Supplemental Readings, Day 3
Global Health and Disasters Course

Influenza

What you need to know about diagnosing and treating TB: a preventable, fatal disease

HIV: Elimination, Cure and Treatment
Supplemental Readings

Influenza

Presented by: Wayne Sullender

Readings
Influenza Section in Module 5 of Pediatric Education in Disasters Manual, pp. 10-18.


http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm
INFLUENZA INFECTIONS

OBJECTIVES

- Understand the influenza virus pathogenesis and epidemiology.
- Describe clinical symptoms of influenza and diagnostic and treatment options.
- Evaluate treatment and prevention methodologies for influenza and incorporate them into preparedness plans.

What is Influenza?

Influenza is a segmented, single-stranded enveloped RNA virus classified into influenza A, B and C based on antigenic differences. Influenza A is a potentially severe illness, causes epidemics and pandemics, is rapidly changing, and infects birds, swine, horses, seals, and humans. Influenza B is more uniform, causes epidemics and only infects humans. Influenza C is of minimal public health impact and infects humans and swine. Further subtyping of influenza A virus is based on the neuraminidase and hemagglutinin proteins on the viral surface. There are 16 different hemagglutinins and 9 different neuraminidase subtypes. Hemagglutinin proteins allow the virus to stick to cells by binding to a specific receptor. The neuraminidase protein helps newly formed viral particles get released from the cell surface so that they have the potential to infect other cells. Only H1N1, H2N2, H3N2 subtypes are associated with widespread epidemics in human. Since 1997, rare but severe infections in humans with influenza A subtype H5N1 viruses have been identified in Asia, Africa, Europe, and the Middle East where these viruses are present in domestic or wild birds.

Repeated seasonal influenza epidemics persist because the type A and type B viruses undergo constant and rapid change due to antigenic drift. Antigenic drift refers to a gradual change in the virus that occurs through a slow series of amino acid changes in the hemagglutinin or neuraminidase surface antigens. Occurring only after a particular viral strain has become established in humans, antigenic drift represents an adaptation to the development of host antibodies. Newly developed antigenic strains of influenza then prevail for a period of 2 to 5 years, only to be replaced by the next emerging strain. This new strain can then trigger a new epidemic, since it is now unfamiliar to the antibody repertoire of the population. The development of yet another set of host antibodies eventually protects the population—at the same time it puts pressure on the virus to drift yet again. Ongoing change caused by antigenic drift requires ongoing reformulation of influenza vaccines usually on an annual basis. The World Health Organization and the Centers for Disease Control and Prevention continually track these changes to better recommend strains to be contained in the next seasonal influenza vaccine.

In contrast to the gradual evolution of strains subject to antigenic drift, antigenic
shift occurs as soon as a type A influenza virus with a completely novel hemagglutinin or neuraminidase moves into humans from another host species. The primary source is birds, certain species of which carry a reservoir of 15 influenza A subtypes. These subtypes either genetically reassort themselves with circulating human influenza virus or are transmitted directly into humans, typically via intermediate hosts such as swine. Antigenic shift of type A influenza viruses occurs less frequently than antigenic drift, but with more dramatic impact that can lead to a pandemic. A pandemic is defined by the emergence and global spread of a new influenza A virus subtype to which the population has little or no immunity and that spreads rapidly from human to human. Pandemics, therefore, can cause increased morbidity and mortality rates compared with seasonal influenza. During the 20th century, there have been four influenza pandemics, in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 2009-10 (H1N1). The recent influenza pandemics of 2009 H1N1 ("swine flu") was caused by genetic reassortment between human, two avian and one swine influenza viruses. Avian influenza (H5N1) continues to cause outbreaks among poultry and wild birds worldwide but has caused relatively few cases of human H5N1 infection although case fatality rates are greater than 50 percent.

Epidemiology
Influenza is spread from person to person primarily by respiratory droplets created by coughing or sneezing. Contact with respiratory droplet-contaminated surfaces or fomites is another possible mode of transmission. During community outbreaks of influenza, the highest attack rates occur among school-aged children. Secondary spread to adults and other children within a family is common. Incidence and disease severity depend, in part, on immunity developed as a result of previous experience (by natural disease) or recent influenza immunization with the circulating strain or a related strain. In temperate climates, seasonal epidemics usually occur during winter months. Peak influenza activity in the United States can occur anytime from November to May but most commonly occurs in January and February. Community outbreaks can last 4 to 8 weeks or longer. Circulation of 2 or 3 influenza virus strains in a community may be associated with a prolonged influenza season of 3 months or more and bimodal peaks in activity. Influenza is highly contagious, especially among semi enclosed institutionalized populations.

Attack rates in healthy children generally have been found to be 10% to 40% each year, but illness rates as low as 3% also have been reported. Children younger than 5 years of age visit clinics or emergency departments for influenza illness at the rate of 1 to 2 children per 100 annually. Influenza and its complications have been reported to result in a 10% to 30% increase in the number of courses of antimicrobial agents prescribed to children during the influenza season. These medical care encounters for children with influenza result in considerable costs and
likely are an important cause of inappropriate antimicrobial use.

**Influenza Pathogenesis and Symptoms**

Influenza in adults typically begins with the sudden onset of fever, often accompanied by chills or rigors, headache, malaise, diffuse myalgia, and nonproductive cough. Subsequently, respiratory tract signs including sore throat, nasal congestion, rhinitis, and cough become more prominent. Conjunctival injection, abdominal pain, nausea, vomiting, and diarrhea are less commonly associated with influenza illness. Influenza symptoms may be different among different age populations with older children and adolescents having more classic adult influenza-like symptoms. Neonates may present with fever and a sepsis-like picture and toddlers may have few respiratory signs but have vomiting and diarrhea as their predominant symptom. The usual incubation period between the time someone is exposed and infected with influenza virus to the time that they experience symptoms of illness ranges from 18 hours to 5 or more days with an average of 2-3 days. Once infected with influenza the principal site of replication is the columnar epithelium in the back of the throat. Viral shedding in respiratory secretions occurs for 1 day before illness and 5-10 days after illness onset. Viral titers are generally higher in young children with shedding lasting 10 days or longer. Peak shedding of virus generally occurs during the first 3 days of illness and correlates with the presence of fever.

**Complications of Influenza**

Post-influenza complications are common. Influenza is an important cause of otitis media. Acute myositis characterized by calf tenderness and refusal to walk has been described especially with influenza type B. In infants, influenza can produce a sepsis-like picture and occasionally can cause croup, bronchiolitis, or pneumonia. Although the large majority of children with influenza recover fully after 3 to 7 days, previously healthy children can have severe symptoms and complications. Neurologic complications associated with influenza range from febrile seizures to severe encephalopathy and encephalitis with status epilepticus, with resulting neurologic sequelae or death. Reye syndrome has been associated with influenza infection and salicylate exposure. Death from influenza-associated myocarditis has been reported. Invasive secondary infections or coinfections with group A streptococcus, Staphylococcus aureus (including methicillin-resistant S. aureus [MRSA]), Streptococcus pneumoniae, or other bacterial pathogens can result in severe disease and death.

Hospitalization rates among children younger than 2 years of age are similar to hospitalization rates among people 65 years of age and older. Children younger than 24 months of age consistently are at substantially higher risk of hospitalization than are older children, and the risk of hospitalization attributable to influenza infection is highest in the youngest chi-
Rates of hospitalization and morbidity attributable to complications, such as bronchitis and pneumonia, are even greater in children with high-risk conditions, including hemoglobinopathies, bronchopulmonary dysplasia, asthma, cystic fibrosis, malignancy, diabetes mellitus, chronic renal disease, and congenital heart disease. Influenza virus infection in neonates also has been associated with considerable morbidity, including a sepsis-like syndrome, apnea, and lower respiratory tract disease. Fatal outcomes, including sudden death, have been reported in both chronically ill and previously healthy children. All influenza-associated pediatric deaths are nationally notifiable and should be reported to the CDC through state health departments.

**Diagnostic Tests**

Specimens for viral culture, immunofluorescent, or rapid diagnostic tests should be obtained if possible during the first 72 hours of illness, because the quantity of virus shed decreases rapidly as illness progresses beyond that point. Rapid enzyme immunoassay diagnostic tests for identification of influenza A and B antigens in respiratory tract specimens are available commercially, although their reported sensitivity (44%–97%) and specificity (76%–100%) compared with viral culture are variable and differ by test and specimen type. Additionally positive and negative predictive values of these influenza screening tests is influenced by the prevalence of circulating influenza viruses resulting in an increased likelihood of false-positive results during periods of low influenza activity. Direct fluorescent antibody (DFA) and indirect immunofluorescent antibody (IFA) staining for detection of influenza A and B antigens in nasopharyngeal or nasal specimens are available at most hospital-based laboratories and can yield results in 3 to 4 hours. Reverse transcriptase-polymerase chain reaction (RT-PCR) testing of respiratory tract specimens may be available at some institutions and offers potential for high sensitivity and specificity in particular with the 2009-2010 H1N1 pandemic strain.

**Treatment of Influenza**

Treatment is mostly supportive with rest, fluids, and antipyretics such as acetaminophen or ibuprofen. Aspirin and other salicylate-containing products should be avoided as it is associated with a rare severe complication called Reye Syndrome. Antivirals administered within 2 days of illness onset may have the greatest benefit to reduce the duration of uncomplicated influenza illness and should be considered for those who are at increased risk of severe or complicated influenza infection. Other candidates for antiviral therapy include healthy children with moderate to severe illness and people with special environmental, family, or social situations where ongoing influenza illness would be detrimental. Antiviral treatment should be continued for 5 days and be discontinued approximately 24 to 48 hours after symptoms resolve. Children with severe influenza
should be evaluated carefully for possible coinfection with bacterial pathogens, such as *Staphylococcus aureus*, that might require antimicrobial therapy.

In the United States, two classes of antiviral medications are available for treatment or prophylaxis of influenza infections: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (amantadine and rimantadine). Treatment has been shown to decrease the duration of flu-related symptoms by 1 to 1.5 days. Oseltamivir has been approved for chemoprophylaxis and treatment of patients older than one year old. Zanamivir has been approved for treatment in patients 7 years and older and chemoprophylaxis of patients age 5 years and older.

Influenza B viruses intrinsically are resistant to adamantanes and since 2005 all H3N2 strains in the United States have been resistant to adamantanes. During the 2008–2009 influenza season, virtually all H1N1 influenza strains were resistant to oseltamivir but remained susceptible to zanamivir, amantadine, and rimantadine. The most recent pandemic 2009–2010 H1N1 strain was once again susceptible to oseltamivir.

These resistance patterns among circulating influenza A virus strains present challenges in selecting antiviral medications for treatment and chemoprophylaxis of influenza and provide additional reasons for clinicians to test patients for influenza virus infection and to consult surveillance data in their community when evaluating people with acute respiratory tract illnesses during the influenza season. Specific drug recommendations for treatment and chemoprophylaxis may vary by season, geographic location, and level of circulating viral resistance. The CDC website provides current recommendations for treatment and chemoprophylaxis of influenza: [www.cdc.gov/flu/professionals/antivirals/index.htm](http://www.cdc.gov/flu/professionals/antivirals/index.htm).

Zanamivir (Relenza®) is available as a dry powder administered via oral inhalation with a plastic device. The dose is two breath-activated inhalations (one 5 mg blister per inhalation = 10 mg) bid for 5 days. Zanamivir is not recommended for use in patients with underlying airway disease including asthma or COPD, because of a lack of safety and efficacy data in these patients. Oseltamivir (Tamiflu®) is available as pills or liquid and is given twice daily for 5 days, with dose adjustments required in renal impairment. Pediatric dosing of oseltamivir for 1 – 12 years is 2 mg/Kg/dose bid x 5 days (max. dose = 75 mg) and for 13 years and older: 75 mg bid x 5 days.

### Chemoprophylaxis

Chemoprophylaxis or prolonged administration of antiviral medications during the periods of highest risk for transmission is an adjunct for control and prevention of influenza in specific situations and is not a substitute for immunization. Chemoprophylaxis should be considered for protection of children at increased risk of severe infection or complications who are unable to receive influenza vaccine due to contraindications and for immunocompromised children who may not respond to
vaccine. Other considerations include the protection of unimmunized high-risk children or children who were immunized less than two weeks before influenza circulation and who may not have developed an adequate immune response, protection of unimmunized close contacts of high-risk children, protection of immunized high-risk children if the circulating influenza strain is a poor match to the strain in the vaccine and for the control of influenza outbreaks in some institutional closed settings.

Prevention of Influenza
Good infection control maintenance is a well known cornerstone of disease management and needs to be the focus of general practice management of all respiratory outbreaks including seasonal and pandemic influenza. Infection control refers to all policies, procedures and activities that aim to prevent or minimize the risk of transmission of infectious diseases. This includes simple measures such as adequate hand hygiene by hand washing or hand rubs, and cough etiquette to more involved measures such as personal protective equipment (PPE).

Hospitalized patients with influenza should be placed on droplet precautions (mask, gown and glove). Respiratory hygiene/cough etiquette (placing masks on patients with a cough when outside of their room) should be incorporated into infection control practices. Visitors who have any respiratory illness symptoms should be discouraged from visiting patients. Health care workers who are ill should be restricted from working until they are healthy.

The primary measure to prevent influenza is vaccination of both patients and families, and healthcare workers. The rapid evolution of new strains of influenza necessitates annual reformulation of the vaccine strains and annual vaccination of vaccine recipients to maintain immunity to current influenza strains. All currently available inactivated and live attenuated influenza vaccines are trivalent, meaning they contain 3 strains that represent the most recent circulating wild-type strains in a given year: A (H3N2), A (H1N1), and B. Initiation of influenza vaccination programs should start as soon as influenza vaccine is available from manufacturers and should be continued throughout the influenza season.

Surveillance and Surge Planning
During the pre-pandemic intervals, healthcare providers and healthcare facilities play an essential role in surveillance for suspected cases of infection with novel strains of influenza and should be on the alert for such cases. Novel strains may include avian or animal influenza strains that can infect humans such as avian influenza A H5N1 or novel influenza A H1N1 and new or re-emergent human viruses that cause cases or clusters of human disease. For detection of cases during the Pre-Pandemic and Pandemic Intervals, hospitals should have predetermined thresholds for activating pandemic influenza surveillance plans.
Influenza pandemics are different from many of the threats for which public health and the healthcare system are currently planning. The pandemic will last much longer than most other emergency events and may include “waves” of influenza activity separated by months (in 20th century pandemics, a second wave of influenza activity occurred 3 to 12 months after the first wave). The numbers of healthcare workers and first responders available to work can be expected to be reduced; they will be at high risk of illness through exposure in the community and in healthcare settings, and some may have to miss work to care for ill family members. It is reasonable to assume that absenteeism may exceed 25%. Resources in many locations could be limited because of how widespread an influenza pandemic would be.

The goal of a pandemic surge plan for an emergency department or other outpatient setting is to provide safe and effective care in the event of an influenza pandemic or similar event, and to optimize resources and mitigate throughput issues in order to provide for maximum surge capacity for pediatric patients presenting to the emergency department for care. Utilizing the all-hazards approach to develop plans for epidemic and pandemic respiratory illness is based on the concept that most disaster-response functions are common to all disaster types, and unified planning provides the strongest basis for effective response.

Critical components of comprehensive plans must address the following: 1) Screening, surveillance, and tracking of exposed individuals; 2) controlled access to the healthcare facility; 3) prevention strategies (isolation and cohorting, PPE use, vaccination, antiviral prophylaxis, modification of environmental controls (i.e., separate areas for ill and non ill patients); 4) disease-specific admission criteria, treatment, and triage algorithms; and 5) enabling the continuity of limited clinical operations.

In all healthcare settings, patients with symptoms of influenza or influenza-like illness (ILI) should be segregated from non-influenza patients as rapidly as possible, especially in a triage setting. When possible, consider having different teams of staff should care for influenza and non-influenza patients. In acute care settings, triage non-ILI patients promptly to specific non-ILI waiting and examining areas, physically separate from the ILI assessment area to prevent their exposure to ILI if possible. Additionally separate entrances and exits should be established for those who believe they may have been exposed to ILI or those that are in need of other types of medical attention if feasible.

Admission policies and testing and treatment algorithms should also be created for determining if a patient needs to be admitted to the hospital or if an alternate care facility may be more appropriate if altered standards of care are being used. If possible, hospitals triage protocols for phone triage may help to educate patients and families and provide help with illness management without accessing the clinic, emergency department or
hospital setting. The diagnosis and treatment algorithms used at the Children’s Hospital Colorado can be found in this module appendix.

**Special Issues in Developing Countries**

Several factors may be involved in the high mortality rates pandemics cause in developing countries. These include lack of access to adequate medical care, weak public health infrastructures, social factors such as housing conditions and population density, and host factors such as nutritional status and co-existing medical conditions. Core interventions to control or mitigate the effects of an influenza pandemic include pharmaceutical interventions such as vaccines and antiviral agents, and nonpharmaceutical interventions such as quarantine, isolation, social distancing, and personal hygiene.

Antiviral agents are particularly useful in the early stages of a pandemic when there is shortage of vaccines. Stockpiling of neuraminidase inhibitors is part of many industrialized countries pandemic preparedness plans however stockpiles of antiviral agents available in developing countries is small and limited. The most critical limiting factor for stockpiling neuraminidase inhibitors in developing countries is their high cost and allocating scarce resources to stockpile sufficient quantities of oseltamivir for an unpredictable influenza pandemic. Because only a limited number of vaccines will be initially available, particularly in the early stages of a pandemic, and most of them would likely be supplied to industrialized countries, developing countries will need to focus initially on nonpharmaceutical interventions. Maintaining a balance between pharmaceutical and nonpharmaceutical interventions is necessary to achieve the best use of limited resources.

During an influenza pandemic, additional essential medical supplies such as gloves, masks, syringes, antipyretics, and antimicrobial agents will also be required. These supplies are insufficient in healthcare facilities in developing countries, even in nonemergency situations. Lack of these supplies may hamper provision of adequate medical care for patients with pandemic influenza. Basic PPE such as disposable gloves and surgical masks are needed for protecting healthcare workers. Anti-microbial agents are expected to be effective for secondary bacterial pneumonia, which can be a major cause of death for patients with pandemic influenza.

Providing better medical care during a pandemic is essential to reduce the health consequences of the pandemic including death. Since the availability of pharmaceutical interventions in developing countries is less likely, nonpharmaceutical interventions such as social distancing and personal hygiene may be the only available interventions. Essential medical supplies such as masks, gloves, and antimicrobial agents should be available in hospitals and clinics. The stockpiles of these basic supplies can be more cost-effective in developing countries than stockpiles of more expensive antiviral agents. Healthcare personnel
should be trained for infection control measures, especially hand hygiene and use of personal protective equipment. The overarching goal is to maintain the current healthcare and public health systems need to minimize the impact of a pandemic. The link to PAHO’s Pandemic Influenza A (H1N1) 2009 manuals that describe preparedness planning, infection prevention and control, nonpharmaceutical strategies and IMCI diagnosis, treatment and management protocols in Spanish, English, Portuguese and French is http://new.paho.org/hq/index.php?option=com_content&task=view&id=2914&Itemid=1084&lang=en.

Lessons Learned from 2009-2010 H1N1 Pandemic
The WHO plans to continue to strengthen influenza surveillance and the early warning system, build capacity to cope with a pandemic, and further coordinate global scientific research and development activities. The current novel influenza A (H1N1) pandemic confirms the need for preparedness plans that focus on both nonpharmaceutical strategies (social distancing, infection control and quarantine), and pharmaceutical strategies (antiviral drugs use for the treatment and prophylaxis of influenza, and the use of influenza vaccines) to mitigate the effect of the pandemic. The importance of building human surge capacity allows the allocation of health resources including the provision of essential health services and determination of the roles each institution plays in the response. Infection prevention and control activities have been critical to protect healthcare workers and to prevent the nosocomial spread of influenza infections.

Additionally, there is an urgent need to have better detection methods for influenza viruses, including the creation or strengthening and scaling-up of laboratory capacity for influenza diagnosis in most settings (low-, middle-, and high-income countries), through international networks of collaboration, technology transfer, and capacity-building efforts. Pharmacologic interventions including the use of antiviral drugs and medical interventions such as antimicrobials to treat secondary bacterial pneumonias, along with the use of supportive medical care such as oxygen, anti-inflammatory drugs, and antipyretics, have also shown to be a critical component of the overall response activities during the current influenza pandemic. Finally, all countries should develop pandemic influenza vaccine deployment or antiviral deployment plans, regardless of the current absence of availability of pandemic influenza vaccine or adequate supplies of antiviral medications.
INTERIM INFLUENZA TESTING ALGORITHM

Currently Influenza A-H1 (Swine), susceptible to oseltamivir (Tamiflu), is the only strain circulating in Colorado. Recommendations will change as strains change in the community - for most current information go to “PlanetCtv/Quicklinks/Influenza info”

Patient presenting to ED/NOC/outpatient clinic

Patients presenting with symptoms consistent with Influenza

1. Place immediately in and rigorously enforce DROPLET PRECAUTIONS
2. Give information sheet that recommends notification of high-risk contacts

Patient requiring hospitalization

Patient NOT requiring hospitalization

Rapid Flu IA* with backup PCR

High-Risk Child

Low-Risk Child

Respiratory Flu IA* with backup PCR

No Test Recommended

Treat presumptively (even if symptoms >48 hrs) until both tests are influenza negative. Use oseltamivir or zanamivir while prevalence of seasonal influenza is low. (See tables)

*High Risk Child per CDC suggestion = Children < 2 yrs (CDC includes those 2-5 yrs but many experts feel that is excessive); children with any of the following medical conditions: chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), neurologic, neuromuscular, or metabolic disorder (including diabetes mellitus); immunosuppression including that caused by medications or by HIV; pregnant women; persons who are receiving long-term aspirin therapy; residents of chronic-care facilities; or children who present with a severe illness.

* Nasopharyngeal Aspirate - Observe droplet precautions + N95 mask and eye protection. Get a good specimen - the quality of the result is directly proportional to the quality of the specimen! Immunofluorescent (IFA) sensitivity alone = 70%.

Note to ordering physicians - Due to the increased number of samples being tested, the microbiology lab will only call physicians for respiratory virus results if positive for influenza. It is the ordering physician's responsibility to follow up for all other testing results.

Recommendations will change when seasonal influenza and/or RSV become more widespread in the community.
## INFLUENZA ANTIVIRALS

### Table 1. Influenza A-H1 (Swine) Oseltamivir dosing recommendations

<table>
<thead>
<tr>
<th>Age group</th>
<th>Treatment</th>
<th>Chemoprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>75-mg capsule twice per day for 5 days</td>
<td>75-mg capsule once per day</td>
</tr>
<tr>
<td>Children (age, 12 months or older), weight:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 kg or less</td>
<td>60 mg per day divided into 2 doses</td>
<td>30 mcg once per day</td>
</tr>
<tr>
<td>16-23 kg</td>
<td>90 mg per day divided into 2 doses</td>
<td>45 mg once per day</td>
</tr>
<tr>
<td>24-40 kg</td>
<td>120 mg per day divided into 2 doses</td>
<td>60 mg once per day</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>150 mg per day divided into 2 doses</td>
<td>75 mcg once per day</td>
</tr>
</tbody>
</table>

### Table 2. Dosing recommendations for antiviral treatment of children younger than 1 year using oseltamivir

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended treatment dose for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td>12 mg twice daily</td>
</tr>
<tr>
<td>3-5 months</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>6-11 months</td>
<td>25 mg twice daily</td>
</tr>
</tbody>
</table>

### Table 3. Summary of Antiviral Resistance, U.S. 2008-09

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>A-H1 (Swine)</th>
<th>A-H1 (Seasonal)</th>
<th>A-H3 (Seasonal)</th>
<th>B (Seasonal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Resistant</td>
<td>No activity</td>
</tr>
<tr>
<td>Rimantadine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir (Tamiflu)</td>
<td>Susceptible</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Zanamivir (Relenza)</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>
Prevention and Control of Influenza with Vaccines: Interim Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2013

This report summarizes recommendations approved on February 21, 2013, by the Advisory Committee on Immunization Practices (ACIP) for the use of influenza vaccines. An expanded 2013 ACIP influenza vaccination recommendation statement is scheduled to be published in MMWR Recommendations and Reports before the start of the 2013–14 influenza season. Providers should consult the expanded 2013 ACIP influenza vaccination statement for complete and updated information.

Vaccine Recommendations

Routine annual influenza vaccination is recommended for all persons aged ≥6 months. Immunization providers should consult Food and Drug Administration-approved prescribing information for 2013–14 influenza vaccines and the 2013–14 ACIP influenza recommendation statement for the most current information concerning indications, contraindications, and precautions.

Available Influenza Vaccines for 2013–14

Influenza vaccines that are currently licensed and expected to be available for the 2013–14 season and their approved age indications are summarized in a table available at http://www.cdc.gov/flu/professionals/acip/2013-interim-recommendations.htm#table1. The information in the table is current as of April 15, 2013. Any changes in product availability or other information will be reflected in the expanded 2013–14 ACIP influenza recommendations statement. The table lists four newly licensed influenza vaccines that are expected to be available during the 2013–14 influenza season. These vaccines are acceptable alternatives to other licensed products listed in the table, to the extent that their specific indications allow. For persons for whom more than one type of vaccine is appropriate and available, ACIP does not express a preference for use of any particular product over another.

Note on Influenza Vaccine Abbreviations

Certain U.S. vaccine abbreviations have been revised by ACIP to refer to currently available influenza vaccines.* The revisions are as follows:

- The abbreviation IIV (trivalent influenza vaccine, previously used for inactivated influenza vaccines) has been replaced with the abbreviation IIV (inactivated influenza vaccine). For 2013–14, IIVs as a class will include 1) egg-based and cell culture-based trivalent inactivated influenza vaccine (IIV3), and 2) egg-based quadrivalent inactivated influenza vaccine (IIV4).
- RIV refers to recombinant hemagglutinin influenza vaccine, which will be available as a trivalent formulation (RIV3) for 2013–14.
- LAIV refers to live, attenuated influenza vaccine, which will be available as a quadrivalent formulation (LAIV4) for 2013–14.
- LAIV, IIV, and RIV denote vaccine categories; a numeric suffix specifies the number of influenza virus antigens contained in the vaccine.
- Where necessary to refer specifically to cell culture-based vaccine, the prefix “cc” is used (e.g., “ccIIV3”).

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Acknowledgments


Supplemental Readings

What you need to know about diagnosing and treating TB: a preventable, fatal disease
Presented by: Robert Belknap

Readings
Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment

Elizabeth L Corbett, Barbara Marston, Gavin J Churchyard, Kevin M De Cock

Rapid scale-up of antiretroviral treatment programmes is happening in Africa, driven by international advocacy and policy directives and supported by unprecedented donor funding and technical assistance. This welcome development offers hope to millions of HIV-infected Africans, among whom tuberculosis is the major cause of serious illness and death. Little in the way of HIV diagnosis or care was previously offered to patients with tuberculosis, by either national tuberculosis or AIDS control programmes, with tuberculosis services focused exclusively on diagnosis and treatment of rising numbers of patients. Tuberculosis control in Africa has yet to adapt to the new climate of antiretroviral availability. Many barriers exist, from drug interactions to historic differences in the way that tuberculosis and HIV are perceived, but failure to successfully integrate HIV and tuberculosis control will threaten the viability of both programmes. Here, we review tuberculosis epidemiology in Africa and policy implications of HIV/AIDS treatment scale-up.

Search strategy and selection criteria

Publications related to tuberculosis or antiretroviral treatment in Africa were identified by systematically searching PubMed and Google Scholar with terms including, but not restricted to, the following combinations: “tuberculosis Africa”, “tuberculosis HIV”, “tuberculosis antiretroviral”, “mortality/survival tuberculosis”. Further publications were identified from references cited in relevant articles, reports, and workshop and conference proceedings. The search was restricted to publications in English, but not restricted by date.
HIV and epidemiology of tuberculosis in Africa

Burden of HIV/AIDS and tuberculosis

Figure 2 summarises the disproportionate burden of HIV and tuberculosis infection and disease in Africa at the start of the new millennium. In 2003, an estimated 8.8 million new cases of tuberculosis resulted in 1.7 million deaths. 27% of these cases and 31% of these deaths arose in Africa, home to only 11% of the world’s population. HIV prevalence in tuberculosis patients is less than 1% in the Western Pacific region but 38% in Africa. In countries with the highest HIV prevalence, more than 75% of cases of tuberculosis are HIV-associated.

In Africa, tuberculosis is often the first manifestation of HIV infection, and it is the leading cause of death among HIV-infected patients. In hospital-based series, 40–65% of HIV-infected African patients with respiratory disease had tuberculosis. In primary health and chest clinic settings, tuberculosis was confirmed in 43–70% of adults with cough for 3 weeks or longer (chronic cough) in Zimbabwe, Kenya, and Malawi. Patients with tuberculosis now commonly present with atypical symptoms: M tuberculosis was isolated from 9% of adults with acute pneumonia in Kenya, 35% of people with cough for less than 3 weeks in Malawi, 23% of febrile HIV-infected inpatients in Tanzania, and 13% of HIV-infected patients with chronic diarrhoea in Kenya. In Cote d’Ivoire, the Democratic Republic of Congo, and Kenya, 38–47% of autopsies in HIV-positive adults indicated tuberculosis as the cause of death, although tuberculosis had been diagnosed during life in only about half of those with autopsy-proven disease.

Increased risk for tuberculosis from HIV infection in Africa

Comparison of HIV prevalence in general populations and tuberculosis patients shows that tuberculosis incidence was 8–3 times higher in HIV-positive than HIV-negative African people in 2003 (figure 3). In 2000, similar methods led to an estimated relative rate of 5.9, whereas estimates from individual cohort studies range from less than 5 to more than 20. Tuberculosis incidence increases with worsening immunosuppression, so that relative rates rise during the course of an HIV epidemic.

Tuberculosis incidence in African countries with high HIV prevalence

Reported tuberculosis case rates rose by 6.4% per year in the WHO African region in the late 1990s, but with up to five-fold increases since 1990 in some countries. Incidence might have peaked in some countries (figure 4) but at very high rates. The high case rate in Africa contributed to a global rise in tuberculosis incidence of 1% in 2003, despite stable or declining rates in the rest of the world.

Southern Africa has the highest prevalence of HIV infection and had the highest incidence of tuberculosis before the HIV/AIDS era. In the six southern African countries with adult HIV prevalence of more than 20%, tuberculosis case-notification rates are 461–719 per 100 000 per year; by comparison, the notification rate in the USA was 5 per 100 000 per year. True yearly rates in Africa are likely to be even higher because of under-diagnosis and under-reporting.

HIV and infectiousness and transmission of tuberculosis

The critical period with respect to infectiousness is before diagnosis, because most patients become non-infectious soon after starting treatment, even if they are HIV-infected. Both intensity and duration of infectiousness are highly variable, with some individuals remaining very infectious for prolonged periods, sometimes with apparently minor symptoms. HIV-positive individuals with tuberculosis are less infectious than HIV-negative patients since they are less often and
less intensely smear-positive and because they remain infectious for a much shorter average duration. The average duration of smear positivity for HIV-negative individuals in resource-poor settings is estimated to be between 1 and 3 years. In two African studies in high HIV settings, mean durations of smear-positivity of only 6 and 8 weeks were estimated for HIV-positive patients with smear-positive tuberculosis, indicating fast progression to symptomatic disease. In both studies, most infectious individuals at any given point in time—the driving force for tuberculosis transmission in the community—were HIV-negative, because of their fairly long duration of infectiousness (figure 5). Thus, HIV-associated tuberculosis contributes greatly to incidence of tuberculosis and deaths, but it might contribute much less to disease transmission because of early diagnosis or death. This combination of exquisite vulnerability to disease by HIV-positive individuals and prolonged transmission from HIV-negative patients with tuberculosis together fuel escalating tuberculosis incidence in areas of high HIV prevalence. This fundamental observation has important implications for tuberculosis control in Africa.

Tuberculosis control in Africa before antiretroviral treatment

Tuberculosis control has been based on the WHO-promoted DOTS strategy, whose philosophical basis is prompt diagnosis and effective treatment of individuals with smear-positive tuberculosis to interrupt continuing transmission. In the face of rising tuberculosis incidence in Africa, international guidance during the 1990s emphasised the need for tuberculosis programmes to focus on diagnosis and treatment of self-presenting patients and to improve adherence and cure rates. HIV services, such as HIV-testing, were only deemed appropriate when priority tuberculosis objectives had been met. While understandable under the circumstances and funding of the time, this approach did not serve the overall medical needs of HIV-infected patients with tuberculosis.

The HIV epidemic has challenged DOTS as a sole tuberculosis control strategy for Africa, because even rigorous programmes cannot adequately compensate for the rising susceptibility to tuberculosis at the population level that occurs as HIV prevalence increases. As an example, despite well-funded control programmes in the South African gold mining industry that adhere to all elements of WHO’s DOTS strategy and screen miners every year, tuberculosis case rates have risen four-fold since 1990, driven by an increase in population HIV prevalence from less than 1% to almost 30%.

Containing tuberculosis transmission and preventing drug resistance might be realistic and important goals for conventional DOTS programmes, but they are not routinely evaluated. Evidence that strong tuberculosis control programmes can control disease transmission is provided by analysis of incidence data stratified by HIV status. Figure 6 shows two possible scenarios of an epidemic of HIV.

In part A, an epidemic of HIV is shown, during which slowly falling tuberculosis transmission rates (from 1%
in 1985 to 0.7% per year in 2010) are maintained despite a rising burden of HIV-related tuberculosis. Disease incidence continues to decline in the HIV-negative subpopulation, but rises in the HIV-positive subpopulation as the proportion of patients with moderate-to-severe immunosuppression increases (maturation of the HIV epidemic). Overall tuberculosis incidence rises to a plateau soon after peak HIV prevalence in 2000. This scenario might describe the course of HIV and tuberculosis in countries with fairly strong tuberculosis control programmes such as Malawi and Tanzania, where peak tuberculosis incidence might already have been reached. In part B, an identical HIV epidemic to that in part A is shown, with the same assumptions about the effect of HIV on susceptibility to tuberculosis disease. However, in this scenario, the potential for HIV-related tuberculosis to increase disease transmission rates is not contained. Tuberculosis incidence rises to very high levels among HIV-positive individuals and increases substantially in the HIV-negative subpopulation as well, because of a rise in yearly risk of infection from 1% in 1985 to 2.7% in 2010. Tuberculosis incidence continues to rise after HIV prevalence peaks. Several countries, including Kenya, Uganda, and Swaziland, might be following a course intermediate between these two scenarios.

Uganda and Kenya have reported continuing rises in tuberculosis case rates despite falling HIV prevalence, associated with a noted rise in yearly risk of *M. tuberculosis* infection in Kenya.\(^4\,18\,51\) Data for Cote d’Ivoire, South Africa, Malawi, and Thailand, however, show stable or declining tuberculosis incidence among HIV-negative individuals despite increasing burdens and incidence of HIV-related tuberculosis.\(^46\,52\) Similarly, in Tanzania, tuberculosis transmission rates have continued to decline while case-notifications have quadrupled.\(^6\) Within the same environment, therefore, strong orthodox tuberculosis control approaches can limit or reduce HIV-negative tuberculosis but not that associated with HIV.\(^52\)

**Effect of antiretroviral treatment on tuberculosis epidemiology**

**Mortality in HIV-infected tuberculosis patients**

Antiretroviral treatment scale-up mainly aims to reduce HIV-associated morbidity and mortality. Tuberculosis case-fatality rates (proportion of patients dying while on antituberculous treatment) in Africa are 16–35% in HIV-positive individuals not receiving antiretroviral treatment and 4–9% in HIV-negative patients.\(^53\) Increased mortality in the first month of treatment seems largely attributable to tuberculosis itself,\(^54\) whereas other HIV-associated pathologies predominate thereafter.\(^55\) The highest death rates are present for people with the lowest CD4+ T-lymphocyte counts (CD4 count).\(^55\) In a 7-year follow-up in Malawi before HIV/AIDS treatment initiatives, only 11% of individuals who were HIV-infected at tuberculosis diagnosis were known to be still living.\(^56\) About a quarter of known deaths arose within 1 month of tuberculosis diagnosis.

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**Figure 6: Simulated time trends in tuberculosis incidence during the course of an HIV epidemic**

Deterministic compartmental model of HIV (uninfected, WHO stages 1–4) and tuberculosis infection and disease (susceptible, latent, diseased, on-treatment, post-treatment), as previously described.\(^50\) Scenarios shown of tuberculosis trends in the whole population and HIV subpopulations under either falling (A) or rising (B) tuberculosis transmission rates. (C) Time course of simulated HIV epidemic in (A) and (B). HIV prevalence refers to adults in the general population (not tuberculosis patients).
Case-fatality rates can be reduced by diagnosis of HIV infection linked to co-trimoxazole prophylaxis and antiretroviral treatment. Mortality in tuberculosis patients in London (UK) fell by 72% after introduction of highly active antiretroviral drugs. Mortality in African people with HIV-associated tuberculosis is similar to that in patients with tuberculosis before effective antituberculous treatment, and provision of antiretroviral drugs could have as revolutionary an effect as antituberculous drugs themselves did when first introduced.

**Tuberculosis incidence and recurrence in HIV-infected people**

Findings of several studies from different countries show that antiretroviral drugs reduce the incidence of tuberculosis in HIV-infected people by 80% or more, with the greatest effect at the lowest CD4 counts. However, clinically important immune dysfunction persists even during successful antiretroviral treatment, and tuberculosis incidence remains well above HIV-negative rates, even at high CD4 counts. Rates of recurrent disease in patients with previous HIV-related tuberculosis are also high, suggesting a need for secondary preventive treatment.

Tuberculosis is an aggressive opportunistic infection that arises at higher median CD4 counts than do most other AIDS-defining disorders. For example, median CD4 counts were 257 per μL for smear-positive patients in Cote d’Ivoire. Current guidelines for resource-poor settings recommend treatment for patients with symptomatic HIV or a CD4 count of 200 per μL or less. The potential effect of antiretroviral treatment on tuberculosis incidence, therefore, is lessened because many HIV-infected patients with tuberculosis present before antiretroviral drugs are prescribed.

Theoretically, even well-functioning antiretroviral programmes could worsen the HIV-associated tuberculosis epidemic if an expanding cohort of patients remains highly susceptible and capable of transmitting tuberculosis for long periods. Mathematical and statistical modelling suggests antiretroviral drug coverage would have to be high, start early, and be combined with tuberculosis preventive treatment to contain disease incidence and reduce mortality.

**Towards a coordinated public-health response to tuberculosis and HIV/AIDS**

One strategy alone is unlikely to succeed: different approaches based on serostatus need to address the vulnerability to tuberculosis disease of HIV-infected individuals and reduce disease transmission from all affected people, including those who are HIV-negative. The need for a coordinated approach towards tuberculosis and HIV control is now stressed at the highest levels. There is understandable reluctance to relinquish the traditional disease model for tuberculosis control: past experience, notably in Zambia, shows that well-intentioned reform can disrupt essential tuberculosis control activities. However, different programme models are now emerging that retain DOTS as the essential but insufficient minimum, while additional elements discussed below are implemented or investigated in collaboration with HIV/AIDS control programmes. Essential outcomes are reduced transmission, disease, and death for both HIV and tuberculosis (panel). Seamless collaboration between tuberculosis and HIV/AIDS treatment programmes is needed, along with a unified public-health vision towards the prevention and treatment of these interacting infectious diseases.

One barrier to closer collaboration is the philosophical difference historically in how HIV/AIDS and tuberculosis surveillance, diagnosis, and treatment have been approached. Tuberculosis control programmes have epitomised the public-health approach of case finding, name-based case notification, and, when possible, screening of contacts. Control of tuberculosis transmission and prevention of drug resistance have been paramount aims, with less emphasis on patient-centred goals such as reduction of deaths. By contrast, HIV/AIDS programmes have focused on an individual approach to HIV testing that is private, confidential, and voluntary, but which has little emphasis on interrupting chains of transmission.

Currently, fewer than 10% of African patients with tuberculosis are tested for HIV, although HIV testing is acceptable to most people when provided in a convenient and confidential way. The major difficulty is that testing is still not routinely offered in most tuberculosis clinics. WHO and UNAIDS guidelines now lend support to diagnostic HIV testing of individuals with HIV-associated disorders, including known and suspected tuberculosis patients, using an opt-out approach, and these organisations have requested routine reporting of the uptake of HIV testing along with the numbers of notified tuberculosis cases.

There are three goals of coordinated tuberculosis and HIV interventions: (1) to optimise diagnosis and treatment to improve outcome for all tuberculosis patients; (2) to reduce HIV-associated tuberculosis incidence and recurrence; and (3) to improve HIV and tuberculosis control overall.

**Optimisation of tuberculosis diagnosis and treatment**

Tuberculosis diagnosis in Africa relies on sputum microscopy followed by broad-spectrum antibiotics and chest radiography if smears are negative. Although specificity is high, major concerns include low sensitivity and delayed diagnosis of smear-negative disease. The accuracy of both microscopy and radiography is reduced by HIV, and so assessment of diagnostic approaches with existing methods and continuing research into new diagnostics are necessary.
Panel: Key interventions for improving tuberculosis and HIV control in Africa

1) Better implementation of existing policies
- Universal HIV testing of patients with confirmed or suspected tuberculosis
- Universal access to high-quality sputum microscopy for individuals with suspected tuberculosis
- Universal directly observed treatment while taking rifampicin-containing tuberculosis regimen
- Antiretroviral treatment according to national guidelines for all HIV-infected individuals, including tuberculosis patients
- Ready access to voluntary counselling and testing for HIV and condoms to prevent HIV transmission

2) More widespread implementation of additional interventions known to be effective
- Use of the most effective short-course chemotherapy for all tuberculosis patients
- Co-trimoxazole prophylaxis for all HIV-infected tuberculosis patients not taking antiretroviral drugs
- Screening of all HIV-infected individuals for tuberculosis infection and disease
- Primary isoniazid preventive treatment for all HIV-infected individuals
- Environmental measures to prevent nosocomial transmission of M tuberculosis

3) Rapid assessment of promising new approaches
- More sensitive sputum smear microscopy
- More rapid and sensitive diagnostic algorithms for smear-negative individuals with suspected tuberculosis
- Expanded access to tuberculosis culture with rapid liquid culture systems
- Secondary preventive treatment for HIV-infected individuals after successful treatment of active tuberculosis
- Early initiation of antiretroviral treatment in newly diagnosed HIV-infected tuberculosis patients
- Co-trimoxazole prophylaxis for HIV-infected tuberculosis patients taking antiretroviral drugs
- Active case-finding for tuberculosis in the community
- Promotion of universal knowledge of HIV serostatus, with emphasis on prevention of transmission from HIV-infected individuals
- Novel HIV prevention interventions

4) Increased resources and support
- Training and retention of health-care workers in joint HIV and tuberculosis management
- Increased funding for integrated tuberculosis and HIV activities
- Increased funding for tuberculosis control programmes to support HIV diagnosis and initiation of HIV care, and more rapid diagnosis and effective treatment of both HIV-positive and HIV-negative patients with tuberculosis

DOTS programmes have focused on smear-positive disease because it is the most infectious type, but much of the increased tuberculosis caseload in Africa is reported as smear-negative.1 HIV-related tuberculosis is more usually smear-negative, extrapulmonary, or disseminated than tuberculosis among HIV-negative individuals. Worsening immunosuppression correlates with increased mycobacterial load and atypical radiological findings: smear-negative tuberculosis has a worse prognosis than smear-positive disease in HIV-positive patients.2–4 In studies based on blood culture, disseminated tuberculosis typically presents as a non-specific febrile disorder that progresses rapidly to death,5 and in autopsy studies, up to 50% of HIV-related tuberculosis deaths go undiagnosed; these findings indicate the diagnostic challenge.6,7 In programmes, a commitment must be made to prioritise smear-negative disease and lower the threshold for starting antituberculous treatment, with appropriate follow-up and outcome assessment.

Major initiatives to increase culture facilities in Africa are underway but without any consensus about their probable effect. Culture outperforms other investigations for early HIV-related tuberculosis8,9 and could be ideal for screening at HIV diagnosis and before starting tuberculosis preventive treatment. For routine investigation of ambulant individuals with suspected tuberculosis, however, the potential gain over sensitive microscopy and radiology is not clear.10–12 Logistic constraints to decentralisation of culture to primary health-care level are considerable,12 and culture might be too slow to contribute much to clinical decision-making.12 Expert groups have prioritised sensitive microscopy over expanded access to culture.13

Active case finding for tuberculosis and HIV

Up to 10% of HIV-infected individuals have active tuberculosis when first seeking knowledge of their HIV status.20 Symptom screening detects most, but not all, active cases,22,23 with culture but not radiology seeming to add substantially to sensitivity.22,23 Every opportunity should be taken to screen HIV-infected African people for active tuberculosis, just as every patient with tuberculosis should be screened for HIV. To increase access to life-prolonging interventions, active case finding for HIV will have to be developed in a way that is acceptable to communities.

Optimisation of antituberculous chemotherapy

The most frequently used treatment for newly diagnosed tuberculosis in Africa is an 8-month regimen introduced in the 1990s to replace thioacetazone-based strategies that were poorly tolerated in patients with HIV infection.25 The 8-month regimen includes rifampicin for 2 months only, but it is inferior to an alternative 6-month regimen containing rifampicin throughout.25 Using rifampicin for 6 months rather than 2 months
extends direct supervision of treatment, which is recommended to prevent rifampicin resistance developing, and it makes treatment choices difficult because of drug interactions between rifamycins and antiretroviral drugs. However, to strive for antiretroviral drug access while tolerating suboptimum tuberculosis treatment is inconsistent, and the 8-month regimen should be phased out as soon as possible.

Prevention of the emergence of multidrug-resistant tuberculosis
Multidrug-resistant strains of M tuberculosis (resistant to at least isoniazid and rifampicin) arise from inadequate treatment of active tuberculosis, and can then be further transmitted. Treatment outcomes are poor for both HIV-positive and HIV-negative patients, with high case-fatality and treatment failure rates. Treatment for multidrug-resistant tuberculosis is expensive, toxic, difficult to combine with antiretroviral drugs, and unavailable in most of Africa. HIV-care settings are prone to outbreaks of nosocomial multidrug-resistant tuberculosis, which can persist for years without intervention. Lack of diagnostic capacity would make early recognition difficult in most of Africa. Data indicate a growing problem, with primary multidrug resistance in more than 2% of patients in parts of South Africa, and a rise in Botswana from 0·2% to 0·8%. Continued commitment, more comprehensive surveillance, better access to drug-sensitivity testing, implementation of fixed-drug combination tablets, and policies for management of multidrug-resistant tuberculosis in HIV care settings are needed. The DOTS strategy focuses on standard treatment regimens and direct observation and has contained and even reduced primary rates of multidrug-resistant tuberculosis in other regions of the world.

Optimisation of antiretroviral therapy in HIV-infected patients with tuberculosis
The high death rate in the first 2 months of tuberculosis treatment provides an argument for antiretroviral drugs to be started as soon as possible. However, challenges favouring a delayed start include drug interactions, combined toxic effects, and non-adherence to treatment. Clear definition of the best time to initiate antiretroviral treatment in patients with tuberculosis awaits results from controlled trials.

Detailed discussions of antiretroviral treatment for tuberculosis patients are available elsewhere. In brief, enzyme induction by rifampicin causes many interactions, with additional concerns of combined toxic effects, especially for nevirapine. Nevirapine-containing antiretroviral regimens are first-line in all African countries apart from South Africa, since the drug is cheap, effective, available in various fixed-drug combinations, and safe in pregnancy. Rifampicin reduces nevirapine concentrations by about a third, and both drugs can cause severe hepatitis. Women with a CD4 count greater than 250 per μL—a substantial subgroup of African patients with tuberculosis—are at highest risk of nevirapine-associated hepatitis. Clinical experience of concurrent use of nevirapine and antituberculous treatment is accruing, but at the time of writing the risks remain unclear.

Patients who start antiretroviral drugs early in their tuberculosis treatment can be predisposed to immune reconstitution inflammatory syndrome, which is frequent, has symptoms overlapping with worsening tuberculosis and drug reactions, and can be life-threatening. WHO guidelines suggest starting antiretroviral drugs within 2 months of tuberculosis treatment at a CD4 count of 200 per μL or less and for extrapulmonary tuberculosis or other manifestations of severe immunosuppression, for patients with CD4 counts less than 50 per μL, treatment initiation is advised within 2 weeks. In such cases, efavirenz-containing regimens are recommended unless contraindicated by pregnancy or the potential to conceive. Use of protease inhibitors other than full-dose ritonavir is not recommended. Nevirapine can be used “in the absence of other options”.

Rifabutin is a less potent enzyme inducer than rifampicin; it can effectively treat tuberculosis and is compatible with antiretroviral drugs, but it is prohibitively expensive at present. Triple nucleoside or nucleotide regimens, such as zidovudine, lamivudine, and tenofovir, have potential as tuberculosis-compatible antiretroviral regimens if shown to be sufficiently potent.

Co-trimoxazole prophylaxis in HIV-infected people with tuberculosis
Results from a placebo-controlled trial of co-trimoxazole in Cote d’Ivoire, showing a 46% reduction in mortality in HIV-infected tuberculosis patients, have been lent support by research in other parts of Africa. Since 1999, WHO and UNAIDS have recommended co-trimoxazole prophylaxis for all individuals with symptomatic HIV disease or CD4 counts less than 500 per μL, but uptake was estimated as only 3% of HIV-infected adults in 2003. The current drive towards roll-out of antiretroviral treatment might greatly enhance co-trimoxazole uptake as systems are put into place for delivery of chronic HIV care. An important question is whether co-trimoxazole benefits patients with tuberculosis who are taking antiretroviral treatment. In the industrialised world, co-trimoxazole can safely be withdrawn when CD4 count is greater than 200 per μL, but in the African environment, benefit could extend to higher CD4 cell counts.

Reduction of tuberculosis incidence and recurrence in HIV-infected individuals
Risk of new tuberculosis disease in HIV-infected individuals can be lowered, but not eliminated, by
isoniazid preventive treatment,69 antiretroviral drugs,70–72 and reducing exposure to M tuberculosis. The benefits of antiretroviral drugs73 and secondary isoniazid preventive treatment74 for recurrent tuberculosis disease have not yet been clearly defined, but the rate of recurrence remains very high even for patients on antiretroviral drugs.75

Isoniazid preventive treatment for 6–9 months reduces tuberculosis prevalence by about 60% in HIV-infected individuals with a positive tuberculin skin test, and by about 40% when used irrespective of skin-test results.76,77 However, this low-cost intervention has been little used in Africa, with only Botswana attempting widespread implementation.78 In part, this low use relates to concerns about possible promotion of drug resistance and past absence of additional funding, but it also exemplifies limited commitment to date to joint tuberculosis and HIV interventions. Definition of screening procedures needed in operational settings remains an important research question.79 Other unresolved issues include the best duration of preventive treatment, since protection wanes with time in HIV-infected individuals not receiving antiretroviral drugs,80,81 and the role and safety of primary and secondary preventive treatment and antiretroviral regimens.

Epidemics of nosocomial tuberculosis have been well documented in industrialised countries, where they stand out against low background rates.82 In Africa, the potential for nosocomial transmission affecting patients and staff is much higher, and facilities are ill-equipped. In two cohort studies in a goldmining workforce, a rise was noted in the incidence of HIV-related recurrent tuberculosis, from 8.2 to 19.1 per 100 person-years, coinciding with the introduction of HIV clinics.83 Models for delivery of coordinated tuberculosis and HIV treatment services

Rapid scale-up of antiretroviral programmes dominates public-health interventions in Africa, but with only limited attention to coordination with tuberculosis programmes.84 Coordination can mean referral between services, some provision of joint services, or complete integration of tuberculosis and HIV/AIDS clinics. Important experience has been gained in Malawi, where the national tuberculosis control programme provides a model for scaling-up delivery of antiretroviral drugs.85 First-line treatment is with stavudine, lamivudine, and nevirapine (provided free of charge); clinical staging is used to define eligibility after a positive HIV test. Uptake of routine (opt-out) HIV testing among tuberculosis patients has reached 70%, with high uptake and adherence to co-trimoxazole but with success rates for starting antiretroviral treatment of 20% or less.86 The main constraints seem to be the 8-week delay between starting tuberculosis treatment and becoming eligible for nevirapine-containing antiretroviral regimens (during which time patients are discharged) and logistic difficulties for patients in accessing centralised antiretroviral services when they also have to attend local health clinics for continued management of tuberculosis.87 These difficulties indicate a major limitation of tuberculosis and antiretroviral services that are linked only by cross-referrals, and they show a need for antiretroviral and tuberculosis management to be decentralised and integrated as far as possible into the local health-care system.

Good uptake rates for antiretroviral treatment have been reported from programmes that offer tuberculosis and antiretroviral drugs from the same clinic, with transfer of care once tuberculosis treatment has been completed (partial integration) or continued treatment as a fully integrated HIV and tuberculosis service.88,89,90 Timely investigation and improved management of patients who develop tuberculosis while on antiretroviral drugs might be a further benefit of completely integrated clinics.91 Integrated care needs planning, retraining, and considerable expansion of tuberculosis programme personnel, but it is more patient-orientated and efficient than current systems.92

Monitoring and assessment

Traditional outcome measures for tuberculosis programmes need cohort analysis of treated patients to establish successful and adverse outcomes. WHO defines targets of 70% case detection (estimated indirectly) and 85% cure rates.93 Collaborative HIV and tuberculosis programmes also need to monitor uptake of HIV testing and antiretroviral treatment, with subsequent measures of adherence, default, and survival. Because antiretroviral regimens, unlike antituberculous treatment, are lifelong, complexity of programmes will be greatly enhanced.94

From a surveillance perspective, universal opt-out HIV testing of tuberculosis patients will provide useful data for HIV prevalence and allow estimation of tuberculosis incidence in HIV-positive and HIV-negative subpopulations (figure 6). HIV-positive tuberculosis trends could usefully be viewed as a surrogate for trends in a country’s overall AIDS epidemic,95 and HIV-negative trends would offer assessment of programme performance in controlling tuberculosis transmission. Demonstration that the incidence of tuberculosis was declining in HIV-negative subpopulations could do much to enhance morale of tuberculosis programmes, whose confidence has been shaken by escalating incidence, as could data showing reduced HIV-positive mortality rates.
Challenges, constraints, and future prospects

Whatever we aim for, limited human resources, weak management and health systems, inadequate clinical and laboratory infrastructure, and absent training programmes for combined tuberculosis and HIV/AIDS care are all formidable barriers to supporting large numbers of patients in long-term care. Despite potential for increased funding, African tuberculosis control programmes remain poor in resources—in absolute terms and relative to those available for HIV/AIDS control. Few areas of the health sector have seen demand escalate to the degree experienced by tuberculosis programmes, yet support has not greatly increased and sometimes has declined in important areas such as personnel. The incidence of AIDS and tuberculosis programmes, yet support has not greatly increased and sometimes has declined in important areas such as personnel. The incidence of AIDS and HIV-associated tuberculosis in Africa is hundreds of times more than that in the industrialised world, but the ratio of health-care workers to population is a tenth of European levels. Programmes cannot succeed without increased funding for basic public-health and clinical infrastructure and appropriate personnel.

Since the tuberculosis epidemic in Africa has been driven by HIV, activities directed towards HIV-associated disease should logically be the most effective response. Paradoxically, results from mathematical modelling suggest that improvements in tuberculosis case-finding and treatment, and reductions in HIV incidence, have a greater potential than interventions targeted to known HIV-positive individuals. Tuberculosis control in Africa remains weak, and large gains can still be made from strengthening basic disease control. Care must be taken to avoid collapse of previously well-functioning tuberculosis control programmes after competition for scarce human resources and to ensure that integration of HIV and tuberculosis services does not compromise core tuberculosis programme functions, such as maintenance of drugs and supplies, prevention of drug resistance, assurance of quality diagnostic microscopy, and cohort analysis of treated patients.

In the same way that HIV fundamentally changed tuberculosis and its epidemiology in Africa, so the introduction of antiretroviral treatment poses important challenges to how tuberculosis control should be approached. Rapid scale-up of antiretroviral programmes in Africa in the past 2 years has not adequately taken patients with tuberculosis into account. Without sufficient coverage of preventive and therapeutic interventions for both diseases, tuberculosis could yet be the limiting factor to the long-term success of antiretroviral programmes because of uncontrolled incidence, recurrence, and institutional transmission. The advent of antiretroviral treatment in Africa is the most important event for tuberculosis patients since the introduction of antituberculosis drugs, and HIV/AIDS and tuberculosis programmes will both have to change greatly to benefit as much as possible from this development.

Conflict of interest statement

We declare that we have no conflict of interest.

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References


Treatment of Latent Tuberculosis Infection: Challenges and Prospects

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It is estimated that one third of the global population, or 2 billion people, are infected with \textit{Mycobacterium tuberculosis} \cite{1}. Among infected persons, approximately 10% progress to the clinically important (and infectious) stage of active tuberculosis over their lifetime \cite{2,3}. The risk is higher in persons with concomitant HIV infection (>20%), evidence of old healed tuberculosis on chest radiograph (>20%), or recent \textit{M. tuberculosis} infection (10% to 20%) \cite{4}. In most infected persons, the host immune response contains the replication of \textit{M. tuberculosis} and prevents the development of disease \cite{5}. Among infected persons who develop active disease, progression occurs either shortly after initial infection (progressive primary disease) or subsequent to the initial infection, when there is a breakdown in the host immune response. A person is at greatest risk of progressing to active disease during the first 2 years after infection with \textit{M. tuberculosis} \cite{2}. In addition to HIV infection and recent \textit{M. tuberculosis} infection, other risk factors for progression to active tuberculosis include silicosis, diabetes mellitus, chronic renal failure, malnutrition, weight loss, leukemia, lymphoma, cancer of the head, neck, and lung, gastrectomy, and jejunoileal bypass surgery \cite{6}.

\textbf{Diagnosis of latent \textit{Mycobacterium tuberculosis} infection}

As discussed elsewhere in this issue, the diagnosis of latent \textit{M. tuberculosis} infection relies primarily on the tuberculin skin test, an intradermal test that utilizes purified protein derivative (PPD). Because the mycobacterial proteins in PPD are not specific for \textit{M. tuberculosis}, persons infected with other mycobacteria (eg, environmental mycobacteria such as \textit{M. avium intracellulare} and \textit{M. bovis}, the organism in the tuberculosis vaccine bacille Calmette-Guerin) may result in a false-positive test. Conversely, the tuberculin skin test has low sensitivity, particularly in immunocompromised persons. Because of these limitations, the definition of a positive tuberculin skin test varies according to the person’s risk of tuberculosis infection and risk of progressing to active disease if infected (Box 1) \cite{6}. The different criteria for a positive test increase its sensitivity in high-risk persons and specificity in low-risk persons.

\textbf{Indications for treatment of \textit{Mycobacterium tuberculosis} infection}

All persons with evidence of latent \textit{M. tuberculosis} infection should be evaluated for the presence of active disease. The evaluation should include an assessment of the signs and symptoms of tuberculosis and a chest radiograph; in persons with symptoms or an abnormal chest radiograph, sputum for acid-
fast smear and culture should also be obtained. Once active disease has been excluded, all persons at increased risk of progressing to active tuberculosis (see Box 1) should receive treatment for latent infection.

**Importance of treatment of *Mycobacterium tuberculosis* infection to decrease the global tuberculosis burden**

Most cases of active tuberculosis arise from persons with latent *M. tuberculosis* infection; treatment of such persons is therefore necessary to achieve tuberculosis elimination. The focus should be on those persons at high risk of progressing to active disease. The strategy of targeted tuberculin skin testing among high-risk groups and treatment of all such persons with a positive tuberculin skin test is recommended in the United States [6,7].

Infection with *M. tuberculosis* is often termed latent because of the absence of clinical manifestations, the slower replication rate of *M. tuberculosis*, and the lower burden of organisms compared with active disease [8]. Because of the relatively low burden of organisms, treatment of latent infection requires fewer drugs than active disease to facilitate cure and prevent the development of drug resistance. Use of a single antituberculosis agent is sufficient for latent infection but not for active disease. As detailed later, treatment of latent *M. tuberculosis* infection dramatically decreases the risk of developing active tuberculosis.

**Regimens to treat *Mycobacterium tuberculosis* infection**

Each of the regimens available to treat latent *M. tuberculosis* infection is reviewed here, with emphasis on both the effectiveness and toxicity of the regimens. The review is limited to studies conducted in adults and published in the English peer-reviewed literature; studies reported only in abstract form are not included. The authors are unaware of studies of the effectiveness of short-course therapy conducted among children. Because the risk of active tuberculosis is substantially higher in HIV-seropositive persons than in HIV-seronegative persons, and because the effectiveness of many regimens has been assessed separately according to HIV serostatus, the data are presented separately for HIV-seropositive and HIV-seronegative persons. Toxicity of therapy may also differ according to HIV sero-

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**Box 1. Criteria for a positive tuberculin skin test based on millimeters of induration after intradermal placement of five tuberculin units of purified protein derivative (Mantoux technique)**

<table>
<thead>
<tr>
<th>Induration Level</th>
<th>Risk Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm</td>
<td>HIV seropositive</td>
</tr>
<tr>
<td>10 mm</td>
<td>Recent contact with a culture-confirmed tuberculosis case</td>
</tr>
<tr>
<td>10 mm</td>
<td>Fibrotic changes on chest radiograph consistent with prior tuberculosis</td>
</tr>
<tr>
<td>10 mm</td>
<td>Chronic immunosuppression (eg, prednisone ≥15 mg/day for at least 30 days)</td>
</tr>
<tr>
<td>10 mm</td>
<td>Immigration from a high-prevalence country within the last 5 years</td>
</tr>
<tr>
<td>10 mm</td>
<td>Injection drug use</td>
</tr>
<tr>
<td>10 mm</td>
<td>Residents and employees of high-risk settings: prisons, jails, nursing homes, and other long-term care facilities, hospitals, residential facilities for AIDS patients, homeless shelters</td>
</tr>
<tr>
<td>10 mm</td>
<td>Mycobacteriology laboratory personnel</td>
</tr>
<tr>
<td>10 mm</td>
<td>Persons at increased risk of developing active tuberculosis: those with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, cancer of the head, neck or lung, weight loss of more than 10% of ideal body weight, gastrectomy, jejunoileal bypass</td>
</tr>
<tr>
<td>15 mm</td>
<td>Children younger than 4 years old</td>
</tr>
<tr>
<td>15 mm</td>
<td>Persons with no risk factors for tuberculosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Randomization unit</th>
<th>Population</th>
<th>Follow-up</th>
<th>Regimen</th>
<th>Active TB n/N (%)</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>United States Public Health Service trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mount, 1962 [67]</td>
<td>Family</td>
<td>Contacts of known active cases PPD+ and –</td>
<td>4 years</td>
<td>INH 5 mg/kg/d for 1 year Placebo</td>
<td>6/1463 (0.41)</td>
<td>54</td>
</tr>
<tr>
<td>Ferebee, 1962 [17]</td>
<td>Family</td>
<td>Household contacts of new active TB 39 US communities, PPD+ and –</td>
<td>3 years</td>
<td>INH 5 mg/kg/d for 1 year Placebo</td>
<td>12/1351 (0.89)</td>
<td>70</td>
</tr>
<tr>
<td>Ferebee, 1963 [68]</td>
<td>Ward</td>
<td>Mental institutions PPD+ and –</td>
<td>5 years</td>
<td>INH 5 mg/kg/d for 1 year Placebo</td>
<td>97/12594 (0.77)</td>
<td>62</td>
</tr>
<tr>
<td>Comstock, 1967 [69]</td>
<td>Household</td>
<td>Alaskan Eskimos in Bethel area Most not PPD tested</td>
<td>6 years</td>
<td>INH 5 mg/kg/d for 1 year Placebo</td>
<td>89/12326 (0.72)</td>
<td>59</td>
</tr>
<tr>
<td><strong>International trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiba, 1963 [70]</td>
<td>Household</td>
<td>Osaka, Japan Household contacts of new active TB</td>
<td>2 years</td>
<td>INH 5 mg/kg/d for 1 year Placebo</td>
<td>11/1096 (1.0)</td>
<td>30</td>
</tr>
<tr>
<td>Nyboe, 1963 [71]</td>
<td>City blocks</td>
<td>Suburb of Tunis City</td>
<td>1 year</td>
<td>INH (very erratic pill taking) Placebo</td>
<td>18/7769 (0.23)</td>
<td>25</td>
</tr>
<tr>
<td>Egsmose, 1965 [72]</td>
<td>Household</td>
<td>Rural northern Kenya PPD+ contacts of new active cases</td>
<td>4 years</td>
<td>INH 5–10 mg/kg/d for 1 year Placebo</td>
<td>25/8141 (0.31)</td>
<td>35</td>
</tr>
<tr>
<td>DelCastillo, 1965 [73]</td>
<td>Household</td>
<td>Philippines Contacts of active cavitary TB</td>
<td>2 years</td>
<td>INH Placebo</td>
<td>1.04</td>
<td>1.6</td>
</tr>
<tr>
<td>Horwitz, 1966 [74]</td>
<td>Village</td>
<td>Greenland villagers</td>
<td>6 years</td>
<td>INH 400 mg 2 × /wk for total 52 doses Placebo</td>
<td>18/129 (14.0)</td>
<td>31</td>
</tr>
<tr>
<td>Veening, 1968 [75]</td>
<td>Individual</td>
<td>Royal Netherlands Navy New PPD+ after exposure to index case</td>
<td>4 years</td>
<td>INH 600 mg × 4 mo, 400 mg × 8 mo Placebo</td>
<td>238/4174 (5.7)</td>
<td>96</td>
</tr>
<tr>
<td>IUAT, 1982 [9]</td>
<td>Individual</td>
<td>7 European countries PPD+ patients with fibrotic lesions</td>
<td>5 years</td>
<td>INH 300 mg/d for 12 weeks Placebo</td>
<td>76/6956 (1.1)</td>
<td>21</td>
</tr>
</tbody>
</table>

**Abbreviations:** INH, isoniazid; IUAT, International Union Against Tuberculosis; PPD, purified protein derivative; TB, tuberculosis.
status, so tolerability data are also presented according to HIV serostatus. Recommended doses of specific drugs have been published previously [6].

**Isoniazid**

**Effectiveness**

**HIV-seronegative persons**

Isoniazid is the best-studied regimen for the treatment of latent *M. tuberculosis* infection. More than 20 randomized, controlled trials have been conducted, which together enrolled more than 100,000 persons. Most of these studies were conducted in the 1950s and 1960s and therefore enrolled only HIV-seronegative persons. These trials are summarized in Table 1.

Most of the studies assessed the effectiveness of 12 months of isoniazid versus placebo. The trial conducted by the International Union Against Tuberculosis (IUAT) assessed 3 versus 6 versus 12 months of therapy and found that 6 months of isoniazid was less effective (65%) than 12 months (75%) [9]. George Comstock [10] subsequently performed an analysis of previously conducted clinical trials and found that 6 months of isoniazid provided insufficient protection; 9 to 10 months of isoniazid seemed to provide optimal protection. Based on these findings, the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) guidelines recommend 9 months of isoniazid [6]. A 9-month regimen of isoniazid has never been compared with a 6- or 12-month course of isoniazid in a clinical trial, however.

**HIV-seropositive persons**

Isoniazid effectiveness has also been studied in HIV-seropositive persons, although not as extensively as in HIV-seronegative persons. The randomized, controlled trials of treatment of latent *M. tuberculosis* infection in HIV-infected persons are summarized in Table 2, and the randomized, placebo-controlled trials of isoniazid are summarized in Table 3. Among tuberculin skin-test–positive persons, isoniazid is clearly more effective than placebo in preventing tuberculosis; this finding has been confirmed in a meta-analysis [11]. Isoniazid has been associated with improved survival in some studies [12–14], but not in all [11,15,16]. Although there has not been a direct comparison of 6 versus 9 versus 12 months of isoniazid, 6 months seems to be less effective than 12 months. Based on the rationale used for HIV-seronegative persons, and to ensure uniformity of recommendations, the ATS/CDC/IDSA guidelines recommend 9 months of isoniazid for HIV-seropositive persons [6]. Although HIV-infected persons are at increased risk of having a negative tuberculin skin test, particularly with advanced immunosuppression, isoniazid is not substantially more effective than placebo in preventing tuberculosis in such persons, and therefore is not recommended (Table 3) [11].

**Toxicity**

**HIV-seronegative persons**

In the initial studies of isoniazid, drug discontinuation rates were low and did not differ from rates among persons receiving placebo [17]. Subsequent studies, however, have noted higher rates of drug discontinuation, as summarized in Tables 4 and 5. Few of these studies have been placebo-controlled. Isoniazid can cause elevated hepatic transaminases [18], but these liver function abnormalities are often transient and are not representative of clinically significant hepatitis. In studies in which serum transaminases were monitored regularly regardless of symptoms, 10% to 22% of participants had at least one elevated transaminase level during the course of therapy [19–25]. Rates of clinically significant hepatitis are lower. In a surveillance study of the US Public Health Service, 236 of 13,838 persons (1.7%) who received isoniazid developed hepatitis. When considering only those persons in whom the hepatitis was probably or possibly related to isoniazid, the rate was 174 in 13,838 (1.3%) [26]. Hepatitis risk increased with age and concomitant alcohol consumption. In another study, a 7-year survey from one public health clinic, 11 of 11,141 patients (0.10%) who started isoniazid developed hepatotoxicity [27]. Isoniazid-associated hepatotoxicity can be fatal, and the risk of death increases with age. It is estimated that the hepatotoxicity-associated case-fatality rate per 10,000 persons initiating isoniazid treatment is 0 for ages 20 to 34 years, 2 for ages 35 to 49 years, and 4 for ages 50 to 64 years [24,26,28,29]. Although never tested in a trial, rates of hepatotoxicity may be lower when there is regular monitoring of signs and symptoms of hepatitis [27,28]. In the United States it is currently recommended that patients receiving isoniazid undergo monthly clinical assessments for adverse effects. They should also be evaluated whenever symptoms develop. Patients should be educated regarding the signs and symptoms of hepatotoxicity and instructed to discontinue the medicine and seek clinical evaluation if symptoms...
<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Trial type</th>
<th>Population</th>
<th>Regimens</th>
<th>N</th>
<th>Mean follow-up</th>
<th>Compliance/follow-up</th>
</tr>
</thead>
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<tr>
<td><strong>INH versus placebo trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pape, 1993 [12]</td>
<td>Randomized</td>
<td>Haiti</td>
<td>INH 300 mg/d for 12 months</td>
<td>118</td>
<td>33 months</td>
<td>No loss to follow-up</td>
</tr>
<tr>
<td>Double-blind</td>
<td></td>
<td>New HIV</td>
<td>PPD+ or --</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td>diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawken, 1997 [76]</td>
<td>Block-randomized</td>
<td>Kenya</td>
<td>INH 300 mg/d for 6 months</td>
<td>684</td>
<td>20 months</td>
<td>70% follow-up</td>
</tr>
<tr>
<td>Double-blind</td>
<td></td>
<td>PPD+ or --</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gordin, 1997 [77]</td>
<td>Randomized</td>
<td>US, mostly NYC</td>
<td>INH 300 mg/d for 6 months</td>
<td>517</td>
<td>33 months</td>
<td>63% completed therapy; 6% INH and 7% placebo lost to follow-up</td>
</tr>
<tr>
<td>Double-blind</td>
<td></td>
<td>Anergic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fitzgerald, 2001 [78]</td>
<td>Randomized</td>
<td>Haiti</td>
<td>INH 300 mg/d for 12 months</td>
<td>237</td>
<td>2.5 years</td>
<td>77% followed to death or study end</td>
</tr>
<tr>
<td>Blinding unclear</td>
<td></td>
<td>PPD--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled</td>
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<td></td>
</tr>
<tr>
<td><strong>Multiregimen trials</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Whalen, 1997 [15]</td>
<td>Block-randomized</td>
<td>Uganda</td>
<td>PPD+: INH 300 mg/d for 6 months or INH 300 mg/d and RIF 600 mg/d for 3 months or INH 300 mg/d, RIF 600 mg/d, and PZA 2000 mg/d for 3 months</td>
<td>2018</td>
<td>15 months</td>
<td>75% urine tests and 80%–89% completed the trials</td>
</tr>
<tr>
<td>Double-blind</td>
<td></td>
<td>(1) PPD+</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Anergic</td>
<td></td>
<td>Zambia</td>
<td>Anergic: INH 300 mg/d for 6 months</td>
<td>718</td>
<td>1.8 years</td>
<td>81% placebo, 66% INH, and 75% RIF/PZA were &gt;80% compliant</td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>Block-randomized</td>
<td>Zambia</td>
<td>INH 900 mg 2 ×/wk for 6 months or RIF 600 mg and PZA 3500 mg 2 ×/wk for 3 months</td>
<td>1053</td>
<td>1.8 years</td>
<td>81% placebo, 66% INH, and 75% RIF/PZA were &gt;80% compliant</td>
</tr>
<tr>
<td>Double-blind</td>
<td></td>
<td>PPD+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordin, 2000 [36]</td>
<td>Randomized</td>
<td>US, Mexico, Haiti, Brazil</td>
<td>INH 300 mg/d for 12 months or RIF 600 mg and PZA 20 mg/kg/d for 2 months</td>
<td>1583</td>
<td>37 months</td>
<td>80% RIF/PZA and 69% INH completed therapy</td>
</tr>
<tr>
<td>Open-label</td>
<td></td>
<td>PPD+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No placebo arm</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halsey, 1998 [40]</td>
<td>Randomized</td>
<td>Haiti</td>
<td>INH 600–800 mg 2 ×/wk for 6 months or RIF 450–600 mg and PZA 1500–2000 mg 2 ×/wk for 2 months (weight-based)</td>
<td>750</td>
<td>2.5 years</td>
<td>55% INH and 74% RIF/PZA had &gt;80% compliance</td>
</tr>
<tr>
<td>Unmasked</td>
<td></td>
<td>PPD+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partly supervised</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>No placebo arm</td>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** INH, isoniazid; PPD, purified protein derivative; PZA, pyrazinamide; RIF, rifampin.
occur. Routine laboratory monitoring is recommended for persons with abnormal baseline liver function tests, persons at increased risk of hepatotoxicity (eg, HIV infection, liver disease, alcoholism, pregnancy), and persons who develop symptoms while on therapy. [6]

Isoniazid can also cause peripheral neuropathy, but the risk is lower with concomitant use of vitamin B6 (pyridoxine) [30,31].

HIV-seropositive persons

The rates of isoniazid-associated toxicity requiring drug discontinuation in HIV-seropositive persons are summarized in Table 5. Although the data are not as extensive as in HIV-seronegative persons, isoniazid is generally well tolerated in this patient population.

Hepatitis C virus and isoniazid-associated hepatotoxicity

Hepatitis C virus (HCV) infection has been associated with an increased risk of hepatotoxicity among persons receiving combination antituberculosis therapy for active disease, particularly HIV-infected persons [32]. HCV infection is common in injection drug users [33], who are also at high risk of progressing to active tuberculosis if latently infected with M. tuberculosis. Two studies have assessed the risk of isoniazid-associated hepatotoxicity in persons with underlying HCV. In a study of 146 injection drug users with M. tuberculosis infection and normal baseline hepatic transaminases, 138 were HCV seropositive; 32 (22%) developed hepatic transaminases levels more than three times the upper limit of normal, and 11 (8%) required drug discontinuation [34]. These rates are comparable to those reported in populations with lower HCV seroprevalence (see preceding discussion and Table 5). In a second study of 415 drug users, of the 214 that were HCV-antibody–positive, 16 (7.5%) developed hepatotoxicity (defined as drug discontinuation in the setting of hepatic transaminase elevation more than five times the upper limit of normal in the presence of symptoms or as transaminase elevation alone on two occasions at least 1 week apart) [35]. On multivariate analysis, HCV infection was not independently associated with hepatotoxicity. Both studies suggest that isoniazid is safe in persons with HCV infection and is not associated with significantly higher rates of hepatotoxicity than in persons without HCV.

Table 3
Results of randomized, controlled trials of isoniazid for the treatment of latent Mycobacterium tuberculosis infection among HIV-seropositive persons

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Rx n/N (%) INH</th>
<th>Control n/N (%) placebo</th>
<th>RR</th>
<th>95% Confidence interval</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pape, 1993 [12]</td>
<td>2/38 (5.2)</td>
<td>6/25 (24.0)</td>
<td>0.22</td>
<td>0.05, 1.00</td>
<td>78</td>
</tr>
<tr>
<td>Hawken, 1997 [76]</td>
<td>5/67 (7.5)</td>
<td>8/69 (11.6)</td>
<td>0.64</td>
<td>0.22, 1.87</td>
<td>36</td>
</tr>
<tr>
<td>Whalen, 1997 [15]</td>
<td>7/536 (1.3)</td>
<td>21/464 (4.5)</td>
<td>0.29</td>
<td>0.12, 0.67</td>
<td>71</td>
</tr>
<tr>
<td>PPD+ cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>6/101 (5.9)</td>
<td>11/60 (18.3)</td>
<td>0.32</td>
<td>0.13, 0.83</td>
<td>68</td>
</tr>
<tr>
<td>PPD negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordin, 1997 [77]</td>
<td>4/260 (1.5)</td>
<td>6/257 (2.3)</td>
<td>0.66</td>
<td>0.19, 2.31</td>
<td>34</td>
</tr>
<tr>
<td>Fitzgerald, 2001 [78]</td>
<td>6/126 (4.8)</td>
<td>4/111 (3.6)</td>
<td>1.32</td>
<td>0.38, 4.56</td>
<td>−32</td>
</tr>
<tr>
<td>Hawken, 1997 [76]</td>
<td>11/235 (4.7)</td>
<td>8/224 (3.6)</td>
<td>1.31</td>
<td>0.54, 3.20</td>
<td>−31</td>
</tr>
<tr>
<td>Pape, 1993 [12]</td>
<td>2/20 (10.0)</td>
<td>5/35 (14.3)</td>
<td>0.70</td>
<td>0.15, 3.28</td>
<td>30</td>
</tr>
<tr>
<td>Whalen, 1997 [15]</td>
<td>9/395 (2.3)</td>
<td>10/323 (3.1)</td>
<td>0.74</td>
<td>0.30, 1.79</td>
<td>26</td>
</tr>
<tr>
<td>anergic cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>27/351 (7.7)</td>
<td>17/166 (10.2)</td>
<td>0.75</td>
<td>0.42, 1.34</td>
<td>25</td>
</tr>
</tbody>
</table>

Results are presented according to the tuberculin skin test status of study patients. Abbreviations: INH, isoniazid; PPD, purified protein derivative; RR, relative risk.

Table 4
Toxicity of isoniazid for treatment of latent Mycobacterium tuberculosis infection in HIV-seronegative patients

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Toxicity requiring discontinuation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INH n/N (%) Placebo n/N (%)</td>
</tr>
<tr>
<td>Scharer, 1969 [18]</td>
<td>2/90 (2.2) No placebo arm</td>
</tr>
<tr>
<td>Byrd, 1972 [22]</td>
<td>16/160 (10) No placebo arm</td>
</tr>
<tr>
<td>Bailey, 1973 [79]</td>
<td>18/427 (7.3) No placebo arm</td>
</tr>
<tr>
<td>Byrd, 1977 [80]</td>
<td>10/120 (8.3) 1/60 (1.7)</td>
</tr>
<tr>
<td>Byrd, 1979 [24]</td>
<td>64/1000 (6.4) No placebo arm</td>
</tr>
<tr>
<td>Stuart, 1999 [25]</td>
<td>26/83 (31.3) No placebo arm</td>
</tr>
</tbody>
</table>

Toxicity is defined as adverse events resulting in discontinuation of therapy. Abbreviation: INH, isoniazid.
Although the efficacy of isoniazid in preventing tuberculosis exceeds 90% among persons who adhere to therapy [9], the effectiveness of isoniazid is lower because of low rates of adherence to the long duration of therapy. This problem of adherence has led to the assessment of regimens that require a shorter course of treatment. These regimens are summarized here.

### Rifampin plus pyrazinamide for 2 months

#### Effectiveness

Among available short-course regimens for the treatment of latent *M. tuberculosis* infection, the regimen with the shortest duration, and therefore the greatest potential for improved adherence, is the 2-month regimen of rifampin plus pyrazinamide.

#### HIV-seronegative persons

Effectiveness of rifampin plus pyrazinamide has not been studied in HIV-seronegative persons. Because of high rates of hepatotoxicity in tolerability studies (see later discussion), it is unlikely that effectiveness will ever be studied in HIV-seronegative persons.

#### HIV-seropositive persons

The effectiveness of the 2-month rifampin plus pyrazinamide regimen has been studied entirely in HIV-seropositive persons. Because the risk of tuberculosis without treatment of latent infection is substantially higher in HIV-seropositive persons than in HIV-seronegative persons, much smaller sample sizes were required to study effectiveness in the former. The results of the studies are summarized in Table 6. In the largest of the studies, the effectiveness of daily rifampin plus pyrazinamide for 2 months was nearly identical to 12 months of daily isoniazid [36].

### Toxicity

#### HIV-seronegative persons

After the effectiveness and tolerability of 2 months of rifampin plus pyrazinamide were demonstrated in HIV-seropositive adults, the regimen was recommended in the United States for both HIV-seropositive and -seronegative adults [6]. Shortly thereafter, however, there were reports of severe hepatotoxicity and death among persons treated with this regimen [37,38]. When such cases continued to be reported, the CDC began collecting retrospective surveillance data on the number of persons treated.

---

**Table 5**

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>INH n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>RR</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pape, 1993 [12]</td>
<td>0/58(0)</td>
<td>0/60(0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gordin, 1997 [77]</td>
<td>24/260(9.2)</td>
<td>24/257(9.3)</td>
<td>0.99</td>
<td>0.58, 1.69</td>
</tr>
<tr>
<td>Hawken, 1997 [76]</td>
<td>11/342(3.2)</td>
<td>5/342(1.5)</td>
<td>2.2</td>
<td>0.77, 6.26</td>
</tr>
<tr>
<td>Whalen, 1997 [15] PPD+</td>
<td>3/536(0.6)</td>
<td>1/464(0.2)</td>
<td>2.60</td>
<td>0.27, 24.88</td>
</tr>
<tr>
<td>Anergic</td>
<td>0/395</td>
<td>0/323</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>26/703(3.7)</td>
<td>3/350(0.9)</td>
<td>4.31</td>
<td>1.32, 14.16</td>
</tr>
</tbody>
</table>

Toxicity is defined as adverse events resulting in discontinuation of therapy.

**Abbreviations:** INH, isoniazid; PPD, purified protein derivative; RR, relative risk.

**Table 6**

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Rx n/N (%)</th>
<th>RIF/PZA n/N (%)</th>
<th>INH RR</th>
<th>95% Confidence interval Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPD positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordin, 2000 [36]</td>
<td>28/791(3.5)</td>
<td>29/792(3.7)</td>
<td>0.97</td>
<td>0.58, 1.61</td>
</tr>
<tr>
<td>Halsey, 1998 [40]</td>
<td>19/380(5.0)</td>
<td>14/370(3.8)</td>
<td>1.32</td>
<td>0.67, 2.56</td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>2/49(4.1)</td>
<td>4/52(7.7)</td>
<td>0.53</td>
<td>0.10, 2.77</td>
</tr>
<tr>
<td><strong>PPD negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>13/173(7.5)</td>
<td>14/178(7.9)</td>
<td>0.96</td>
<td>0.46, 1.96</td>
</tr>
</tbody>
</table>

Results are presented according to the tuberculin skin test status of study patients.

**Abbreviations:** INH, isoniazid; PPD, purified protein derivative; PZA, pyrazinamide; RIF, rifampin; RR, relative risk.
with this regimen so that the risk of toxicity could be determined [39]. Data were collected for persons initiating therapy between January 2000 and June 2002 and reported to CDC by June 6, 2003. Of the 7737 persons reported to have started rifampin plus pyrazinamide treatment during the survey period, 204 persons developed aspartate aminotransferase concentrations more than five times the upper limit of normal (2.6/100 treatment initiations), and an additional 146 patients discontinued therapy because of symptoms of hepatitis (1.9/100 treatment initiations). There were 48 cases of severe hepatotoxicity (defined as resulting in hospitalization or death); 11 patients died. The estimated rate of death caused by hepatotoxicity was 0.9 per 1000 treatment initiations [39]. The estimates were limited because data were obtained retrospectively, and the risk associated with isoniazid was not determined concurrently. Nonetheless, the risk of severe hepatotoxicity and death seemed to be approximately 10 times greater than the risk associated with isoniazid, and it was therefore recommended that rifampin plus pyrazinamide should generally not be offered for treatment of latent tuberculosis infection [39]. The toxicity data from clinical trials are summarized in Table 7.

**HIV-seropositive persons**

The regimen was very well tolerated in all of the clinical trials conducted among HIV-seropositive persons (Table 8) [36,40,41], even upon repeat analysis specifically addressing hepatotoxicity [42]. Because of the relatively small sample sizes of the studies, and an event rate of severe hepatotoxicity of approximately 1 per 1000, it is possible that such serious events were not detected in these studies. The CDC therefore recommends that rifampin plus pyrazinamide should generally not be offered, regardless of HIV serostatus [39].

**Isoniazid plus rifampin for 3 months**

**Effectiveness**

There are few studies of isoniazid plus rifampin for the treatment of latent *M. tuberculosis* infection. In the only study among HIV-seronegative adults, the efficacy among adherent patients of 3 months of isoniazid plus rifampin was 41% [43]. Among HIV-seropositive adults, the regimen was 59% effective in

### Table 7

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Toxicity requiring discontinuation of therapy</th>
<th>Hepatotoxicity requiring discontinuation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIF/PZA n/N (%)</td>
<td>INH n/N (%)</td>
</tr>
<tr>
<td>Bock, 2001 [40]</td>
<td>13/168 (7.7)</td>
<td>No INH arm</td>
</tr>
<tr>
<td>Chaisson, 2002 [81]</td>
<td>12/589 (2.0)</td>
<td>No INH arm</td>
</tr>
<tr>
<td>Jasmer, 2002 [60]</td>
<td>28/307 (9.1)</td>
<td>8/282 (2.8)</td>
</tr>
<tr>
<td>Lee, 2002 [82]</td>
<td>26/148 (17.6)</td>
<td>No INH arm</td>
</tr>
<tr>
<td>McNeill, 2003 [83]</td>
<td>14/110 (12.7)</td>
<td>5/114 (4.4)</td>
</tr>
<tr>
<td>Stout, 2003 [84]</td>
<td>8/114 (7.0)</td>
<td>No INH arm</td>
</tr>
<tr>
<td>Van Hest, 2004 [85]</td>
<td>14/166 (8.4)</td>
<td>17/528 (3.2)</td>
</tr>
</tbody>
</table>

Toxicity is defined as adverse events resulting in discontinuation of therapy.

**Abbreviations:** INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RR, relative risk.

*In these studies, the patient population was predominantly HIV-seronegative, with a small minority of HIV-seropositive patients.*

### Table 8

<table>
<thead>
<tr>
<th>First author/date [reference]</th>
<th>Toxicity leading to discontinuation of therapy</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halsey, 1998 [40]</td>
<td>0/380 (0)</td>
<td></td>
</tr>
<tr>
<td>Mwinga, 1998 [41]</td>
<td>14/351 (4.0)</td>
<td>1.17 0.55, 2.50</td>
</tr>
<tr>
<td>Gordin, 2000 [36,42]</td>
<td>75/791 (9.5)</td>
<td>1.56 1.09, 2.22</td>
</tr>
<tr>
<td>Narita, 2003 [86]</td>
<td>5/135 (3.7)</td>
<td></td>
</tr>
</tbody>
</table>

Toxicity is defined as adverse events resulting in discontinuation of therapy.

**Abbreviations:** INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RR, relative risk.

*In these studies, the patient population was predominantly HIV-seronegative, with a small minority of HIV-seropositive patients.*
preventing tuberculosis [15]. Extensive programmatic experience with the regimen among children in Great Britain suggests its effectiveness, but there are no clinical trial data [44]. In the United States, this regimen is not among the recommended treatment regimens, perhaps because of the limited available data [6].

**Toxicity**

The regimen has been well tolerated, although relatively few studies have been conducted to date. In the study among HIV-seronegative adults, 8 of 167 persons (5%) discontinued therapy because of adverse drug reaction [43]; the rate among HIV-seropositive adults was 13 of 556 (2.3%) [15]. In a pooled analysis of 6105 persons who received isoniazid plus rifampin, 156 (2.5%) developed hepatitis [45].

**Rifampin for 4 months**

**Effectiveness**

Among persons who are intolerant of isoniazid, or among close contacts of tuberculosis cases in which the isolate of *M. tuberculosis* is resistant to isoniazid, rifampin can be used to treat latent *M. tuberculosis* infection. There are, however, only limited data from randomized clinical trials and uncontrolled observational studies regarding the effectiveness and tolerability of the regimen. Given the importance of rifampin in the treatment of active tuberculosis, it is particularly important to exclude active disease before treating for latent *M. tuberculosis* infection, because treatment of undiagnosed active tuberculosis with rifampin monotherapy will lead to rifampin resistance.

**HIV-seronegative persons**

The only randomized trial to evaluate the effectiveness of rifampin was conducted in Hong Kong among persons with latent *M. tuberculosis* infection and silicosis. Among all persons initiating therapy, 20 of 165 (12.1%) randomly assigned to receive rifampin for 3 months developed tuberculosis, compared with 36 of 159 persons (22.6%) who received placebo, for an effectiveness of 46% [43]. Among persons who completed the 5-year study, rates were 17 of 103 (17%) and 34 of 99 (34%), respectively, for an effectiveness of 50% [43]. In an observational study among homeless persons with documented tuberculin skin-test conversion during an epidemic of tuberculosis resistant to isoniazid and streptomycin, 49 persons received rifampin. The average duration of therapy was 6.4 months. None of the 49 persons developed tuberculosis, compared with 6 of 71 persons (8.6%) who received no therapy [46]. In a study of 157 tuberculin skin-test–positive adolescent close contacts of persons with isoniazid-resistant tuberculosis, all were treated with a 6-month course of rifampin; none developed tuberculosis during the 2-year evaluation period [47]. Although the effectiveness of 4 months of rifampin has never been studied, it is the currently recommended duration in the ATS/CDC/IDSA guidelines [6].

**HIV-seropositive persons**

There are no studies of the effectiveness of rifampin for the treatment of latent *M. tuberculosis* infection among HIV-seropositive persons. Because of the lack of studies, and because active disease is more difficult to exclude in persons with HIV, one should use rifampin in this patient population with much caution, if at all.

**Toxicity**

**HIV-seronegative persons**

Although data on the tolerability of rifampin are limited, it seems to be well tolerated. In the randomized trial conducted in Hong Kong, 6 of 172 patients (3.5%) discontinued therapy during the study because of adverse drug reaction. None of these patients developed hepatotoxicity [43]. In the study among homeless persons in Boston, 7 of 49 persons (14%) developed adverse effects requiring discontinuation of therapy, but there were no reports of hepatotoxicity [46]. Of the 157 adolescents who received rifampin, 18 (11.5%) interrupted therapy temporarily, and 2 (1.3%) permanently discontinued therapy [47]. In a recent study of persons randomly assigned to receive either 4 months of rifampin or 9 months of isoniazid, 2 of 58 persons (3%) receiving rifampin developed adverse events requiring permanent drug discontinuation; none developed hepatitis [48].

**HIV-seropositive persons**

There are no data on the safety of this regimen in HIV-seropositive persons.
Special situations

Pregnant/breastfeeding women

Pregnancy does not increase the risk of progression from latent infection to active disease. Because of the morbidity associated with tuberculosis in the pregnant mother and neonate, treatment of latent *M. tuberculosis* infection is recommended for pregnant women at high risk of progression to active disease (ie, those with recent *M. tuberculosis* infection or with coinfection with *M. tuberculosis* and HIV) [6]. Given the proven effectiveness of isoniazid and its safety in pregnancy, it is the preferred regimen. Because of the low levels of isoniazid in breast milk, its use is not contraindicated in breastfeeding women.

Children

The only treatment regimen that has been extensively studied in children is isoniazid. Isoniazid may be more effective in children than in adults, with a reported effectiveness of 70% to 90% [49,50]. Because the effectiveness of short-course regimens has not been studied in children, such regimens are not recommended by the ATS/CDC/IDSA [6].

Contacts of persons with drug-resistant tuberculosis

If persons are infected with a strain of *M. tuberculosis* that is resistant to rifampin but susceptible to isoniazid, isoniazid is effective for treatment. For persons exposed to a case of tuberculosis resistant to isoniazid, treatment with rifampin is recommended, as discussed previously [6]. The optimal treatment is unknown for persons with evidence of latent *M. tuberculosis* infection who have been exposed to multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid plus rifampin. No clinical studies have assessed the effectiveness of specific regimens, and such studies will probably never be conducted because of the difficulty in enrolling a sufficient sample size. Recommended regimens include a fluoroquinolone plus pyrazinamide or ethambutol plus pyrazinamide [51]. The optimal duration of these regimens is unknown, although 6 to 12 months is recommended. They often are poorly tolerated [52].

Tumor necrosis factor-alpha antagonists

Drugs that block the inflammatory cytokine tumor necrosis factor-alpha (TNF-α), such as infliximab, etanercept, and adalimumab, are used to treat autoimmune diseases such as rheumatoid arthritis and Crohn’s disease. Use of these drugs increases the risk of progressing from latent *M. tuberculosis* infection to active disease in persons with either remote or recent *M. tuberculosis* infection [53–55]. Before initiating the use of a TNF-α antagonist, patients should be evaluated for latent *M. tuberculosis* infection and, if symptomatic, for active tuberculosis. In immunocompromised persons, induration of 5 mm or greater is considered a positive tuberculin skin test (see Box 1). Treatment of latent infection may be considered in persons with an induration of less than 5 mm if epidemiologic and clinical circumstances suggest recent *M. tuberculosis* infection [54,55]. Treatment for latent *M. tuberculosis* infection should be initiated (and preferably completed) before starting treatment with the TNF-α antagonist [55].

Difficulties and challenges of treatment of latent *Mycobacterium tuberculosis* infection

Low rates of treatment initiation

Not all persons who are eligible for treatment of latent tuberculosis infection initiate therapy. In a study of close contacts of smear-positive pulmonary tuberculosis cases, 95 HIV-infected persons were eligible for treatment of latent infection; of these, only 30 (32%) initiated therapy [56]. In another study of close contacts of tuberculosis cases, of the 630 persons with newly documented positive tuberculin skin tests (all of whom were eligible for therapy), treatment was recommended in 447 (71%), and was started in only 398 (63%) [57]. Efforts must be made to improve the use of treatment of latent infection, particularly in those at highest risk of progression to active disease, such as HIV-infected persons and close contacts.

Low treatment-completion rates

Among persons who start therapy, treatment-completion rates are low. In the second study of close contacts mentioned previously, 203 of 398 persons starting therapy (51%) completed it; 203 of 630 of those eligible for therapy (32%) completed it [57]. In a study of isoniazid treatment of latent infection in an inner-city population, 84 of 409 persons eligible for therapy (21%) completed it [58]. Low treatment-completion rates can result in continued transmission of *M. tuberculosis* and additional cases [59]. The low completion rates may result from a lack
of understanding on the part of the patient of the importance of treatment, the absence of symptoms related to tuberculosis, the toxicity of the regimen, and the prolonged duration of therapy. Even if toxicity is relatively mild and infrequent, patients may be less likely to tolerate adverse effects because they do not have symptomatic tuberculosis disease. Shorter treatment duration may improve completion rates [36,40], but this result has not been noted uniformly [60].

Direct observation of treatment of latent infection can improve adherence [61,62] but is often not feasible for tuberculosis treatment programs because of its high cost.

**Monitoring for toxicity**

As discussed previously, the potentially severe toxicity associated with the treatment of latent *M. tuberculosis* infection necessitates monitoring, particularly in persons at increased risk for toxicity. Routine monitoring for symptoms of toxicity is recommended. Monitoring of laboratory tests (eg, hepatic transaminases) to prevent toxicity, or at least identify toxicity in its early stages, is a reasonable approach in persons at high risk for toxicity, although the utility of such a strategy (and the optimal monitoring strategy) has never been assessed in a clinical trial.

**Logistical difficulties in implementing treatment of latent tuberculosis infection**

Treatment of latent *M. tuberculosis* infection has been a cornerstone of efforts to control tuberculosis in the United States for the past several decades. This approach has been possible because of the relatively low number of tuberculosis cases and available public health resources in the United States. In areas of the world where tuberculosis case rates are substantially higher and resources are more limited, treatment of latent *M. tuberculosis* infection is limited; the focus in these countries is to identify and treat cases of active tuberculosis.

**Prospects for improvements in the treatment of latent *Mycobacterium tuberculosis* infection**

There is clearly a need for safe and effective short-course treatment of latent *M. tuberculosis* infection. Studies are underway to assess the tolerability and effectiveness of once-weekly isoniazid plus rifapentine for 3 months. A study assessing the tolerability of this regimen has recently completed enrollment in Brazil, and data analysis is underway. A comparison of isoniazid plus rifapentine versus the standard regimen of daily isoniazid is underway in South Africa and in a multinational study being conducted by the Tuberculosis Trials Consortium of the CDC (US Public Health Service Study 26). If effective and well-tolerated, isoniazid plus rifapentine would provide a relatively simple short-course regimen for the treatment of latent tuberculosis infection, which could improve treatment completion rates.

Data from the mouse model of tuberculosis, which has correlated closely with human tuberculosis [63,64], have demonstrated that moxifloxacin, a newer fluoroquinolone, has excellent activity against *M. tuberculosis*. This drug may allow shorter and more effective treatment of active tuberculosis [65,66] and may be effective for the treatment of latent tuberculosis infection. Additional studies are warranted.

The Tuberculosis Epidemiologic Studies Consortium of the CDC has launched a large study of the treatment of latent tuberculosis infection in the United States (Task Order 13), including an assessment of the regimens used and the factors associated with acceptance of, adherence to, and tolerability of current treatment regimens. A better understanding of these factors will allow the development of interventions to improve the treatment of latent *M. tuberculosis* infection in the United States and throughout the world.

**References**


[Update. Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of...]

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Treatment of Active Tuberculosis: Challenges and Prospects

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bDepartment of Medicine, University of North Texas Science Center, Texas College of Osteopathic Medicine, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, USA

In the past 5 years, the Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control and Prevention has completed several large studies that have improved the understanding of pharmacotherapy of tuberculosis. Insights gained from these studies have resulted in major changes in drug therapy of tuberculosis in HIV-infected and non-infected individuals [1–5]. These advances require that tuberculosis drug therapy now be individualized. Recommended treatment regimens are based on a patient’s risk profile that is determined by a combination of hematologic, microbiologic, clinical, and radiographic findings [6]. These studies have resulted in substantial changes in the treatment guidelines. Although they are more complicated than the previous guidelines, they allow treatment to be refined so that it can be extended in patients at high risk for treatment failure and allow shorter, more convenient treatment regimens in patients who can be identified as being at very low risk for failure [2]. This article reviews the basic principles of drug treatment of tuberculosis, individual pharmacologic agents, current treatment recommendations, and several special situations that clinicians are likely to encounter in medical practice.

Axioms of chemotherapy of tuberculosis

Effective tuberculosis drug therapy requires not one but at least two effective drugs. This axiom emerged from the first studies of drug therapy of tuberculosis initiated in the late 1940s. These studies evaluated monotherapy with streptomycin and subsequently para-aminosalicylic acid (PAS) [7–9]. They demonstrated that drug resistance developed frequently in persons treated with monotherapy. During 3 months of monotherapy with streptomycin, 92% of persons who remained culture-positive developed streptomycin resistance [3]. Resistance also developed commonly during monotherapy with PAS and was found in approximately one third of patients during 4 months of treatment [9]. It was also observed that resistance was much less common in persons treated with the combination of streptomycin and PAS, and that many more patients treated with the two-drug regimen became bacteriologically negative with 4 months of therapy [9]. Ten percent or less of persons treated simultaneously with streptomycin and PAS developed streptomycin resistance [7,8]. It also was observed that development of resistance was associated with a worse prognosis and with more severe disease [3]. From these early observations came the principle that tuberculosis treatment must include simultaneous treatment with at least two effective drugs.

The microbiologic basis for these early observations was not identified until the early 1960s and remains as important today to understand the design of current treatment regimens [10]. Persons with cavitary disease are estimated to have bacterial populations of approximately $10^8$ organisms in each cavity [10,11]. During division, *Mycobacterium tuberculosis* bacilli mutate from drug-susceptible to drug-resistant status spontaneously, randomly, and at a predictable rate [12]. The proportion of naturally oc-
Corollaries of the treatment axiom that tuberculosis treatment must include simultaneous treatment with at least two effective drugs are important for designing effective tuberculosis regimens and tuberculosis control programs. Because of the possibility of resistance, a single drug is never added to a failing drug-treatment regimen. Optimal design of re-treatment regimens should include at least two medications to which the patient is naïve, and clinicians designing initial treatment regimens must consider prevailing tuberculosis-susceptibility patterns in the community where the infection probably was acquired. It is equally important to successful treatment that the patient actually take the two probably effective drugs. The only way to ensure that a patient actually takes drug therapy as prescribed is direct observation of therapy. If three separate drugs are prescribed for a patient with tuberculosis, the patient may, for many reasons, take a single drug at a time. Short-term single-drug therapy in a person with high bacillary burden can lead to emergence of drug resistance [7–9]. If a patient happens to be initially resistant to one drug and takes a combination of two drugs, including the one to which he or she is resistant, drug resistance to the second drug will emerge. Similarly, if the patient is resistant to two drugs and takes these two drugs and a single effective drug, resistance to the third will emerge. Therefore, poor adherence, inadequate prescribing, or both may result in the development of multidrug resistance. Although these axioms may seem self-evident, the growing number of persons worldwide with drug-resistant tuberculosis is testimony that these principles are not being implemented successfully [14].

The last 50 years of tuberculosis drug treatment can be summarized succinctly. First, it was demonstrated that proper chemotherapy and the cooperation of the patient are the most important factors influencing response to treatment [15]. Second, it has been proven that the social factors such as those corrected during sanatoria treatment of tuberculosis (which provided bed rest, airy accommodations, a well-balanced diet, good nursing care, and psychologic balance) have had no effect on outcome in persons prescribed drug therapy and cooperating with treatment [15]. Third, a few new antituberculosis drugs have been developed. For the most part, however, progress has been made in learning to use available drugs more effectively, with treatment regimens becoming refined to the current treatments that are shorter, have fewer side effects, and are more convenient [6].

Pharmacology and toxicity of antimycobacterial agents

The current drugs approved by the Food and Drug Administration (FDA) for the treatment of tuberculosis include isoniazid, pyrazinamide, rifampin, rifapentine, ethambutol, cycloserine, ethionamide, capreomycin, PAS, and streptomycin. Drugs that commonly are recommended by expert panels for use in the treatment of tuberculosis but are not FDA approved include rifabutin, the aminoglycosides including amikacin, kanamycin, and the fluoroquinolones including ciprofloxacin, moxifloxacin, and levofloxacin. Of the approved drugs, isoniazid, rifampin, ethambutol, and pyrazinamide are considered first-line antituberculosis drugs. Rifapentine and rifabutin can also be considered first-line drugs under special conditions discussed later. The others are categorized as second-line drugs, which are used when the first-line drugs are unsuitable because of drug intolerance or infection with drug-resistant tuberculosis. Additionally clarithromycin, amoxicillin/clavulanate, and linezolid have been used in the treatment of patients with drug-resistant tuberculosis.

Drug-level monitoring is not routinely an important aspect of treatment in a patient with active tuberculosis. Therapeutic drug monitoring is most useful when there is a direct relationship between serum concentrations and therapeutic response and when serum concentrations serve as a surrogate for drug concentrations at the site of action. Therapeutic
drug monitoring is also important when there is a narrow range of concentrations that are effective and safe and when toxicity or lack of effectiveness puts the patient at great risk [16,17]. Examples of situations in which therapeutic drug monitoring is useful for safety include persons treated with aminoglycosides and persons treated with ethambutol or cycloserine with renal impairment.

**Isoniazid**

Isoniazid is used for the treatment of both latent and active tuberculosis and works primarily by inhibiting cell wall synthesis. It is usually administered orally but has been given successfully intramuscularly or intravenously [6]. Isoniazid is cleared predominantly through the liver by acetylation. A patient’s acetylation status and the associated differences in plasma isoniazid concentrations are not associated with isoniazid-induced liver injury [18]. Additionally, no association was found between plasma isoniazid concentrations and isoniazid-induced liver injury [19]. Isoniazid is distributed throughout the body with peak concentrations occurring within 1 to 2 hours after the administration of an oral dose [20]. The usual dose for isoniazid is 3 to 5 mg/kg body weight/day in adults with a maximum dose of 300 mg/day [6].

Isoniazid generally is well tolerated. Hepatic side effects are perhaps the best known of the untoward effects associated with isoniazid use. Less well known is the asymptomatic elevation of liver aminotransferases of up to five times the upper limits of normal, which occurs in approximately 20% of patients receiving isoniazid. This asymptomatic mild elevation of liver aminotransferases is not progressive, is not an indication of progressive liver toxicity, and when asymptomatic does not require discontinuation of isoniazid treatment [6]. Isoniazid-induced hepatitis does occur, but recent studies indicate it is less common than previously thought. Isoniazid-induced hepatitis is estimated to occur in 0.15% of those starting and in 0.15% of those completing treatment for latent tuberculosis infection [21]. The rate of isoniazid-induced hepatitis is higher when isoniazid is combined with rifampin [22]. It is also more common in older persons, heavy alcohol consumers, and persons with underlying liver disease [23]. Based on a large survey, the risk of isoniazid-induced fatal hepatitis is much lower than previously thought—0.001%—when patients are monitored routinely for liver toxicity [24,25]. The risk increases slightly in patients over the age of 35 years.

Peripheral neuropathy also is associated occasionally with use of isoniazid. Neuropathy occurs more commonly among persons who have other risks for neuropathy. Persons at increased risk of peripheral neuropathy include those who are nutritionally deficient, alcoholics, diabetics, pregnant women, breastfeeding mothers, and patients with renal disease. Vitamin B₆ (pyridoxine) supplements usually are given with isoniazid to prevent development of peripheral neuropathy [6].

Hypersensitivity reactions including arthralgias, irriatability, seizures, and lupuslike syndrome have also been reported in patients receiving isoniazid. Although as many as 20% of patients treated with isoniazid develop a positive antinuclear antibody test, systemic lupus rarely occurs [26].

Isoniazid has clinically important reactions with other concomitantly used medications. Isoniazid can affect the levels of certain antiseizure medications, such as phenytoin and carbamazepine. Levels of these medications must be monitored during isoniazid therapy [6].

**Rifamycins**

The rifamycins, which include rifampin, rifabutin, and rifapentine, work by interfering with RNA synthesis, even in bacilli with minimal metabolic activity [27]. The rifamycins are variable inducers of the cytochrome P450 system. Rifampin, rifabutin, and rifapentine are each first-line drugs for the treatment of tuberculosis in different circumstances. Rifampin generally is given orally, but formulations are available for parenteral therapy. The usual dose for rifampin in adults is 10 mg/kg to a maximum of 600 mg daily. It is distributed well throughout the body and reaches effective concentrations in all tissues [6]. Rifampin is a necessary component of all short-course regimens [6].

Rifampin is generally a well-tolerated drug. The most common side effect of rifampin use is an orange discoloration of the urine, tears, and other body fluids. The change in the color of the urine or other body fluids can be disconcerting to persons treated with rifampin if they are not warned. This discoloration has been associated with discoloration of soft contact lenses and clothing. This staining must be rare, however, because the author and colleagues have treated many contact lens wearers with rifampin and never have had a complaint of discoloration of contact lenses, even though they routinely warn patients of this potential side effect. Rifampin can also cause pruritus [28]. Gastroin-
testinal upset, including diarrhea, nausea, and ab-
dominal pains, can occur but rarely require drug
discontinuation and are usually self limiting [29].
Transient elevation of serum bilirubin may be ob-
served during rifampin administration. Hepatitis is
more common when rifampin is administered with
isoniazid [30].

A more serious side effect of rifampin use is an
influenzalike syndrome. Symptoms often mistaken
by patients and physicians for influenza, including
fevers, chills, faintness, headaches, myalgia, and ar-
thralgia, occur alone or in combination. This hyper-
sensitivity syndrome seems to be immune mediated
and develops primarily when rifampin is given
intermittently or in larger doses than are currently
recommended. It most commonly develops after 3 to
6 months but can occur at any time during treatment
[31]. Among persons receiving once-weekly rifampin
as part of the antituberculosis regimen, 35% to 57%
of persons who received 1200 to 1800 mg rifampin
developed a flulike syndrome; the rates were 22% to
31% among those receiving 900 mg/week and 10%
among persons taking 600 mg/week [32]. In contrast,
for persons who received twice-weekly rifampin, a
flulike syndrome was reported in 8% of those
receiving 900 mg/week and in 4% of those receiving
600 mg/week. Symptoms usually appear 1 to 2 hours
after administration of the drug and last up to 8 hours
[31,32]. The hypersensitivity syndrome can be ac-
companied by other manifestations that may be
severe and, rarely, life threatening. The incidence
of individual adverse drug reactions included in the
hypersensitivity syndrome is not well described for
persons treated for tuberculosis. A study of
20,667 patients treated for leprosy with rifampin,
600 mg/day for 3 months, noted the following
incidence rates: rash (0.07%), acute renal failure
(0.1%), thrombocytopenia (0.01%), and hypotension
(0.01%) [33]. Rifabutin use is also associated with
rare immune-related reactions. These reactions tend
to be hematologic, such as leukopenia and thrombo-
cytopenia [33,34].

Rifampin can interact with a large number of
medications because it is a potent inducer of several
enzymes. Rifampin induction of hepatic enzymes can
reduce serum concentrations of oral contraceptives,
resulting in pregnancy, and women relying on hor-
monal methods of contraception need to use addi-
tional means of contraception. Rifampin can increase
the metabolism of methadone and glucocorticoids,
resulting in narcotic withdrawal syndrome and ad-
renal insufficiency or exacerbation of the illness
being treated by glucocorticoid. The interactions of
rifampin with other drugs are so extensive that all
concurrent medications must be checked for inter-
actions with rifampin.

**Ethambutol**

Ethambutol is used in combination with isoniazid
and rifampin in the initial treatment of active tuber-
culosis and has been proven effective in primary
treatment of pulmonary tuberculosis [35]. Ethambutol
is used with isoniazid and rifampin to prevent
selecting resistant organisms when resistance to
one of the primary drugs is present. Like isoniazid,
ethambutol inhibits cell wall synthesis. It is available
only in the oral form. Because it is secreted through
the kidneys, it can accumulate in patients with renal
insufficiency. The usual dose for ethambutol is 15 to
20 mg/kg/day or 50 mg/kg two times per week.

Ethambutol generally is very well tolerated, but,
rarely, it can cause retrobulbar neuritis. This syn-
drome first manifests as decreased red-green color
discrimination and visual acuity. Although it can
result in irreversible vision loss, recognition of the
symptoms and prompt discontinuation of the drug
usually results in return of normal vision. Reducing
the dose of ethambutol to 15 mg/kg/day can minimize
the risk [36].

**Fluoroquinolones**

Levofloxacin, moxifloxacin, and gatifloxacin
all are active against mycobacterium tuberculosis
[37,38]. Although they are not approved by the
FDA for the treatment of tuberculosis, they are
used frequently in treating drug-resistant tubercu-
losis or when patients are intolerant of first-line
agents [39,40]. The adult dose for levofloxacin is
500 to 1000 mg/day orally. Moxifloxacin is admin-
istered at 400 mg/day. Central nervous system (CNS)
concentrations of fluoroquinolones have been found
to be around 16% to 20% of serum after admin-
istration of a standard dose of levofloxacin [41].
Microbial resistance to fluoroquinolones is common
in the community setting; therefore it is imperative
that fluoroquinolones be used only when appropriate.
The most common side effects reported with the use
of this group of antimicrobials are gastrointestinal
symptoms such as nausea, anorexia, dyspepsia, ab-
dominal pain, followed by CNS disturbances (head-
ache, dizziness, drowsiness, abnormal vision) and
liver enzyme abnormalities [42]. Fluoroquinolones
were not developed with the expectation that they
would be used for months; however most experts in
the field of TB have reported a good safety profile
and tolerability with long-term use. Controlled stud-
ies are in progress by CDC/TBTC to look at fluoroquinolones as there is a dearth of information on the efficacy of long-term fluoroquinolone treatment (either daily or intermittently) as is required for multi-drug resistant TB.

**Pyrazinamide**

Pyrazinamide is the primary drug used in the initial intensive phase of active tuberculosis therapy to reduce the total length of therapy. It has a sterilizing effect and helps eliminate potential persisters and consequently is used in the first two months of intensive therapy to reduce the total length of therapy [43]. It is administered orally and is first broken down by the liver. The remaining metabolites are excreted through the kidney [44]. It is more hepatotoxic than isoniazid; therefore, liver function tests should be monitored. It can exacerbate gout and arthralgias by elevating serum uric acid levels [45]. The adult dose for pyrazinamide, based on estimated lean body weight, is 25 mg/kg for daily oral administration orally, 37.5 mg/kg for trice-weekly administration, and 50 mg/kg for twice-weekly administration [6].

**Aminoglycosides**

Amikacin [46], kanamycin [47], and capreomycin are three aminoglycosides that are second-line agents used in treatment of patients who have resistant tuberculosis. They are available for both intramuscular and intravenous administration. All three are administered at 15 mg/kg/day (maximum, 1.0 g/day). Sensitivity tests have shown incomplete cross-resistance between amikacin and capreomycin but complete cross-resistance between amikacin and kanamycin [48]. Adverse effects most commonly associated with the use of these drugs are ototoxicity and nephrotoxicity. Patients receiving these medications should have regular audiograms, vestibular and Romberg testing, and monitoring of renal function.

**Treatment guidelines**

Tuberculosis treatment guidelines for the United States have been prepared by and endorsed by the American Thoracic Society, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention. These regimens are, for the most part, evidence based. These guidelines rate treatments according to the strength of the evidence supporting their use, using a system developed by the United States Public Health Service and the Infectious Diseases Society of America (Box 1) [6].

The guidelines recommend four regimens for treating persons with drug-susceptible tuberculosis [6]. These regimens contain recommendations for regimen modification under circumstances determined by a combination of hematologic, microbiologic, clinical, and radiographic findings [6]. Each regimen has an initial intensive phase of 2 months followed by several options for the continuation phase of 4 or 7 months’ duration. These regimens, together with the number of doses specified by the regimen, are described in Table 1. The initial phases are denoted by a number (1, 2, 3, or 4), and the continuation phases associated with the initial phase are denoted by the number of the initial phase plus a letter designation for the continuation phase (a, b, or c).

The continuation phase can be given daily, two times per week, or three times per week with iso-
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Interval and doses(^c) (minimal duration)</th>
<th>Continuation phase</th>
<th>Interval and doses(^c,d) (minimal duration)</th>
<th>Range of total doses (minimal duration)</th>
<th>Rating(^a) (evidence)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH</td>
<td>7 d/wk for 56 doses (8 wk) or 5 d/wk(^e)</td>
<td>1a INH/RIF</td>
<td>7 d/wk for 128 doses (18 wk) or 5 d/wk for 90 doses (18 wk)(^f)</td>
<td>182–130 (26 wk)</td>
<td>A (I) A (II)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>for 40 doses (8 wk)(^g)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>PZA</td>
<td></td>
<td>1b INH/RIF</td>
<td>2×/wk for 36 doses (18 wk)</td>
<td>92–76 (26 wk)</td>
<td>A (I) A (II)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td>1c(^g) INH/RPT</td>
<td>1×/wk for 18 doses (18 wk)</td>
<td>74–68 (26 wk)</td>
<td>A (I) E (I)</td>
</tr>
<tr>
<td>2</td>
<td>INH</td>
<td>7 d/wk for 14 doses (2 wk), then 2×/wk for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk)(^h) then 2×/wk for 12 doses (8 wk)</td>
<td>2a INH/RIF</td>
<td>2×/wk for 36 doses (18 wk)</td>
<td>62–68 (26 wk)</td>
<td>A (II) B (II)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td></td>
<td>2b(^h) INH/RPT</td>
<td>1×/wk for 18 doses (18 wk)</td>
<td>44–40 (26 wk)</td>
<td>B (I) E (I)</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
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<tr>
<td></td>
<td>EMB</td>
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<tr>
<td>3</td>
<td>INH</td>
<td>3×/wk for 24 doses (8 wk)</td>
<td>3a INH/RIF</td>
<td>3×/wk for 54 doses (18 wk)</td>
<td>78 (26 wk)</td>
<td>B (I) B (II)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
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<td>PZA</td>
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<td></td>
<td>EMB</td>
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<tr>
<td>4</td>
<td>INH</td>
<td>7 d/wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)(^g)</td>
<td>4a INH/RIF</td>
<td>7 d/wk for 217 doses (31 wk) or 5 d/wk for 156 doses (31 wk)(^i)</td>
<td>273–195 (39 wk)</td>
<td>C (I) C (II)</td>
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<tr>
<td></td>
<td>RIF</td>
<td></td>
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<tr>
<td></td>
<td>EMB</td>
<td></td>
<td>4b INH/RIF</td>
<td>2×/wk for 62 doses (31 wk)</td>
<td>118–102 (39 wk)</td>
<td>C (I) C (II)</td>
</tr>
</tbody>
</table>

**Abbreviations:** EMB, Ethambutol; HIV\(^–\), HIV-negative; HIV\(^+\), HIV-positive; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

\(^a\) Definitions of evidence ratings: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given.

\(^b\) Definitions of evidence ratings: I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

\(^c\) When directly observed therapy is used, drugs may be given 5 d/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

\(^d\) Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 wk; either 217 doses [7×/wk] or 62 doses [2×/wk]) continuation phase.

\(^e\) Five d/wk administration is always given by DOT. Rating for 5 d/wk regimens is A III.

\(^f\) Not recommended for HIV-infected patients with CD4\(^+\) cell counts <100 cells/µL.

\(^g\) Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from 2-month specimen, treatment should be extended an extra 3 months.

Corticoids. Dexamethasone treatment was tuberculous meningitis has clarified the role of glucocorticoids in an attempt to reduce mortality and morbidity has been controversial. For these patients, the continuation phase should be extended for an additional 3 months. It is critically important to have sputum cultures at the time of completion of the initial phase of treatment to identify patients at increased risk of relapse. The treatment of tuberculosis in persons with HIV is discussed elsewhere in this issue.

Treatment of tuberculosis may be delayed for many reasons. The current treatment guidelines defined completion of adequate therapy by the number of doses ingested as well as by the duration of treatment administration. The minimum goal for adequate therapy is delivery of the full number of doses in no more than 150% of the expected delivery duration.

Special situations

Central nervous system tuberculosis is one of the most devastating presentations of human tuberculosis. Disability and death occur despite antituberculosis therapy. The best antimicrobial agents for the treatment of central nervous system tuberculosis have not been validated by well-designed, randomized, clinical trials. Isoniazid and pyrazinamide penetrate the meninges in all stages of inflammation. Rifampin, ethambutol, and aminoglycosides penetrate the blood–brain barrier in the presence of meningeal inflammation but poorly in its absence. The use of glucocorticoids in an attempt to reduce mortality and morbidity has been controversial. Recently, a large trial of dexamethasone adjunct therapy for persons 14 years of age and older with tuberculosis meningitis has clarified the role of glucocorticoids. Dexamethasone treatment was started as soon as possible after starting antituberculosis treatment. Patients were stratified by Glasgow Coma Scale and given intravenous dexamethasone for 4 weeks for severe disease and for 2 weeks for mild disease. Subsequently, all patients were given tapering doses of dexamethasone orally for an additional 4 weeks. Dexamethasone adjunctive treatment improved survival. Adverse and severe adverse events were reduced significantly in the dexamethasone-therapy group. There was no demonstrable improvement in the broader prespecified combined end points of death or severe disability after 9 months.

There have been many reports of an increased risk of tuberculosis in persons receiving tumor necrosis factor-α (TNF-α) antagonists. These agents, which include infliximab, etanercept, and adalimumab, are used for the treatment of an expanding group of diseases and work by blocking TNF-α; an inflammatory cytokine. TNF-α is expressed by activating macrophages, T cells, and other immune cells and is an important part of the host response against Mycobacterium tuberculosis and other intracellular organisms. Current expert opinion on this emerging problem in tuberculosis treatment is that the TNF-α antagonist should be discontinued if tuberculosis develops during TNF-α antagonist therapy. The optimal time for resuming TNF-α antagonist therapy is undetermined. It is recommended that TNF-α antagonist therapy be withheld at least until treatment with the tuberculosis regimen has been started, and the patient’s condition has improved.

Tuberculosis occurring in pregnancy is a danger to the pregnant woman and her child, and treatment should not be delayed because of the pregnancy. Infants born to women with untreated tuberculosis may be of lower birth weight than those born to women without tuberculosis and can acquire congenital tuberculosis. Of the first-line medications, pyrazinamide is not recommended for general use in pregnant women in the United States because of insufficient data to determine safety. Aminoglycosides should not be used to treat tuberculosis in pregnancy, because they are associated with birth defects. There is little information about the safety of second-line antituberculosis drugs during pregnancy. The recommended initial treatment regimen in pregnancy should consist of isoniazid, rifampin, and ethambutol. If the organism is confirmed to be susceptible to isoniazid and rifampin, the ethambutol may be discontinued and isoniazid and rifampin continued for a minimum of 9 months. It is recommended that pregnant women receiving isoniazid also be given pyridoxine (25 mg/day). Breastfeeding should not be discouraged for women being treated with first-line agents, because the small concentrations of these drugs in breast milk do not produce toxic effects in the nursing infant.

Renal insufficiency increases the risk for developing tuberculosis, and treatment of the two conditions concurrently is a complex and common situation. Isoniazid and rifampin are metabolized in the liver, and dosages need not be changed in persons with chronic renal failure. Metabolites of
pyrazinamide are excreted renally and can accumulate in patients with renal insufficiency [61]. Approximately 80% of ethambutol is cleared by the kidneys, so ethambutol may accumulate in patients with renal insufficiency [59,61]. Reducing the dosage may avoid toxicity, but the peak serum concentrations achieved may be too low to be effective. Therefore increasing the dosing interval is recommended [60]. For patients undergoing hemodialysis, administering all drugs for tuberculosis after dialysis is a way to facilitate directly observed treatment and simultaneously to avoid removal of drugs such as pyrazinamide [6]. To avoid toxicity, it is important to monitor serum drug concentrations in persons with renal failure who are taking aminoglycosides, cycloserine, or ethambutol [60]. Data are unavailable for the effect of peritoneal dialysis on the clearance of antituberculosis drugs.

The challenges facing patients with tuberculosis and underlying liver disease are great. Clinicians must choose antituberculosis agents that, with a few exceptions, are metabolized by the liver and can potentially cause additional liver damage [62–64]. This damage can be life threatening for a person with marginal hepatic function [62–65]. Hepatic dysfunction can also alter absorption and distribution of drugs that are metabolized or excreted by the liver [65]. In the setting of severe liver disease, it is reasonable to include fewer hepatotoxic medications and to extend the period of treatment [6,65]. This change can be accomplished using a single hepatotoxic drug, generally rifampin, in combination with ethambutol, a quinolone, and an aminoglycoside. Isoniazid can be substituted for rifampin, if rifampin cannot be given [6]. For these complicated patients, expert opinion should be obtained [6].

**Summary**

Insights gained from studies done by the TBTC have resulted in major changes in the recommendations for drug therapy of tuberculosis in HIV-infected and noninfected individuals [1–5]. Although the goals for the treatment of tuberculosis remain the same, these advances require that tuberculosis drug therapy now be more individualized. Treatment regimens are based on a patient’s risk profile based on a combination of hematologic, microbiologic, clinical, and radiographic findings [6]. Although they are more complicated than the previous guidelines, they allow treatment to be refined so that it can be extended in patients at high risk for treatment failure and allow shorter, more convenient treatment regimens in patients who can be identified as being at very low risk for failure [2].

**Acknowledgments**

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[12] David HL. Probability distribution of drug-resistant


Selecting Interventions

- Infectious Disease, Reproductive Health, and Undernutrition
- Noncommunicable Disease and Injury
- Risk Factors
- Consequences of Disease and Injury
Despite the availability of drugs to cure tuberculosis (TB) since the 1940s, TB remains an important cause of death from an infectious agent, second only to the human immunodeficiency virus, or HIV (WHO 2004f). TB control is high on the international public health agenda, not only because of the enormous burden of disease, but also because short-course chemotherapy (SCC) is recognized as one of the most cost-effective of all health interventions (Jamison and others 1993). That recognition is partly attributable to an influential series of studies done in three of the poorest countries of southeastern Africa (Malawi, Mozambique, and Tanzania), which suggested that a year of healthy life could be gained for less than about US$5 (de Jonghe and others 1994; Murray and others 1991). This evidence has been central to the global promotion of the DOTS strategy, the package of measures combining best practices in the diagnosis and treatment of patients with active TB, in which direct observation of treatment during SCC is a key element (WHO 2002a, 2004c).

Although the World Health Organization (WHO) has fostered the implementation of DOTS over the past decade, four recent developments have drawn attention to a wider range of options for TB control:

- First, many more studies have investigated the costs, efficacy, and cost-effectiveness of different approaches to TB control. They are mostly studies of ways to improve the delivery of first-line drug treatment for active disease, but they include some investigations of preventive therapy (treatment of latent infection), treatment of multidrug-resistant TB (MDR-TB) using both first- and second-line drugs, and different approaches to diagnosis. They have been carried out in a variety of settings, in richer as well as poorer countries. The results have not been fully synthesized but may suggest ways to enhance DOTS.
- Second, striking increases in TB have been associated with the spread of HIV infection and drug resistance, suggesting that DOTS alone may not be enough to bring TB under control, especially in Africa and in the countries of the former Soviet Union.
- Third, there is now substantially more investment in new tools for TB control, including multimillion-dollar initiatives to develop better diagnostics, drugs, and vaccines, many of which operate under the umbrella of the Stop TB Partnership (see http://www.stoptb.org). Some of the possible products of this new research would stimulate reevaluations of the current reliance on chemotherapy, especially the development of a new high-efficacy vaccine.
- Fourth, interest in TB is resurgent, not simply as the outcome of mycobacterial infection, but also as the consequence of exposure to exacerbating risks, such as tobacco smoke, air pollution, malnutrition, overcrowding, and poor access to health services. Research directed at quantifying these risks will also suggest ways to minimize them.

These developments set a big agenda for analysis. To make some inroads, this chapter presents an overview of the value for money and potential effect of the principal modes of TB control around the world. The starting point is a review of the natural history and clinical characteristics of TB and the geographical distribution of and trends in TB cases and deaths. This introduction sets the context for a discussion of the interventions that are now available to control TB and of how they have been used. We use a new method for evaluating the cost-effectiveness of infectious disease control and apply
TUBERCULOSIS INFECTION, DISEASE, AND DEATH

Human TB is caused by infection with mycobacteria, principally *Mycobacterium tuberculosis*. Individuals with pulmonary or laryngeal TB produce airborne droplets while coughing, sneezing, or simply talking. Inhaled infectious droplets lodge in the alveoli, and bacilli are taken up there by macrophages, beginning a series of events that results in either the containment of infection or the progression to active disease (Frieden and others 2003). Following uptake by macrophages, *M. tuberculosis* replicates slowly but continuously and spreads through the lymphatic system to hilar lymph nodes. In most infected people, cell-mediated immunity, associated with a positive tuberculin test, develops two to eight weeks after infection. Activated T lymphocytes and macrophages form granulomas, which limit the further replication and spread of bacilli. Unless a later defect occurs in cell-mediated immunity, the infection remains contained within the granulomas.

The immune mechanisms are, in their details, far more complex. For example, following antigenic challenge, a suite of different T cells is responsible for the induction and suppression of protective immunity, delayed hypersensitivity, cytolyis, and the production of antibodies and memory cells. Helper T cells mature into two functionally different populations; in *M. tuberculosis* infection, the T_{H1} response is associated with granuloma formation and protection, whereas the T_{H2} response results in tissue-necrotizing hypersensitivity and the progression of disease. The processes that determine the balance of the two responses affect, for example, the interaction between *M. tuberculosis* and other infectious agents (Grange 2003).

When the immune response cannot suppress replication, primary infection leads to active TB (progressive primary TB). The most common clinical manifestation is pulmonary disease, typically in the parenchyma of the middle and lower lung. In the most infectious patients, bacilli can be seen microscopically on stained sputum smears (60 to 70 percent of pulmonary cases; Marais and others 2004; Styblo 1991). Smear-negative patients may also be infectious but, per patient, contribute relatively little to transmission (Behr and others 1999; Hernandez-Garduño and others 2004). Extrapulmonary tuberculosis accounts for 10 to 30 percent of the disease but is more common among women and children (particularly lymphatic TB) and in people infected with HIV (Aaron and others 2004; Rieder 1999; Rieder, Snider, and Cauthen 1990; Shafer and Edlin 1996).

In the absence of other predisposing conditions, only about 5 percent of infected people develop progressive primary disease within five years of infection (Comstock, Livesay, and Woolpert 1974; Sutherland 1968, 1976). After five years, the annual risk of developing TB by the reactivation of latent infection is much lower (≈10^{-1} per capita per year). The risk of progressing to active disease is relatively high in infancy and lower in older children; it increases quickly during adolescence (earlier in girls) and then more slowly throughout adulthood (Comstock, Livesay, and Woolpert 1974; Nelson and Wells 2004; Sutherland, Svandova, and Radhakrishna 1982; Vynnycky and Fine 1997). Whether latent bacilli remain viable for the full life span of all infected people is unknown, but the risk of reactivation certainly persists into old age. The lifetime risk of developing TB following infection clearly depends on the prevailing transmission rate; the rule of thumb is 10 percent, but it has been calculated at 12 percent for all forms of pulmonary disease in England and Wales during the second half of the 20th century (Vynnycky and Fine 2000).

Besides the strong innate resistance to developing disease, infection is associated with an acquired immune response. This response is only partially protective (Dye and others 1998; Sutherland, Svandova, and Radhakrishna 1982; Vynnycky and Fine 1997), which helps explain why developing an effective vaccine has been difficult (few manufactured vaccines are more protective than natural immunity; Andersen 2001; Fordham von Reyn and Vuola 2002; Young and Stewart 2002). Consequently, individuals who carry a latent infection and who continue to be exposed are at risk of TB following reinfection. The importance of reinfection remains controversial, but mathematical modeling shows that the decline of TB in Europe cannot easily be explained without reinfection (Dye and others 1998; Vynnycky and Fine 1997). In addition, molecular fingerprinting has produced direct evidence that TB commonly arises from infection and reinfection in endemic areas (de Viedma and others 2002; Richardson and others 2002; van Rie and others 1999; Vervel and others 2004), especially where subjects are infected with HIV (Glynn and others 2004).
The low incidence of infection and the low probability of breakdown to disease explain why TB is relatively rare. Its importance among infectious diseases is attributable not so much to the number of cases as to the high case-fatality rate among untreated or improperly treated patients. About two-thirds of untreated smear-positive patients will die within five to eight years, the majority within the first 18 months (Styblo 1991). Most of those who are still alive after eight years will have quiescent TB (self-cures, susceptible to relapse), and a few will become chronic excretors of bacilli. The case-fatality rate for untreated smear-negative cases is lower, but still of the order of 10 to 15 percent (Krebs 1930; Rieder 1999). Even among smear-positive patients receiving antituberculosis drugs, the case-fatality rate can exceed 10 percent if adherence to treatment is low or if rates of HIV infection and drug resistance are high (WHO 2004c). Online annex 1 contains more information about factors that affect the risk to individuals of contracting infection and developing disease and the distribution of TB in populations.

**EPIDEMIOLOGICAL BURDEN AND TRENDS**

Surveys of the prevalence of infection and disease, assessments of the performance of surveillance systems, and death registrations yield an estimated 8.8 million new cases of TB in 2003, fewer than half of which were reported to public health authorities and WHO (online annex 2). Approximately 3.9 million cases were sputum-smear positive, the most infectious form of the disease (Corbett and others 2003; Dye and others 1999; WHO 2005). The African region has the highest estimated incidence rate (345 per 100,000 population annually), but the most populous countries of Asia harbor the largest number of cases: Bangladesh, China, India, Indonesia, and Pakistan together account for half the new cases arising each year. In terms of the total estimated number of new TB cases arising annually, about 80 percent of new cases occur in the top-ranking 22 countries.

In most countries (but not all), more cases of TB are reported among men than women. This differential is partly because women have less access to diagnostic facilities in some settings (Hudelson 1996), but the broader pattern also reflects real epidemiological differences between men and women, both in exposure to infection and in susceptibility to disease (Borgdorff and others 2000; Hamid Salim and others 2004; Radhakrishna, Frieden, and Subramani 2003). Where the transmission of *M. tuberculosis* has been stable or increasing for many years, the incidence rate is highest among young adults, and most cases are caused by recent infection or reinfection. As transmission falls, the caseload shifts to older age groups, and a higher proportion of cases comes from the reactivation of latent infection.

Globally, the TB incidence rate per capita appears to be growing slowly (online annex 2). Case numbers have been declining more or less steadily for at least two decades in Western and Central Europe, the Americas, and the Middle East. Striking increases have occurred in countries of Eastern Europe (mainly the former Soviet republics) since 1990 and in Sub-Saharan Africa since the mid 1980s, although trends in case notifications suggest that the rate of increase in both regions has slowed significantly since the mid 1990s (WHO 2005).

TB has increased in Eastern European countries because of economic decline and the general failure of TB control and other health services since 1991 (Shilova and Dye 2001). Periodic surveys indicate that more than 10 percent of new TB cases in Estonia, Latvia, and, some parts of the Russian Federation are multidrug-resistant—that is, resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs (Espinal and others 2001; WHO 2004a). Drug resistance is likely to be a by-product of the events that led to TB resurgence in these countries, not the primary cause of it, for three reasons. First, resistance is generated initially by inadequate treatment caused, for example, by interruption of the treatment schedule or use of low-quality drugs. Second, resistance tends to build up over many years, and yet TB incidence increased suddenly in Eastern European countries after 1991. Third, although formal calculations have not been done, resistance rates are probably too low to attribute all of the increase in caseload to excess transmission from treatment failures.

Globally, 12 percent of new adult TB cases were infected with HIV in 2003, but there was marked variation among regions—from an estimated 33 percent in Sub-Saharan Africa to 2 percent in East Asia and the Pacific (online annex 2). HIV infection rates in TB patients have so far remained below 1 percent in Bangladesh, China, and Indonesia. The increase in TB incidence in Africa is strongly associated with the prevalence of HIV infection (Corbett and others 2002), and in populations with higher rates of HIV infection, women 15–24 years old constitute a higher proportion of TB patients (Corbett and others 2002). The rise in the number of TB cases in Africa is slowing, almost certainly because HIV infection rates are also beginning to stabilize or fall (Asamoah-Odei, Garcia Calleja, and Boerma 2004). HIV has probably had a smaller effect on TB prevalence than on incidence because HIV significantly reduces the life expectancy of TB patients (Corbett and others 2004). Where HIV infection rates are high in the general population, they are also high among TB patients; estimates for 2003 suggested that more than 50 percent of TB patients infected with HIV in Botswana, South Africa, Zambia, and Zimbabwe, among other countries.

Approximately 1.7 million people died of TB in 2003 (Corbett and others 2003), including 229,000 patients who were also infected with HIV (online annex 2). Although these
are usually reported as AIDS deaths under the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10), and by WHO, TB control programs need to know the total number of TB deaths, whatever the underlying cause.

**INTERVENTIONS AGAINST TUBERCULOSIS**

TB can be controlled by preventing infection, by stopping progression from infection to active disease, and by treating active disease. The principal intervention is the DOTS strategy and its variations, centered on the diagnosis and treatment of the most severe and most infectious (smear-positive) forms of TB but including treatment for smear-negative and extrapulmonary cases as well. Anti-TB drugs can also be used to treat latent *M. tuberculosis* infection and active TB in patients with HIV coinfection, and the widely used bacillus Calmette-Guérin (BCG) vaccine prevents (mainly) severe forms of TB in childhood. These biomedical interventions directed specifically against TB can be implemented in a variety of ways through medical services and public action and can be supported by other efforts to reduce environmental risk factors (online annex 1).

**Vaccination**

Currently, the only means of immunizing against TB is with the live attenuated vaccine BCG, although other vaccines are under development (Fruth and Young 2004; Goonetilleke and others 2003; Horwitz and others 2000; Letvin, Bloom, and Hoffman 2001; Reed and others 2003; Young and Stewart 2002). Randomized controlled trials and case-control studies have shown consistently high protective efficacy of BCG against serious forms of disease in children (73 percent [95 percent confidence limits 67–79 percent] for meningitis and 77 percent [95 percent confidence limits 58–87 percent] for miliary TB) but highly variable—and often very low—efficacy against pulmonary TB in adults (Bourdin Trunz, Fine, and Dye, forthcoming; Fine 2001; Rieder 2003). Thus, even with the high coverage now achieved, BCG is unlikely to have any substantial effect on transmission. In parts of Europe and North America that did and did not use BCG, TB declined at rates that were not measurably different (Styblo 1991). In areas of high incidence, BCG vaccination is recommended for children at birth or at first contact with health services. Vaccination is being discontinued in many low-incidence countries because the risk of infection is low and because the response to BCG confounds the interpretation of tuberculin skin tests used to track persons infected during occasional outbreaks. BCG may have substantial nonspecific effects on child mortality—that is, in reducing deaths from causes other than TB—but this possibility is still controversial (Kristensen, Aaby, and Jensen 2000).

Reported BCG vaccination coverage has increased throughout the world during the past 25 years, reaching about 100 million infants, or 86 percent of all infants, in 2002. An estimated 92 percent of children were vaccinated in Europe and 62 percent in Africa in 2002 (WHO 2001). During the past 15 years, coverage has generally been most variable among African countries and least variable in Europe and the Americas. The most complete analysis of the effect of BCG vaccination suggests that BCG given to children born in 2002 prevents about 29,700 cases of childhood meningitis and 11,500 cases of miliary TB during the first five years of life, or one case for every 3,400 and 9,300 vaccinations, respectively (Bourdin Trunz, Fine, and Dye, forthcoming).

**Treatment of Latent Infection**

Individuals at high risk of TB who have a positive tuberculin skin test but not active disease (for example, associates of active cases, especially children and immigrants to low-incidence countries) can be offered treatment for latent TB infection (TLTI), most commonly with the relatively safe and inexpensive drug isoniazid. Studies among those who have contacts with active cases have demonstrated that 12 months of daily isoniazid gives 30 to 100 percent protection against the development of active TB (Cohn and El-Sadr 2000; Comstock 2000). For patients who may be carrying a strain resistant to isoniazid, rifampicin daily for 4 months is an acceptable alternative (or rifabutin, if used with protease inhibitors for HIV-infected people; Cohn 2003; Menzies and others 2004). Nevertheless, TLTI is not widely used. The main reason is that compliance with long-term daily treatment tends to be poor among healthy people—a relatively high risk of TB among those who are latently infected is usually still a low risk in absolute terms. An additional reason is that the tuberculin skin test tends to be less specific when applied to individuals who have been vaccinated with BCG. Although it is sometimes possible to make separate estimates of the number of individuals in a population who have been infected and who have received BCG (Neuenschwander and others 2002), distinguishing the responses to BCG and infection is harder in any given individual.

The exceptionally high risk of TB among persons coinfected with *M. tuberculosis* and HIV is a reason for encouraging wider use of TLTI, especially in Africa. However, there are significant barriers to making TLTI effective for coinfected individuals living in areas of high transmission (in addition to those listed earlier). Although trials of TLTI with individuals infected with HIV whose tuberculin skin test was positive have averaged about 60 percent protection for up to three years (with a good deal of variability), the effects have been lost soon afterward, and little or no effect has been seen on mortality (Buchner and others 1999; Johnson and others 2001; Mwinga and others 1998; Quigley and others 2001; Whalen and others 1997; Wilkinson,
Squire, and Garner 1998). In addition, identifying \textit{M. tuberculosis} infection is more difficult in HIV-positive individuals than in those who are HIV-negative because the former are often anergic and are, therefore, unresponsive to tuberculin. Early studies have also experienced problems with uptake and compliance. In a pilot project in Zambia, for example, only 35 percent of HIV-infected individuals identified through HIV testing and counseling services actually started TLTI, and, of those who started, only 23 percent completed at least six months of treatment (Terris-Prestholt and Kumaranayake 2003).

TLTI has been used as a component of intensive, local control campaigns, such as those carried out for North American and Greenland Eskimos, but probably had effects secondary to the prompt treatment of active disease (Comstock, Baum, and Snider 1979; Styblo 1991). At present, TLTI plays no more than an accessory role in TB control in any setting, although the number of recipients around the world has been neither directly quantified nor indirectly estimated.

**Treatment of Active Disease: The DOTS Strategy**

The cornerstone of TB control is the prompt treatment of active cases with SCC using first-line drugs, administered through the DOTS strategy (WHO 2002a) within targets framed by the MDGs. The DOTS strategy has five elements:

- political commitment
- diagnosis primarily by sputum-smear microscopy among patients attending health facilities
- SCC with effective case management (including direct observation of treatment)
- a regular drug supply
- systematic monitoring to evaluate the outcomes of every patient started on treatment.

Standard SCC can cure more than 90 percent of new, drug-susceptible TB cases, and high cure rates are a prerequisite for expanding case finding. Although the DOTS strategy aims primarily to provide free treatment for smear-positive patients, most DOTS programs also treat smear-negative patients, usually without a fee. DOTS can be used as the basis for more complex TB control strategies where rates of drug resistance or HIV infection are high.

Mathematical modeling and practical experience suggest that the incidence of TB will decline at 5 to 10 percent per year when 70 percent of infectious cases are detected through passive case finding and 85 percent of these cases are cured, even though that level represents a treatment success rate among all infectious cases of only 60 percent (Dye 2000; Dye and others 1998). In principle, TB incidence could be forced down more quickly, by as much as 30 percent per year, if new cases could be found soon enough to eliminate transmission. In general, the decline will be faster where a larger fraction of cases arises from recent infection (that is, in areas where transmission rates have recently been high) and slower where there is a large backlog of asymptomatic infection. As TB transmission and incidence go down, a higher proportion of cases comes from the reactivation of latent infection and the rate of decline in incidence slows. These facts explain why it should be easier to control epidemic than endemic disease: during an outbreak in an area that previously had little TB, the reservoir of latent infection will be small, and most new cases will come from recent infection.

In the control of endemic TB, largely by chemotherapy, the best results have been achieved in communities of Alaskan, Canadian, and Greenland Eskimos, where incidence was reduced at 13 to 18 percent per year from the early 1950s (Styblo 1991). Over a much wider area in Western Europe, TB declined at 7 to 10 percent per year after drugs became widely available during the 1950s, although incidence was already falling at 4 to 5 percent per year before chemotherapy (Styblo 1991). More recently, between 1994 and 2000, the incidence of pulmonary TB among Moroccan children 0 to 4 years of age fell at more than 10 percent per year, suggesting that the risk of infection was falling at least as quickly (S. Ottmani, personal communication 2005). The overall reduction in pulmonary TB was only 4 percent per year, in part because of the large reservoir of infection in adults. DOTS was launched in Peru in 1991, and high rates of case detection and cure appear to have pushed down the incidence rate of pulmonary TB by 6 percent per year (Suarez and others 2001). For epidemic TB, as a result of aggressive intervention following an outbreak in New York City, the number of MDR-TB cases fell at a rate of more than 40 percent per year (Frieden and others 1995).

Although the long-term aim of TB control is to eliminate all new cases, cutting prevalence and death rates is arguably more important. About 86 percent of the burden of TB, as measured in terms of disability-adjusted life years (DALYs) lost, is attributable to premature death rather than illness, and prevalence and mortality can be reduced faster than incidence in chemotherapy programs. Thus, the TB death rate among Alaskan Eskimos dropped at an average of 30 percent per year in the period 1950–70 and at an average of 12 percent per year throughout the Netherlands from 1950 to 1990. Indirect assessments of the effect of DOTS suggest that 70 percent of the TB deaths expected in the absence of DOTS were averted in Peru between 1991 and 2000, and more than half the TB deaths expected in the absence of DOTS are prevented each year in DOTS provinces of China (Dye and others 2000; Suarez and others 2001). There have been few direct measures of the reduction in TB prevalence over time, but surveys done in China in 1990 and 2000 showed a 32 percent (95 percent confidence limits 9–51 percent) reduction in the prevalence rate of all forms of TB in DOTS areas, as compared with the change in the
prevalence rate in other parts of the country (China Tuberculosis Control Collaboration 2004; PRC Ministry of Health 2000). These findings imply that the targets of halving prevalence and death rates between 1990 and 2015 are technically feasible, at least in countries that are not burdened by high rates of HIV infection or drug resistance.

Many of the 182 national DOTS programs in existence by the end of 2003 have shown that they can achieve high cure rates: the average treatment success rate was 82 percent (that is, the percentage that were sputum-smear negative at the end of treatment plus the percentage that had completed treatment but for whom cure was not confirmed by sputum smear), not far below the 85 percent international target (WHO 2005). The outstanding deviations below that average were in Africa (73 percent) and some former Soviet republics (for example, 67 percent in Russia). Although the completion of treatment was almost a guarantee of cure before the spread of HIV and drug resistance, “completed” is an unsatisfactory way to report the outcome of treatment if cure is in doubt.

Although most TB patients probably receive some form of treatment, only 45 percent of all estimated new smear-positive cases were reported by DOTS programs to WHO in 2003. The case-detection rate in DOTS programs has been accelerating globally since 2000, but the annual increment must be still greater if the 70 percent target is to be reached by the end of 2005. Observations on the way DOTS is presently implemented suggest that a ceiling on case detection might be reached at about 50 to 60 percent (Dye and others 2003; WHO 2005). This fraction is about the same as the percentage of all cases reported annually to WHO from all sources (that is, from DOTS and non-DOTS programs). The problem is that, as DOTS programs have expanded geographically, they have not yet reached far beyond existing public health reporting systems.

ALTERNATIVE AND COMPLEMENTARY APPROACHES TO THE DIAGNOSIS AND TREATMENT OF ACTIVE DISEASE

The limitations of the DOTS strategy have stimulated numerous initiatives to improve program performance (including treatment protocols for patients carrying drug-resistant bacilli or who are infected with HIV), active case finding, collaborations within and between public and private sector health services, schemes for outpatient and community-based treatment, and integration of the management of TB and other illnesses.

Management of Drug-Resistant Disease

The higher the proportion of patients carrying drug-resistant bacilli is, the greater the need for accurate resistance testing and for the provision of alternative regimens that include at least three drugs to which bacilli are fully susceptible. Of greatest importance is resistance to the two principal first-line drugs, isoniazid and rifampicin (that is, MDR-TB). The introduction of resistance testing, second-line drugs, longer treatment regimens (12 to 18 months), and rigorous bacteriological and clinical monitoring all increase program costs without necessarily ensuring high cure rates (equal to or greater than 85 percent). Indeed, achieving the same cure rates for MDR-TB patients as for patients carrying fully susceptible strains may not be possible. The cost-effectiveness of this component of a TB control program is therefore lower by an amount that depends on the nature of the resistance, the methods of testing and monitoring, and the choice of regimen. The higher costs and lower cure rates associated with treating drug-resistant TB are part of the argument for preventing the spread of resistance in the first place, as can be investigated with models of selection and transmission (Dye and Espinal 2001; Dye and others 2002; Dye and Williams 2000). Suarez and others (2002) have investigated the cost-effectiveness of managing drug-resistant TB in Peru, but because studies in other settings have yet to be published, an empirical overview is not yet possible. Further data will be available from studies in Estonia, the Philippines, and Russia in 2005.

Treatment of HIV Coinfection

Antiretroviral therapy for HIV-positive individuals is unlikely to prevent a large fraction of TB cases unless treatment can be given shortly after HIV infection is acquired (Sonnenberg and others 2005; Williams and Dye 2003). In general, antiretroviral therapy is likely to be most effective, not in reducing TB incidence, but in extending the life expectancy of HIV-positive patients successfully treated for TB (Friedland and others 2004). Antiretroviral therapy and DOTS are formally synergistic, because without undergoing both together, HIV-infected TB patients have a short life expectancy, typically less than five years.

Where the prevalence of HIV infection has been rising quickly, as in eastern and southern Africa, even the most energetic programs of TB chemotherapy may not be able to reverse the rise in TB incidence. However, mathematical modeling indicates that, even in the midst of a major HIV epidemic, early detection and cure are the most cost-effective ways of minimizing TB cases and deaths (Currie and others, 2005). One reason is that DOTS programs treat all TB cases, not just those linked with HIV. The alternatives—the prevention of HIV infection, TLTI, and antiretroviral therapy—are less promising strategies to control TB, at least for the coming decade, although they could be used in combination with DOTS.

Active Case Finding

The DOTS strategy is based on passive case detection for three reasons: (a) the majority of incipient TB cases develop active
smear-positive, infectious disease more quickly than any reasonable interval between successive rounds of mass screening for TB symptoms or x-ray abnormalities; (b) the majority of patients severely ill with a life-threatening disease are likely to seek help quickly (Toman 1979); and (c) countries that have not yet implemented effective systems for passive case detection are not in a position to pursue cases more actively. The drawback of passive case finding is that the delays to diagnosis among symptomatic patients are often long, and health services never see some patients. To shorten delays and increase the proportion of cases detected, studies of risk can identify subpopulations in which TB tends to be relatively common. Systematic surveys of these subpopulations for active TB may be logistically feasible and affordable. The target populations include individuals infected with HIV, refugees (Marks and others 2001), contacts of active cases (Claessens and others 2002; Noertjojo and others 2002), health workers (Cuhadaroglu and others 2002), and drug users and prisoners (Nyangulu and others 1997). Despite the practical possibilities and the potential effect on transmission (Murray and Salomon 1998), active case finding is rarely done in high-burden countries, where the emphasis is still on implementing the basic DOTS strategy.

Case Finding and Treatment in the Private Sector

It is well known that many TB patients first seek treatment from private practitioners and that diagnosis and treatment in the private sector often do not meet internationally accepted standards (Uplekar, Pathania, and Raviglione 2001). A new scheme to deliver DOTS through the private sector (Public-Private Mix DOTS) operates through the provision of free drugs, by information exchange and patient referral, and with some financial support from participating governments. Two pilot projects in Hyderabad and Delhi, India, improved case-detection rates by 26 percent and 47 percent, respectively, and maintained treatment success close to the target of 85 percent (WHO 2004b). Other such projects are under way elsewhere in India as well as in Bangladesh, Indonesia, Nepal, the Philippines, and Vietnam (WHO 2004d).

Outpatient and Community-Based Treatment

Early studies of the cost-effectiveness of TB control found that full ambulatory treatment, eliminating hospitalization during the first two months (intensive phase), was cheaper and did not compromise cure rates (de Jonghe and others 1994; Murray and others 1991). Partly as a result, ambulatory treatment has become the standard of care in many high-burden countries. The natural extension, to home- and community-based treatment, has proved to be just as effective in several African settings, and even lower in cost (Adatu and others 2003; Dudley and others 2003; Floyd and others 2003; Floyd, Wilkinson, and Gilks 1997; Moalosi and others 2003; Okello and others 2003; Sinanovic and others 2003; Vassall and others 2002; Wilkinson, Floyd, and Gilks 1997). Various schemes have been used to provide TB care in the community, in which nongovernmental organizations, volunteers (Okello and others 2003), or appointed “guardians” (Floyd and others 2003) supervise treatment, sometimes with financial incentives (Sinanovic and others 2003). Consequently, community-based care is being adopted in some countries (for example, Uganda) as standard procedure.

Integrated Management of Tuberculosis and Other Respiratory Illnesses

Surveys in nine countries found that up to one-third of patients over five years of age attending primary health centers had respiratory symptoms, of whom 5 to 10 percent were TB suspects, but only 1 to 2 percent had TB (WHO 2004e). Because TB is rare among respiratory diseases, comanaging TB with other conditions has clear advantages. The purpose of the WHO’s Practical Approach to Lung Health (PAL) project is to encourage a syndromic approach to management of patients, to standardize health service delivery through the development and implementation of clinical guidelines, and to promote the necessary coordination within national health services. Preliminary investigations in the Kyrgyz Republic and Morocco suggest that PAL projects can improve the accuracy of diagnosis, encourage better practice in prescribing drugs, and strengthen primary care. However, a full analysis of costs and effects in the nine-country study remains to be done.

COST-EFFECTIVENESS OF INTERVENTIONS AGAINST TUBERCULOSIS

Some questions about investing in TB control are broad and strategic (for example, should money be spent on the control of TB rather than on the control of some other condition?); others are specific and technical (for example, which laboratory diagnostic procedures should be used?). On whatever level the question is posed, cost-effectiveness analysis (CEA) has become a prominent method for evaluating and choosing among different health interventions.

Background

Between 1980 and 2004, 32 studies of the cost-effectiveness of TB control were published from the low- and middle-income countries considered by the Disease Control Priorities Project (table 16.1; online annex 3 summarizes the 32 studies that have been published according to the country and year of publication, the question being addressed, the strategies compared, the
subjects and costs considered, the effectiveness of measures used, whether or not transmission is considered, and the main results and conclusions). Almost all of these studies (28, or 88 percent) have concerned ways of finding, diagnosing, and treating patients with active TB, and most (18, or 56 percent) have been done in eight countries in Sub-Saharan Africa (Floyd 2003). Three studies (all in Sub-Saharan Africa) have investigated TLTI, and one study in Indonesia has examined BCG vaccination. The principal findings are that short-course chemotherapy for active TB is a comparatively cost-effective intervention and one of the most cost-effective of all health interventions. TB patients can be treated more cheaply and conveniently outside hospitals on an ambulatory basis, by health staff or with the help of family and community members, without compromising the success of treatment. Supplementary methods, such as standardized second-line drug treatment for MDR-TB, appear to be affordable and cost-effective in some settings.

What does not emerge from this compilation of data is a comprehensive overview of the value for money provided by current and potential interventions against TB in all major regions of the world, expressed using a common measure of effectiveness and based on a consistent approach to the evaluation of transmission. (The returns on investment in infectious disease control include the immediate benefits to individuals treated—for example, those vaccinated or given drug therapy—plus the longer-term benefits gained by preventing secondary cases through reduced transmission.) Little work has been done in China, India, and other large countries in Asia, even though Asia carries the largest burden of TB, and only limited information is available for Europe and Central Asia, Latin America and the Caribbean, and the Middle East and North Africa. Of the 32 studies, only 10 used a measure of effectiveness that allows comparison with other diseases (table 16.2), and only 9 attempted to include an estimate of the benefits gained from reduced transmission (table 16.1). The benefits from reduced transmission are usually assessed through mathematical modeling (using computer simulations) for a given epidemiological situation, an approach that produces specific solutions for each setting rather than results that are generally applicable. In addition, although the benefits from prevented transmission are lower when TB is endemic, existing studies do not make a clear distinction between the cost-effectiveness of interventions in epidemic (outbreak) and endemic situations.

### Methods

In this study, a general analytical framework was used to evaluate the total costs and total effects (defined as cases prevented, deaths averted, and DALYs gained) of the principal interventions against TB across six regions of the world (see online annexes 4–7 for further details). A dynamic infectious disease model (online annex 4) was used to derive general formulas for calculating the cost-effectiveness of interventions...
to control endemic (online annex 5) and epidemic (online annex 6) TB in a wide variety of settings. The formulas are approximate, but they are simple and able to provide insights into the strategies that give value for money under a wide variety of epidemiological circumstances. The model was then supplied with cost and efficacy data (online annex 7) for each of the six World Bank regions for four main groups of interventions:

- immunization with BCG (proportion of infants, \( m \), assumed to be protected against severe, noninfectious childhood TB only), or a new vaccine that prevents infection and progression to pulmonary and extrapulmonary TB in children and adults
- isoniazid treatment of latent TB infection (TLTI, given at per capita rate \( \rho \)), for people infected with \( M. \) tuberculosis, with or without HIV coinfection and with or without the use of radiography to exclude patients with active disease
- short-course chemotherapy, delivered as a component of the DOTS strategy, for smear-positive or smear-negative pulmonary disease and extrapulmonary disease (with a combination of drugs given at per capita rate \( \tau \)), and for patients infected with HIV, with or without supporting antiretroviral therapy
- treatment for MDR-TB using a standardized regimen including first- and second-line drugs or using individualized regimens of first- and second-line drugs that are tailored to each patient’s drug susceptibility pattern.

Costs were considered from a health system or provider perspective. They were calculated by combining estimates of the quantities of resources required for each intervention (per patient or per person treated) with the unit prices of those resources (in 2001 U.S. dollars) using the cost categories and unit prices defined in the Disease Control Priorities costing guidelines.

**COST-EFFECTIVENESS OF MANAGING ENDEMIC TUBERCULOSIS**

The primary problem in global TB control is the management of disease in countries where incidence has been roughly stable for many years (that is, where TB is endemic).

**Cost per Case Prevented**

In monetary terms, the cost-effectiveness (\( C/E \)) of a new program of treatment for active infectious disease (here defined as sputum-smear positive), per case prevented, can be calculated from \( C/E = P/eKT \), where \( P \) is the cost of treatment, \( e \) is the efficacy of treatment, \( k \) is a constant determined by the mode of action of the intervention, and \( T \) is the duration of the intervention in years (online annex 5). The cost per case prevented is mostly in the range of US$1,000 to US$10,000, depending on the region of the world (figure 16.1). The exception is Europe and Central Asia, where costs are high because patients are currently treated for long periods in hospitals rather than on an

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**Table 16.2 Number of Studies on the Cost-Effectiveness of TB Control by Effectiveness Measure and Intervention, 1980–2004**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cases detected or cases diagnosed</th>
<th>Cases prevented</th>
<th>Cure or successful treatment rate</th>
<th>Deaths prevented</th>
<th>Years of life saved</th>
<th>QALYs gained</th>
<th>DALYs gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG vaccination</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLTI</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Treatment of active disease: the DOTS strategy</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Variations on DOTS: Management of drug-resistant disease</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Treatment of HIV coinfection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Active case finding and diagnosis</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Outpatient and community-based treatment</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>All interventions</td>
<td>5</td>
<td>5</td>
<td>18</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Source: Authors.

QALY = quality-adjusted life year.

Note: The total for all interventions is greater than the number of studies because some studies use more than one measure of effectiveness.
Source: Authors.

Note: Where shown, bar 7 is for ambulatory (outpatient) treatment in Sub-Saharan Africa. The treatment of active disease saves no additional cases of TB when the effects of reducing transmission are excluded, so the cost per case prevented cannot be calculated. Cost-effectiveness of vaccination and TLTI is calculated for an initial incidence rate of 100 per 100,000 population per year. Cost-effectiveness ratios are plotted on a logarithmic scale. Error bars are 90 percent confidence limits. The horizontal gray line in the third chart marks a cost-effectiveness of US$1 per day of healthy life gained.

Figure 16.1 Cost-Effectiveness of Different Interventions against Endemic TB
ambulatory basis. These cost-effectiveness ratios (CERs) are computed from the total costs and total effects of treatment. Costs are therefore the same as the incremental costs for new programs. If costs and effects are compared with those of a previous treatment program, CERs for the treatment of active disease are often negative; that is, the program sooner or later saves money, as well as preventing TB cases. The positive CERs reported here for new treatment programs are, in this sense, upper estimates.

The cost of TLTI per active case prevented also depends on the initial incidence rate (I) and is calculated from $C/E = \frac{P/e}{\text{KIT}}$ (online annex 5). The cost is substantially higher than that for the treatment of active TB: US$20,000 to US$40,000 when radiography is used to exclude patients with active disease, but it is less (US$13,000 to US$20,000) if active TB can be ruled out on the basis of symptoms and clinical examination (figure 16.1). TLTI is less cost effective than the treatment of active TB because preventive treatment would be given to latently infected individuals, most of whom were not recently infected and who are at small risk of developing active disease. In an endemic setting, there is no feasible method of identifying individuals who have recently acquired infection and who will proceed rapidly to active TB.

A new vaccine that prevents infection and, hence, the progression to pulmonary TB among people who were previously uninfected would be extremely competitive (US$90 to US$200) per case prevented if the costs were the same as those for BCG. BCG is cheap to manufacture and administer (US$1 to US$3 per dose) but less cost-effective (US$2,000 to US$8,500 per case prevented) than the treatment of active disease because it is assumed to protect against severe forms of childhood TB only and because it does not affect transmission (figure 16.1).

Cost per Death Prevented and DALY Gained

The wider benefits of treating active TB are revealed when allowing for the additional reduction in case fatality. For a 10-year program of treatment for infectious TB, the cost per death prevented is typically US$150 to US$750, and the cost per DALY gained is US$5 to US$50 for all regions except Europe and Central Asia (figure 16.1). When TB is close to the endemic equilibrium, the extra benefits gained from reducing transmission under DOTS are small: the cost per DALY gained is only 60 percent higher when transmission benefits are excluded. The treatment of nonfectious TB is less cost-effective (US$60 to US$200 per DALY gained), not primarily because transmission is unaffected, but because the case fatality of untreated smear-negative and extrapulmonary disease is relatively low. Treating infectious MDR-TB is between two and ten times more costly than treating drug-susceptible TB per death prevented (greater than US$2,000), or per DALY gained (greater than US$90), assuming resistant bacilli are as transmissible and pathogenic as susceptible bacilli.

BCG vaccination is not much less cost-effective than the treatment of active disease (US$40 to US$170 per DALY gained; higher where the risk of infection is lower). If a new vaccine with 75 percent efficacy against pulmonary disease and other forms of TB costs the same as BCG, it would be almost as cost-effective (US$20 to US$100 per DALY gained) as the ambulatory treatment of active TB. As expected from the preceding analysis, TLTI is much more expensive than all other options (US$5,500 to US$26,000 per DALY gained) and most costly where the death rate from TB among adults is already relatively low—for example, because an effective DOTS program already exists. Although the cost-effectiveness of each intervention varies among regions, the variation among strategies is much greater, whatever the outcome measure (figure 16.1).

**COST-EFFECTIVENESS OF MANAGING TUBERCULOSIS OUTBREAKS**

The basic case reproduction number, $R_0$, is a ready-made epidemiological tool for relating effort and reward in the management of outbreaks. $R_0$ is the average number of secondary cases generated by a primary case introduced into a previously uninfected population (Anderson and May 1991). No country is presently free of TB, but some countries have recently suffered “epidemic” increases in incidence from previously low levels. The algebraic expression of $R_0$ for TB reveals how the various components of a disease's natural history and the different kinds of intervention interact with each other to influence transmission and the generation of new cases (online annex 4). For example, the cost-effectiveness of chemotherapy per M. tuberculosis generation is $C/E = \frac{P/e}{R_0}$, where $P/e$ is the number of TB patients treated per prevalent case per unit time, and $\sigma$ is the proportion of new cases that is infectious.

The biggest resurgences of TB in recent history have been driven by the spread of HIV in Africa and are linked to the rise of drug resistance in former Soviet republics; this analysis is confined to interventions associated with these two phenomena (figure 16.2; online annex 6). Indeed, in this study, interventions related to TB with HIV are considered only in the epidemic context.

If multidrug-resistant strains of M. tuberculosis are assumed to have the same intrinsic transmissibility and pathogenicity as drug-susceptible strains, and given the spread of MDR-TB as an independent epidemic (Dye and Williams 2000), then treatment of MDR-TB with a standard regimen including second-line drugs is more costly per DALY gained than treatment of fully susceptible disease in Sub-Saharan Africa, but it is marginally less costly than TLTI (with an x-ray screen) over most rates of case detection and treatment (online annex 6).
Figure 16.2 Cost-Effectiveness of Managing Epidemic TB

Source: Authors.

Note: Five interventions used in the management of TB epidemics that are linked with HIV and MDR-TB (TLTI for people coinfected with TB and HIV, treatment of infectious MDR-TB with a standard or individual regimen, treatment of HIV-infected TB patients with TB drugs, treatment of HIV-infected TB patients with TB and antiretroviral drugs) are compared with two standard methods (TLTI, with active disease excluded by x-ray screen, and treatment of active infectious disease, allowing for transmission). Cost-effectiveness ratios (plotted on a logarithmic scale) vary with the treatment rate (online annex 6); for illustration here, 20 percent of eligible people are treated annually with each intervention. The horizontal gray line in the third figure marks a cost-effectiveness of US$1 per day of healthy life gained. Error bars are 90 percent confidence limits.
For example, at the fixed rate of treatment used to generate figure 16.2, treatment of MDR-TB with a standard regimen costs US$91 to US$846 per DALY gained, depending on the region, as compared with US$6 to US$31 for the treatment of drug-susceptible TB. The treatment of MDR-TB with regimens tailored to the resistance patterns of individual patients is more costly but also more efficacious than standardized treatment for MDR-TB and, therefore, almost equally cost-effective under this set of assumptions.

TB patients infected with HIV are more costly to treat per DALY gained than HIV-negative patients, either without antiretroviral therapy (low cost, short life expectancy) or with such therapy (high cost, long life expectancy). TLTI is a more attractive option for the management of epidemic TB than for endemic TB (compare figures 16.1 and 16.2), because during an outbreak, TLTI is directed at recent rather than remote infection. TLTI is even more cost-effective in the control of TB and HIV coinfection, because it prevents the rapid breakdown to active disease caused by immunodeficiency.

These results are indicative rather than definitive, because the calculations assume, among other things, that HIV-infected populations exist in isolation; in reality, HIV-infected people also acquire TB infection from TB patients who are not infected with HIV. Neither does this analysis address all the important questions about managing outbreaks of drug-resistant or HIV-related TB. Fuller investigations should assess, for example, the benefits to whole populations of giving antiretroviral therapy to HIV-infected individuals before they develop TB and of investing in DOTS to prevent multidrug-resistant epidemics from arising in the first place.

**SUMMARY OF COST-EFFECTIVENESS ANALYSES**

Box 16.1 summarizes the results of these calculations of the cost-effectiveness of managing epidemic and endemic TB. The findings are one justification for maintaining and expanding DOTS programs, on the basis of SCC for patients with active disease, as the dominant mode of TB control around the world. BCG vaccination and the treatment of MDR-TB (standard or individualized regimens) or HIV-infected TB patients (with or without supporting antiretroviral therapy) are more costly in absolute terms, but they typically cost less than US$1 per day of healthy life gained, which is less than the average economic productivity of workers in the least developed countries. TLTI appears to be relatively poor value for money, even though this analysis assumes that one course of treatment prevents active

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**Box 16.1**

**Cost-Effectiveness of TB Interventions: Main Findings**

- The cost-effectiveness of TB control depends not only on local costs but also on the local characteristics of TB epidemiology (for example, epidemic or endemic, low or high rates of HIV infection and drug resistance) and on the rate of application of any chosen intervention.
- Short-course chemotherapy for the treatment of infectious and noninfectious TB patients through the DOTS strategy is highly cost-effective for the control of either epidemic or endemic TB (US$5 to US$50 per DALY gained, for regions excluding Eastern and Central Europe). When a new treatment program is compared with a previous program, DOTS often saves money as well as preventing cases and deaths.
- Some variations on DOTS are less cost-effective but still good value for money, including the treatment of patients with MDR-TB (standard or individualized drug regimens) and with HIV infection (with or without supporting antiretroviral therapy). For these additional interventions, the cost per DALY gained is less than the annual average economic productivity per capita in the least developed countries.
- Even with relatively favorable assumptions, the treatment of latent TB infection where TB is endemic and populations are unaffected by HIV is the least cost-effective of the interventions examined here (US$5,500 to US$26,000 per DALY gained). TLTI is more cost-effective during outbreaks (US$150 to US$500 per DALY gained) and for people who are coinfected with TB and HIV (US$15 to US$300 per DALY gained).
- BCG vaccination to prevent severe forms of childhood TB is much less effective than SCC but nearly as cost-effective (US$40 to US$170 per DALY gained).
- A new vaccine that prevents pulmonary TB with high efficacy (equal to or greater than 75 percent) would be more cost-effective than BCG if the cost of immunization were the same as BCG (US$20 to US$100 per DALY gained).
- For any intervention with the potential to cut transmission (that is, excluding BCG vaccination), control of epidemic disease produces more favorable cost-effectiveness ratios than control of endemic disease, because the benefits gained from reduced transmission are greater during outbreaks.

*Source: Authors.*
TB for life. TLTI is more cost-effective in epidemic than in endemic settings, and it is more cost-effective when it is used to treat individuals coinfected with TB and HIV. A new, high-efficacy vaccine that prevents infection and the progression to pulmonary TB in adults, to be directed at the control of endemic TB, would be more cost-effective than BCG at the same price and almost as cost-effective as SCC.

Averted and Avertable Burden of Tuberculosis

Trends in case notifications can be used, judiciously, to assess regional and global trends in TB incidence, but no satisfactory large-scale analysis has been done of the number of cases prevented by chemotherapy (as distinct from the reductions in transmission and susceptibility associated with improved living standards). One approach to evaluating the averted and avertable burden of TB begins with the observation that 86 percent of the years of healthy life lost that are attributable to TB are from premature death, and only 14 percent are from illness. Because DALYs lost are dominated by premature death, a conservative estimate of the burden of TB alleviated can be obtained in terms of the number of deaths and associated DALYs gained, regionally and globally, since the introduction of the DOTS strategy in 1991.

Figure 16.3 is derived from recent estimates of cases and deaths and their trends by region, including those attributable to HIV coinfection (Corbett and others 2003; WHO 2004c). In the MDG baseline year, 1990, approximately 1.5 million TB deaths (28 per 100,000) occurred. BCG vaccination saved roughly 650,000 deaths from extrapulmonary TB among children between 1990 and 2003. If chemotherapy is assumed to reduce only the case-fatality rate and to have no effect on transmission and incidence, 23 million deaths (44 percent) would have been saved in non-DOTS treatment programs. The expansion to 45 percent case-detection rate under DOTS during the same period saved an estimated 2.3 million (~5 percent) additional deaths, the largest numbers in Sub-Saharan Africa (1.1 million), East Asia and the Pacific (358,000), and South Asia (408,000). Further analysis shows that, if 70 percent of TB cases (smear positive and smear negative) can be treated under DOTS before MDG target year 2015, an estimated 1.9 million TB deaths (26 per 100,000) will occur in that year, a greater number than in 1990, but a 7 percent lower death rate per capita (Dye and others 2005).

The calculations for Africa assume that treatment cures TB in the majority of HIV-infected patients even though, without antiretroviral therapy, many of these patients will die anyway. Despite these favorable assumptions, the number of TB deaths was evidently still rising in Africa in 2003, whereas it was falling in Asia, aided by the large programs of DOTS expansion in China (1991–97) and India (from 1998).

Reducing the TB death rate sufficiently to meet the MDG target requires a significant cut in incidence, as well as in case fatality. An extension of this assessment suggests that case detection must reach at least 70 percent and the TB incidence rate must fall by 5 to 6 percent annually between 2003 and 2015 (Dye and others 2005). For the world, excluding Sub-Saharan Africa and former Soviet republics, the incidence rate would have to fall at a more modest 2 percent per year.

New diagnostics, drugs, and vaccines would also help reduce the global TB burden more quickly. The most desirable of these is a vaccine that prevents pulmonary disease, whether or not vaccination subjects are already infected (a pre- or postexposure vaccine), and that confers lifetime immunity (Andersen 2001; Fordham von Reyn and Vuola 2002; McMurray 2003; Young and Stewart 2002). A new vaccine with high efficacy against pulmonary TB would almost certainly change immunization practice: mass vaccination campaigns among adults (rather than infants) would have dramatic effects, going far beyond the expectations of DOTS programs (figure 16.4; Dye 2000). A postexposure vaccine that stops progression to disease among those already infected, as well as preventing infection in others, would have greater effect than a preexposure vaccine that only prevents infection (Lietman and Blower 2000). However, such calculations are at present highly speculative, because the mode of action and efficacy of any new vaccine is unknown.

Economic Benefits of Tuberculosis Control

Preventing TB deaths brings no savings in the costs of TB control unless it is accompanied by a reduction in incidence so that fewer patients require treatment. The prompt and effective
treatment of active disease is almost certainly reducing transmission around the world, but because the effect on incidence is necessarily slow, it has been hard to quantify in all but a few countries, notably Peru (Suarez and others 2001).

The monetary savings implied by a reduction in incidence of one-quarter (26 percent) between 2000 and 2015—which may be enough to achieve the MDG targets—could be magnified or diminished by adjustments to the DOTS strategy. On the one hand, without compromising cure rates, chemotherapy can be delivered more cheaply to outpatients than inpatients and with less reliance on X-ray diagnosis and surgical procedures. On the other hand, various additions to DOTS—contact tracing, active case finding, antiretroviral therapy for HIV-infected patients, second-line drugs for patients carrying resistant bacilli, or joint public–private schemes for the management of TB—might be desirable but more costly per year of healthy life gained. Whether the savings made by reducing incidence and improving efficiency offset the costs of DOTS add-ons will, therefore, depend on the setting.

Besides the possibility of reducing diagnostic and treatment costs, improved health and longevity yield other economic benefits, but the quantification of those benefits is always controversial. This difficulty is reflected in the limited number of cost-benefit analyses of TB control; among the few examples, one detailed study in India estimated the potential societal benefits of DOTS to be worth US$8.3 billion in 1993–94, or 4 percent of the gross domestic product (Dholakia 1996). Without attempting to extend such analyses here, we note that the preceding results also imply that large-scale treatment programs for TB are likely to give net returns on investment or at least to appear to be good value for money in ways that go beyond the arguments from cost-effectiveness (Jack 2001).

The analysis earlier in this chapter showed that SCC typically costs up to US$30 per DALY gained for the treatment of infectious TB and up to US$200 per DALY gained for the treatment of noninfectious TB (excluding Europe and Central Asia). These figures can be compared with a recent estimate of US$1.5 billion as the annual global cost of treating 70 percent of cases with 85 percent cure (WHO 2004c). Reaching these targets would prevent approximately 2.1 million of all the TB deaths expected if no treatment were available in 2003, including 391,000 deaths prevented by DOTS (figure 16.3). Because each TB death prevented gains approximately 20 DALYs (WHO 2002b), the total cost per DALY gained would be about US$36. This rough calculation excludes any benefits in reduced transmission but includes the costs of treating smear-negative and extrapulmonary TB and is of the same order of magnitude as the results from CEA.

However the calculation is done, the cost of gaining a year of healthy life under DOTS is substantially less than the annual average productivity per capita in the low-income (gross national income [GNI] less than or equal to US$735) or least developed (GNI average US$290, http://www.worldbank.org) countries, and it is probably less than the marginal productivity of labor in the poorest communities. It is also less than twice the average annual income per capita, which has also been proposed as a benchmark for assessing whether an intervention is cost-effective (Garber and Phelps 1997). Moreover, it is less than the World Bank’s definition of absolute poverty (living on US$1 per day or less, close to average GNI per capita for the least developed countries) and is certainly less than the monetary values that are typically placed on the value of a human life year (for example, a life was valued at US$100,000 by the 2004 Copenhagen Consensus panel, http://www.copenhagenconsensus.com). All these comparisons suggest not only that the basic DOTS strategy, and perhaps even an enhanced DOTS strategy, are cost-effective but that they also have very favorable cost-benefit ratios.

**RESEARCH AND DEVELOPMENT**

The preceding review and analysis suggest at least six areas for economic and epidemiological research and development:

1. **DOTS expansion.** Refinement of existing cost estimates of scaling up DOTS programs to reach and move beyond targets for case detection (70 percent) and cure (85 percent) in the poorest countries—notably in Africa—through more comprehensive planning and budgeting exercises. The analyses should include the costs of developing fully staffed...
health services, with expanded and renovated infrastructure and improved management capacity where necessary, and the costs of the new initiatives that will be required to improve case detection and cure rates.

2. **Service delivery.** Assessment of the potential for health service restructuring to detect, diagnose, and treat TB patients more efficiently through syndromic management of respiratory diseases at primary health centers and through collaborations between public and private health services, between different parts of the public sector health service, and between TB and HIV/AIDS control programs.

3. **Complementary strategies.** Further investigation of the costs and effectiveness of strategies that are potentially complementary to DOTS, including active case finding and TLDI in high-risk populations, and the management of drug resistance and of patients infected with HIV.

4. **Impact and targets.** Evaluation of the actual and potential effects of the tools (mostly drugs) now being used for TB control. This research requires a better understanding of the ways human population density, age structure, migration, HIV coinfection, and drug resistance affect TB epidemiology. The analyses should check the internal consistency of international targets for the implementation and effect of chemotherapy programs, as defined by the MDGs. The analyses should also make better use of the rich body of routine surveillance data collected by all national TB control programs around the world.

5. **Risk factors.** Assessment of the reductions in TB cases and deaths that could be made by reducing exposure to environmental risk factors, notably indoor and outdoor air pollution, tobacco smoking, and malnutrition. These risk factors affect the establishment of infection, the progression to active disease, and the outcome of treatment.

6. **New diagnostics, drugs, and vaccines.** A sensitive and specific test for active TB that is cheap and simple to use at the first point of contact between patients and health services would be a major advance in diagnosis. Mycobacterial culture, which detects a higher proportion of active TB patients than sputum-smear microscopy, is a prerequisite for screening for drug resistance. However, present culture methods are slow, taking four to six weeks to obtain a result. Technology based on phage amplification and nucleic acid amplification can establish whether cultures are positive in days or hours, but this technology needs to be packaged for use in developing countries (Albert and others 2002, 2004; Johansen and others 2003; Woods 2001). The tuberculin skin test is being superseded in many developed countries by more specific methods for detecting infection (Doherty and others 2002; Pai, Riley, and Colford 2004). A test that can predict who will progress from latent to active disease, as yet hypothetical, would greatly increase the feasibility of treating latent infection.

Among a growing list of new vaccine antigens (Fruth and Young 2004), three of the most promising are now undergoing phase 1 safety trials in humans. One trial has evaluated mycobacterial antigen 85, delivered as a recombinant smallpox vaccine (Goonetilleke and others 2003). Another is testing a live attenuated BCG bacterium (rBCG30) that overexpresses antigen 85B protein and that provides guinea pigs with greater protection than BCG alone (Horwitz and others 2000). A third trial is assessing a fusion protein of two different antigens in an avian adjuvant, referred to as Mtb72f, that is likely to be used as a booster to either BCG or rBCG30 (Reed and others 2003).

Compounds that could form the basis of new drugs and new drug regimens include the nitroimidazopyran PA-824. Experiments with a mouse model of TB have shown that PA-824 has bactericidal activity similar to that of isoniazid and sterilizing activity that may rival that of rifampicin and that it is particularly active against dormant bacilli.

Among the most important recent discoveries is a diarylquinoline with a novel mode of action on the ATP synthase of *M. tuberculosis* that powerfully inhibits both drug-sensitive and drug-resistant strains of bacilli (Andries and others 2004). Alongside these laboratory studies, analytical and operational research are needed to find out what kinds of new tools will give the best returns on investment. Investigations of this kind will contribute to the introduction of new vaccines, drugs, and diagnostics and will inform the work of the Foundation for Innovative New Diagnostics (http://www.finddiagnostics.org), the Global Alliance for TB Drug Development (http://www.tballiance.org), and the AerasGlobal TB Vaccine Foundation (http://www.aeras.org).

**CONCLUSIONS**

After more than a decade of climbing incidence rates in Africa and former Soviet republics, the global TB epidemic appears once again to be on the threshold of decline. The spread of HIV and drug resistance, respectively, in those two regions has exacerbated the problems of TB control, but at the same time it has helped keep TB on the international public health agenda. The global incidence rate was still rising in 2003, but more slowly each year. This slowdown is not only (or even mainly) because of direct intervention through DOTS programs but because HIV epidemics are approaching peak levels in Africa and because incidence is now starting to fall again in some former Soviet republics, including Russia. Where TB incidence is already falling, prevalence and death rates should be dropping more quickly, although little evidence demonstrates this decrease yet.

The prompt diagnosis and treatment of active TB has been the mainstay of TB control and will continue to be so for the foreseeable future. Short-course chemotherapy, delivered
through the DOTS strategy, is, at typically US$5 to US$350 per DALY gained, the most cost-effective among current methods for the management of TB, and in most high-burden countries, the cost is toward the lower end of this range. A comparison of the costs of treating active TB with the costs of running a previous program suggests that DOTS could actually save money in the long run. In addition, DOTS provides an operational framework for the introduction of more specialized methods in certain risk groups. The extensions to DOTS investigated here include the treatment of MDR-TB with second-line drugs, preventive therapy (TLTI) during outbreaks and for people coinfected with M. tuberculosis and HIV, and antiretroviral therapy for HIV-infected TB patients. Those interventions cost more than the basic DOTS strategy but are still less than a dollar for each day of healthy life gained, which provides an economic argument for their integration into enhanced DOTS programs.

Although the analyses in this chapter show that DOTS and its extensions are good value for money, they conceal various features of health systems, as yet poorly defined, that may facilitate the implementation of treatment programs. For example, if broader investment in the health sector is needed before TB control programs can work in some parts of some countries, then the full cost of DOTS could be greater. By contrast, a more integrated approach to the management of TB and other respiratory diseases in primary health facilities could lead to cost savings. Those possibilities have not yet been investigated.

The only development that could radically alter the current approach to TB control—shifting the emphasis from cure to prevention—is the discovery of a new vaccine that protects adults against infectious pulmonary disease. Whether such a vaccine would be more or less cost-effective than BCG (US$40 to US$1,600 per DALY gained) depends on price and efficacy, but the potential epidemiological effect would be far greater than that of BCG, perhaps justifying mass adult vaccination. If research and development proceed according to plan, a new vaccine of some kind could be licensed between 2010 and 2015. New drugs and diagnostics should be available earlier, shortening the delay to, and duration of, treatment.

Although cost-effectiveness studies show that DOTS is a good investment, they do not formally show that the strategy is affordable. The analytical difficulty is that CEA does not solve the practical problem of how to allocate money to TB control in combination with other interventions, or even how to combine different approaches to TB control (Tan-Torres Edejer and others 2004). Interpreted literally, CEA says that the best return on total investment is obtained by ranking interventions according to CER and then fully implementing each intervention, from smallest to largest CER, allowing for diminishing returns, until the total budget is spent. This method is unlikely to lead to a balanced health care portfolio in the poorest countries. Besides, the evidence is rarely available to carry out such a complete analysis. The results of CEA are therefore typically used more informally, along with other evidence and constraints, when a mix of health interventions is chosen.

Although this problem will recur in discussions about allocating health budgets, the case for large-scale programs of TB treatment has now been accepted in many parts of the world. That is the fruit of more than 10 years' work on burden, cost, efficacy, effectiveness, and cost-effectiveness. The governments of the less poor members of the group of 22 high-burden countries have demonstrated that they can budget for, and provide, most of the funds needed to reach target levels of case detection and cure (WHO 2004c, 2005). Some of the poorer countries among the 22 are now receiving sufficient external assistance to fill the gaps in their budgets for TB control, principally from the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Consequently, the total reported budget deficit for the high-burden countries in 2005 was remarkably small—just US$119 million—and concentrated in the poorest countries (WHO 2005).

From those findings and observations arise two key questions for global TB control: If the estimated budget gap is filled, would the money be enough to ensure that enhanced DOTS programs reach 70 percent case detection and 85 percent cure—and by when? And if those targets are reached, will the effort be sufficient to achieve the MDG objectives of halving prevalence and death rates by 2015?

As yet, there are only partial answers. On the costs, it is clear that, by moving treatment out of hospitals and into the community, DOTS can often be made cheaper and more convenient for patients and health services without compromising treatment outcome. However, planning for TB control in the poorest countries is still inadequate, and budgets commonly underestimate the real costs of scaling up national TB control programs (WHO 2004c, 2005). Despite those weaknesses in the budgeting and funding process, the overall expenditure on TB control in high-burden countries has increased since 2000, and the injection of extra effort and money has led to a small acceleration in case finding globally. As a result, case detection under DOTS could reach 50 to 60 percent by 2005, and treatment success should be close to the target level of 85 percent.

A case-detection rate of 50 to 60 percent may not be enough. The analysis in this chapter suggests that the MDG objective of halving the death rate can be reached with 70 percent case detection globally, provided this case detection also generates a 5 to 6 percent annual reduction in the incidence rate between 2003 and 2015. The DOTS program in Peru generated a 6 to 7 percent annual reduction in the incidence rate of pulmonary TB, but that result has not yet been repeated in other high-burden countries with good control programs (for example, India, Morocco, and Vietnam). It is unlikely to be achieved in African countries that currently have high rates of HIV infection.
Although others have emphasized that the costs of infectious disease control can be related to the benefits in complex ways (Brandeau, Zaric, and Richter 2003), we advocate the use of a powerful new method of carrying out CEA, which is based on the observation that mathematical models can be used to generate simple (albeit approximate) and general formulas that relate reward to effort in the management of both epidemic (based on $R_0$) and endemic (based on dynamics in the vicinity of equilibrium) TB. The results are similar to those obtained by using more complex simulations in specific settings, and they are accurate enough to offer a choice between interventions (Currie and others, 2005). The generality of the method exposes more clearly the reasons some interventions are comparatively cost-effective and indicates the range of conditions under which specific cost-effectiveness results apply. The scope for using this approach for other infectious diseases remains to be explored, but it should be readily applicable in the evaluation of new approaches to TB control, whether through vaccination, drug treatment, the reduction of environmental risks, or improved service delivery.

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REFERENCES


Multidrug-resistant (MDR) tuberculosis is a growing clinical and public-health concern. To evaluate existing evidence regarding treatment regimens for MDR tuberculosis, we used a Bayesian random-effects meta-analysis of the available therapeutic studies to assess how the reported proportion of patients treated successfully is influenced by differences in treatment regimen design, study methodology, and patient population. Successful treatment outcome was defined as cure or treatment completion. 34 clinical reports with a mean of 250 patients per report met the inclusion criteria. Our analysis shows that the proportion of patients treated successfully improved when treatment duration was at least 18 months, and if patients received directly observed therapy throughout treatment. Studies that combined both first-line and second-line drugs at substantially reduced prices). Some treatment programmes use only self-administered therapy, some use DOT only for the intensive phase, and others incorporate DOT throughout treatment. MDR tuberculosis treatment programmes also vary in other characteristics, including the size of drug regimens, duration of treatment, definitions of cure, and follow-up protocols. The impact of these variations on the probability that patients will achieve treatment success is unknown.

Previous reviews of MDR tuberculosis therapy have not identified which factors are the most important contributors to treatment success. One review found that initial drug resistance and treatment composition could predict the development of acquired drug resistance and treatment failure for patients receiving first-line drug regimens, but did not present outcomes specifically from MDR tuberculosis patients or examine the impact of other treatment programme characteristics. Other reviews have assessed treatment outcomes in patients with MDR tuberculosis, but included too few studies to statistically determine which factors specifically affect treatment success.

In this study, we did a systematic review and meta-analysis of available therapeutic studies to characterise factors associated with improved treatment outcomes among patients with MDR tuberculosis who were treated with second-line drugs. Our analysis assesses the role of individualised versus standardised treatment regimens, characteristics of patients and programmes, study settings, and outcome definitions on the reported efficacy of MDR tuberculosis treatment.

Methods
We did our meta-analysis in accordance with QUOROM guidelines.

Multidrug-resistant (MDR) tuberculosis: systematic review and meta-analysis


Multidrug-resistant (MDR) tuberculosis is a growing clinical and public-health concern. An estimated 489,000 cases of multidrug-resistant (MDR) tuberculosis (defined as resistance to at least isoniazid and rifampin) occurred worldwide in 2006. Treatment of drug-resistant tuberculosis is expensive and complex because it necessitates the use of second-line tuberculosis drugs, which are associated with a greater incidence of adverse reactions, and require a longer treatment duration than first-line drugs. However, comprehensive treatment programmes have shown the efficacy of MDR tuberculosis treatment, and mathematical models have suggested that this therapy is cost-effective in resource-poor settings. Nevertheless, current guidelines for MDR tuberculosis management are largely based on expert opinion and case series, rather than on the results of clinical trials. Guidelines in different countries are based on variable health-system approaches to MDR tuberculosis treatment. Some programmes use second-line drug-susceptibility testing to design individualised treatment regimens for patients with MDR tuberculosis, minimising amplification of resistance and sparing patients from otherwise toxic drugs. Other programmes use standardised drug regimens based on population surveys of local drug-susceptibility patterns in the context of limited laboratory capacity or pharmaceutical access (such as lack of participation in the WHO Green Light Committee programme, which provides countries with access to quality-assured second-line drugs at substantially reduced prices).

Programmes differ in their use of strategies to promote adherence such as directly observed therapy (DOT). Some treatment programmes use only self-administered therapy, some use DOT only for the intensive phase, and others incorporate DOT throughout treatment. MDR tuberculosis treatment programmes also vary in other characteristics, including the size of drug regimens, duration of treatment, definitions of cure, and follow-up protocols. The impact of these variations on the probability that patients will achieve treatment success is unknown.

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Search strategy
To assess the effect of study characteristics on treatment success for MDR tuberculosis, we searched for English language publications in the MEDLINE database, the Cochrane Library, EMBASE, CINAHL, and the ISI Web of Science with combinations of the keywords “tuberculosis”, “multi-drug resistant”, “MDR TB”, and “treatment outcomes”. In addition, the online archives of the International Journal of Tuberculosis and Lung Disease were reviewed for applicable studies not found in the previous search. All database searches were updated in December, 2008. We did not exclude any articles on the basis of publication date.

Study selection
The list of publications obtained through this search was narrowed to studies considered relevant to our analysis. References from the selected studies were also assessed to ensure that relevant studies were not omitted. Articles were independently assessed by two reviewers (EWO and JRA), with disagreements mitigated by a third author (SB). Studies were required to meet the following inclusion criteria: (1) confirmation that patients had MDR tuberculosis using drug-susceptibility testing on cultured M tuberculosis; (2) treatment outcome definitions specified by mycobacterial culture endpoints (eg, cure defined as at least five consecutive negative cultures during the last 12 months of treatment); (3) clearly defined treatment protocols including second-line drugs; and (4) outcomes reported according to WHO classifications of success (including cure or treatment completion), failure, default (treatment interruption), and death.6 Studies in which all patients had extensively drug-resistant tuberculosis were excluded.

Data abstraction
We recorded treatment outcomes according to WHO classifications of treatment success (cure and treatment completion), failure, default, and death.7 Patients still on treatment who were classified as “probable cure” or “probable failure” were added to the success and failure categories, respectively. Patients who remained on treatment but were not assigned an interim outcome were not included in this analysis. All patients who were classified as “transfer out” were added to the default category.

Study characteristics
We examined differences in tuberculosis treatment outcomes for studies using second-line regimens to determine which treatment programme characteristics were associated with a higher proportion of patients achieving treatment success. For each study, we gathered data on patients’ characteristics, treatment protocols, and study definitions. Patients’ characteristics included previous tuberculosis treatment history, HIV prevalence, and the mean number of drugs to which patients’ isolates were resistant. Data on treatment protocols included the mean number of drugs in the regimen, duration of treatment, duration of DOT, and whether the regimen was standardised or individualised. Studies in which all patients received the same second-line regimen in addition to any susceptible first-line drugs after MDR tuberculosis diagnosis were categorised as having used a standardised treatment approach. Studies that tailored treatment regimens to each individual patient’s drug-susceptibility testing results were categorised as using an individualised treatment approach. We hypothesised that studies that used an individualised approach would have a higher proportion of patients achieving treatment success than reports of standardised treatment.8 In addition, we recorded length of follow-up and definition of cure if available.
Quantitative data synthesis

Pooled percentages for each tuberculosis outcome from every study category were included in a Bayesian random-effects meta-analysis. We chose a Bayesian model because of the direct interpretation of credible intervals of the posterior-effect estimates as belief that the effect lies in that region. Given the large number of variables and the small number of studies in our analysis, we deemed that the correlation to belief would be useful in the context of subjective clinical judgment in MDR tuberculosis. The Bayesian model was repeated with five initialisations using vague prior distributions, and convergence was assessed using Brooks-Gelman criteria. Data reported in each study were used to calculate 95% credible intervals (CIs). Non-overlapping CIs indicated significant differences between groups with a 95% probability of a true difference.

Heterogeneity across studies was estimated by calculating $I^2$, an index of the proportion of total variation across studies that is due to heterogeneity rather than to

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<th>Study location</th>
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<th>HIV prevalence (%)</th>
<th>Length of treatment (months)</th>
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<td>6 (4-9)</td>
<td>5</td>
<td>Self-administered</td>
<td>2 or more consecutive negative cultures</td>
</tr>
<tr>
<td>Kim et al16</td>
<td>Korea</td>
<td>1011</td>
<td>100%</td>
<td>··</td>
<td>18 [2]</td>
<td>5</td>
<td>3</td>
<td>Self-administered</td>
<td>2 or more negative cultures</td>
</tr>
<tr>
<td>Yen et al14</td>
<td>Hong Kong</td>
<td>71</td>
<td>65%</td>
<td>0</td>
<td>14 (9-24)</td>
<td>4.7 (3-6)</td>
<td>3.2**</td>
<td>Throughout treatment</td>
<td>Culture negative for at least 6 consecutive months</td>
</tr>
<tr>
<td>Chiang et al25</td>
<td>Taiwan</td>
<td>299</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>3 (0-7)</td>
<td>3 (2-6)</td>
<td>Throughout treatment</td>
<td>2 negative cultures, no clinical evidence of tuberculosis</td>
</tr>
<tr>
<td>Munhoff et al16</td>
<td>USA</td>
<td>574</td>
<td>92%</td>
<td>74%</td>
<td>18 (1-83)</td>
<td>8 (2-15)</td>
<td>5 (2-10)</td>
<td>68% directly observed</td>
<td>12 months of treatment after the last negative culture</td>
</tr>
<tr>
<td>Tahaoglu et al20</td>
<td>Turkey</td>
<td>158</td>
<td>100%</td>
<td>··</td>
<td>18 $\pm$ 55 (3-9)</td>
<td>4.4 (2-9)</td>
<td></td>
<td>During hospitalisation</td>
<td>WHO guidelines</td>
</tr>
<tr>
<td>Nanta et al17</td>
<td>USA</td>
<td>80</td>
<td>60%</td>
<td>53%</td>
<td>125</td>
<td>4.3 (1-8)</td>
<td>4.7 (2-11)</td>
<td>56% directly observed</td>
<td>CDC guidelines</td>
</tr>
<tr>
<td>Kwon et al18</td>
<td>Korea</td>
<td>2014</td>
<td>88%</td>
<td>0</td>
<td>24 (18-30)</td>
<td>6 (5-7)</td>
<td>5 (3-6)</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Mitnick et al24</td>
<td>Peru</td>
<td>75</td>
<td>100%</td>
<td>··</td>
<td>23</td>
<td>6 (5-9)</td>
<td>6 (2-32)</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Palmero et al17</td>
<td>Argentina</td>
<td>141</td>
<td>64%</td>
<td>0</td>
<td>18</td>
<td>4.2 (3-5)</td>
<td>4.1 (2-7)</td>
<td>Self-administered</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Kim et al16</td>
<td>South Korea</td>
<td>168</td>
<td>-</td>
<td>0</td>
<td>25 (1-136)</td>
<td>6 (3-11)</td>
<td></td>
<td>Not reported</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Saravia et al29</td>
<td>Peru</td>
<td>1997-2001</td>
<td>100%</td>
<td>··</td>
<td>18-24</td>
<td>5</td>
<td>4</td>
<td>Throughout treatment</td>
<td>Culture negative for the last 12 months of treatment</td>
</tr>
<tr>
<td>Ulfred et al26</td>
<td>France</td>
<td>1998-1999</td>
<td>47%</td>
<td>20%</td>
<td>12</td>
<td>37</td>
<td>3</td>
<td>Self-administered</td>
<td>Clinical improvement plus 1 negative culture</td>
</tr>
<tr>
<td>Nathanson et al26</td>
<td>Estonia, Latvia, Peru, Philippines</td>
<td>1999-2001</td>
<td>87%</td>
<td>1.8%</td>
<td>18-24</td>
<td>57</td>
<td>-</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Mitnick et al24</td>
<td>Peru</td>
<td>2002</td>
<td>100%</td>
<td>··</td>
<td>24</td>
<td>5</td>
<td>3</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Tuapai et al21</td>
<td>Philippines</td>
<td>2002</td>
<td>97%</td>
<td>15%</td>
<td>18 $\pm$ 53</td>
<td>5</td>
<td>42</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Holtz et al21</td>
<td>Latvia</td>
<td>2000</td>
<td>74%</td>
<td>18</td>
<td>5</td>
<td>5.6 (4-8)</td>
<td>5</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Leimane et al21</td>
<td>Latvia</td>
<td>2000</td>
<td>58%</td>
<td>18-38</td>
<td>5.6 (3-8)</td>
<td>4 (2-7)</td>
<td>Throughout treatment</td>
<td>Culture negative for the last 12 months of treatment</td>
<td></td>
</tr>
<tr>
<td>Minaei et al21</td>
<td>Iran</td>
<td>2002</td>
<td>100%</td>
<td>0</td>
<td>18 $\pm$ 5 (7-36)</td>
<td>5.2</td>
<td>3</td>
<td>During hospitalisation</td>
<td>WHO guidelines</td>
</tr>
<tr>
<td>Shin et al21</td>
<td>Russia</td>
<td>2002</td>
<td>100%</td>
<td>0</td>
<td>18 $\pm$ 5 (1-43)</td>
<td>5.8</td>
<td>4.7 (3-9)</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Kim et al21</td>
<td>Korea</td>
<td>2002</td>
<td>1407</td>
<td>72%</td>
<td>5</td>
<td>5 (2-9)</td>
<td>4.2</td>
<td>26% directly observed</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Keshavjee et al21</td>
<td>Russia</td>
<td>2004-2004</td>
<td>97%</td>
<td>0.9%</td>
<td>18 $\pm$ 55</td>
<td>5</td>
<td>53</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Bartu21</td>
<td>Czech Republic</td>
<td>2001-2004</td>
<td>53%</td>
<td>0</td>
<td>4.5 (0-6)</td>
<td>4.7</td>
<td>-</td>
<td>Culture negative, no clinical evidence of tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Riekstina et al21</td>
<td>Latvia</td>
<td>2002</td>
<td>75</td>
<td>0</td>
<td>&lt;24</td>
<td>-</td>
<td>-</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Cox et al21</td>
<td>Uzbekistan</td>
<td>2003-2005</td>
<td>87%</td>
<td>100%</td>
<td>22 (18-30)</td>
<td>7 (5-10)</td>
<td>4</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
<tr>
<td>Eker et al21</td>
<td>Germany</td>
<td>2004-2006</td>
<td>53%</td>
<td>4.9%</td>
<td>18 (9-27)</td>
<td>-</td>
<td>4.7</td>
<td>Throughout treatment</td>
<td>Laserson definition</td>
</tr>
</tbody>
</table>

(Continues on next page)
The median length of treatment and range is shown if reported. †For studies using standardised therapy regimens, the number of drugs in the regimen is given for the intensive and subsequent phases separated by commas. ‡The mean number of drugs and range is shown if reported. CDC guidelines (1994) defined “probable cure” as two negative cultures followed by 12 months of treatment with at least two effective drugs; WHO MDR guidelines (1999) defined “probable cure” as 6 months of negative smears and cultures, and “cure” as 18–24 months of negative cultures; Laserson standard definition defines cure as at least five consecutive negative cultures during the last 12 months of treatment. §Only includes hospitalisation time; afterwards, the patient was discharged to the referring physician to continue treatment, but was not followed in the study. ¶After culture conversion. **Only did drug-sensitivity testing for first-line drugs. ††Remaining patients had self-administered treatment.

Table 1: Characteristics of patients, study design, and cure definition in 34 reports of multidrug-resistant (MDR) tuberculosis treatment outcomes, 1973–2006

<table>
<thead>
<tr>
<th>Study location</th>
<th>Years</th>
<th>Sample size</th>
<th>Proportion previously treated (%)</th>
<th>HIV prevalence (%)</th>
<th>Length of treatment†‡ (months)</th>
<th>Drugs in regimen† (n drugs)</th>
<th>Average resistance§ (n drugs)</th>
<th>Directly observed treatment</th>
<th>Definition of cure§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Deun et al16 Bangladesh</td>
<td>1997–1999</td>
<td>58</td>
<td>–</td>
<td>–</td>
<td>21</td>
<td>7, 5, 2</td>
<td>3, 2</td>
<td>During intensive phase</td>
<td>Culture negative at end of treatment and 2 previous occasions</td>
</tr>
<tr>
<td>Sánchez et al17 Peru</td>
<td>1997–1999</td>
<td>466</td>
<td>100%</td>
<td>–</td>
<td>18</td>
<td>5, 4</td>
<td>3</td>
<td>Self-administered</td>
<td>Two negative culture results at the end of treatment</td>
</tr>
<tr>
<td>Saravia et al18 Peru</td>
<td>1997–2001</td>
<td>39</td>
<td>100%</td>
<td>–</td>
<td>18</td>
<td>5, 4</td>
<td>4</td>
<td>Throughout treatment</td>
<td>Culture negative for the last 12 months of treatment</td>
</tr>
<tr>
<td>Park et al19 South Korea</td>
<td>1998–2000</td>
<td>126</td>
<td>100%</td>
<td>–</td>
<td>18</td>
<td>5, 4, 3</td>
<td>4, 5 (2–10)</td>
<td>During hospitalisation</td>
<td>Culture negative for 18 months</td>
</tr>
<tr>
<td>Masjedi et al20 Iran</td>
<td>2002–2006</td>
<td>43</td>
<td>100%</td>
<td>–</td>
<td>24</td>
<td>5, 4</td>
<td>–</td>
<td>Laserson definition</td>
<td></td>
</tr>
</tbody>
</table>

*The median length of treatment and range is shown if reported. †For studies using standardised therapy regimens, the number of drugs in the regimen is given for the intensive and subsequent phases separated by commas. ‡The mean number of drugs and range is shown if reported. CDC guidelines (1994) defined “probable cure” as two negative cultures followed by 12 months of treatment with at least two effective drugs; WHO MDR guidelines (1999) defined “probable cure” as 6 months of negative smears and cultures, and “cure” as 18–24 months of negative cultures; Laserson standard definition defines cure as at least five consecutive negative cultures during the last 12 months of treatment. §Only includes hospitalisation time; afterwards, the patient was discharged to the referring physician to continue treatment, but was not followed in the study. ¶After culture conversion. **Only did drug-sensitivity testing for first-line drugs. ††Remaining patients had self-administered treatment.

Results

565 publications were obtained through the literature search. We narrowed these to 253 studies deemed relevant to this analysis, of which 76 were pursued for full analysis. After adding studies from references and reviews, 95 articles were reviewed. Of these, 33 studies (34 published reports) met the inclusion criteria, including 28 studies of individualised therapy for MDR tuberculosis, four studies of standardised therapy, and one study that had an individualised group and a standardised group (figure 1). These reports came from 20 countries, including treatment outcomes for a mean of 250 patients per report (range 17–1407). All of the studies were retrospective observational cohort studies of treatment outcomes for MDR tuberculosis patients who were receiving second-line drugs. These included 29 studies done from 1973 to 2006 that used individualised treatment regimens and five reports from 1997 to 2006 that used standardised second-line regimens (table 1).

Heterogeneity among studies

Characteristics of the patient population, study design, and cure definition differed among the included studies, and reporting procedures varied widely (table 1). The number of patients previously treated for tuberculosis ranged from 0 to 100% in 30 of the 34 reviewed reports; other studies omitted this statistic. HIV prevalence ranged from 0 to 100% in 30 of the 34 reviewed reports; other studies omitted this statistic. HIV prevalence ranged from 0 to 74% in the 16 studies in which it was reported. The median duration of treatment ranged from 11 months to 25 months. The duration of treatment for individual patients varied widely, with some patients receiving as long as 136 months of therapy based on their culture results and clinical indications.21 21 studies reported the length of follow-up after treatment, which often varied between patients within the same study. 16 studies included DOT throughout treatment, nine maintained DOT during the intensive phase of therapy or directly observed some but not all patients, six studies used self-administered therapy, and three studies did not report the degree to which treatment was observed. The mean number of drugs used ranged from 3·7 to 8 (median 5·5). The mean size of drug regimens was equal between studies of individualised and standardised therapy, although the range among standardised studies was smaller (range 5–7). 13 of the 29 reports of individualised regimens and all five reports of standardised regimens listed which specific drugs or drug classes were given. Four additional studies reported the
The proportion of patients receiving a fluoroquinolone. The mean number of drugs to which isolated organisms were resistant ranged from 2·8 to 6.

The definition of cure varied among studies. 14 studies followed the current standard definition, which requires at least five negative cultures during the last year of treatment. Seven additional studies required that the patient be culture negative for at least 12 months, and one study mandated 6 months; however, the number of actual cultures taken was not defined for these five studies. In 12 studies, three or fewer negative cultures were necessary to be classified as “cured”.

### Treatment outcomes

Across all studies that used second-line drugs in individualised or standardised protocols, the overall treatment success estimate, defined as the proportion of patients who were cured or completed treatment, was 62% (95% CI 58–67%). However, the heterogeneity in study characteristics led to significant variation in reported treatment outcomes. Among the 29 reports of individualised treatment regimens for patients with MDR tuberculosis (mean 268 patients; range 17–1407), the mean proportion of patients achieving treatment success was 64% (95% CI 59–68%; figure 2). The mean proportion of patients whose outcomes were treatment failure, default, and death were 6%, 12%, and 11%, respectively. Among the five studies in which patients with MDR tuberculosis were treated with a standardised regimen (mean 146 patients; range 39–466), the mean proportion achieving treatment success was lower than that for individualised treatment, but not significantly different.

![Figure 2: Treatment success and other treatment outcomes for individualised and standardised treatment of multidrug-resistant tuberculosis](image)

Treatment effects and summaries were calculated using a Bayesian random effects model weighted by study population size. 95% credible intervals (CIs) are shown. Saravia et al had an individualised arm and a standardised arm, which are reported separately.
length of treatment, level of direct observation of therapy, regimen design, number of drugs in the regimen, percentage of patients receiving fluoroquinolones, start year of the study, or cure definition (table 2). Differences in population characteristics, including prevalence of HIV, mean number of resistant drugs, and proportion of patients previously treated for tuberculosis, also did not lead to significantly different outcomes.

Although the proportion of patients achieving treatment success was not significantly different on the basis of any individual factor, studies that combined the two factors with the largest effect on success (treatment length of at least 18 months and use of DOT throughout) had a pooled success proportion that surpassed all other subgroups. In the 12 studies that incorporated both factors into their study methods, the pooled success was 69% (95% CI 64–73%), which was significantly greater than the pooled success estimate for the other 22 studies that did not meet both criteria (58%; 95% CI 52–64%; figure 3).

Discussion

To determine which patient and programme characteristics facilitate the greatest treatment success, we analysed data from 33 studies in 20 countries that included treatment outcomes for a total of 8506 patients receiving second-line drug treatment for MDR tuberculosis. Although the proportion of patients achieving treatment success was better in studies that used individualised treatment regimens, the difference was not significant. In fact, no individual patient or programme characteristic was associated with a significantly greater proportion of patients achieving treatment success. Studies that incorporated both treatment for longer than 18 months and DOT throughout the entire treatment period had a significantly greater proportion of patients achieving treatment success than all other studies. When treatment programmes included both of these factors, 69% (95% CI 64–73%) of patients were successfully treated. Only 58% (95% CI 52–64%) were successfully treated when a maximum of one of the two factors was used. However, substantial heterogeneity in study designs, patient populations, and reporting limit the scope of this analysis. Prospective trials may be necessary to elucidate specific programme components that promote MDR tuberculosis treatment success.

All of the 12 studies associated with a higher proportion of patients achieving success that featured extended duration of treatment and DOT throughout therapy used individualised treatment regimens. However, standardised second-line therapy programmes may also benefit from simultaneously implementing extended treatment duration together with DOT throughout treatment. Among the five reports of standardised treatment in this analysis, the two studies with the highest proportion of patients treated successfully both treated patients for a duration exceeding 18 months.
WHO guidelines for the treatment of MDR tuberculosis encourage a minimum of 18 months of treatment after culture conversion and DOT throughout treatment.49 Our meta-analysis underscores the importance of these particular recommendations and emphasises their use in combination. Previous reviews have discussed the use of individualised therapy and the number and choice of drugs in the regimen,12,13 but have not focused on the duration of treatment or DOT throughout therapy. A longer duration of treatment has been associated with lower likelihood of early relapse for drug-susceptible tuberculosis.50 Similarly, DOT has been shown to promote treatment success in non-MDR tuberculosis,7 although not all studies show clinical improvement,12 and increased population coverage of DOT programmes has been associated with countrywide treatment success.51

Substantial heterogeneity in study characteristics prevents a more conclusive determination of what factors have the most effect on the proportion of patients that achieve treatment success and limits the validity of this analysis. We found that treatment protocols and reporting of key patient and study characteristics were inconsistent across studies. Several studies omitted the exact protocol used in treatment regimen design, length of follow-up, and the average number of drugs to which each patient’s tuberculosis isolate was resistant.

![Figure 3: Treatment success and other treatment outcomes by treatment duration and whether study included directly observed treatment regimens](image)

Effect sizes and summaries were calculated using a Bayesian random effects model weighted by study population size. Individual studies can have different treatment effects in figure 2 and figure 3 caused by differences in the other studies being analysed simultaneously. 95% credible intervals (CIs) are shown. Saravia et al15 had an individualised arm and a standardised arm, which are reported separately.
outcomes among patients receiving treatment for MDR and extensively drug-resistant tuberculosis,24,25 was assessed in fewer than half of the studies reviewed. This absence despite the confluence of the HIV and tuberculosis epidemics exemplifies the heterogeneity in tuberculosis epidemics and associated treatment strategies. Similarly, fluoroquinolone use was only reported in 13 of 34 studies, despite its association within studies with treatment success for MDR tuberculosis.24,25 Thus, the lack of significant findings associated with certain variables in this analysis may be due to reporting insufficiency, rather than the absence of a real association. Furthermore, these variations in the recording of data necessary for assessing treatment outcomes underscore the need for standardised data collection and reporting in programmes and studies of MDR tuberculosis,24 possibly through the use of an international registry of treatment outcomes. The absence of a registry of individual treatment outcomes or outcome studies precluded the possibility of estimating publication bias in this meta-analysis. Standards in outcome reporting are particularly important in light of the emergence of extensively drug-resistant tuberculosis.

Many programme characteristics that were reported in most studies also varied widely. Even within studies, different patients had highly variable treatment durations,20,24,30,32 and the size of drug regimens ranged from very few to very many drugs.20,24,27,30,31,42 In addition, factors that cannot be measured or were not reported may have confounded the results of this study. Issues such as logistics, programme resources, transportation, food assistance, and social support that are accounted for in different ways by different programmes but often not reported in published studies may have affected the proportion achieving treatment success independently of factors analysed in this study. Prospective trials comparing specific aspects of treatment recommendations for MDR tuberculosis in similar populations would provide greater insight into improving MDR tuberculosis treatment protocols. For example, one prospective trial suggests that addition of high-dose isoniazid as adjuvant therapy to second-line regimens may improve MDR tuberculosis treatment.14

The “Stop TB” strategy developed by WHO set the goal of curing 85% of all detected tuberculosis cases by 2005.17 MDR tuberculosis has presented challenges to achieving this objective in many areas. Nonetheless, appropriate second-line treatment for more than 18 months together with DOT throughout therapy might lead to treatment success more readily, and should be further investigated in current trials of MDR tuberculosis therapy. In the absence of randomised clinical trials, more systematic documentation of programmatic components and outcomes of MDR tuberculosis treatment can strengthen the evidence base for treatment. Comprehensive treatment of MDR tuberculosis is of vital importance in promoting public health to slow the spread and reduce the impact of drug-resistant tuberculosis around the world.

Conflicts of interest
We declare that we have no conflicts of interest.

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Supplemental Readings

HIV: Elimination, Cure and Treatment
Presented by: Lisa Abuogi

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection
http://www.who.int/hiv/pub/guidelines/arv2013/en/

Global update on HIV treatment 2013: Results, impact and opportunities

Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive
CONSOLIDATED GUIDELINES ON
THE USE OF ANTIRETROVIRAL DRUGS
FOR TREATING AND PREVENTING HIV INFECTION
RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH
JUNE 2013
CONSOLIDATED GUIDELINES ON
THE USE OF ANTIRETROVIRAL DRUGS
FOR TREATING AND PREVENTING HIV INFECTION
RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH
JUNE 2013
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<tr>
<td>3TC</td>
<td>lamivudine</td>
</tr>
<tr>
<td>ABC</td>
<td>abacavir</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral (drug)</td>
</tr>
<tr>
<td>ATV</td>
<td>atazanavir</td>
</tr>
<tr>
<td>ATV/r</td>
<td>atazanavir/ritonavir</td>
</tr>
<tr>
<td>AZT</td>
<td>zidovudine (also known as ZDV)</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CD4</td>
<td>T–lymphocyte cell bearing CD4 receptor</td>
</tr>
<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>d4T</td>
<td>stavudine</td>
</tr>
<tr>
<td>DALYs</td>
<td>death- and disability-adjusted life-years</td>
</tr>
<tr>
<td>DBS</td>
<td>dried blood spot</td>
</tr>
<tr>
<td>ddl</td>
<td>didanosine</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRV</td>
<td>darunavir</td>
</tr>
<tr>
<td>DRV/r</td>
<td>darunavir/ritonavir</td>
</tr>
<tr>
<td>EFV</td>
<td>efavirenz</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ETV</td>
<td>etravirine</td>
</tr>
<tr>
<td>FPV</td>
<td>fosamprenavir</td>
</tr>
<tr>
<td>FPV/r</td>
<td>fosamprenavir/ritonavir</td>
</tr>
<tr>
<td>FTC</td>
<td>emtricitabine</td>
</tr>
<tr>
<td>GNP+</td>
<td>Global Network of People Living with HIV</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HPTN</td>
<td>HIV Prevention Trials Network</td>
</tr>
<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td>INH</td>
<td>isoniazid</td>
</tr>
<tr>
<td>IPT</td>
<td>isoniazid preventive therapy</td>
</tr>
<tr>
<td>IRIS</td>
<td>immune reconstitution inflammatory syndrome</td>
</tr>
<tr>
<td>LPV</td>
<td>lopinavir</td>
</tr>
<tr>
<td>LPV/r</td>
<td>lopinavir/ritonavir</td>
</tr>
<tr>
<td>MDR</td>
<td>multidrug-resistant TB, resistant to at least isoniazid and rifampicin</td>
</tr>
<tr>
<td>MTCT</td>
<td>mother-to-child transmission (of HIV)</td>
</tr>
<tr>
<td>NFV</td>
<td>nelfinavir</td>
</tr>
<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse-transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside reverse-transcriptase inhibitor</td>
</tr>
<tr>
<td>NVP</td>
<td>nevirapine</td>
</tr>
<tr>
<td>OST</td>
<td>opioid substitution therapy</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PI</td>
<td>protease inhibitor</td>
</tr>
<tr>
<td>PICO</td>
<td>Population, Intervention, Comparison and Outcomes</td>
</tr>
<tr>
<td>PCP/PJP</td>
<td><em>Pneumocystis (jirovecii)</em> pneumonia</td>
</tr>
<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child transmission of HIV</td>
</tr>
<tr>
<td>PrEP</td>
<td>pre-exposure prophylaxis of HIV</td>
</tr>
<tr>
<td>RAL</td>
<td>raltegravir</td>
</tr>
<tr>
<td>RBV</td>
<td>ribavirin</td>
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<tr>
<td>RIF</td>
<td>rifampicin</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RTV</td>
<td>ritonavir</td>
</tr>
<tr>
<td>sd-NVP</td>
<td>single-dose nevirapine</td>
</tr>
<tr>
<td>TAM</td>
<td>thymidine analogue mutation</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>TPV</td>
<td>tipranavir</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>UNODC</td>
<td>United Nations Office on Drugs and Crime</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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DEFINITION OF KEY TERMS

GENERAL

HIV refers to human immunodeficiency virus. There are two types of HIV: HIV-1 and HIV-2. HIV-1 is responsible for the vast majority of HIV infections globally. Within these guidelines, HIV refers to both HIV-1 and HIV-2 unless otherwise specified.

AGE GROUPS AND POPULATIONS

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these consolidated guidelines, as well as with other WHO guidelines. It is recognized that other agencies may use different definitions.

An adult is a person older than 19 years of age unless national law defines a person as being an adult at an earlier age.

An adolescent is a person aged 10 to 19 years inclusive.

A child is a person 19 years or younger unless national law defines a person to be an adult at an earlier age. However, in these guidelines when a person falls into the 10 to 19 age category they are referred to as an adolescent (see adolescent definition).

An infant is a child younger than one year of age.

These guidelines define key populations to include both vulnerable and most-at-risk populations. They are important to the dynamics of HIV transmission in a given setting and are essential partners in an effective response to the epidemic. People living with HIV are considered a key population in all epidemic contexts.

These guidelines define most-at-risk populations as men who have sex with men, transgender people, people who inject drugs and sex workers. Most-at-risk populations are disproportionately affected by HIV in most, if not all, epidemic contexts.

Vulnerable populations are groups of people who are particularly vulnerable to HIV infection in certain situations or contexts, such as adolescents (particularly adolescent girls), orphans, street children, people in closed settings (such as prisons or detention centres), people with disabilities and migrant and mobile workers. Each country should define the specific populations that are particularly vulnerable and key to their epidemic and response based on the epidemiological and social context.

Serodiscordant couples are couples in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these is referred to as a partner in the relationship. How individuals define their relationships varies considerably according to cultural and social context.

HEALTH CARE SERVICES

Continuum of HIV care refers to a comprehensive package of HIV prevention, diagnostic, treatment and support services provided for people living with HIV and their families ranging across: initial HIV diagnosis and linkage to care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second-line and third-line ART; and palliative care.
A public health approach addresses the health needs of a population or the collective health status of the people rather than just individuals. A public health approach involves a collaborative effort by all parts of the health sector, working to ensure the well-being of society through comprehensive prevention, treatment, care and support. For HIV, this involves: simplified limited formularies; large-scale use of fixed-dose combinations for first-line treatment for adults and children; care and drugs given free at the point of service delivery; decentralization; and integration of services, including task shifting and simplified clinical and toxicity monitoring.

**HIV TESTING AND PREVENTION**

**Voluntary counselling and testing** (also referred to as client-initiated testing and counselling) describes a process initiated by an individual who wants to learn his or her HIV status. Since there are now many different community approaches to providing HIV testing and counselling and people often have mixed motivations for seeking testing (both recommended by a provider and sought by a client), WHO prefers to use the term **HIV testing and counselling**. All forms of HIV testing and counselling should be voluntary and adhere to the five C’s: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services. Quality assurance of both testing and counselling is essential in all approaches to HIV testing and counselling.

**Provider-initiated testing and counselling** is HIV testing and counselling recommended by a health-care provider in a clinical setting. Provider-initiated testing and counselling, as with all forms of HIV testing and counselling, should be voluntary and adhere to the five C’s.

**Combination prevention** refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

**ART (ANTIRETROVIRAL THERAPY)**

**ARV (antiretroviral) drugs** refer to the medicines themselves and not to their use. **ART** refers to the use of a combination of three or more ARV drugs to achieve viral suppression. This generally refers to lifelong treatment. Synonyms are combination ART and highly active ART.

**ART for prevention** is used to describe the HIV prevention benefits of ART.

**Eligible for ART** refers to people living with HIV for whom ART is indicated according to the definitions of clinical and immunological eligibility in WHO treatment guidelines. The term is often used interchangeably with “needing treatment”, although this implies an immediate risk or an obligation to initiate treatment.

**Viral suppression** refers to the aim of ART to maintain viral load below the level of detection of available assays, generally less than 50 copies per ml. The current WHO virological criterion for treatment failure is 1000 copies per ml or more.

**Universal access to ART** is defined broadly as a move to a high level of access (≥80% of the eligible population) for the most effective interventions that are equitable, accessible, affordable, comprehensive and sustainable over the long term; this does not necessarily mean 100% coverage.
HEALTH WORKFORCE

**Community health workers** are health workers who have received standardized and nationally endorsed training outside the nursing, midwifery or medical curricula.

**Midwives** are people trained to assist in childbirth, including registered and enrolled midwives.

**Non-physician clinicians** are professional health workers capable of many of the diagnostic and clinical functions of a physician but who are not trained as physicians. These types of health workers are often known as health officers, clinical officers, physician assistants, nurse practitioners or nurse clinicians.

**Nurses** include professional nurses, enrolled nurses, auxiliary nurses and other nurses such as dental or primary care nurses.

EPIDEMIOLOGY

**Concentrated HIV epidemic**: HIV has spread rapidly in one or more defined subpopulation but is not well established in the general population. Numerical proxy: HIV prevalence is consistently over 5% in at least one defined subpopulation but is less than 1% among pregnant women in urban areas.

**Generalized HIV epidemic**: HIV is firmly established in the general population. Numerical proxy: HIV prevalence consistently exceeding 1% among pregnant women. Most generalized HIV epidemics are mixed in nature, in which certain (key) subpopulations are disproportionately affected.

**Mixed epidemics**: people are acquiring HIV infection in one or more subpopulations and in the general population. Mixed epidemics are therefore one or more concentrated epidemics within a generalized epidemic.

**Low-level epidemic**: epidemics in which the prevalence of HIV infection has not consistently exceeded 1% in the general population nationally or 5% in any subpopulation.

**Low-, moderate- and high-uptake ART settings** refer to settings in which the uptake of ART among those eligible for ART is less than 50%, 50–80% and greater than 80%, respectively.
A setting with a high burden of TB and HIV refers to settings with adult HIV prevalence ≥1% or HIV prevalence among people with TB ≥5%.

HIV incidence is the number of new people acquiring HIV infection in a given period in a specified population.

HIV prevalence refers to the number of people living with HIV at a specific point in time and is expressed as a percentage of the population.

**PMTCT (PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV)**

In these guidelines, WHO is moving away from the previous terms “Options A, B and B+”. Instead, these guidelines recommend two options: (i) providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage or (ii) providing ART (ARV drugs) for pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health. In settings that are not implementing lifelong ART for all pregnant and breastfeeding women living with HIV, the distinction between prophylaxis (ARV drugs given for a limited time during the risk period for transmitting HIV from mother to child to prevent this) and treatment (ART given both for the mother’s health, based on current adult eligibility, and to prevent vertical transmission) is still important.

**ARV drugs for women living with HIV during pregnancy and breastfeeding** refers to a triple-drug ARV drug regimen provided to mothers living with HIV primarily as prophylaxis during pregnancy and throughout breastfeeding (when there is breastfeeding) to prevent mother-to-child transmission of HIV. In this option, the mother’s regimen is continued lifelong after delivery or after the breastfeeding ends only if she meets the ART eligibility criteria for her own health based on CD4 count or clinical stage. Previous WHO guidance referred to this as option B.

**Lifelong ART for all pregnant and breastfeeding women living with HIV** refers to the approach in which all pregnant women living with HIV receive a triple-drug ARV regimen regardless of CD4 count or clinical stage, both for their own health and to prevent vertical HIV transmission and for additional HIV prevention benefits. Previous WHO guidance referred to this as option B+.
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With this publication, WHO issues its first consolidated guidelines for the use of antiretroviral drugs to treat and prevent HIV infection. The guidelines are ambitious in their expected impact, yet simplified in their approach, and firmly rooted in evidence. They take advantage of several recent trends, including a preferred treatment regimen that has been simplified to a single fixed-dose combination pill taken once per day, which is safer and affordable.

The guidelines also take advantage of evidence demonstrating the multiple benefits of antiretroviral therapy. With the right therapy, started at the right time, people with HIV can now expect to live long and healthy lives. They are also able to protect their sexual partners and infants as the risk of transmitting the virus is greatly reduced.

The guidelines represent another leap ahead in a trend of ever-higher goals and ever-greater achievements. In Africa, the region that bears the brunt of the HIV epidemic, an estimated 7.5 million people were receiving treatment at the end of 2012, compared with only 50,000 a decade earlier. Worldwide, some 9.7 million people were receiving treatment, indicating that the global target of providing antiretroviral therapy to 15 million people by 2015 is within reach. The present achievement represents the fastest scale-up of a life-saving public health intervention in history.

A key way to accelerate progress is to start treatment earlier, as recommended in the guidelines. As the evidence now shows, earlier treatment brings the dual advantage of keeping people healthier longer and dramatically reducing the risk of virus transmission to others.

Earlier treatment has the further advantage of simplifying the operational demands on programmes. The guidelines recommend that pregnant women and children under the age of five years start treatment immediately after diagnosis. The same once-per-day combination pill is now recommended for all adults living with HIV, including those with tuberculosis, hepatitis, and other co-infections.

Additional recommendations in the guidelines aim to help programmes get services closer to people’s homes; expedite test results; integrate HIV treatment more closely with antenatal, tuberculosis, drug dependence and other services; and use a wider range of health workers to administer treatment and follow-up care.
Countries asked WHO for simplified guidance on the use of antiretroviral drugs. I believe these consolidated guidelines go a long way towards meeting that request. They offer recommendations for all age groups and populations. They bring clinical recommendations together with operational and programmatic guidance on critical dimensions of treatment and care, from testing through enrollment and retention, and from general HIV care to the management of co-morbidities.

The new guidelines ask programmes to make some significant changes. They also require increased investments. I am personally convinced that the future of the HIV response will follow the pattern of the recent past: that is, a constant willingness to build on success and rise to new challenges.

WHO estimates that doing so will have an unprecedented impact: global implementation of the guidelines could avert an additional 3 million deaths between now and 2025, over and above those averted using 2010 guidelines, and prevent around 3.5 million new infections.

Such prospects – unthinkable just a few years ago – can now fuel the momentum needed to push the HIV epidemic into irreversible decline. I strongly encourage countries and their development partners to seize this unparalleled opportunity that takes us one more leap ahead.

Dr Margaret Chan
Director-General, WHO
EXECUTIVE SUMMARY

These consolidated guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. They are structured along the continuum of HIV testing, care and treatment. Behavioural, structural and biomedical interventions that do not involve the use of ARV drugs are not covered in these guidelines.

The 2013 consolidation process combines and harmonizes recommendations from a range of WHO guidelines and other documents, including the 2010 guidelines on using antiretroviral therapy (ART) for HIV infection in adults and adolescents, in infants and children and for treating pregnant women living with HIV and preventing HIV infection in infants. Comprehensive guidance is now provided on using ARV drugs across age groups and populations of adults, pregnant and breastfeeding women, adolescents, children and key populations. The guidelines also aim to consolidate and update clinical, service delivery and programmatic guidance.

The 2013 guidelines reflect important advances in HIV responses during the past three years. Since 2010, new technologies, including CD4 point-of-care testing and new service delivery approaches, allow HIV testing and treatment monitoring to be diversified and decentralized. Simple, safer, once-daily, single-pill ARV regimens that are suitable for use in most populations and age groups have become more affordable and more widely available in low- and middle-income countries. Countries are moving towards earlier initiation of triple-drug regimens and simplified programming for the prevention of mother-to-child transmission of HIV (PMTCT) that emphasizes the long-term health of pregnant women and mothers living with HIV and preventing HIV infection among their children. The broader HIV prevention benefits of ARV drugs are being recognized: in addition to improving health and prolonging lives, ART prevents the sexual transmission of HIV, while pre-exposure prophylaxis of HIV with ARV drugs expands HIV prevention options and post-exposure prophylaxis of HIV continues to play an important role in managing HIV exposure in certain populations and settings, including for those who have been sexually assaulted. Although countries are at different stages of ART coverage and implementing the 2010 WHO guidelines, there is a consistent global trend towards initiating HIV treatment earlier.

Consistent with previous WHO guidelines, the 2013 guidelines are based on a public health approach to the further scaling up of ARV drugs for treatment and prevention that considers feasibility and effectiveness across a variety of resource-limited settings. The new clinical recommendations in these guidelines promote expanded eligibility for ART with a CD4 threshold for treatment initiation of 500 cells /mm³ or less for adults, adolescents and older children. Priority should be given to individuals with severe or advanced HIV disease and those with CD4 count of 350 cells /mm³ or less. ART is recommended to be initiated regardless of CD4 count for certain populations, including people with active tuberculosis (TB) disease who are living with HIV, people with both HIV and hepatitis B virus (HBV) infection with severe chronic liver disease, HIV-positive partners in serodiscordant couples, pregnant and breastfeeding women and children younger than five years of age. Harmonization of ARV regimens for adults and children is recommended whenever possible, with a new, preferred first-line ARV regimen. The need to phase out d4T in first-line ARV regimens for adults and adolescents is being reinforced.
Viral load testing is now recommended as the preferred approach to monitoring ART success and diagnosing treatment failure, complementing clinical and immunological monitoring of people receiving ART.

The guidelines emphasize that ARV drugs should be used within a broad continuum of HIV care. Additional new recommendations provide guidance on community-based HIV testing and counselling and HIV testing of adolescents. Apart from new recommendations, summaries of and links to existing WHO guidance are provided for HIV testing and counselling, HIV prevention, general care for people living with HIV, the management of common coinfections and other comorbidities and monitoring and managing drug toxicities. Some existing recommendations need to be updated, and new recommendations will need to be reviewed in the next few years, as new evidence emerges.

Expanded eligibility for ART and a wider range of options for using ARV drugs provide new opportunities to save lives, improve clinical outcomes and reduce HIV incidence but also pose challenges to policy-makers and implementers in many countries. New operational guidance in 2013 provides recommendations for strengthening key aspects of the continuum of HIV care and improving linkages across the health system. This guidance focuses on strategies to improve retention in care and adherence to ART and on decentralizing the provision of ART to primary care, maternal and child health clinics, TB clinics and services to treat drug dependence. The operational guidance also addresses the implications of new clinical recommendations for laboratory services and supply systems for ARV drugs and other commodities.

Guidance specifically developed for HIV programme managers addresses decision-making and planning for the strategic use of ARV drugs in the context of national governance processes, HIV epidemiology, health systems capacity, available financial resources and ethical and human rights considerations. Implementation considerations especially relevant to programme managers are provided for major new recommendations. A concluding chapter on monitoring and evaluation provides preliminary guidance on monitoring the implementation of new recommendations.

The revision process for the 2013 guidelines was conducted in accordance with procedures established by the WHO Guidelines Review Committee. New clinical and operational recommendations in the guidelines are based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to reviewing evidence and decision-making. Modelling, expert consultations and country case studies have informed clinical, operational and programmatic guidance. The process has identified key gaps in knowledge that will guide the future research agenda. In addition to new recommendations based on the GRADE system, the guidelines summarize existing recommendations from other WHO guidelines. Most of these recommendations were developed using the GRADE system or a modification of the GRADE rating of the strength of the recommendations and the quality of the evidence.

The primary audience for these guidelines is national HIV programme managers, especially in low- and middle-income countries. The guidelines are anticipated to guide country policy decisions and planning the scaling up of ART. They will also be a valuable resource for clinicians and informing the priorities of development agencies, international organizations, nongovernmental organizations and other implementing partners during the next few years.

The 2013 guidelines represent an important step towards achieving universal access to ARV drugs for treating and preventing HIV, increasing the efficiency, impact and long-term sustainability of ARV programmes and realizing the ultimate goal of ending the HIV epidemic.
The following table summarizes the new WHO recommendations formulated for the 2013 guidelines on HIV testing and counselling, antiretroviral therapy (ART) and HIV service delivery. It also summarizes the guidance provided in Chapter 10 for programme managers. Where the recommendations remain unchanged from 2010 ART guidelines, this is clearly stated in the table.

The table is not comprehensive and does not include all WHO recommendations referred to in these guidelines, specifically recommendations that have been drawn from other, already existing WHO guidelines. The existing WHO recommendations referred to can be found in: Chapter 5 on HIV testing and counselling and HIV prevention, Chapter 6 on general care for people living with HIV, Chapter 8 on the management of common coinfections and other comorbidities and in section 7.4 on monitoring and management of drug toxicities.

### HIV testing and counselling

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Community-based testing                       | - In generalized HIV epidemics, community-based HIV testing and counselling with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (strong recommendation, low-quality evidence).  
- In all HIV epidemic settings, community-based HIV testing and counselling for key populations, with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (strong recommendation, low-quality evidence). |
| HIV testing and counselling of adolescents¹   | - HIV testing and counselling, with linkages to prevention, treatment and care, is recommended for adolescents from key populations in all settings (generalized, low and concentrated epidemics) (strong recommendation, very-low-quality evidence).  
- HIV testing and counselling with linkage to prevention, treatment and care is recommended for all adolescents in generalized epidemics (strong recommendation, very-low-quality evidence).  
- We suggest that HIV testing and counselling with linkage to prevention, treatment and care be accessible to all adolescents in low and concentrated epidemics (conditional recommendation, very-low-quality evidence).  
- We suggest that adolescents be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose (conditional recommendation, very-low-quality evidence). |
When to start ART in people living with HIV

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **When to start ART in adults and adolescents** | • As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).  
  • ART should be initiated in all individuals with HIV with CD4 count >350 cells/mm³ and ≤500 cells/mm³ regardless of WHO clinical stage (strong recommendation, moderate-quality evidence).  
  • ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:  
    • Individuals with HIV and active TB disease (strong recommendation, low-quality evidence).  
    • Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease (strong recommendation, low-quality evidence).  
    • Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence). |
| **When to start ART in pregnant and breastfeeding women** | • All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (strong recommendation, moderate-quality evidence).  
  • For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (conditional recommendation, low-quality evidence).  
  • In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased (conditional recommendation, low-quality evidence). |

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*An adolescent is a person aged 10 to 19 years inclusive.*
## When to start ART in people living with HIV (continued)

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVs and duration of breastfeeding</td>
<td>The key principles and recommendations established in 2010 remain, including:</td>
</tr>
<tr>
<td></td>
<td>National or subnational health authorities should decide whether health services will mainly counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context.</td>
</tr>
<tr>
<td></td>
<td>In settings where national authorities have decided that maternal and child health services will mainly promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival:</td>
</tr>
<tr>
<td></td>
<td>• Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided <em>(strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months).</em></td>
</tr>
<tr>
<td>When to start ART in children</td>
<td>• ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.</td>
</tr>
<tr>
<td></td>
<td>• Infants diagnosed in the first year of life <em>(strong recommendation, moderate-quality evidence)</em></td>
</tr>
<tr>
<td></td>
<td>• Children infected with HIV one year to less than five years of age <em>(conditional recommendation, very-low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>• ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤500 cells/mm³, regardless of WHO clinical stage.</td>
</tr>
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<td></td>
<td>• CD4 count ≤350 cells/mm³ <em>(strong recommendation, moderate-quality evidence)</em></td>
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<tr>
<td></td>
<td>• CD4 count between 350 and 500 cells/mm³ <em>(conditional recommendation, very-low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>• ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count <em>(strong recommendation, moderate-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>• ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection <em>(strong recommendation, low-quality evidence)</em></td>
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</table>
### What ARV regimens to start with

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td><strong>First-line ARV regimens for adults</strong></td>
<td></td>
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</tbody>
</table>
- First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).
  - TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
  - If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended:
    - AZT + 3TC + EFV
    - AZT + 3TC + NVP
    - TDF + 3TC (or FTC) + NVP (strong recommendation, moderate-quality evidence).
- Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence). |
| **First-line ART for pregnant and breastfeeding women and their infants** |  
- A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped (strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants).
- Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding). |
## What ARV regimens to start with (continued)

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
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</table>
| **First-line ART for children younger than 3 years of age** | - A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen (*strong recommendation, moderate-quality evidence*).  
- Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained (*conditional recommendation, low-quality evidence*).  
- For infants and children infected with HIV younger than three years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ARV regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (*strong recommendation, moderate-quality evidence*). |
| **First-line ART for children 3 years of age and older (including adolescents)** | - For children infected with HIV three years of age and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (*strong recommendation, low-quality evidence*).  
- For children infected with HIV three years to less than 10 years old (and adolescents weighing less than 35 kg), the NRTI backbone for an ARV regimen should be one of the following, in preferential order:  
  - ABC + 3TC  
  - AZT or TDF + 3TC (or FTC) (*conditional recommendation, low-quality evidence*). |
| | - For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ARV regimen should align with that of adults and be one of the following, in preferential order:  
  - TDF + 3TC (or FTC)  
  - AZT + 3TC  
  - ABC + 3TC (*strong recommendation, low-quality evidence*). |
### Monitoring ART response and diagnosis of treatment failure

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| All populations      | • Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure *(strong recommendation, low-quality evidence).*  
|                      | • If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure *(strong recommendation, moderate-quality evidence).* |

### Second-line ART: what ARV regimen to switch to

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| What ARV regimen to switch to in adults and adolescents *(includes pregnant and breastfeeding women)* | • Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).  
|                      | • The following sequence of second-line NRTI options is recommended:  
|                      |   • After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.  
|                      |   • After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.  
|                      | • Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach *(strong recommendation, moderate-quality evidence).*  
|                      | • Heat-stable fixed-dose combinations ATV/r and LPV/r are the preferred boosted PI options for second-line ART *(strong recommendation, moderate-quality evidence).* |
## Second-line ART: what ARV regimen to switch to (continued)

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| What ARV regimen to switch to in children (including adolescents) | • After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI *(strong recommendation, moderate-quality evidence)*.  
• After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken *(conditional recommendation, very-low-quality evidence)*.  
• After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI *(conditional recommendation, low-quality evidence)*.  
• After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC *(strong recommendation, low-quality evidence)*.  
• After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC) the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC) *(strong recommendation, low-quality evidence)*. |

## Third-line ART

<table>
<thead>
<tr>
<th>Topic and population</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| All populations      | • National programmes should develop policies for third-line ART *(conditional recommendation, low-quality evidence)*.  
• Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs *(conditional recommendation, low-quality evidence)*.  
• Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen *(conditional recommendation, very low-quality evidence)*. |
| Special considerations for children | Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used in treating adults such as ETV, DRV and RAL may be possible. Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed. |
## Operations and service delivery

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions to optimize adherence to ART</strong></td>
<td>- Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions <em>(strong recommendation, moderate-quality evidence).</em></td>
</tr>
<tr>
<td><strong>Service integration and linkage</strong></td>
<td>- In generalized epidemic settings, ART should be initiated and maintained in eligible pregnant and postpartum women and in infants at maternal and child health care settings, with linkage and referral to ongoing HIV care and ART, where appropriate <em>(strong recommendation, very-low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>- In settings with a high burden of HIV and TB, ART should be initiated for an individual living with HIV in TB treatment settings, with linkage to ongoing HIV care and ART <em>(strong recommendation, very-low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>- In settings with a high burden of HIV and TB, TB treatment may be provided for an individual living with HIV in HIV care settings where TB diagnosis has also been made <em>(strong recommendation, very-low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>- ART should be initiated and maintained in eligible people living with HIV at care settings where opioid substitution therapy (OST) is provided <em>(strong recommendation, very-low-quality evidence).</em></td>
</tr>
<tr>
<td><strong>Decentralization of treatment and care</strong></td>
<td>The following options should be considered for decentralization of ART initiation and maintenance.</td>
</tr>
<tr>
<td></td>
<td>- Initiation of ART in hospitals with maintenance of ART in peripheral health facilities <em>(strong recommendation, low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>- Initiation and maintenance of ART in peripheral health facilities <em>(strong recommendation, low-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>- Initiation of ART at peripheral health facilities with maintenance at the community level (that is, outside health facilities in settings such as outreach sites, health posts, home-based services or community-based organizations) between regular clinical visits <em>(strong recommendation, moderate-quality evidence).</em></td>
</tr>
</tbody>
</table>
### Operations and service delivery (continued)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Task-shifting</strong></td>
<td>• Trained non-physician clinicians, midwives and nurses can <strong>initiate</strong> first-line ART <em>(strong recommendation, moderate-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>• Trained non-physician clinicians, midwives and nurses can <strong>maintain</strong> ART <em>(strong recommendation, moderate-quality evidence).</em></td>
</tr>
<tr>
<td></td>
<td>• Trained and supervised community health workers can <strong>dispense</strong> ART between regular clinical visits <em>(strong recommendation, moderate-quality evidence).</em></td>
</tr>
</tbody>
</table>

### Guidance for programme managers

<table>
<thead>
<tr>
<th>Topic</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guidance for programme managers</strong></td>
<td>For deciding on the implementation of the clinical and operational recommendations, it is recommended that:</td>
</tr>
<tr>
<td></td>
<td>• The national authorities do so using a transparent, open and informed process. This process should have broad stakeholder engagement, including meaningful participation from the affected communities, and take into account the specifics of the recommendations under discussion.</td>
</tr>
<tr>
<td></td>
<td>• The decision-making process take into account data on the national and local HIV epidemiology, current ART programme performance and the socioeconomic, policy and legal context, including the budgetary, human resource requirements and other health system implications. The latter would identify which inputs and systems are currently available and which areas require additional investment.</td>
</tr>
<tr>
<td></td>
<td>• The decision-making process take into account the ethics, equity and human rights, the impact and cost-effectiveness and the opportunity and risk dimensions of alternative implementation options.</td>
</tr>
</tbody>
</table>
INTRODUCTION

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1. INTRODUCTION

1.1 Background and context

WHO first published guidelines on the use of ART for HIV infection among adults and adolescents in 2002 (1) and on the use of ARV drugs for PMTCT in 2001 and 2004 (2). The 2006 updates of the guidelines (3–5) introduced the concept of a public health approach, with simplified and harmonized ARV regimens (6). These publications and their updates, most recently in 2010 (7–9), have provided important guidance to countries that have scaled up national ARV programmes during the past decade. In 2013, for the first time, WHO has revised and combined these and other ARV-related guidance documents into one set of consolidated guidelines that addresses the use of ARV drugs for HIV treatment and prevention across all age groups and populations, based on the broad continuum of HIV care.

These guidelines were updated in late 2012 and early 2013. The ARV regimens now available, even in the poorest countries, are safer, simpler, more efficacious and more affordable than ever before. New testing strategies and approaches are enabling earlier diagnosis of HIV in a wider range of settings, and new, more affordable technologies for monitoring people receiving ART are becoming available. Countries are moving towards triple-drug regimens and simplified programming for PMTCT that emphasizes the long-term health of pregnant women and mothers living with HIV as well as their children. Important new evidence has shown that ARV drugs offer significant benefits in preventing HIV transmission (10). Although countries are at different stages of ART coverage and implementation of the 2010 guidelines (7–9) and there are still important gaps in research, there is a consistent global trend towards expanding access and the earlier initiation of treatment.

Expanding the eligibility criteria for ART and the options for using ARV drugs creates opportunities to save lives and reduce HIV transmission but can pose significant technical, operational, programmatic and ethical challenges to policy-makers and implementers in many low- and middle-income countries. These include implementing a strategic mix of approaches to ensure more timely diagnosis of HIV infection in both health facility and community settings. Effective linkage and referrals between care settings, innovative, decentralized approaches to delivering ART services and effective adherence support and interventions are also needed to ensure that people are retained in long-term care. Reliable, quality-assured and affordable laboratory monitoring tools, adequate health workforce capacity and uninterrupted drug supplies are also essential.

At the programmatic level, countries often encounter difficulties in reaching the people who need ARV drugs the most. They may face difficult choices in allocating limited resources and determining programme priorities to make the best use of ARV drugs for treatment and prevention in combination with other HIV prevention methods. National HIV programmes may need to justify increased investment in ARV programmes by assessing the costs and benefits and demonstrating how they impact on HIV morbidity, mortality and incidence.

1.2 Rationale for consolidated guidelines

The consolidated guidelines offer the following anticipated benefits.

Guidance on using ARV drugs is presented within the context of the continuum of HIV-related prevention, treatment and care. In addition to providing recommendations on the clinical use of ARV drugs for treatment, the guidelines address other major aspects of HIV-related care.
The guidelines address the use of ARV drugs for all age groups and populations. Previously separate WHO guidelines on using ART among adults and adolescents have been combined with those for children and for PMTCT, harmonizing ARV regimens and treatment approaches to the extent possible across age groups and populations.

**New and existing guidance is harmonized.** Consolidation has allowed for new recommendations to be harmonized with relevant, existing WHO guidance.

**Consolidation promotes the consistency of approaches and linkage between settings.** Consolidated recommendations help to facilitate linkage and promote consistency of approaches across the various settings in which ARV drugs and related services may be provided, including specialized HIV care, primary care, community-based care, maternal and child health services, TB services and services for people who use drugs.

**Updates will be more timely and comprehensive.** Consolidated guidelines enable key clinical, operational and programmatic implications of new science and emerging practice in the use of ARV drugs to be comprehensively reviewed every two years across populations, age groups and settings.

### 1.3 Objectives

The objectives of the consolidated guidelines are:

- to provide updated, evidence-based clinical recommendations outlining a public health approach to providing ARV drugs for HIV treatment and prevention in the context of the continuum of HIV care, with a focus on settings with limited capacity and resources in the health system;
- to provide guidance on key operational and service delivery issues that need to be addressed to increase access to HIV services, strengthen the continuum of HIV care and further integrate the provision of ARV drugs into health systems; and
- to provide programmatic guidance for decision-makers and planners at the national level on adapting, setting priorities for and implementing the clinical and operational recommendations and monitoring their implementation and impact.

### 1.4 Target audience

The guidelines are intended primarily for use by national HIV programme managers. They will also be of interest to the following audiences:

- national HIV treatment and prevention advisory boards;
- national TB programme managers;
- managers of maternal, newborn and child health and reproductive health programmes;
- clinicians and other health service providers;
- managers of national laboratory services;
- people living with HIV and community-based organizations; and
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in resource-limited settings.
1.5 **Scope and components**

The guidelines address clinical, operational and programmatic aspects of using ARV drugs for HIV treatment and prevention (Fig. 1.1).

1.5.1 **Introductory chapters**

The guidelines include several introductory chapters.

- **Chapter 1:** Describes the background, context, rationale and objectives of the guidelines and the target audience.
- **Chapter 2:** Outlines the guiding principles that underpin the guidelines.
- **Chapter 3:** Describes the methods and process for developing the guidelines.
- **Chapter 4:** Presents the format used to present new recommendations.

1.5.2 **Clinical guidance**

The recommendations in Chapters 5, 6 and 7 address key aspects of using ARV drugs for HIV treatment and prevention for all age groups and populations along the continuum of care from HIV-related diagnosis to care and treatment.

- **Chapter 5:** Summarizes HIV testing and counselling approaches, with links to existing WHO guidance. In addition, it summarizes approaches to using ARV drugs for preventing HIV transmission (pre-exposure prophylaxis and post-exposure prophylaxis of HIV and ARV drugs for prevention in serodiscordant couples) within the context of comprehensive combination HIV prevention, with links to existing WHO guidance. Note that the guidelines do not address behavioural, structural and biomedical prevention interventions that do not involve the use of ARV drugs.

- **Chapter 6:** Summarizes general HIV care for individuals from the time that they are diagnosed with HIV infection to the time that they are initiated on ART, including practices for linking people diagnosed with HIV infection to HIV care and treatment, the components of a general care package and preparing individuals for starting ART.

- **Chapter 7:** Includes recommendations on ART for adults (including pregnant and breastfeeding women), adolescents and children, including updated recommendations applicable to the majority of populations regarding the optimal timing for initiating ART (when to start); updated recommendations on the most effective and feasible first- and second-line treatment regimens (what to start and what to switch to); updated recommendations for monitoring the response to and toxicity of ART; and a discussion of third-line ART.

- **Chapter 8:** Includes a summary of approaches to preventing and managing common HIV-related opportunistic infections, other coinfections and other comorbidities, with links to existing WHO guidance.

1.5.3 **Operational and service delivery guidance**

- **Chapter 9:** Includes recommendations in six major operational and service delivery areas in which action is essential to further scaling up ARV programmes and ensuring their effectiveness and sustainability across the health system. These areas are: retention in care; adherence to ART; human resources; models of service delivery, focusing on decentralizing ART to primary health care services and integrating ART with TB treatment, antenatal care and maternal and child health programmes and drug dependence services; laboratory services; and drug supply management.
1.5.4 Guidance for programme managers

Chapter 10: Aims to assist countries in decision-making and programme planning. Implementation will involve various policy mixes based on local context, including the prevalence and dynamics of HIV infection; modes of transmission; the organization and capacity of health systems; relative income; and the current coverage of interventions. The chapter proposes steps to ensure fair, inclusive and transparent decision-making processes at the country level; discusses parameters to consider in assessing and adapting the global recommendations in countries; and suggests tools for costing and planning. Considerations for implementation across the health system and for specific, key recommendations in the guidelines are also discussed.

1.5.5 Monitoring and evaluation

Chapter 11: Provides guidance on the implications for monitoring of key new recommendations in these guidelines. It proposes a range of indicators that may be used to track the implementation of new recommendations and indicators to monitor the performance of programmes across the continuum of care. Chapter 11 also highlights opportunities provided by new recommendations to review and strengthen monitoring and evaluation systems.

Fig. 1.1 Components of the consolidated guidelines
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<tbody>
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<td>2.3 Strengthening health systems through innovation and learning</td>
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<td>2.5 Promoting human rights and health equity</td>
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<tr>
<td>2.6 Implementation based on local context</td>
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2. GUIDING PRINCIPLES

2.1 Contribution to global health goals

Implementing these guidelines will contribute to achieving universal access to HIV prevention, treatment, care and support in accordance with the goals and targets articulated in the 2006 Political Declaration on HIV/AIDS (1) and the 2011 Political Declaration on HIV and AIDS: Intensifying Our Efforts to Eliminate HIV and AIDS (2). These guidelines will also contribute to attaining specific health sector goals in the Global Health Sector Strategy on HIV/AIDS 2011–2015 (3) and the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (4). Major targets for 2015 include reducing by half the percentage of young people 15–25 years who are infected with HIV compared with 2009; reducing the number of children newly infected with HIV by 90% compared with 2009; reducing the number of people dying from HIV-related causes by 25% compared with 2009; reducing by half the number of HIV-related maternal deaths compared with 2009; reducing by half the number of people dying from TB compared with 2004; and having 15 million people on ART in low- and middle-income countries. In the longer term, the guidelines will contribute to and inform efforts to achieve universal health coverage, a key pillar of the post-2015 development agenda.

2.2 Public health approach

In accordance with WHO guidance on HIV since 2002, these guidelines are based on a public health approach to scaling up the use of ARV drugs for HIV treatment and prevention (5). The public health approach seeks to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings.

2.3 Strengthening health systems through innovation and learning

The recommendations and innovations in service delivery described in these guidelines should be implemented with a view to strengthening the continuum of HIV care and broader health systems, especially primary care and chronic care.

HIV services are already being integrated at lower-level health facilities in many settings with a high burden of HIV infection, while services for PMTCT are increasingly becoming core elements of maternal and child health services. HIV, TB, hepatitis, drug dependence and harm reduction services are being integrated to varying degrees. As people receiving ART begin to age and HIV infection becomes a chronic, manageable condition, improving the integration of HIV services with care for noncommunicable diseases will also become more important. In accordance with these trends, the guidelines promote the adaptation of service delivery models that strengthen the continuum of HIV care and enable the timely initiation of ART in a variety of settings, ensuring that people are appropriately referred to services and are retained in and adhere to lifelong treatment.

National HIV programmes should consider undertaking implementation research to determine how best to adopt and adapt these guidelines to their local context and bringing to scale more efficient and effective services.
2.4 **Increasing the effectiveness and efficiency of programmes**

In the context of limited financial resources, competing priorities and health system constraints, countries may face difficult choices among an expanding range of options for using ARV drugs to reduce HIV morbidity, mortality and transmission. These guidelines are based on the principle that countries should further scale up and optimize the effectiveness and efficiency of HIV programmes through a strategic approach to using ARV drugs that involves:

- giving priority to providing ARV drugs to people living with HIV who are eligible for treatment and most in need;
- exploring opportunities to enhance the impact of ARV drugs on HIV prevention by starting treatment earlier in certain populations;
- increasing the effectiveness and reach of ARV programmes across the continuum of care through a strategic mix of quality-assured HIV testing approaches, improving adherence and retention, innovative service delivery, integrating ART in a wider range of settings and strengthening links between services; and
- engaging in both short- and longer-term efforts to optimize and harmonize drug regimens and increase their affordability and to develop and implement simpler and more affordable point-of-care diagnostics and laboratory services.

2.5 **Promoting human rights and health equity**

Access to HIV prevention, treatment, care and support should be recognized as fundamental to realizing the universal right to health, and these guidelines should be implemented based on core human rights and ethical principles. In general, HIV programmes need to ensure that ARV drugs and related interventions are accessible to the people who need them most, including pregnant women, children and key populations, and that they are provided in an environment that minimizes stigma and discrimination. Informed consent – notably for HIV testing but also for initiating ART – should always be obtained. Adequate safeguards must be in place to ensure confidentiality.

Some countries may face significant ethical challenges as they seek to implement these guidelines in the context of constraints on resources and health systems. A key challenge may involve the need to give priority to ensuring ART for the people who are most ill and those already receiving treatment, while also striving to implement expanded eligibility criteria. Each country will need to plan its own approach to ensuring that current ARV programmes are not disrupted and that expanded access is fair and equitable.

2.6 **Implementation based on local context**

Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness. A strong recommendation for a specific approach to service delivery should not necessarily be viewed as an endorsement of that model over an effective service delivery model already in place in a country.
3.1 Overview

3.2 Information sources

3.3 External participation
   3.3.1 Guideline Development Groups and peer review process
   3.3.2 Conflicts of interest

3.4 Process of formulating recommendations

3.5 Other methods

3.6 Dissemination
3. METHODS AND PROCESS FOR DEVELOPING THE GUIDELINES

3.1 Overview
The 2013 consolidated guidelines compile new recommendations, existing recommendations and other guidance across the continuum of HIV care. This includes guidance on HIV diagnosis, general HIV care and the strategic use of ARV drugs for treating and preventing HIV infection, based on a public health approach. New clinical and operational recommendations were developed in accordance with procedures outlined by the WHO Guidelines Review Committee (1) and are based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system (2–11). Most recommendations cited from existing guidance were developed using the GRADE system. In a few cases where GRADE was not used, the text notes this. Chapter 10 did not use the GRADE approach, since the programmatic guidance does not contain any formal recommendations.

3.2 Information sources
The following sources of information were used in developing new recommendations.

- **Systematic reviews** were commissioned on 41 topics framed using Population, Intervention, Comparison and Outcome (PICO) format by the WHO Guideline Steering Group (3) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The 41 topics covered the continuum of HIV care (9 on when to start; 11 on what to start; 4 on monitoring the response to treatment; 6 on monitoring toxicity; 11 on various aspects of service delivery; and 5 on adherence interventions). The WHO Guideline Steering Group established the critical outcomes for the reviews of clinical evidence (mortality, morbidity, transmission and severe adverse reactions) and for the reviews of operational service delivery (mortality, morbidity, transmission, access, retention in care, viral suppression and adherence) in consultation with the Guidelines Development Groups. Systematic reviews were outsourced to researchers who developed search protocols and conducted reviews of the available scientific evidence. Searches of electronic databases (MEDLINE/PubMed, Embase, CENTRAL), conference databases (Aegis, AIDSearch, NLM Gateway and hand searches) and clinical trial registers (http://clinicaltrials.gov, www.controlled-trials.com and www.pactr.org) used relevant keywords and search strings. The Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes) includes the search protocols, the full list of review questions and the GRADE tables and evidence summaries for each topic.

- A standardized **GRADE evidence table** was used to present quantitative summaries of the evidence and assessment of its quality for each PICO question by outcome. The GRADE system was used to rate the quality of evidence (4–10) and the strength of the recommendations (11) (Box 3.1; Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

- **Community consultations** on values and preferences in priority areas for the guidelines were conducted through an online e-survey and moderated e-forum discussions with civil society networks and coordinated by the International HIV/AIDS Alliance and the Global Network of People Living with HIV (GNP+). Focus group discussions were also held in Uganda and Malawi on the experiences of pregnant women with lifelong ART, and on PMTCT and paediatric ART in South Africa (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).
3. Methods and process for developing the guidelines

- **Two global community and civil society consultations** on service delivery across the continuum of care in generalized and concentrated epidemic settings.

- **Consultations with health workers** working with adults and with children on the values and preferences related to priority areas in the guidelines were conducted through an e-survey (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).


- **Mathematical modelling** on the impact and cost-effectiveness of earlier ART in various populations and settings, based on data from countries with both generalized and concentrated epidemics (India, Kenya, South Africa, Viet Nam and Zambia), together with modelling of various treatment monitoring strategies were undertaken by the HIV Modelling Consortium (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

- **An impact assessment** using the Spectrum model to estimate the increased number of adults and children eligible for ART based on various eligibility criteria (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

- **Reports on country implementation experiences** were provided on using option B+ for PMTCT in Malawi; introducing TDF in first-line ARV regimens in Zambia; phasing out d4T in Zimbabwe; and scaling up viral load monitoring in Médecins Sans Frontières programmes in southern Africa.

- **An electronic e-survey of country-level end-users** was undertaken of WHO guidelines on ARV drugs to identify areas for improvement in format, presentation and dissemination (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

### 3.3 External participation

#### 3.3.1 Guideline Development Groups and peer review process

The process was supported by four, separate, external Guideline Development Groups (Adult; Maternal and Child Health; Operational and Service Delivery; and Programmatic, comprising 108 individuals) and an external peer review group of over 100 individuals. The acknowledgements list the members of these Groups. The composition of the Groups was in accordance with WHO procedures for developing guidelines (1) and included HIV experts, researchers, programme managers, guideline methodologists, epidemiologists, human rights experts, development agencies, United Nations partners, civil society representatives and representatives from networks of people living with HIV. Appropriate representation by geography and sex was considered. Community group members were selected following an open call for nominations. A full draft of the guidelines was circulated for comment to members of the Guideline Development Groups and the external peer review group.

#### 3.3.2 Conflicts of interest

All members of the Guideline Development Groups and peer review group completed WHO declaration of interest forms (including participation in consulting and advisory panels, research support and financial investment). A total of 21 Guideline Development Group members and 12 peer reviewers declared membership of pharmaceutical industry or other advisory panels or receipt of consulting fees, and 23 Guideline Development Group members and 13 peer reviewers declared pharmaceutical industry financial support through grants for research.
The focus of the 2013 guidelines was on the development of new or updated recommendations on the use of ARV drugs in adults, adolescents, children and pregnant women. The WHO secretariat and co-chairs of each Guideline Development Group considered that important areas for potential conflict of interest would be evidence for exclusive engagement with one pharmaceutical company, or a major role within completed, ongoing or planned trials on either the timing of ART, or evaluation of specific ARV regimens. The WHO Guideline Steering Group reviewed all declarations, and found no case where there was exclusive membership of an advisory group panel, receipt of consulting fees or financial support through research grants from only one pharmaceutical company. There was also a further declaration at the Guideline Development Group meeting of the involvement of members as investigators in key trials and studies. Overall, the WHO Guideline Steering Group and co-chairs of each Guideline Development Group were satisfied that there had been a transparent declaration of interests, and that no case necessitated exclusion from the deliberations. The broad range of constituencies represented on the different Guideline Development Group panels was also noted, and that the majority of members had no declared interests. All individuals with declared interests therefore proceeded to participate fully in the Guideline Development Group meetings or to act as peer reviewers.

3.4 Process of formulating recommendations

Four Guideline Development Group meetings were held in Geneva, Switzerland between November 2012 and January 2013 (Operational and Service Delivery Guideline Development Group, November 2012; Adult Guideline Development Group and Maternal and Child Health Guideline Development Group, December 2012; and Programmatic Guideline Development Group, January 2013). The systematic reviews, evidence tables prepared in accordance with GRADE and other relevant information described in section 3.2 were presented and discussed at these meetings and made available through a password-protected web site. The proposed recommendations were then considered, informed by a standardized decision-making table for each topic (Box 3.1) encompassing the following elements: existing and proposed recommendations; summary of the evidence; benefits and risks; community and health care worker values and preferences; costs and resource implications; cost-effectiveness; feasibility and barriers to implementation; equity, ethics and human rights implications; the suggested rating of the strength of recommendations (strong or conditional) and quality of the evidence; research gaps and needs; and the overall rationale for the recommendations.

The Guideline Development Groups discussed both the proposed wording of the recommendations and the rating of its strength (strong or conditional). All decisions were reached by discussion and consensus on the recommendations, including their strength and, where appropriate, the conditions to be attached to the recommendations. Disagreements were resolved through e-mail discussions, teleconferences and redrafting recommendations and rationale. Early drafts of sections of the guidelines were circulated to Guideline Development Group members, and a full draft of the guidelines was circulated to Guideline Development Group members and peer reviewers for comment. The extensive comments from more than 100 reviewers were addressed where possible and incorporated into the revised guidelines.
Box 3.1 Approach to rating the quality of evidence and strength of recommendations using the GRADE system

Since 2008, WHO has followed the GRADE system. GRADE separates the rating of the quality of evidence from the rating of the strength of the recommendation.

The **quality of evidence** is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low and very low (Table 3.1) (4–10). Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including the risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if multiple studies show the same effect, if evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect (10). The higher the quality of evidence, the more likely a strong recommendation can be made.

The **strength of a recommendation** reflects the extent to which the Guideline Development Group was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The strength is influenced by the following factors: the quality of the evidence, the balance of benefits and harms, values and preferences, resource use and the feasibility of the intervention (Table 3.2).

The GRADE system classifies the strength of a recommendation in two ways: “strong” and “conditional” (11). A **strong recommendation** is one for which the Guideline Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects. A **conditional recommendation** is one for which the Guideline Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the Guideline Development Group is not confident about these trade-offs. Table 3.3 summarizes the implications of a strong or conditional recommendation for individuals, clinicians and policy-makers.

The reasons for making a conditional recommendation include the absence of high-quality evidence; imprecision in outcome estimates; variability in the values and preferences of individuals regarding the outcomes of interventions; small benefits; applicability in all settings versus specific settings; and benefits that may not be worth the costs (including the costs of implementing the recommendation).
### Table 3.1 GRADE classification of the level of evidence

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an estimate of effect and is likely to change the estimate of effect</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>

### Table 3.2 Key domains considered in determining the strength of recommendations

<table>
<thead>
<tr>
<th>Domain</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits and risks</td>
<td>Desirable effects (benefits) need to be weighed against undesirable effects (risks). The more that the benefits outweigh the risks, the more likely that a strong recommendation will be made.</td>
</tr>
<tr>
<td>Values and preferences (acceptability)</td>
<td>If the recommendation is likely to be widely accepted or highly valued, a strong recommendation will probably be made. If there are strong reasons that the recommended course of action is unlikely to be accepted, a conditional recommendation is more likely to be made.</td>
</tr>
<tr>
<td>Costs and financial implications (resource use)</td>
<td>Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness will more likely result in a strong recommendation.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is more probable.</td>
</tr>
</tbody>
</table>

### Table 3.3 Implications for strong and conditional recommendations for individuals, clinicians and policy-makers

<table>
<thead>
<tr>
<th></th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not</td>
</tr>
<tr>
<td>Clinician</td>
<td>Most individuals should receive the recommended course of action</td>
<td>Be prepared to help individuals to make a decision that is consistent with their own values</td>
</tr>
<tr>
<td>Policy-maker</td>
<td>The recommendation can be adapted as a policy in most situations</td>
<td>There is a need for substantial debate and involvement of stakeholders</td>
</tr>
</tbody>
</table>
**3.5 Other methods**

**Recommendations from existing guidelines.** In addition to new recommendations based on the GRADE system, the guidelines summarize existing relevant recommendations from other WHO guidelines. Most of these recommendations were developed using the GRADE system or an alternative grading used prior to 2008 (A (strongly recommended) to C (optional)) and I–IV (level of evidence) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). For these existing recommendations, no new evidence reviews were undertaken. Recommendations that require updating are noted, and it is clearly stated where updated guidelines are planned.

Where systematic reviews and GRADE assessment of quality of evidence to support new recommendations were not possible or appropriate, qualitative reviews of the literature were undertaken and presented. This applies to specific topics in Chapter 9, including retention across the continuum of care, but this did not lead to formal recommendations.

**Guidance for programme managers on programmatic decision-making.** Chapter 10 and Chapter 11 did not involve formulating recommendations or rating of the quality of evidence and therefore did not follow the GRADE system. The process involved a narrative review of literature on both the process and criteria for evidence-based ethical decision-making, a review of relevant WHO policies and World Health Assembly resolutions, and results from mathematical modelling on the impact and cost–effectiveness of earlier ART in various populations and settings. Structured discussions were held among Guideline Development Group members regarding setting priorities for key clinical recommendations in various epidemic scenarios (settings with generalized and concentrated epidemics and with low, moderate and high ART coverage).

**3.6 Dissemination**

The guidelines will be disseminated as a printed publication and electronically on the WHO web site in the six official United Nations languages. The web version will include all annexes. A short version will summarize key new and existing recommendations for easy reference. A library of all supporting documentation and evidence will also be made available on the web site. WHO headquarters will work closely with regional and country offices and implementing partners to ensure their wide dissemination through regional and subregional meetings. Assistance will be provided to Member States to adapt the guidelines to their national contexts.

An evaluation of how users have implemented the guidelines has been developed to assess the uptake of the recommendations and the barriers to effective implementation. A review of the guidelines is planned for 2015. Interim technical and programmatic updates may be developed if important new evidence becomes available.
4 Continuum of care 56
4.1 Structure of presentation for new recommendations 58
4.2 Structure of presentation of selected recommendations from existing guidelines 58
4.3 How to use the guidelines for specific populations 59
  4.3.1 Pregnant and breastfeeding women 59
  4.3.2 Adolescents 61
  4.3.3 Children 63
  4.3.4 Key populations 64
4. ORGANIZATION OF THE GUIDELINES

Continuum of care
4. Organization of the guidelines

- **ART INITIATION (FIRST LINE ART)**
  - Sections 7.1 and 7.2

- **RETENTION AND ADHERENCE**
  - Sections 9.2 and 9.3

- **SECOND AND THIRD LINE ART**
  - Sections 7.3 and 7.4
  - Section 7.5

- **MONITORING ART RESPONSE**
- **MONITORING ARV TOXICITY**
4.1 Structure of presentation for new recommendations

New recommendations in these guidelines are flagged by a symbol NEW. These include existing recommendations that have been updated, where a new evidence review was undertaken as part of this guidelines process. When the original recommendation remained unchanged, this is clearly indicated. They are presented in the following format to reflect the full evidence review and discussion held within the Guideline Development Group for new recommendations.

- **Recommendation**. The new recommendation and the strength of the recommendation, and quality of the evidence assessed using the GRADE system are stated.

- **Background**. Previous WHO guidance in this area and key developments since recommendations were last published are described. When the recommendation relates to a specific population, the key issues for that population may be briefly summarized.

- **Rationale for recommendation and supporting evidence**. The new evidence on which the recommendation is based and other key operational and programmatic considerations that informed the development of the recommendation are summarized.

- **Clinical or implementation considerations**. In some cases, key clinical implementation issues specific to the recommendation are listed. For several key recommendations, discussion of implementation considerations relevant to programme managers is presented in Chapter 10.

- **Key research gaps**. In some cases, critical issues requiring further research are briefly described or listed, where these are integral to the recommendations.

- The references relating to each section are listed at the end of the guidelines by chapter number.

4.2 Structure of presentation for selected recommendations from existing guidelines

Two chapters summarize recommendations from existing WHO guidelines: Chapter 5 on HIV testing and counselling as well as the use of ARV drugs for prevention; and Chapter 8 on general HIV care, including prevention and management of coinfections and comorbidities. In general, these are presented in the following format:

- **Background**;

- **Source(s) for recommendation(s)**;

- **Additional guidance (where appropriate)**; and

- **Existing recommendation(s)**.

The recommendations and the strength of the recommendation, and quality of the evidence assessed using the GRADE system (or an alternative method) are stated.
4.3 How to use the guidelines for specific populations

These guidelines include recommendations for adults, pregnant and breastfeeding women, adolescents, children, and key populations. The populations relevant to each recommendation are clearly specified and also marked by an appropriate symbol for quick reference.

Tables 4.1–4.4 also summarize the chapter and section number of key recommendations and guidance for specific populations: pregnant and breastfeeding women, adolescents, children and infants, and key populations. The tables highlight selected topics that are particularly relevant to the respective populations. However, the topics listed are not exhaustive and many of the recommendations and other guidance are relevant across different populations.

4.3.1 Pregnant and breastfeeding women

Table 4.1 summarizes the location of key guidance and recommendations relevant to pregnant and breastfeeding women.

Table 4.1. Key recommendations and guidance for pregnant and breastfeeding women

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
<th>Chapter subsections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 5: HIV diagnosis and ARV drugs for HIV prevention</td>
<td>HIV testing and counselling in health facilities</td>
<td>Section 5.1.2</td>
</tr>
<tr>
<td></td>
<td>Community-based HIV testing and counselling</td>
<td>Section 5.1.3</td>
</tr>
<tr>
<td></td>
<td>HIV testing and counselling in specific populations: Couples</td>
<td>Section 5.1.4.1</td>
</tr>
<tr>
<td></td>
<td>HIV testing and counselling in specific populations: Pregnant and postpartum women</td>
<td>Section 5.1.4.2</td>
</tr>
<tr>
<td></td>
<td>HIV testing and counselling in specific populations: Early infant diagnosis</td>
<td>Section 5.1.4.3</td>
</tr>
<tr>
<td></td>
<td>ART for prevention among serodiscordant couples</td>
<td>Section 5.2.2</td>
</tr>
<tr>
<td>Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment</td>
<td>General care for people living with HIV</td>
<td>Section 6.3</td>
</tr>
<tr>
<td></td>
<td>Preparing people living with HIV for ART</td>
<td>Section 6.4</td>
</tr>
<tr>
<td></td>
<td>What to expect in the first months of ART</td>
<td>Section 6.5</td>
</tr>
<tr>
<td>Chapter</td>
<td>Topic</td>
<td>Chapter subsections</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Chapter 7: Antiretroviral therapy</td>
<td>When to start ART in pregnant and breastfeeding women</td>
<td>Section 7.1.2</td>
</tr>
<tr>
<td></td>
<td>ARV drugs and duration of breastfeeding</td>
<td>Section 7.1.3</td>
</tr>
<tr>
<td></td>
<td>Special considerations for the care and management of pregnant women</td>
<td>Section 7.1.3; Box 7.1</td>
</tr>
<tr>
<td></td>
<td>First-line ART for pregnant and breastfeeding women and ARV drugs for their infants</td>
<td>Section 7.2.2</td>
</tr>
<tr>
<td></td>
<td>Monitoring response to ART and diagnosis of treatment failure (includes pregnant and breastfeeding women)</td>
<td>Section 7.3</td>
</tr>
<tr>
<td></td>
<td>Monitoring and substitutions for ARV drug toxicities (includes pregnant and breastfeeding women)</td>
<td>Section 7.4</td>
</tr>
<tr>
<td></td>
<td>Second-line ART for adults and adolescents (includes pregnant and breastfeeding women)</td>
<td>Section 7.5.1</td>
</tr>
<tr>
<td></td>
<td>Third-line ART (includes pregnant and breastfeeding women)</td>
<td>Section 7.6</td>
</tr>
<tr>
<td>Chapter 8: Managing common coinfections and comorbidities</td>
<td>Prevention, screening and management of coinfections</td>
<td>Section 8.1</td>
</tr>
<tr>
<td></td>
<td>Preventing and managing other comorbidities and chronic care for people living with HIV</td>
<td>Section 8.2</td>
</tr>
<tr>
<td>Chapter 9: Guidance on operations and service delivery</td>
<td>Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adherence to ART: Pregnant and postpartum women</td>
<td>Section 9.2.1</td>
</tr>
<tr>
<td></td>
<td>Delivering ART in antenatal care and maternal and child health settings</td>
<td>Section 9.4.2.1</td>
</tr>
<tr>
<td></td>
<td>Decentralization and Task shifting</td>
<td>Sections 9.4.3 and 9.5.2</td>
</tr>
<tr>
<td>Chapter 10: Guidance for programme managers</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Implementation considerations for key recommendations: moving to lifelong ART for all pregnant and breastfeeding women</td>
<td>Section 10. 6; Box 10.4</td>
</tr>
<tr>
<td>Chapter 11: Monitoring and evaluation</td>
<td>Monitoring implications of new recommendations</td>
<td>Section 11.2</td>
</tr>
<tr>
<td>Annexes</td>
<td>Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children</td>
<td>Chapter 12</td>
</tr>
<tr>
<td></td>
<td>Annex 3. Algorithms for the 2013 recommendations for pregnant and breastfeeding women</td>
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<tr>
<td></td>
<td>Annex 6. Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annex 7. Dosages of recommended ARV drugs for adults and adolescents (includes pregnant and breastfeeding women)</td>
<td></td>
</tr>
</tbody>
</table>
4.3.2 Adolescents

WHO defines adolescence as 10–19 years old. Adolescents with HIV include those surviving perinatal infection and those newly acquiring infection as they become sexually active or are exposed through injecting drug use, other unsafe injections and blood transfusions. Adolescents may access care in a variety of settings, including paediatric and antenatal care clinics, as well as adult clinics. Since few health systems provide adolescent-specific services it can be challenging for adolescents to access health care and maintain adherence to treatment regimens.

In general, in these guidelines, clinical and general care recommendations for adults apply to adolescents. Where guidance for adolescents is addressed in recommendations for children, this is clearly indicated. There are four specific recommendations on testing and counselling taken from additional recent adolescent-specific guidance. The 2013 Guidance on HIV testing and counselling for adolescents and care for adolescents living with HIV contains recommendations on HIV testing and counselling and delivery of services for adolescents (Table 4.2).

Table 4.2. Key recommendations and guidance for adolescents

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
<th>Chapter subsections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 5: HIV diagnosis and ARV drugs for HIV prevention</td>
<td>HIV testing and counselling in health facilities</td>
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</tr>
<tr>
<td></td>
<td>Community-based HIV testing and counselling</td>
<td>Section 5.1.3</td>
</tr>
<tr>
<td></td>
<td>HIV testing and counselling in specific populations: Adolescents</td>
<td>Section 5.1.4.4</td>
</tr>
<tr>
<td>Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment</td>
<td>General care for people living with HIV</td>
<td>Section 6.3</td>
</tr>
<tr>
<td></td>
<td>Preparing people living with HIV for ART</td>
<td>Section 6.4</td>
</tr>
<tr>
<td></td>
<td>What to expect in the first months of ART</td>
<td>Section 6.5</td>
</tr>
<tr>
<td>Chapter 7: Antiretroviral therapy</td>
<td>When to start ART in adults and adolescents</td>
<td>Section 7.1.1</td>
</tr>
<tr>
<td></td>
<td>First-line ART for children three years and older (includes adolescents)</td>
<td>Section 7.2.4</td>
</tr>
<tr>
<td></td>
<td>TB co-treatment in children with HIV</td>
<td>Section 7.2.5</td>
</tr>
<tr>
<td></td>
<td>Monitoring response to ART and the diagnosis of treatment failure (includes adolescents)</td>
<td>Section 7.3</td>
</tr>
<tr>
<td></td>
<td>Monitoring and substitutions for ARV drug toxicities (includes adolescents)</td>
<td>Section 7.4</td>
</tr>
<tr>
<td></td>
<td>Key ARV drug interactions (includes adolescents)</td>
<td>Table 7.16</td>
</tr>
<tr>
<td></td>
<td>Second-line ART for adults and adolescents</td>
<td>Section 7.5.1</td>
</tr>
<tr>
<td></td>
<td>Second-line ART for children (includes adolescents)</td>
<td>Section 7.5.2</td>
</tr>
<tr>
<td></td>
<td>Third-line ART (includes adolescents)</td>
<td>Section 7.6</td>
</tr>
<tr>
<td>Chapter</td>
<td>Topic</td>
<td>Chapter subsections</td>
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<tr>
<td><strong>Chapter 8: Managing common coinfections and comorbidities</strong></td>
<td>Prevention, screening and management of coinfections</td>
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</tr>
<tr>
<td></td>
<td>Preventing and managing other comorbidities and chronic care for people living with HIV</td>
<td>Section 8.2</td>
</tr>
<tr>
<td></td>
<td>Nutritional care and support among adolescents and adults living with HIV</td>
<td>Section 8.2.4.1</td>
</tr>
<tr>
<td><strong>Chapter 9: Guidance on operations and service delivery</strong></td>
<td>Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adherence to ART: Adolescents</td>
<td>Section 9.2.1</td>
</tr>
<tr>
<td></td>
<td>Decentralization and Task shifting</td>
<td>Sections 9.4.3 and 9.5.2</td>
</tr>
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<td>Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Implementation considerations for key recommendations for programme managers: raising the CD4 threshold for initiating ART in adults and adolescents from 350 to 500 cells/mm³</td>
<td>Section 10.6; Box 10.2</td>
</tr>
<tr>
<td><strong>Chapter 11: Monitoring and evaluation</strong></td>
<td>Monitoring implications of new recommendations</td>
<td>Section 11.2</td>
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<td><strong>Annexes</strong></td>
<td>Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children</td>
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<td></td>
<td>Annex 2. Algorithm for the 2013 recommendations for adults and adolescents</td>
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<tr>
<td></td>
<td>Annex 7. Dosages of recommended ARV drugs for adults and adolescents</td>
<td></td>
</tr>
</tbody>
</table>
4.3.3 Children

The location of the most important guidance and recommendations specific to children (younger than 10 years) is summarized in Table 4.3.

Table 4.3. Key recommendations and guidance for children

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
<th>Chapter subsections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 5: HIV diagnosis and ARV drugs for HIV prevention</td>
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<td></td>
<td>Community-based HIV testing and counselling</td>
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</tr>
<tr>
<td></td>
<td>HIV testing and counselling in specific populations: Infants and children</td>
<td>Section 5.1.4.3</td>
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<tr>
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<td>Section 6.5</td>
</tr>
<tr>
<td>Chapter 7: Antiretroviral therapy</td>
<td>When to start ART in children</td>
<td>Section 7.1.4</td>
</tr>
<tr>
<td></td>
<td>First-line ART for children younger than 3 years of age</td>
<td>Section 7.2.3</td>
</tr>
<tr>
<td></td>
<td>First-line ART for children 3 years of age and older</td>
<td>Section 7.2.4</td>
</tr>
<tr>
<td></td>
<td>TB co-treatment in children with HIV</td>
<td>Section 7.2.5</td>
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<td></td>
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<td></td>
<td>Monitoring and substitutions for ARV drug toxicities (includes children)</td>
<td>Section 7.4</td>
</tr>
<tr>
<td></td>
<td>Key ARV drug interactions (includes children)</td>
<td>Table 7.16</td>
</tr>
<tr>
<td></td>
<td>Third-line ART (includes children)</td>
<td>Section 7.6</td>
</tr>
<tr>
<td>Chapter 8: Managing common coinfections and comorbidities</td>
<td>Prevention, screening and management of coinfections (includes children)</td>
<td>Section 8.1</td>
</tr>
<tr>
<td></td>
<td>Immunizations</td>
<td>Section 8.1.7</td>
</tr>
<tr>
<td></td>
<td>Preventing and managing other comorbidities and chronic care for people living with HIV</td>
<td>Section 8.2</td>
</tr>
<tr>
<td></td>
<td>Nutritional care and support among children living with HIV</td>
<td>Section 8.2.4.2</td>
</tr>
<tr>
<td>Chapter 9: Guidance on operations and service delivery</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Adherence to ART: Infants and children</td>
<td>Section 9.2.1</td>
</tr>
<tr>
<td></td>
<td>Decentralization and Task shifting</td>
<td>Sections 9.4.3 and 9.5.2</td>
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</table>
Table 4.3 (continued)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
<th>Chapter subsections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 10: Guidance for programme managers</td>
<td>Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.</td>
<td></td>
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<tr>
<td></td>
<td>Implementation considerations of key recommendations: scaling up treatment for children</td>
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<tr>
<td></td>
<td>Implementation considerations of key recommendations: phasing out d4T</td>
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<td>Annexes</td>
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<td>Annex 4. Algorithm for the 2013 recommendations for children</td>
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<td>Annex 5. Algorithm for early infant diagnosis</td>
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<tr>
<td></td>
<td>Annex 7. Weight-based dosing for ARV formulations for children</td>
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</tr>
</tbody>
</table>

4.3.4 Key populations

In these guidelines, key populations include both vulnerable and most-at-risk populations. Most-at-risk populations include men who have sex with men, transgender people, people who inject drugs and sex workers.

The use of ART in key populations should follow the same general principles and recommendations as for adults. There is one recommendation on community-based HIV testing, that is specific to key populations.

The location of the most important guidance and recommendations specific to key populations is summarized in Table 4.4.

Table 4.4 Key recommendations and guidance for key populations

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
<th>Chapter subsections</th>
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<tbody>
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<td>Chapter 5: HIV diagnosis and ARV drugs for HIV prevention</td>
<td>HIV testing and counselling in health facilities</td>
<td>Section 5.1.2</td>
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<tr>
<td></td>
<td>Community-based HIV testing and counselling</td>
<td>Section 5.1.3</td>
</tr>
<tr>
<td></td>
<td>HIV testing and counselling in specific populations: Key populations</td>
<td>Section 5.1.4.5</td>
</tr>
<tr>
<td>Chapter</td>
<td>Topic</td>
<td>Chapter subsections</td>
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<tr>
<td><strong>Chapter 6:</strong> Linking people diagnosed with HIV infection to HIV care and treatment</td>
<td>General care for people living with HIV</td>
<td>Section 6.3</td>
</tr>
<tr>
<td></td>
<td>Preparing people living with HIV for ART</td>
<td>Section 6.4</td>
</tr>
<tr>
<td></td>
<td>What to expect in the first months of ART</td>
<td>Section 6.5</td>
</tr>
<tr>
<td><strong>Chapter 7:</strong> Antiretroviral therapy</td>
<td>When to start ART in adults and adolescents (includes key populations)</td>
<td>Section 7.1.1</td>
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<tr>
<td></td>
<td>First-line ART for adults (includes key populations)</td>
<td>Section 7.2.1</td>
</tr>
<tr>
<td></td>
<td>Monitoring response to ART and the diagnosis of treatment failure (includes key populations)</td>
<td>Section 7.3</td>
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<tr>
<td></td>
<td>Monitoring and substitutions for ARV drug toxicities (includes key populations)</td>
<td>Section 7.4</td>
</tr>
<tr>
<td></td>
<td>Second-line ART for adults and adolescents (includes key populations)</td>
<td>Section 7.5.1</td>
</tr>
<tr>
<td></td>
<td>Third-line ART (includes key populations)</td>
<td>Section 7.5.3</td>
</tr>
<tr>
<td><strong>Chapter 8:</strong> Managing common coinfections and comorbidities</td>
<td>Prevention, screening and co-management of coinfections</td>
<td>Section 8.1</td>
</tr>
<tr>
<td></td>
<td>Preventing and managing common coinfections and comorbidities</td>
<td>Section 8.2</td>
</tr>
<tr>
<td></td>
<td>Drug use and drug use disorders</td>
<td>Section 8.2.3</td>
</tr>
<tr>
<td><strong>Chapter 9:</strong> Guidance on operations and service delivery</td>
<td>Adherence to ART: Most-at-risk populations (including sex workers, men who have sex with men, transgender people and people who inject drugs)</td>
<td>Section 9.2.1</td>
</tr>
<tr>
<td></td>
<td>ART in settings providing opioid substitution therapy, integrating and linking services</td>
<td>Section 9.4.2.3</td>
</tr>
<tr>
<td></td>
<td>Decentralization and Task shifting</td>
<td>Sections 9.4.3 and 9.5.2</td>
</tr>
<tr>
<td><strong>Chapter 10:</strong> Guidance for programme managers</td>
<td>Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues</td>
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</tr>
<tr>
<td></td>
<td>Socioeconomic, policy and legal context</td>
<td>Section 10.3.4</td>
</tr>
<tr>
<td></td>
<td>Ethics, equity and human rights</td>
<td>Section 10.4.1</td>
</tr>
<tr>
<td></td>
<td>Implementation considerations for key recommendations: raising the CD4 threshold for initiating ART in adults from 350 to 500 cells/mm³</td>
<td>Section 10.6; Box 10.2</td>
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</tbody>
</table>
### Table 4.4 (continued)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
<th>Chapter subsections</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Monitoring implications of new recommendations</td>
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<tr>
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<td>Chapter 12</td>
</tr>
<tr>
<td></td>
<td>Annex 7: Dosages of recommended antiretroviral drugs</td>
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</tbody>
</table>
Goal of this chapter

To provide a summary of existing and new evidence-based clinical recommendations outlining a public health approach to diagnosing HIV infection and providing ARV drugs for prevention in the context of the broad continuum of HIV care, with a focus on settings with limited health system capacity and resources.
5. CLINICAL GUIDELINES ACROSS THE CONTINUUM OF CARE: HIV DIAGNOSIS AND ARV DRUGS FOR HIV PREVENTION

5.1 HIV testing and counselling

5.1.1 Introduction

People access HIV treatment, care and prevention through the gateway of HIV testing and counselling. It is currently estimated globally that about half of the people living with HIV do not know their HIV status. The people who do know often test late, and poor linkages from HIV testing and counselling to care – including failure to assess rapidly for ART eligibility – mean that many people start treatment when they are already significantly immunocompromised, resulting in poor health outcomes and ongoing HIV transmission. The overall HIV testing and counselling goal for a national HIV programme should be to identify as many people living with HIV as early as possible after acquiring HIV infection, and link them appropriately and in a timely manner to prevention, care and treatment services. The people tested who are not infected should be linked to appropriate prevention services, such as voluntary male medical circumcision in the priority countries in sub-Saharan Africa, or harm reduction services for those who use drugs, and encouraged to retest at a later time.

Diverse models of HIV testing and counselling services are available to increase access to HIV diagnosis, including testing services in health care facilities, freestanding sites and a wide range of community-based approaches. These are described in detail in the WHO 2012 strategic HIV testing and counselling framework (1). The use of rapid HIV diagnostic tests that can be used at point of care has become an important strategy to expand access, increase the return of same-day results and enable appropriate referral and follow-up. Countries should choose a strategic mix of service delivery models to achieve equitable access to HIV testing and counselling, based on the local context, the nature of the epidemic, cost–effectiveness and available resources. The mix should facilitate diagnosing as many people living with HIV as early as possible to enable timely linkage to ART. Strategies should be able to reach the people who are most vulnerable, most-at-risk and marginalized (Box 5.1).

The use of a single HIV test to diagnose HIV infection is not sufficient; it must be confirmed by following the steps outlined in the updated WHO 2012 HIV testing strategies (algorithms) (1). Quality assurance systems should be put in place to minimize false-positive and false-negative results. Failure to do this will lead to people being given incorrect test results, with potential serious adverse long-term consequences. Quality assurance and quality improvement measures are also important for the counselling process to ensure that HIV testing and counselling is always conducted in an acceptable and effective manner.
5. Clinical guidelines across the continuum of care: HIV diagnosis and ARV drugs for HIV prevention

5.1. HIV testing and counselling in health facilities

Background
WHO recommends routinely offering HIV testing and counselling in clinical settings (known as provider-initiated testing and counselling) as an efficient and effective way to identify people with HIV who could benefit from treatment.

Source for recommendations

Box 5.1 HIV testing and counselling: guiding principles

All forms of HIV testing and counselling should be voluntary and adhere to the five C’s: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services.

Mandatory or coerced testing is never appropriate, whether that coercion comes from a health care provider or from a partner or family member.

The following key principles apply to all models of HIV testing and counselling and in all circumstances.

- People receiving HIV testing and counselling must give informed consent (verbal consent is sufficient and written consent is not required) to be tested and counselled. They should be informed of the process for HIV testing and counselling and their right to decline testing.

- HIV testing and counselling services are confidential, meaning that what the HIV testing and counselling provider and the person discuss will not be disclosed to anyone else without the expressed consent of the person being tested. Although confidentiality should be respected, it should not be allowed to reinforce secrecy, stigma or shame. Counsellors should raise, among other issues, whom else the person may wish to inform and how they would like this to be done. Shared confidentiality with a partner or family members and trusted others and with health care providers is often highly beneficial.

- HIV testing and counselling services must be accompanied by appropriate and high-quality pre-test information (which can be provided as group pre-test information in some settings) and post-test counselling. Quality assurance mechanisms and supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling.

- HIV testing and counselling providers should strive to provide high-quality testing services, and quality assurance mechanisms should be in place to ensure the provision of correct test results. Quality assurance may include both internal and external measures and should include support from the national reference laboratory as needed.

- Connections to prevention, care and treatment services should include the provision of effective referral to appropriate follow-up services as indicated, including long-term prevention and treatment support.

Quality assurance of both testing and counselling is essential in all approaches used.
5.1.3 Community-based HIV testing and counselling

In addition to providing HIV testing and counselling in clinical settings, HIV testing and counselling can be offered in a variety of settings in the community.

New recommendations (2013)

- In generalized HIV epidemics, community-based HIV testing and counselling with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (strong recommendation, low-quality evidence).

- In all HIV epidemic settings, community-based HIV testing and counselling for key populations, with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (strong recommendation, low-quality evidence).

Background

These guidelines include expanded criteria for eligibility for ART for children, adolescents, adults and pregnant and breastfeeding women living with HIV. To maximize the individual and public health benefits of these recommendations, people living with HIV must be diagnosed and linked to care early in the course of HIV infection. Although facility-based testing is a key approach, people living with HIV are often identified late in the course of HIV disease in clinical settings, and some populations, including men and adolescents, and especially key populations, have low utilization of health care services. Community-based
testing approaches may reach people with HIV earlier in the course of HIV disease than provider-initiated testing and counselling, as well as reaching populations that may not normally attend health services.

The use of rapid HIV diagnostic tests using blood from a finger-prick sample taken by trained lay counsellors and community health workers has facilitated the expansion of HIV testing and counselling in community settings including homes, transport stations, religious facilities, schools, universities, workplaces and venues frequented by key populations. Continued expansion of community-based testing to complement facility-based testing is an important consideration in achieving universal knowledge of HIV status and earlier diagnosis linked to care and treatment. Community-based HIV testing and counselling includes using mobile, door-to-door, index, campaign, workplace and school-based HIV testing and counselling approaches (1).

Rationale and supporting evidence

The recommendations are based on evidence and on operational and programmatic considerations. The systematic review identified four randomized studies (3,4) and eight observational studies (5–10) comparing community-based testing to facility-based testing in generalized epidemics (Web Annex: www.who.int/hiv/pub/guidelines/arv2013/annexes). Overall, community-based approaches had increased rates of people testing for the first time and adults diagnosed with CD4 counts exceeding 350 cells/mm³. However, the frequency of positive test results was higher in health facility–based testing than in many community settings. The systematic review found that HIV testing and counselling coverage at the district level increased as a result of offering community-based HIV testing and counselling (using either door-to-door or mobile approaches) in combination with facility-based HIV testing and counselling.

An additional review covering key populations identified three studies comparing community-based testing to facility-based testing in key populations (11–13). Although increased uptake was observed in community-based approaches, the rate of participants receiving their first HIV test was comparable in both the community- and facility-based approaches.

Fifteen studies examined potential negative consequences of community-based testing (10,14–25). These studies discussed both the clients’ positive testing experiences and their fears. Eight articles reported that a minority of participants refused HIV testing and counselling because of fear of status disclosure or stigma (10,14–17,21,23,25). The studies did not demonstrate that community-based approaches either reduced stigma or fear or increased them or other harms.

The few studies comparing the cost per person tested using facility- and community-based testing found that the cost per person tested was similar in both approaches (Web Annex: www.who.int/hiv/pub/guidelines/arv2013/annexes).

Although the review provided low-quality evidence overall, there was consensus that the critical programmatic advantages of community-based HIV testing and counselling and an assessment of values, preferences, costs and feasibilities provided sufficient basis for the Guideline Development Group to propose strong recommendations.

Community-based testing should be implemented in addition to provider-initiated testing and counselling. Multiple approaches are needed, which may include stand-alone sites, home-based testing, mobile outreach (including in workplaces, schools, universities, special testing campaigns and events) and multi-disease campaigns tailored to epidemiological and social contexts.
5.1.4 HIV testing and counselling in specific populations

5.1.4.1 Couples

Background

Studies in several countries have shown that couples HIV testing and counselling is acceptable, feasible and effective. It can identify seroconcordant positive couples who can be linked to treatment and receive treatment adherence support. It also identifies couples with serodiscordant HIV test results who can benefit from HIV prevention interventions. Services should be offered to married and cohabiting couples, premarital couples, polygamous unions and any other partnerships. As with all HIV testing and counselling approaches, couples HIV testing and counselling should be voluntary. Health providers must be aware of the potential for intimate partner–based violence and should support individuals when they do not want to test with their partners. Couples HIV testing and counselling can be offered in all settings where HIV testing and counselling is provided, including antenatal care and TB services. Support to encourage the testing of the partners of people living with HIV is also an efficient and effective way of identifying additional people living with HIV, who then can benefit from treatment. Further, couples HIV testing and counselling can be an important intervention to increase access to earlier ART and reach more men with treatment. Offering family counselling and testing to couples where one or both are living with HIV can identify children, adolescents and other household members who have not previously been diagnosed.

Source for recommendations


Existing recommendations (26)

- Couples and partners should be offered voluntary HIV testing and counselling with support for mutual disclosure (strong recommendation, low-quality evidence).
- Couples and partners in antenatal care settings should be offered voluntary HIV testing and counselling with support for mutual disclosure (strong recommendation, low-quality evidence).
- Couples and partner voluntary HIV testing and counselling with support for mutual disclosure should be offered to individuals with known HIV status and their partners (strong recommendation, low-quality evidence for all people with HIV in all epidemic settings; conditional recommendation, low-quality evidence for HIV-negative people depending on the country-specific HIV prevalence).
5.1.4.2 Pregnant and postpartum women

Background

Provider-initiated testing and counselling for pregnant women and linkage to prevention and care are needed to promote the mother’s health and prevent new paediatric infections and can contribute to a strategy for couples testing.

Source for recommendations


Existing recommendations (2)

Generalized epidemics

- Provider-initiated testing and counselling is recommended for women as a routine component of the package of care in all antenatal, childbirth, postpartum and paediatric care settings.
- Re-testing is recommended in the third trimester, or during labour or shortly after delivery, because of the high risk of acquiring HIV infection during pregnancy.

Low-level and concentrated epidemics

- Provider-initiated testing and counselling should be considered for pregnant women. Many countries prioritize provider-initiated testing and counselling in antenatal care as a key component of their effort to eliminate the mother-to-child transmission of HIV and are effectively bundling HIV testing with syphilis screening, hepatitis testing or other key tests relevant to the setting as well as prioritizing the strengthening of underlying maternal and child health system.

5.1.4.3 Infants and children

Background

HIV-exposed infants and children younger than 18 months should be tested within four to six weeks of birth so that those already infected with HIV can start ART. Mortality is very high among untreated infants infected with HIV in the first year of life, making early HIV testing, prompt return of results and rapid initiation of treatment essential. In this population, HIV infection can only be definitively confirmed using virological tests because of the presence of persisting maternal HIV antibody in the child up to 15–18 months of age. Virological tests include assays to detect viral nucleic acid (HIV DNA, RNA or total nucleic acid) or p24 antigen. Currently, virological testing is most commonly performed on dried blood spot (DBS) specimens, with collection at local sites and transport and testing at centralized laboratories. While early testing is increasing, there are ongoing challenges of access, return of results and initiation of early treatment in infants testing positive. Point-of-care virological testing, in development, is expected to greatly improve early diagnosis and treatment. Because some infants are not identified as HIV-exposed or are lost to postpartum follow-up, provider-initiated
testing and counselling should be implemented in infant care settings for additional case-finding. Final diagnosis (or definitive diagnosis) at the end of the risk period for mother-to-child transmission (breastfeeding period) should be ensured. A negative HIV antibody test in a known HIV-exposed infant can be useful to exclude HIV infection if there is no ongoing exposure. (See Annex 5 for the algorithm on HIV diagnosis in children less than 18 months of age.)

For children 18 months of age and older (who are not being breastfed or who stopped breastfeeding at least six weeks earlier), standard HIV serological tests such as rapid diagnostic tests can be used to reliably determine HIV infection status. WHO recommends provider-initiated testing and counselling for all children who are malnourished, have TB, are admitted to hospital or have other signs or symptoms of HIV infection. Other approaches such as testing all children in childhood vaccination programmes have been implemented in some settings to increase chances of finding HIV-infected children. The recommendations on diagnosis of HIV infection in infants and children will be reviewed in the coming year.

<table>
<thead>
<tr>
<th>Category</th>
<th>Test required</th>
<th>Purpose</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well, HIV-exposed infant</td>
<td>Virological testing at 4–6 weeks of age</td>
<td>To diagnose HIV</td>
<td>Start ART if HIV-infected</td>
</tr>
<tr>
<td>Infant – unknown HIV exposure</td>
<td>Maternal HIV serological test or infant HIV serological test</td>
<td>To identify or confirm HIV exposure</td>
<td>Need virological test if HIV-exposed</td>
</tr>
<tr>
<td>Well, HIV-exposed infant at 9 months</td>
<td>HIV serological test (at last immunization, usually 9 months)</td>
<td>To identify infants who have persisting HIV antibody or have seroreverted</td>
<td>Those HIV seropositive need virological test and continued follow up; those HIV negative, assume uninfected, repeat testing required if still breastfeeding</td>
</tr>
<tr>
<td>Infant or child with signs and symptoms suggestive of HIV infection</td>
<td>HIV serological test</td>
<td>To confirm exposure</td>
<td>Perform virological test if &lt;18 months of age</td>
</tr>
<tr>
<td>Well or sick child seropositive &gt;9 months and &lt;18 months</td>
<td>Virological testing</td>
<td>To diagnose HIV</td>
<td>Reactive – start HIV care and ART</td>
</tr>
<tr>
<td>Infant or child who has completely discontinued breastfeeding</td>
<td>Repeat testing six weeks or more after breastfeeding cessation – usually initial HIV serological testing followed by virological testing for HIV-positive child and &lt;18 months of age</td>
<td>To exclude HIV infection after exposure ceases</td>
<td>Infected infants and children &lt;5 years of age, need to start HIV care, including ART</td>
</tr>
</tbody>
</table>

Table 5.1 Summary of recommended testing approaches for infants (27)
Source for recommendations


**Existing recommendations (27)**

- It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health care facilities at or around birth or at the first postnatal visit (usually 4–6 weeks), or other child health visit, have their HIV exposure status ascertained (**strong recommendation, high-quality evidence**).

- It is strongly recommended that all HIV-exposed infants have HIV virological testing at four to six weeks of age or at the earliest opportunity thereafter (**strong recommendation, high-quality evidence**).

- For infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. Immediate initiation of ART saves lives and should not be delayed while waiting for the results of the confirmatory test (**strong recommendation, high-quality evidence**).

- It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing (**strong recommendation, low-quality evidence**).

- It is strongly recommended that well, HIV-exposed infants undergo HIV serological testing at around nine months of age (or at the time of the last immunization visit). Infants who have reactive serological assays at nine months should have a virological test to identify HIV-infected infants who need ART (**strong recommendation, low-quality evidence**).

- It is strongly recommended that children 18 months of age or older with suspected HIV infection or HIV exposure, have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults (**strong recommendation, high-quality evidence**).

**Existing recommendation (28)**

- Children of school age should be told their HIV-positive status and their parents or caregiver’s status; younger children should be told their status incrementally to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure (**strong recommendation, low-quality evidence**).
5.1.4.4 Adolescents

Background
Adolescents are often underserved and given insufficient priority in many HIV programmes, with poor access to and uptake of HIV testing and counselling and linkage to prevention and care. Adolescents with HIV include those surviving perinatal infection and those newly acquiring infection as they become sexually active or are exposed through injecting drug use, other unsafe injections and blood transfusions. In generalized epidemic settings, many vertically infected infants are not diagnosed through programmes for PMTCT and would benefit from earlier HIV diagnosis and treatment. In many settings, adolescent girls and adolescents from key populations are also vulnerable to HIV infection and would benefit from access to acceptable and effective HIV services, including HIV testing and counselling. Consent issues may pose a barrier to access for adolescents in some settings and are discussed in detail in the WHO 2013 guidelines for adolescents (29).

Source for recommendations

New recommendations (2013) (29)
- HIV testing and counselling, with linkages to prevention, treatment and care, is recommended for adolescents from key populations in all settings (generalized, low and concentrated epidemics) (strong recommendation, very-low-quality evidence).
- HIV testing and counselling with linkage to prevention, treatment and care is recommended for all adolescents in generalized epidemics (strong recommendation, very-low-quality evidence).
- We suggest that HIV testing and counselling with linkage to prevention, treatment and care be accessible to all adolescents in low and concentrated epidemics (conditional recommendation, very-low-quality evidence).
- We suggest that adolescents be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose (conditional recommendation, very-low-quality evidence).
Rationale and supporting evidence

These recommendations were developed as part of new HIV guidelines for adolescents from WHO, UNESCO, UNFPA, UNICEF and GNP+ published in 2013 and are based on systematic reviews of the evidence, community consultations to assess values and preferences of adolescents and health providers and consideration by the respective Guideline Development Group. For the most part, published evidence for adolescent-specific recommendations is lacking; for these guidelines, considerable weight is given to expert opinion, values and preferences of adolescents and their health care providers, and to the field experience of practitioners. Further details are provided in the summary of evidence in the full Guidance on HIV testing and counselling for adolescents and care for adolescents living with HIV (29).

5.1.4.5 Key populations

Background

HIV testing and counselling has been provided to key populations since HIV tests were first developed. WHO produced guidance for testing people who inject drugs in 2006, for prisoners and refugees in 2009, for men who have sex with men and for transgender people in 2011 and for sex workers in 2012.

For key populations, especially those who are criminalized, HIV testing and counselling services are sometimes used in punitive or coercive ways. Both existing and new recommendations for HIV testing and counselling for these most-at-risk and vulnerable groups therefore emphasize consent and confidentiality as well as ensuring that HIV testing and counselling is part of a comprehensive prevention, care and treatment programme.

The 2012 WHO HIV testing and counselling strategic framework (1) summarizes HIV testing and counselling guidance for all of these groups and populations (Tables 5.2 and 5.3).

Additional guidance

Table 5.2 Summary of HIV testing and counselling recommendations for generalized epidemics

<table>
<thead>
<tr>
<th>Who to test</th>
<th>When to test</th>
<th>Where to test</th>
<th>Relevant WHO guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everyone attending health facilities</td>
<td>Integrate in all health care encounters</td>
<td>All settings, including primary health care, outpatient medical and surgical wards, antenatal care and maternal and child health, TB, family planning and sexually transmitted infection clinics</td>
<td>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</td>
</tr>
</tbody>
</table>
| Partners and couples                                   | Premarital, pregnancy, after separations, new partnerships and at the start of care and ART | Primary health care settings, voluntary counselling and testing sites, ART clinics, antenatal care, family planning clinics, sexually transmitted infection clinics, community and mobile outreach | Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)  
Delivering HIV test results and messages for re-testing and counselling in adults (32) |
| Families of index cases                                | As soon as possible after the family member is diagnosed                     | Primary health care settings, ART clinics, maternal and child health and antenatal care settings, homes and community and mobile outreach | Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)  
Planning, implementing and monitoring home-based HIV testing (33) |
| Key populations: people who inject drugs, men who have sex with men, transgender people, sex workers, prisoners, and partners of people who inject drugs | Every 6–12 months                                                            | Primary health care settings, sexually transmitted infections clinics and outreach services, including harm reduction and other sites providing services to key populations | Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (30)  
Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach (31)  
Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)  
Delivering HIV test results and messages for re-testing and counselling in adults (32) |
Table 5.2 (continued)

<table>
<thead>
<tr>
<th>Who to test</th>
<th>When to test</th>
<th>Where to test</th>
<th>Relevant WHO guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women and male partners</td>
<td>At first antenatal care visit</td>
<td>Antenatal care, delivery,</td>
<td>Guidance on provider-initiated HIV testing and counselling in health facilities (2) [Delivering HIV test results and messages for re-testing and counselling in adults (32)]  [Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)]</td>
</tr>
<tr>
<td></td>
<td>Re-test in third trimester or peripartum</td>
<td>postpartum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Offer partner testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants and children &lt;18 months</td>
<td>Early infant diagnosis at 4–6 weeks for all infants whose mothers are living</td>
<td>Maternal and child health</td>
<td>WHO recommendations on the diagnosis of HIV infection in infants and children (27)</td>
</tr>
<tr>
<td>old</td>
<td>HIV or if maternal HIV status is unknown; determine the final infant HIV     services</td>
<td>Immunization clinics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>infection status after 18 months and/or when breastfeeding ends</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Establish HIV status for all health contacts</td>
<td>Child inpatients and</td>
<td>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>outpatients, immunization</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>clinics</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>Integrate into all health care encounters</td>
<td>Primary health care,</td>
<td>Delivering HIV test results and messages for re-testing and counselling in adults (32)</td>
</tr>
<tr>
<td></td>
<td>Annually if sexually active; with new sexual partners</td>
<td>outpatients, inpatients,</td>
<td>Guidelines on HIV testing and counselling for adolescents and care and treatment for adolescents living with HIV (29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>voluntary counselling and</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>testing sites, youth-</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>friendly services, family</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>planning and sexually</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>transmitted infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>clinics</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5.3 Summary of HIV testing and counselling recommendations for low-level and concentrated epidemics

<table>
<thead>
<tr>
<th>Who to test</th>
<th>When to test</th>
<th>Where to test</th>
<th>Relevant WHO guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with signs or symptoms of HIV infection</td>
<td>Integrate in health care encounter</td>
<td>Sexually transmitted infection clinics, TB clinics, medical wards, other clinics</td>
<td>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</td>
</tr>
<tr>
<td>Partners of people with HIV</td>
<td>As soon after partner diagnosis as possible</td>
<td>Clinical settings including primary health care settings, ART, TB, sexually transmitted infection clinics, voluntary counselling and testing</td>
<td>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</td>
</tr>
<tr>
<td></td>
<td>For the negative person in serodiscordant couples, offer re-testing every 6–12 months</td>
<td></td>
<td>Delivering HIV test results and messages for re-testing and counselling in adults (32)</td>
</tr>
<tr>
<td>Families of index cases</td>
<td>As soon as possible after the family member is diagnosed</td>
<td>ART clinics, maternal and child health and antenatal care settings, homes, community outreach</td>
<td>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Planning, implementing and monitoring home-based HIV testing (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</td>
</tr>
<tr>
<td>Key populations: people who inject drugs, men who have sex with men, transgender people and sex workers</td>
<td>Every 6–12 months</td>
<td>Sexually transmitted infection clinics, outreach services for key populations and harm-reduction services</td>
<td>Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach (31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delivering HIV test results and messages for re-testing and counselling in adults (32)</td>
</tr>
</tbody>
</table>
Table 5.3 (continued)

<table>
<thead>
<tr>
<th>Who to test</th>
<th>When to test</th>
<th>Where to test</th>
<th>Relevant WHO guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>At the first antenatal care visit</td>
<td>Antenatal care</td>
<td>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</td>
</tr>
<tr>
<td>Infants and children &lt;18 months old</td>
<td>Early infant diagnosis at 4-6 weeks for all infants whose mothers are living with HIV or if maternal HIV status is unknown; determine the final infant HIV infection status after 18 months and/or when breastfeeding ends</td>
<td>Maternal and child health services</td>
<td>WHO recommendations on the diagnosis of HIV infection in infants and children (27)</td>
</tr>
<tr>
<td>Children with signs or symptoms of HIV infection or who have a family member living with HIV</td>
<td>Integrate in health care encounter</td>
<td>In all health settings</td>
<td>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</td>
</tr>
</tbody>
</table>
| Adolescents from key populations                | Every 6–12 months                                                            | Youth-friendly services, sexually transmitted infection clinics, outreach           | Delivering HIV test results and messages for re-testing and counselling in adults (32)  
Guidelines on HIV testing and counselling for adolescents and care and treatment for adolescents living with HIV (29) |
5.2 HIV prevention based on ARV drugs

5.2.1 Oral pre-exposure prophylaxis

Background

Oral pre-exposure prophylaxis of HIV (PrEP) is the daily use of ARV drugs by HIV-uninfected people to block the acquisition of HIV. Clinical trials of daily oral PrEP have shown evidence of effectiveness with serodiscordant heterosexual couples (34), men and transgender women who have sex with men (35), high risk heterosexual couples (36), people who inject drugs (37).

Source for recommendations


Existing recommendations (38)

Existing WHO recommendations (38) are for the use of oral PrEP in demonstration projects for serodiscordant couples and men and transgender women who have sex with men.

- Serodiscordant couples. When serodiscordant couples are identified and where additional HIV prevention choices for them are needed, daily oral PrEP (either TDF or the combination of TDF + FTC) may be considered as a possible additional intervention for the uninfected partner (conditional recommendation, high-quality evidence).

If oral PrEP is to be provided for the HIV-negative partner in same-sex, male serodiscordant couples, the combination of TDF + FTC should be used, as evidence of effectiveness and safety in male-to-male penetrative sex is available for this regimen only.

- Men and transgender women. Where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (specifically the combination of TDF + FTC) may be considered as a possible additional intervention (conditional recommendation, high-quality evidence).

Chapter 7 covers other aspects of ARV drugs as prevention, including PMTCT.
5.2.2 ART for prevention among serodiscordant couples

Source for recommendations

Existing recommendations (26)
- People with HIV in serodiscordant couples who start ART for their own health should be advised that ART is also recommended to reduce HIV transmission to the uninfected partner (strong recommendation, high-quality evidence).
- HIV-positive partners with a CD4 count ≥350 cells/mm³ in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence).

5.2.3 Post-exposure prophylaxis for occupational and non-occupational exposure to HIV

Background
Post-exposure prophylaxis is short-term ART to reduce the likelihood of acquiring HIV infection after potential exposure either occupationally or through sexual intercourse. Within the health sector, post-exposure prophylaxis should be provided as part of a comprehensive package of universal precautions that reduces the exposure of personnel to infectious hazards at work. WHO post-exposure prophylaxis guidelines for occupational exposure have not been reviewed since 2006 and will be updated by 2014. The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure. The choice of post-exposure prophylaxis drugs should be based on the country’s first-line ARV regimen for HIV. A recent recommendation (39) relates specifically to post-exposure prophylaxis in the case of sexual assault.

Source for recommendation

Existing recommendation (2013) (39)
- Consider HIV post-exposure prophylaxis for women presenting within 72 hours of a sexual assault. Use shared decision-making with the survivor to determine whether HIV post-exposure prophylaxis is appropriate (strong recommendation, very-low-quality evidence).
5.2.4 Combination HIV prevention

**Background**

People’s HIV prevention needs change during their lifetime, and a combination approach helps people to access the types of interventions that best suit their needs at different times. Combining approaches may also result in synergies that have greater impact than single interventions alone. Although ARV drugs play a key role in HIV prevention, they should be used in combination with an appropriate mix of the following.

- **Other biomedical interventions** that reduce HIV risk practices and/or the probability of HIV transmission per contact event, including the following.
  - **Male and female condoms.** Male condoms reduce heterosexual transmission by at least 80% and offer 64% protection in anal sex among men who have sex with men (40), if used consistently and correctly. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect (41).
  - **Needle and syringe programmes** are highly associated with a reduction in HIV transmission through injecting drug use (42).
  - **Opioid substitution therapy with methadone or buprenorphine** is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behaviour and transmission through injecting drug use. Opioid substitution therapy also provides adherence support to people on ART (43-44).
  - **Voluntary medical male circumcision** reduces the risk of acquisition of HIV for men by up to 66% and offers significant lifelong protection (45).

- **Behavioural interventions** reduce the frequency of potential transmission events, including the following.
  - **Targeted information and education.** Programmes that use various communication approaches – for example, school-based sex education, peer counselling and community-level and interpersonal counselling – to disseminate behavioural messages designed to encourage people to reduce behaviour that increases the risk of HIV and increase the behaviour that is protective (such as safer drug use, delaying sexual debut, reducing the frequency of unprotected sex with multiple partners, using male and female condoms correctly and consistently and knowing your and your partner’s HIV status).

- **Structural and supportive interventions** affect access to, uptake of and adherence to behavioural and biomedical interventions. Such interventions address the critical social, legal, political and environmental enablers that contribute to HIV transmission, including legal and policy reform, measures to reduce stigma and discrimination, the promotion of gender equality and prevention of gender-based violence, economic empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.
Goal of this chapter

To provide an overview of issues and interventions related to general HIV care for individuals from the time that they are diagnosed with HIV infection to the time that they are initiated on ART, including practices for linking people diagnosed with HIV infection to HIV care and treatment, the components of a general care package, and preparing individuals for starting ART.
6. CLINICAL GUIDELINES ACROSS THE CONTINUUM OF CARE: LINKING PEOPLE DIAGNOSED WITH HIV INFECTION TO HIV CARE AND TREATMENT

6.1 Introduction

It is critical for people living with HIV to enrol in care as early as possible. This enables both early assessment of their eligibility for ART and timely initiation of ART as well as access to interventions to prevent the further transmission of HIV, prevent other infections and comorbidities and thereby to minimize loss to follow-up. The 2012 WHO strategic HIV testing and counselling programme framework (1) especially emphasizes the importance of ensuring linkage between HIV testing and counselling programmes and prevention, treatment, care and support services.

6.2 Good practices for linkage to care

Interventions to improve linkage to care need to be more rigorously evaluated. However, several systematic reviews and observational studies suggest that several good practices can improve linkage to care (2–4). These include integrating HIV testing and counselling and care services; providing on-site or immediate CD4 testing with same-day results; assisting with transport if the ART site is far from the HIV testing and counselling site; involving community outreach workers to identify the people lost to follow-up; ensuring support from peers or expert patients; and using new technologies, such as mobile phone text messaging.

6.3 General care for people living with HIV

Countries should establish a package of general HIV care interventions, in addition to ART, for people living with HIV to reduce HIV transmission, prevent illness and improve their quality of life. Not all people living with HIV are eligible for ART and, of those eligible, not all will be able to access ART immediately. Others may choose to defer ART to later. Enrolment in care provides an opportunity for close clinical and laboratory monitoring and early assessment of eligibility for ART and timely initiation, and aims to minimize loss to follow-up. Many care interventions are relevant across the full continuum of care, including HIV-exposed individuals and people living with HIV before initiating, and during ART.

General care includes basic HIV prevention, promoting the health of people living with HIV and the screening, prophylaxis and management of HIV-related co-infections and comorbidities. WHO has produced summary guidance on general care and prevention interventions (5–7), and in 2008, recommended a package of 13 prevention interventions for adults and adolescents living with HIV in resource-limited settings (5). These include (1) psychosocial counselling and support; (2) disclosure and partner notification; (3) co-trimoxazole preventative therapy (CPT); (4) TB counselling, screening and preventive therapy; (5) preventing common fungal infections; (6) preventing sexually transmitted infections and supporting reproductive health needs, including prevention of and screening for cervical cancer; (7) malaria (co-trimoxazole, bed-nets and preventing malaria among pregnant women); (8) selected vaccine-preventable diseases; (9) nutrition; (10) family planning; (11) PMTCT; (12) needle and syringe programmes for people
who inject drugs; and (13) water, sanitation and hygiene.

A general care package will vary according to the epidemic type, populations affected and prevalence of coinfections, other comorbidities and health conditions. Table 6.1 provides an overview of elements of a general care package for people living with HIV. Section 8.1 summarizes key recommendations from existing WHO guidelines on the screening, prophylaxis and timing of ART with the most common coinfections, comorbid conditions and other health conditions.

Table 6.1 Overview of key elements of general care over the continuum of HIV care for people living with HIV

<table>
<thead>
<tr>
<th>Service</th>
<th>At HIV diagnosis</th>
<th>At enrolment into care</th>
<th>At initiation of ART</th>
<th>Stable while receiving ART</th>
<th>At treatment failure and switching ARV regimen</th>
<th>Comment and cross-references</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO clinical staging</td>
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<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Past and current HIV-related conditions</td>
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<td>Pregnancy status</td>
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</tr>
<tr>
<td>Family planning and Contraception</td>
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<td></td>
<td></td>
<td>Sections 7.1.2 and 7.2.2</td>
</tr>
<tr>
<td>PMTCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support for disclosure and partner notification</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Section 5.1.4</td>
</tr>
<tr>
<td>Risk reduction counselling and combination HIV prevention approaches</td>
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<td>✓</td>
<td>✓</td>
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<td>Section 5.2.4</td>
</tr>
<tr>
<td>Screening for, preventing and managing comorbidities and noncommunicable diseases</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Section 8.2.1</td>
</tr>
<tr>
<td>Screening for and managing mental health problems and substance use</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Sections 8.2.2 and 8.2.3</td>
</tr>
</tbody>
</table>
Table 6.1 (continued)

<table>
<thead>
<tr>
<th>Service</th>
<th>At HIV diagnosis</th>
<th>At enrolment into care</th>
<th>At initiation of ART</th>
<th>Stable while receiving ART</th>
<th>At treatment failure and switching ARV regimen</th>
<th>Comment and cross-references</th>
</tr>
</thead>
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<tr>
<td><strong>General care</strong></td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Section 8.2.5</td>
</tr>
<tr>
<td>Managing pain and symptoms</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
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<td></td>
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<tr>
<td>Nutritional assessment and counselling</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Section 8.2.4</td>
</tr>
<tr>
<td>Nutritional, growth and development assessment in children and adolescents</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Sections 7.1.3 and 8.2.4</td>
</tr>
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<td>Infant and child feeding</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Preventing and treating coinfections</strong></td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Intensified TB case-finding</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td></td>
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</tr>
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<td></td>
<td></td>
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<tr>
<td>Screening for hepatitis B and C</td>
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<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Section 8.1.4</td>
</tr>
<tr>
<td>Malaria prevention (insecticide-treated bed-nets and prophylaxis)</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td></td>
<td>Section 8.1.5</td>
</tr>
<tr>
<td>Screening for sexually transmitted infections</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Section 8.1.6</td>
</tr>
<tr>
<td>Prevention of and screening for cervical cancer</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Section 8.1.7</td>
</tr>
</tbody>
</table>
6.4 Preparing people living with HIV for ART

Before people start ART, it is important to have a detailed discussion with them about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits. For children with HIV, this conversation should directly involve the carer and include discussion about disclosing their HIV status (see Chapter 5). Retesting all people living with HIV before initiating ART is good practice to ensure correct diagnosis of HIV infection. Initiation of ART should always consider nutritional status, any comorbidities and potentially interacting medications for possible contraindications or dose adjustment.

The choice to accept or decline ART ultimately lies with the individual person or his or her caretaker, and if they choose to defer initiation, ART can be offered again at subsequent visits. If there are mental health, substance use or other problems that are major barriers to adherence, appropriate support should be provided, and readiness to initiate ART should be reassessed at regular intervals. A wide range of patient information materials as well as community and peer support can help the person’s readiness and decision to start therapy.

People starting treatment and carers should understand that the first ARV regimen offers the best opportunity for effective virological suppression and immune recovery, and that successful ART requires them to take the medications exactly as prescribed. They should be advised that many adverse effects are temporary or may be treated, or that substitutions can often be made for problematic ARV drugs. (See section 9.2 for strategies to support adherence to an ARV regimen). People receiving ART and carers should also be asked regularly about any other medications that are taken, including herbal remedies and nutritional supplements.

People receiving ART should understand that, while the ARV drugs reduce the risk of HIV transmission, they cannot be relied on to prevent other people from acquiring infection. They should be given advice on safer sex (including condom use) and avoidance of other high-risk activities, such as sharing of injecting equipment, to prevent transmitting HIV to other people.
6.5 What to expect in the first months of ART

Although taking ART is a lifelong commitment, the first six months of therapy are especially important. Clinical and immunological improvement and virological suppression are expected when individuals adhere to ART, but opportunistic infections and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of ART. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are commonest when the people starting ART already have advanced HIV disease with severe immunodeficiency and existing coinfections and/or comorbidities, severely low haemoglobin, low body mass index and very low CD4 counts or are severely malnourished (8,9).

CD4 recovery

In most adults and children, CD4 cell counts rise when ART is initiated and immune recovery starts. Generally, this increase occurs during the first year of treatment, plateaus, and then continues to rise further during the second year (10). However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count when initiating ART. Failure to achieve some CD4 recovery should alert the health care provider to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for opportunistic infections such as co-trimoxazole preventive therapy.

Immune reconstitution inflammatory syndrome (IRIS)

IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART. It is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy (11,12). It may present in two different ways: paradoxical IRIS, when an opportunistic infection or tumour diagnosed before ART initially responds to treatment but then deteriorates after ART starts; or unmasking IRIS, in which initiating ART triggers disease that is not clinically apparent before ART. It should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity.

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumours and non-infectious conditions (11,12). The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposis’s sarcoma and herpes zoster. BCG vaccine–associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is routine. A low CD4+ cell count (<50 cells/mm³) at ART initiation, disseminated opportunistic infections or tumours and a shorter duration of therapy for opportunistic infections before ART starts are the main risk factors (11,12). IRIS is generally self-limiting, and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of or poor adherence to ART.

The most important steps to reduce the development of IRIS include: earlier HIV diagnosis and initiation of ART before a decline to below 200 CD4 cells/mm³; improved screening for opportunistic infections before ART, especially TB and Cryptococcus; and optimal management of opportunistic infections before initiating ART. Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed. Chapter 8 summarizes existing WHO recommendations for the optimal timing of ART among people with TB (see section 8.1.2) and cryptococcal disease (see section 8.1.3) based on evidence from randomized clinical trials.
Goal of this chapter

To provide updated, evidence-based clinical recommendations outlining a public health approach to ART in the context of the continuum of HIV care, with a focus on resource and capacity limited settings.
7. CLINICAL GUIDANCE ACROSS THE CONTINUUM OF CARE:
ANTIRETROVIRAL THERAPY

7.1 When to start ART

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. The 2013 Guidelines Development Group recommends that national HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm³ or less, giving priority to initiating ART among those with severe/advanced HIV disease (see Annex 1) or a CD4 count of 350 cells/mm³ or less. It is also recommended to initiate ART in people with active TB disease and HBV coinfection with severe chronic liver disease, all pregnant and breastfeeding women with HIV, all children younger than five years living with HIV and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count (Table 7.1).

Table 7.1 Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Adults and adolescents (≥10 years) | Initiate ART if CD4 cell count ≤500 cells/mm³  
• As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³ |
|                                 | Initiate ART regardless of WHO clinical stage or CD4 cell count  
• Active TB disease  
• HBV coinfection with severe chronic liver disease  
• Pregnant and breastfeeding women with HIV  
• HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk) |
| Children ≥5 years old            | Initiate ART if CD4 cell count ≤500 cells/mm³  
• As a priority, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³ |
|                                 | Initiate ART regardless of CD4 cell count  
• WHO clinical stage 3 or 4  
• Active TB disease |
| Children 1–5 years old⁺         | Initiate ART in all regardless of WHO clinical stage or CD4 cell count  
• As a priority, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count ≤750 cells/mm³ or <25%, whichever is lower |
| Infants <1 year old⁺            | Initiate ART in all infants regardless of WHO clinical stage or CD4 cell count |

⁺ Initiate ART in all HIV-exposed children below 18 months of age with presumptive clinical diagnosis of HIV infection.
7.1.1 When to start ART in adults and adolescents

New recommendations

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).

- ART should be initiated in all individuals with HIV with a CD4 count >350 cells and ≤500/mm³ regardless of WHO clinical stage (strong recommendation, moderate-quality evidence).a

- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:
  - Individuals with HIV and active TB disease (strong recommendation, low-quality evidence).
  - Individuals coinfected with HIV and HBV with evidence of severe chronic liver diseaseb (strong recommendation, low-quality evidence).
  - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence).
  - Pregnant and breastfeeding women with HIV (see section 7.1.2 for recommendations).

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a There is insufficient evidence and/or favourable risk–benefit profile to support initiating ART at a CD4 cell count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage in the following situations: individuals with HIV older than 50 years, individuals with HIV-1 infected or coinfected with HIV-2, individuals with HIV coinfected with HCV and key populations with HIV with a high risk of transmission (such as people who inject drugs, men who have sex with men, transgender people and sex workers). ART initiation in these populations should therefore follow the same principles and recommendations as for other adults with HIV.

b There is insufficient evidence and/or favourable risk-benefit profile to support initiating ART in everyone coinfected with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is therefore recommended among people with evidence of severe chronic liver disease, who are at greatest risk of progression of liver disease and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.
Background

Since 2002, WHO guidelines on ART have evolved as the body of evidence to support the earlier initiation of ART has progressively increased (1). The 2010 WHO guidelines for adults and adolescents (2) recommended initiating ART for all individuals (including pregnant women) with a CD4 count ≤350 cells/mm³ regardless of WHO clinical stage and for those with severe or advanced HIV disease (WHO clinical stages 3 or 4) regardless of CD4 count. This strong recommendation was based on moderate-quality evidence from randomized controlled trials (3,4) and observational studies (5–8) showing that initiating ART at or below this CD4 threshold reduced mortality, disease progression (including TB), vertical HIV transmission and serious adverse events. Mathematical modelling simulations also suggested that initiating ART earlier could impact on both sexual and vertical HIV transmission if there is high treatment coverage and full adherence (9). For people with active TB disease or HBV coinfection requiring HBV treatment, the 2010 guidelines (2) recommended initiating ART regardless of CD4 cell count.

Global ART coverage for those eligible according to the 2010 recommendations (CD4 ≤350 cells/mm³) had reached 54% – or more than 8 million people – by the end of 2011 (10), but coverage varies across regions, ranging from 15% to 68% (11). Only 9 low-and middle-income countries have reported coverage exceeding 80%, and 68 countries have reported coverage of less than 50%. Nevertheless, policy changes in countries have been significant. A recent survey in 92 countries (Web Annex www.who.int/hiv/pub/guidelines/arv2013/...
annexes) showed that more than 90% had adopted the CD4 threshold for initiating ART of 350 cells/mm³ or less, and several other countries have moved their CD4 threshold above 350 cells/mm³. The median CD4 count at the time ART is initiated, although increasing, has been far lower than 350 cells/mm³ in almost all settings, including high-income countries (12,13), and late presentation for treatment is associated with high early mortality rates and poor retention in care (6,14). Increasing knowledge of HIV status, strengthening links between testing and care and ensuring optimal long-term retention and adherence remain significant challenges in many settings.

**Rationale and supporting evidence**

Since 2010, evidence and programmatic experience have continued to shift the risk-benefit ratio towards initiating ART earlier. Increasing evidence also indicates that untreated HIV may be associated with the development of several non-AIDS-defining conditions (including cardiovascular disease, kidney disease, liver disease, several types of cancer and neurocognitive disorders) (15–17) and that initiating ART earlier reduces such events and improves survival. Recent evidence (18) also show that ART substantially reduces sexual transmission in HIV-serodiscordant couples, but not all studies have reported survival benefits. At the same time, more convenient and less toxic regimens have become more widely available, and ARV costs have continued to fall. How early ART should be started is still debated, and the Guidelines Development Group paid close attention to evaluating the potential benefits and harms to the individual and community in developing these new recommendations.

**Initiating ART in individuals with symptomatic and asymptomatic HIV disease at a CD4 count ≤350 cells/mm³ as a priority**

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 counts. The 2013 Guidelines Development Group did not change the strength and quality of evidence for this recommendation established in the 2010 ART guidelines (2). Moderate-quality evidence from two randomized controlled trials and several observational studies shows that initiating ART at CD4 ≤350 cells/mm³ significantly reduces mortality, disease progression and the incidence of opportunistic diseases, especially TB and non-AIDS-defining conditions (2).

**Initiating ART at a CD4 count between 350 and 500 cells/mm³**

The risk-benefit analysis of the rationale for ART initiation between 350 and 500 CD4 cells/mm³ in these guidelines was debated. The Guidelines Development Group agreed that impact on HIV transmission is strongly supported by the evidence. The quality of evidence for clinical benefit of earlier ART initiation was rated as moderate using the GRADE system, as it mostly relies on observational data mainly from high-income countries. The Guidelines Development Group strongly recommended earlier ART as a public health approach. In settings where feasibility of implementation is a concern, the Guidelines Development Group suggested conducting operational research during implementation to assess context-specific factors such as feasibility, linkage to and retention in care, adherence and resource allocation.
The recommendation for initiating ART at CD4 counts between 350 and 500 cells/mm³ is based on a systematic review with GRADE evidence profiles (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) that assessed the quality and strength of the evidence from 21 observational studies (8,19–39) and three randomized controlled trials (3,18,40) reporting morbidity, mortality and immunological and virological outcomes. They showed that initiating ART at a CD4 count >350 cells/mm³ compared with treatment at a CD4 count ≤350 cells/mm³ reduced the risk of progression to AIDS and/or death, TB, development of a non-AIDS-defining illness and increased the likelihood of immune recovery. Although no studies suggest that earlier ART causes individual harm, these studies were of limited duration.

The pooled analysis of the observational studies found a consistent decreased risk of death with earlier initiation of ART in 13 studies (21–23,26,29–31,34–39) and a decreased risk of progression to AIDS or death in 9 studies (21,23,26,27,30,33,34,36,39) and 3 randomized controlled trials (3,18,40), with a low level of heterogeneity, supporting moderate-quality evidence for earlier treatment. A further subgroup analysis showed a reduced risk of mortality with a CD4 threshold for initiating ART of 500 cell/mm³. The impact on immune recovery was inconsistent and rated as low- to very-low-quality evidence (20,24,28). Two studies found no significant difference in the likelihood of virological failure and viral rebound when treatment is initiated at higher or lower CD4 cell counts (20,36).

In the pooled analysis of two randomized controlled trials (3,18) there was low-quality evidence supporting ART initiation at higher CD4 thresholds for reducing mortality, disease progression or the combined outcome of death and/or progression and, in one trial, the risk of non-AIDS-defining illnesses. The risk of severe adverse events did not differ significantly, but the risk of Grade 3 or 4 laboratory abnormalitieswas increased in one randomized controlled trial (40). Since treatment in the delayed arm of the SMART trial (3) was initiated when the CD4 count fell below 250 cells/mm³ (rather than 350 cells/mm³), the quality of the evidence for clinical benefit was graded as low because of imprecision and indirectness.

A separate systematic review (41) identified one randomized clinical trial (18) and two observational studies (42,43) reporting a decreased risk of TB when individuals initiated ART with CD4 counts exceeding 350 cells/mm³. ART also reduces recurrent TB by about 50% (44). Dynamic models have suggested ART initiation above 350 cells/mm³ could lead to a more substantial reduction in population tuberculosis incidence (45).

Finally, there is high-quality evidence from one randomized controlled trial (18) indicating that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners. This is supported by the secondary outcomes of a trial that also found a 92% reduction in HIV sexual transmission from partners with HIV taking ART (46).

Cost and cost–effectiveness

The Guidelines Development Group reviewed mathematical simulations of the costs and epidemiological benefits of initiating ART at a CD4 count ≤350 cells/mm³, CD4 count ≤500 cells/mm³ and for all adults with HIV regardless of CD4 cell count. These models suggest that expanding the ART eligibility criteria to ≤500 cells/mm³ could lead to substantial health benefits and be cost-effective in both generalized and concentrated epidemic settings; the increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing

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ii Grade 3 and 4 laboratory abnormalities are considered as severe drug adverse reactions and usually requires discontinuation of ARV drugs until the patient is stabilized and substitution for an alternative drug (See Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes)
new HIV infections (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). However, these benefits depend on a high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The models also show that, because the greatest costs are associated with full implementation of the 2010 ART guidelines (2) (initiating ART at CD4 count ≤350 cells/mm$^3$), the incremental cost of moving the ART initiation criterion from a CD4 count ≤350 cells/mm$^3$ to ≤500 cells/mm$^3$ is relatively small, especially if countries already have a substantial number of people with HIV with a CD4 cell count less than 350 cells/mm$^3$ already receiving ART. These modelling findings support the recommendation to initiate ART in adults and adolescents with HIV with a CD4 count ≤350 cells/mm$^3$ as a priority. However, the cost implications at the regional and country levels should be explored further, since countries have different levels of treatment coverage and local cost considerations depending on their context and resources.

**Potential harms**

Not all observational studies have consistently demonstrated the beneficial impact of initiating ART earlier on mortality and the incidence of non-AIDS events associated with chronic inflammation and ongoing viral replication, and longer follow-up is needed to evaluate potential harms and benefits. The long-term safety profile of ART and the implications of earlier initiation on drug resistance and toxicity will also need to be closely monitored.

**Feasibility**

According to cohort and national programme data, the number of people needing treatment could increase by up to 25% if eligibility is based on CD4 counts increasing from ≤350 cells/mm$^3$ to ≤500 cells/mm$^3$ (47,48) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). However, country experience has also shown that moving to a higher CD4 threshold for ART initiation may not necessarily lead to a significant immediate increase in the numbers of people who actually access treatment in the absence of increased uptake of HIV testing and counselling, stronger linkages to care, adequate treatment monitoring and sustained adherence support.

Implementing the recommendation to initiate ART in individuals with HIV with CD4 counts between 350 and 500 cells/mm$^3$ may involve additional human, infrastructure and financial resources. Chapter 10 discusses these issues in further detail.

**Initiating ART regardless of CD4 cell count**

**HIV-positive partners in HIV-serodiscordant couples**

The results of the HPTN052 study (18) strongly support the use of ART to prevent HIV transmission among HIV-serodiscordant couples. The Guidelines Development Group therefore endorsed the recommendations established in the 2012 WHO guidance on HIV testing and counselling including ART for treatment and prevention in serodiscordant couples (49) that the sexual partner with HIV in such a couple should be offered ART regardless of CD4 count.

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*An HIV-serodiscordant couple is a couple in which one of the sexual partners is HIV-positive and one is HIV-negative. Although one partner is currently HIV-negative, this does not mean that this partner is immunized or protected against getting HIV in the future.*
Treating active TB disease

In 2010, WHO recommended starting ART in all people with HIV and active TB regardless of CD4 cell count, and that TB treatment should be started first, followed by ART, as soon as possible afterwards (and within the first eight weeks). The Guidelines Development Group reviewed evidence from three randomized clinical trials that showed for people with TB and severe immunodeficiency (CD4 count ≤ 50 cells/mm³), starting ART before eight weeks has a clinical benefit compared with deferring treatment to later than eight weeks (50–52), and endorsed the 2010 recommendations. Implementation of the recommendations on HIV and TB management may be facilitated by integration of services (Chapter 9).

HIV and HBV coinfection with evidence of severe chronic liver disease

HIV coinfection affects almost every aspect of the natural history of HBV infection. The consequences include higher rates of chronicity; less spontaneous HBV clearance; accelerated liver fibrosis progression with increased risk of cirrhosis and hepatocellular carcinoma; higher liver-related mortality and decreased ARV response (53–56). Liver disease has emerged as a leading cause of death in people coinfected with HIV and HBV (57,58).

The 2010 WHO ART guidelines (2) recommended initiating ART among all individuals coinfected with HIV and HBV who require treatment for their HBV infection (defined as chronic active hepatitis), regardless of CD4 cell count or WHO clinical stage. However, in the absence of routine screening for HBV, most people are unaware of their HBV status. In addition, there is limited access to costly diagnostic tools for staging liver disease (liver biopsy, transient elastography, HBV-DNA and serum biomarkers) needed to establish the presence of chronic active liver disease and eligibility for HBV treatment.

A meta-analysis (59) and a subgroup analysis of a randomized controlled trial (60) provide low-quality evidence of the overall impact of ART on liver-related morbidity and mortality among individuals coinfected with HIV and HBV, but these studies did not examine the benefit of initiating ART at higher CD4 counts.

Overall, the Guidelines Development Group considered that there was not sufficient evidence and/or a favourable risk–benefit profile to support initiating ART among all people coinfected with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 count or stage of liver disease. There are also risks associated with initiating ART earlier (hepatotoxicity, immune reconstitution inflammatory syndrome and hepatic flares).

However, the Guidelines Development Group does recommend providing ART to all people coinfected with HIV and HBV regardless of CD4 count in people with evidence of severe chronic liver disease, who are at greatest risk of liver disease progression and mortality. The term severe chronic liver disease was used instead of chronic active hepatitis (as in the 2010 guidelines), as this is a term that is more widely understood and applicable using clinical criteria alone. In settings where ART cannot be provided to all individuals with HIV with CD4 counts ≤ 500 cells/mm³, giving priority to diagnosing and treating individuals coinfected with HIV and HBV should be considered.

As reported in the 2010 WHO ART guidelines (2), data from one randomized controlled trial support the use of at least two agents with activity against HBV (TDF + 3TC or FTC) in terms of improved viral load response and reduced development of HBV drug resistance (61,62).

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* Active TB disease refers to TB infection where the person has symptoms and clinical disease. Latent TB infection refers to TB infection where the person does not have symptoms or clinical disease. Not all persons with latent TB infection will develop TB disease, but the risk of progressing to disease is very high in people with HIV.

* Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).
Critical research gaps in this area include the need for more data on the impact of ART on liver-related outcomes in HBV-coinfected people in resource-limited settings and on the relative impact of ART in people with CD4 cell counts >500 cells/mm³ and early-stage liver disease.

**Populations for which no specific new recommendation is made**

The Guidelines Development Group did not find evidence and/or favourable risk–benefit profiles to support recommendations for initiating ART at CD4 cell count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage in the following populations.

**Individuals with HIV who are 50 years of age and older**

A pooled analysis of data from 13 cohorts from Europe and North America showed increased risk of death and disease progression in people with HIV older than 50 years of age (26). However, these data were not stratified by CD4 cell count and do not support initiating ART at CD4 counts > 500 cells/mm³ for this group.

**Individuals with HIV-2**

The lack of randomized treatment studies in individuals with HIV-2 makes it difficult to determine the optimal timing of ART initiation in this population. A systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) evaluated observational data from 15 studies and showed no significant differences between initiating ART at a CD4 count ≤350 cells/mm³ and >350 cells/mm³, considering the outcomes of mortality, disease progression, increase in CD4 cell count, virological response and risk of drug resistance. The quality of evidence was rated as low to very low, with serious risk of bias and imprecision (few events) for all these outcomes.

**Individuals coinfected with HIV and HCV**

Observational studies have shown that coinfection with HIV and HCV accelerates HCV-related progression of liver fibrosis and leads to a higher rate of end-stage liver disease (63) and mortality (63–65).

There is consistent but low-quality observational data about the overall benefit of ART on mortality and progression of liver disease in individuals coinfected with HIV and HCV based on evidence from a meta-analysis (66), and a review of nine cohort studies that examined the relationship between ART and hepatic fibrosis showing that ART was associated with a decreased rate of liver fibrosis progression, although this was not evaluated by the level of CD4 count (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The Guidelines Development Group endorsed the special note in the 2010 guidelines (2) that initiating ART among people coinfected with HCV should follow the same principles as in HIV mono-infection. Initiating ART regardless of CD4 cell count was not recommended because of lack of evidence.

There are challenges in diagnosing and treating active HCV infection in settings with limited access to HCV antibody and RNA assays, diagnostic tools for staging of liver disease (such as biopsy) and HCV therapy and in certain populations such as people who inject drugs. However, limited access to HCV testing or treatment and/or high rates of HCV infection should not be barriers to initiating ART.

WHO hepatitis guidelines forthcoming in 2014 will provide detailed guidance on HCV screening, treatment and care. People coinfected with HIV and HCV receiving ART and HCV drugs require close monitoring because of potential drug interactions and increased risk for drug toxicity between HCV drugs (such as interferon, ribavirin and newer directly acting agents) and ARV drugs.
Key populations

The scale-up of ARV drugs for preventing HIV infection or reducing HIV incidence in key populations has been evaluated in community-wide and ecological studies and mathematical models (67–79). Some of these studies showed a reduction in the community viral load, with and without an associated decline in HIV incidence, invariably where ART coverage is high or access to ART is expanding rapidly. However, the Guidelines Development Group concluded that there is insufficient evidence to recommend earlier initiation of ART in key populations regardless of CD4 cell count. The initiation of ART in key populations should follow the same general principles and recommendations as in other adults and adolescents with HIV.

Clinical considerations

Section 10.6 (Checklist 10.3) discusses implementation considerations for moving the CD4 threshold from 350 cells/mm$^3$ to 500 cells/mm$^3$ of relevance to programme managers.

Key research gaps

Further research is required to determine more fully the clinical benefits and disadvantages of earlier ART initiation. Two large randomized trials are examining the optimal timing for initiating ART, with results expected in 2014 to 2015. The Strategic Timing of Antiretroviral Therapy (START) trial in ARV-naive adults aged 18 years and older is comparing immediate ART in those with CD4 cell counts above 500 cells/mm$^3$ to ART deferred until the CD4 count falls below 350 cells/mm$^3$ or an AIDS event develops (80). The TEMPRANO trial (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis against Tuberculosis in HIV-infected Adults – ANRS 12136) is comparing the benefits and risks of initiating ART according to the 2010 WHO guidelines ($\leq$350 cells/mm$^3$) (2) to the benefits and risks of initiating ART immediately among adults with CD4 counts $>$350 cells/mm$^3$ in Côte d’Ivoire (81). These studies will inform future WHO recommendations.

Other research priorities include assessing the incidence of severe adverse events as a result of increased exposure to ART and assessing ART acceptability, uptake, adherence and long-term retention in care for people who initiate ART at higher CD4 counts, and the magnitude of the prevention benefit of immediately initiating ART in key populations.

7.1.2 When to start ART in pregnant and breastfeeding women

New recommendations

- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (strong recommendation, moderate-quality evidence).
- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (conditional recommendation, low-quality evidence).
- In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased (conditional recommendation, low-quality evidence).
Table 7.3 Programme options for ART for PMTCT

<table>
<thead>
<tr>
<th>National PMTCT programme option</th>
<th>Pregnant and breastfeeding women with HIV</th>
<th>HIV-exposed infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use lifelong ART for all pregnant and breastfeeding women (&quot;Option B+&quot;)</td>
<td>Regardless of WHO clinical stage or CD4 cell count</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td></td>
<td>Initiate ART and maintain after delivery and cessation of breastfeeding</td>
<td>6 weeks of infant prophylaxis with once-daily NVP</td>
</tr>
<tr>
<td>Use lifelong ART only for pregnant and breastfeeding women eligible for treatment (&quot;Option B&quot;)</td>
<td>Eligible for treatment(^a)</td>
<td>Not eligible for treatment(^a)</td>
</tr>
<tr>
<td></td>
<td>Initiate ART and maintain after delivery and cessation of breastfeeding (^b)</td>
<td>Initiate ART and stop after delivery and cessation of breastfeeding (^b) (^c)</td>
</tr>
</tbody>
</table>

\(^a\) CD4 count ≤500 cells/mm\(^3\) or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

\(^b\) Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

\(^c\) In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery.

Background

ARV drugs are used for pregnant and breastfeeding women with HIV primarily for the mother’s health and to prevent the exposed child from becoming infected. It may also offer benefits for preventing the sexual transmission of HIV. The 2010 WHO PMTCT guidelines (82) recommended lifelong ART for women eligible for treatment (based on the 2010 eligibility criteria of CD4 counts ≤350 cells/mm\(^3\) or presence of WHO clinical stage 3 or 4 disease) and ARV prophylaxis for PMTCT for women with HIV not eligible for treatment. For those not eligible for treatment, two prophylaxis regimens were recommended: “Option A”, AZT for the mother during pregnancy, single-dose NVP (sd-NVP) plus AZT and 3TC for the mother at delivery and continued for a week postpartum; and “Option B”, triple ARV drugs for the mother during pregnancy and throughout breastfeeding. Prophylaxis was recommended to start as early as 14 weeks of gestation, and both prophylaxis options included four to six weeks of peripartum NVP or AZT for the infant, regardless of whether the mother was breastfeeding. Countries were advised to choose a national approach for their ARV option for PMTCT based on operational considerations.

To accelerate the rapid global scaling up of ART and PMTCT in resource-limited settings, ensure equitable access to ART for pregnant women and achieve the global goal of eliminating new paediatric infections and keeping mothers alive (83), recommendations need to be further simplified, standardized and harmonized. In 2011, Malawi implemented a new approach of lifelong ART for all pregnant and breastfeeding women with HIV regardless of CD4 count or clinical stage, commonly referred to as “Option B+” (84–86). WHO issued a programmatic update in April 2012 (87) outlining some of the operational advantages of Option B and the emerging strategy of Option B+. 
These 2013 guidelines recommend ART (one simplified triple regimen) for all pregnant and breastfeeding women with HIV during the period of risk of mother-to-child HIV transmission and continuing lifelong ART either for all women or for the women meeting eligibility criteria for their own health. Option A is no longer recommended.

**Rationale and supporting evidence**

**Advantages of a standardized ARV regimen for all pregnant and breastfeeding women with HIV**

Although available data continue to show that the Option A and B prophylaxis regimens have similar efficacy in clinical trial settings (88–92), the complexities of Option A have been an impediment to scaling up PMTCT in many countries. These complexities include different treatment and prophylaxis regimens; the requirement for CD4 measurement to determine treatment eligibility and type of regimen; changing antepartum-intrapartum-postpartum regimens; the need for an additional postpartum ARV “tail” in mothers; and extended NVP prophylaxis in infants.

By contrast, providing an optimized, fixed-dose combination first-line ARV regimen of TDF + 3TC (or FTC) + EFV (see section 7.2.2) to all pregnant and breastfeeding women with HIV provides important programmatic and clinical benefits, including the following.

- **Ease of implementation.** The same simplified ARV regimen is administered to all pregnant women (regardless of “eligibility” for treatment) and continued during pregnancy and labour and postpartum.
- **Harmonized regimens.** The optimized first-line fixed-dose combination regimen can be harmonized with guidelines for ART in non-pregnant adults.
- **Increased coverage of ART.** This ensures that immunocompromised women who do not have access to CD4 testing receive appropriate ART without delay.
  - **Vertical transmission benefit.** Provides coverage with ART to maximize the prevention of infant infections.
  - **Maternal health benefit.** Will delay disease progression over the course of treatment (93).
- **Acceptability.** Reviews conducted for these guidelines generally indicated strong community preference and acceptability for this approach.
- **Sexual prevention benefit.** ART will reduce sexual transmission of HIV to sexual partners (18).

The Guidelines Development Group also considered the overall evidence from the systematic review of 21 observational studies (19–39) and three randomized controlled trials (3,18,40) used in the evaluation of when to start ART in adults (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes; see section 7.1.1). The recommendation to increase the use of ART in pregnant and breastfeeding women is made with the understanding that there are limited ARV drug options in resource-limited countries. It also recognizes the need to balance the benefits of starting ART in pregnant and breastfeeding women with the possible risks of ARV drug toxicity to the mother and fetus and infant during pregnancy and breastfeeding. Other issues the Guidelines Development Group considered included costs; cost–effectiveness and health system burden (94,95); issues related to adherence and retention (96), HIV drug resistance, ART failure and the availability of future treatment options; and ensuring treatment access for all people who meet current guidelines on eligibility for treatment.
Lifelong ART versus stopping ART after the risk of mother-to-child HIV transmission ends

The recommendation to provide lifelong ART to all pregnant and breastfeeding women with HIV or to continue ART only for those meeting treatment eligibility criteria for the woman’s health is conditional, based on the epidemic setting and country programme, and because of the lack of conclusive evidence on the impact and efficacy of fully implementing lifelong ART for all pregnant and breastfeeding women.

In generalized epidemic settings and in settings with limited access to CD4 testing, limited partner testing, long duration of breastfeeding or high rates of fertility, the benefits of lifelong ART for all pregnant and breastfeeding women with HIV are clear. It will assure maximum coverage for those needing treatment for their own health, avoid stopping and starting drugs with repeat pregnancies, provide early protection against mother-to-child transmission in future pregnancies, reduce the risk of HIV transmission to HIV-serodiscordant partners and improve maternal health. With the new treatment eligibility threshold of CD4 ≤500 cells/mm³, approximately 60% of HIV-infected pregnant women will meet treatment eligibility criteria for their own health (97). Although not well quantified, it is likely that at least an additional 10–20% of women would become eligible for treatment over the subsequent two years after birth.

In countries with concentrated epidemics that have high access to CD4 testing, adequate capacity to provide ART to the pregnant and breastfeeding women eligible for treatment, low fertility rates and/or where breastfeeding for mothers with HIV is not recommended, consideration can be given to stopping the ARV drugs in women not eligible for ART after the period of mother-to-child transmission risk has ended. Regardless of the approach, special effort and supportive initiatives are needed to optimize adherence, especially during breastfeeding, where many programmes currently have poor follow-up, and to assure effective linkages to long-term treatment. Chapter 10 provides additional guidance for national programmes on making the decision between lifelong ART and stopping ART (Box 10.4).

Enhanced ARV toxicity surveillance for exposure throughout pregnancy and the breastfeeding period is critical to evaluate the safety of this approach for women, the fetus and the child. This is especially true as an increasing number of women already receiving ART become pregnant, resulting in much higher levels of ARV drug exposure during early gestation (see Sections 7.2.2 on “What ARV regimen to start with” and 7.4 on “Monitoring and substitutions for ARV drug toxicities”). In addition, implementation research is important to ensure that the many gaps in knowledge associated with lifelong ART are addressed.

Transition from the 2010 guidelines to the 2013 guidelines

The new 2013 guidelines recommend that countries currently implementing Option A based on the 2010 guidelines (82) should transition, with appropriate planning, to initiating ART for all pregnant and breastfeeding women with HIV; the 2013 guidelines no longer recommend Option A. Countries moving towards Option B and those currently implementing Option B should consider the advantages and disadvantages of implementing lifelong ART for all pregnant and breastfeeding women in their setting.

Clinical considerations

Section 10.6 (Implementation considerations for key recommendations, Box 10.4) discusses clinical and implementation considerations relevant to programme managers for moving towards lifelong ART for all pregnant and breastfeeding women. A toolkit for managing the transition to lifelong ART for pregnant and breastfeeding women has been developed (98), including a readiness assessment checklist (Annex 6).
**Key research gaps**

The Guidelines Development Group emphasized the need for more research to support the new recommendations, to inform programmatic decisions and to promote optimal implementation. Key research gaps include the following.

**ARV toxicity surveillance.** Additional research is needed on the safety and acceptability of lifelong ART for pregnant and breastfeeding women, and their infants, especially in low-resource settings, where malnutrition and comorbidities are more common than in resource-rich countries and monitoring capacity is limited. Better data are needed on mothers’ health outcomes, pregnancy outcomes (such as stillbirth, low birth weight and prematurity) birth defects and health outcomes for infants and young children (see Box 7.2).

**Maternal and child health outcomes.** Research is needed to better define the long-term outcomes in terms of both mother-to-child transmission at the end of breastfeeding and maternal health. In addition to short-term outcomes (such as impact on early mother-to-child transmission rates, which are now commonly measured at six weeks), assessments of long-term outcomes with maternal ART are critical to measure final transmission rates at the end of breastfeeding and HIV-free survival; the health of the mother and children infected or uninfected with HIV; retention in care (for those with both low and high CD4 counts); the long-term success of first-line ART; and HIV drug resistance.

**Adherence and retention.** Research is needed to determine how to optimize acceptability, adherence and retention on ART in pregnant and breastfeeding women, including among the women initiating lifelong ART who do not meet current eligibility criteria for their own health. Research is also needed on health systems and community interventions to optimize lifelong ART for pregnant and breastfeeding women with HIV, and the potential impact of different ART initiation strategies in different populations.

### 7.1.3 ARV drugs and duration of breastfeeding

#### Recommendations

The key principles and recommendations established in 2010 remain, including:

National or subnational health authorities should decide whether health services will mainly counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context.

In settings where national authorities have decided that maternal and child health services will mainly promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival.

- Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided (strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months).
Background

The primary aim of WHO recommendations regarding HIV and infant feeding is to improve the HIV-free survival of HIV-exposed infants. This includes reducing the risk of HIV transmission through breast-milk, primarily by providing ARV drugs, while avoiding malnutrition and the increased risk of serious infections in infants and children through unsafe feeding practices.

In 2010, WHO recommended that ARV drugs be provided either to the mother or the infant throughout breastfeeding to reduce the risk of postnatal HIV transmission (82, 99). In countries that recommended breastfeeding with ARV drugs, it was recommended that women with HIV should “continue breastfeeding for the first 12 months of life” and “only stop once a nutritionally adequate and safe diet without breast-milk can be provided” (99). This recommendation was based on evidence that the maximum benefit of breastfeeding in preventing mortality from diarrhoea, pneumonia and malnutrition is in the first 12 months of life and that the risk of transmitting HIV to infants through breastfeeding is low in the presence of ARV drugs (100,101). At that time, there was uncertainty about the mothers’ adherence to ARV drugs as prophylaxis and their ability to give ARV drugs to their breastfeeding infants over longer periods of time up to 18 or 24 months of age. Consequently, there was uncertainty about the level of protection against HIV transmission for children breastfeeding beyond 12 months. Finally, there were limited data on potential adverse events among infants exposed to prolonged – though low-dose – ARV drugs through breast-milk (102–104).

Since 2010, country-level recommendations on the appropriate duration of breastfeeding for women with HIV and their infants (where breastfeeding is recommended) have varied from 12 to 24 months; in some cases, the duration is not specified. Data on ARV drug coverage and adherence during breastfeeding and effective postpartum follow-up of mother–infant pairs remain limited. With increasing antenatal coverage of ARV drugs in PMTCT programmes, the relative proportion of infants infected during breastfeeding may be increasing because of inadequate ARV drug coverage during breastfeeding, emphasizing the importance of an effective postpartum prevention strategy.

The option of providing lifelong ART to all pregnant women with HIV, regardless of CD4 count or clinical stage (section 7.1.2), raises the question of whether these mothers need to limit the duration of breastfeeding.

The Guidelines Development Group therefore considered whether, in the context of pregnant women with HIV receiving lifelong ART regardless of CD4 count or clinical stage, to maintain the recommendation on the duration of breastfeeding as continued breastfeeding for the first 12 months of life or whether to recommend unrestricted duration of breastfeeding. The Guidelines Development Group considered a revision because of the potential operational advantages of extending the breastfeeding period, including:

- simplifying the recommendations for mothers with HIV and their infants and harmonizing them with those for mothers without HIV would likely simplify public health messaging and improve infant-feeding practices in the entire community; and
- decreasing stigma and possible increasing acceptability by mothers and communities.

Ultimately, the Guidelines Development Group decided not to change the 2010 recommendations on HIV and infant feeding.
Rationale for not changing the 2010 WHO recommendations on HIV and infant feeding

Overall, there is no new evidence to support changing the 2010 recommendation.

The main concern about promoting unrestricted breastfeeding among mothers with HIV is that mothers may not adhere to ART throughout breastfeeding, placing their infants at risk of HIV transmission. Although this is important at any time when the infant is breastfeeding, it is of particular concern after the infant reaches 12 months of age. Before 12 months of age, breastfeeding provides major protection to the infant against death from diarrhoea, pneumonia and malnutrition. Although breastfeeding continues to provide a range of benefits to the child after 12 months of age, reductions in mortality from these conditions become less significant.

WHO recommendations acknowledge that some mothers may not be able to provide a safe and adequate diet to children beyond 12 months of age without breastfeeding and, in these situations, suggest that breastfeeding should continue. However, evidence to support this as a general approach, including the additional risk of HIV transmission and ARV toxicity surveillance data to exclude possible ARV-related adverse health outcomes for the infant, is not currently available.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for using ARV drugs during breastfeeding include:

- postnatal prophylaxis for infants remains critical: infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP (section 7.2.2);
- specific interventions (such as integrated follow-up with immunization and other well-child services) should be considered to improve postpartum follow-up of mother–infant pairs, which is often weak in most programmes; and
- communicating clearly and effectively with the community and users the value of breastfeeding with ARV drugs and local considerations regarding the duration of breastfeeding.

In addition, the Guidelines Development Group emphasized the need to support enhanced monitoring for potential toxicities from prolonged exposure to ARV drugs (such as sentinel site monitoring of infant cohorts during the first two years of life), for the next three to five years, and to continue monitoring as new drugs are introduced, to assess the effects of ARVs especially on neurodevelopmental outcomes and renal and bone health.

Key research gaps

- the risk of postpartum transmission in the context of ART, with variable duration of breastfeeding and different programme settings;
- short- and long-term infant health outcomes related to prolonged, low-dose exposure to ARV drugs (especially EFV and TDF) through breast-milk, including neurodevelopmental outcomes, nutritional status (including micronutrients), bone metabolism and growth; and
- interventions to improve adherence to postnatal ARV drugs during breastfeeding and whether initiating lifelong ART in all pregnant and postpartum women enhances adherence to ARV drugs during breastfeeding, which would enable women with HIV to breastfeed without any time restriction.
Box 7.1. Special considerations for the care and management of pregnant women
(See also Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes)

Sources of guidance:


General guidance

- Pregnant women with HIV should receive at least the minimum package of recommended antenatal visits and pregnancy care, and additional interventions such as screening for sexually transmitted infections, nutritional support and infant feeding and family planning counselling should be considered.

- There is a high risk of HIV transmission during labour and delivery. This risk can be minimized by following several key principles and practices, including reinforcing recommended antenatal clinic visits, especially high-risk management in the late third trimester; promoting facility-based delivery by trained skilled birth attendants; avoiding unnecessary instrumentation and premature rupture of membranes by using a partograph to monitor stages of labour; and non-invasive suction of nasogastric secretions and washing away blood in the newborn.

Additional measures to reduce HIV transmission include the following:

- The early identification of mothers with HIV and providing ARV drugs to both the mother and the newborn baby are essential.

- For mothers presenting at labour with unknown HIV status, rapid HIV testing should be done during labour or immediately postpartum.

- For women testing positive, ARV drugs should be provided to both the mother and child in accordance with current treatment recommendations and with consideration of extended prophylaxis to the infant (see section 7.2.2).

- Health care workers should follow universal precautions for all deliveries, including those involving mothers with HIV.

- Special efforts should be made to ensure that delivery care is provided in a non-stigmatizing and supportive manner.

- Although Caesarean section has been shown to protect against HIV transmission, especially in the absence of ARV drugs or in the case of high viral load, WHO does not recommend it in resource-limited settings specifically for HIV infection; rather it is recommended for obstetric and other medical indications.
Women with HIV and women of unknown HIV status who deliver outside health facilities should be encouraged to be medically assessed at a maternal and child health facility as soon as possible after delivery and to begin or continue appropriate HIV interventions. Providing follow-up, linkages to care and treatment and postpartum care are especially important for women with HIV and their HIV-exposed infants. Initial care of the child is usually scheduled at the first immunization visit at four to six weeks, including reinforcement of safe feeding practices, review of ARV coverage and early infant diagnosis testing. Follow-up care for the mother should ideally be scheduled at the same time and should include a postpartum check, family planning counselling, review of ARV regimen and adherence support.

7.1.4 When to start ART in children

**New recommendations**

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count
  - Infants diagnosed in the first year of life (strong recommendation, moderate-quality evidence)
  - Children infected with HIV one year to less than five years of age (conditional recommendation, very low-quality evidence).
- ART should be initiated in all HIV-infected children five years of age and older with CD4 cell count ≤500 cells/mm$^3$, regardless of WHO clinical stage
  - CD4 count ≤350 cells/mm$^3$ (strong recommendation, moderate-quality evidence)
  - CD4 count between 350 and 500 cells/mm$^3$ (conditional recommendation, very-low-quality evidence).
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (strong recommendation, moderate-quality evidence).
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection (strong recommendation, low-quality evidence).

1 This recommendation is conditional because of the lack of evidence supporting earlier initiation in this age group, but this approach is expected to provide significant programmatic advantages in settings with limited access to immunological testing, high burden of paediatric HIV disease and low ART coverage among children, since simplifying eligibility criteria for initiating ART is likely to increase ART coverage in children infected with HIV and improve their health outcomes. Priority for ART initiation should be given to children younger than two years of age, regardless of WHO clinical stage or CD4 cell count, because of higher mortality risk, and to children between two and five years of age with advanced disease (WHO HIV clinical stages 3 and 4) or with CD4 count ≤750 cells/mm$^3$ or <25%, whichever is lower, regardless of WHO clinical stage (strong recommendation, very-low-quality evidence) (105).

2 This recommendation is conditional because of the lack of evidence in this population for individual benefit as a result of initiating ART earlier; however, this approach is expected to provide significant programmatic advantages in settings with high coverage of paediatric ART and a programmatic need to align with ARV drug recommendations for adults. If this recommendation is not adopted, ART should be initiated at WHO HIV clinical stages 3 and 4 or with CD4 count ≤350 cells/mm$^3$ regardless of WHO clinical stage (strong recommendation, very-low-quality evidence) (105).

3 See Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes
**Table 7.4. Summary of recommendations on when to start ART in children**

<table>
<thead>
<tr>
<th>Age</th>
<th>When you start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (&lt;1 year)</td>
<td>Treat all individuals</td>
</tr>
<tr>
<td>1 year to less than 5 years</td>
<td>Treat all individuals (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or &lt;25% as a priority)</td>
</tr>
<tr>
<td>5 years and above</td>
<td>WHO stage 3 or 4 or CD4 ≤500 cells/mm³ (CD4 ≤350 cells/mm³ as a priority)</td>
</tr>
</tbody>
</table>

**Background**

Infants and young children have an exceptionally high risk of poor outcomes from HIV infection. Up to 52% of children die before the age of two years in the absence of any intervention (106). By five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults (107,108).

The scaling up of early infant diagnosis programmes has increased the identification of infants infected with HIV, but initiating ART early for those who have been found to be infected remains poor. Most HIV-infected children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults (28% versus 57% globally in 2011) (11).

Diagnosing and retaining children exposed to HIV and children infected with HIV in care also presents unique challenges because of their dependence on a caregiver. Loss to follow-up has been particularly high along the continuum of care (109), with retention especially challenging for children who are in HIV care but not yet eligible for ART.

Some countries are already introducing immediate ART for children younger than five years based on operational and programmatic grounds (110,111).

The 2010 WHO guidelines aligned clinical and immunological criteria for ART eligibility for children older than five years with those for adults (that is, treat for WHO clinical stage 3 or 4 disease or CD4 ≤350 cells/mm³) (105). They also recommended treating all children infected with HIV younger than two years of age regardless of clinical or immunological status. For children between two and five years of age, it was recommended that those with WHO stage 3 or 4, clinical disease or CD4 <25% or ≤750 cells/mm³ be treated (105).

The review of evidence in 2013, together with operational considerations and values and preferences expressed by care providers, has led to revised recommendations to simplify and expand treatment in children, including initiating ART in all children up to five years and to increase the CD4 count threshold for ART initiation to ≤500 cells/mm³ in children 5 years and older, aligning with the new threshold in adults.
Rationale and supporting evidence

These recommendations are based on strong operational and programmatic advantages resulting from simplification of criteria for initiating ART, despite the lack of clinical benefits to support treatment regardless of CD4 or clinical stage beyond infancy. Similarly, for programmatic purposes and given that disease progression in children five years and older is comparable to that of young adults, alignment with ART initiation criteria for adults was considered of high value.

Evidence for increasing the age threshold for early ART to five years

CD4 count and WHO clinical stage can identify children at increased risk of disease progression and death. Previous recommendations were based on observational studies demonstrating that untreated children in the second year of life continue to experience high rates of death and illness compared with children without HIV (106). Child-survival curves suggest that the mortality for children older than two years of age and with CD4 exceeding 25% is about 1–2% per year (107,108).

A systematic review identified only one randomized clinical trial, PREDICT (112), informing this issue (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The trial enrolled 300 children (1–12 years old, median age 6.4 years) with CD4 counts above 15% and without CDC clinical stage C disease, randomizing them to either immediate treatment or deferred treatment until the CD4 count fell below 15%. AIDS-free survival, neurodevelopmental outcomes and growth parameters did not differ between groups (113).

A causal modelling study was also undertaken using prospective data collected by the IeDEA-Southern Africa network on 5732 ART-naive children 24–59 months old (median age 3.3 years) who had CD4 counts above the existing eligibility thresholds of 25% or 750 cells/mm$^3$ (114) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The study did not show any survival benefit from early treatment in this population, but a large proportion of children in this age range would rapidly become eligible under the existing criteria, since most children with CD4 count of 750 cells/mm$^3$ or higher at enrolment into care reached the CD4 treatment threshold within three years. More specifically, 32% of this subset of the cohort fell below the thresholds for eligibility after one year and 60% after two years.

Operational and programmatic advantages

Despite the lower risk of progression in children 2–5 years old compared with children younger than two years and the low quality of evidence, the Guidelines Development Group emphasized the operational and programmatic advantages of removing the CD4 barrier to treatment for children under 5 years of age. Treating all children younger than five years of age is expected to simplify paediatric treatment and facilitate a significant expansion of ART coverage for young children. Although this has not been assessed as an outcome, programmatic data suggest that retention is better among children on ART than among those in care but not started on ART (109). Increasing ART coverage and targeting these children for HIV care may also facilitate the treatment of other preventable causes of under-five mortality. This approach will likely represent a small increased burden on current systems (115). Note that late diagnosis is still occurring, and a large proportion of the children identified as infected with HIV would already be eligible for ART based on the 2010 recommendations.

Community values and preferences

Expanding ART to every child younger than five years of age is expected to be well accepted. Assessment of the values and preferences of people living with HIV, caregivers and health care providers of children with HIV showed that earlier initiation is preferable because it is believed to facilitate family-based care, prevent loss to follow-up and improve adherence (116). Nevertheless, there is a risk of resistance if treatment is initiated early in young children and
adherence is poor or drug supplies are suboptimal; this is particularly the case for the youngest children, among whom harmonizing the formulations for children and adults is most difficult. However, the benefits of treatment are likely to outweigh these risks.

Where access to immunological testing is limited, the burden of paediatric HIV disease is high and paediatric ART coverage is low, simplifying the eligibility criteria for initiating ART may significantly improve the overall health outcomes for children with HIV (117). National programmes need to determine how best to implement this recommendation and whether to recommend universal treatment for all children younger than five years or to focus on universal treatment for infants younger than one year and apply clinical or immunological criteria for children one to five years old. When ART initiation is expanded regardless of clinical or immunological status beyond infancy to all children younger than five years, treatment of children younger than two years should be given priority because of their higher risk of death and rapid disease progression. In addition, expanding ART services will require ensuring retention in care and should be matched with concomitant expansion of interventions to support adherence.

Evidence for increasing the CD4 threshold to 500 cells/mm³

The criteria for initiating ART in children five years of age and older are the same as for adults. Although there are limited data to assess the clinical impact of treating children with a CD4 count between 350 and 500 cells/mm³ and the benefits of ARV drugs in preventing sexual transmission are not a factor for this population, this approach has programmatic advantages resulting from harmonizing the criteria with those for adults. It may be most feasible in settings with high ART coverage. As in the case of adults, treating children with CD4 counts ≤350 cells/mm³ should be a high priority since they have the highest risk of disease progression.

Coinfection with HIV and HBV

Small cohort studies in which both HIV and HBV are endemic report rates of chronic HBV among children with HIV between 1% and 49% (118). HBV is often acquired in infancy or early childhood and, unlike among adults, may have an immunotolerant phase that lasts throughout childhood and adolescence. Unfortunately, the natural history of the disease among children with HIV is still poorly known, and the benefits from initiating ART earlier in these children remain to be assessed.

Clinical considerations for scaling up ART among children

Section 10.6 discusses implementation considerations relevant to programme managers (see Box 10.6). An additional important implementation consideration for clinicians and other health care providers is that expanding the initiation of ART regardless of clinical or immunological status to children younger than five years eliminates the need for determining the CD4 count to initiate treatment in this age group and avoids delaying ART in settings without access to CD4 testing. However, the availability of CD4 testing, including determining the baseline CD4 count and percentage, remains important to ensure appropriate treatment monitoring in the absence of viral load monitoring.

Key research gaps

More data are needed to define potential clinical benefits and the impact of initiating ART early on morbidity for children younger than five years as well as immunological response and virological response over time. The impact of initiating ART earlier on retention, adherence and potential HIV drug resistance among children with less advanced disease needs to be investigated further. Data are also needed to inform the optimal approach to initiating ART in children coinfected with HBV.
7.2 What ARV regimen to start with (first-line ART)

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising a non-thymidine NRTI backbone (TDF + FTC or TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than three years. For children younger than three years, a PI-based regimen is the preferred approach (Table 7.5).

Table 7.5 Summary of first-line ARV regimens for adults, adolescents, pregnant and breastfeeding women and children

<table>
<thead>
<tr>
<th>First-line ART</th>
<th>Preferred first-line regimens</th>
<th>Alternative first-line regimens&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alternative first-line regimens&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)</td>
<td>TDF + 3TC (or FTC) + EFV</td>
<td>AZT + 3TC + EFV</td>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td>Adolescents (10 to 19 years) ≥35 kg</td>
<td>ABC + 3TC + EFV</td>
<td>ABC + 3TC + NVP</td>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td>Children 3 years to less than 10 years and adolescents &lt;35 kg</td>
<td>ABC + 3TC + EFV</td>
<td>ABC + 3TC + NVP</td>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td>Children &lt;3 years</td>
<td>ABC (or AZT) + 3TC + LPV/r</td>
<td>ABC + 3TC + NVP</td>
<td>AZT + 3TC + NVP</td>
</tr>
</tbody>
</table>

<sup>a</sup> For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

<sup>b</sup> ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.
7.2.1 First-line ART for adults

New recommendations

- First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI)
  - TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART *(strong recommendation, moderate-quality evidence).*
  - If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended:
    - AZT + 3TC + EFV
    - AZT + 3TC + NVP
    - TDF + 3TC (or FTC) + NVP *(strong recommendation, moderate-quality evidence).*
  - Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities *(strong recommendation, moderate-quality evidence).*

Table 7.6 Summary of first-line ARV regimens for adults

<table>
<thead>
<tr>
<th>First-line ART for adults (including pregnant and breastfeeding women and people with TB and HBV coinfection)</th>
<th>TDF + 3TC (or FTC) + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimens</td>
<td>TDF + 3TC (or FTC) + EFV</td>
</tr>
<tr>
<td>Alternative regimens</td>
<td>AZT + 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + NVP</td>
</tr>
<tr>
<td>Special circumstances c</td>
<td>Regimens containing ABC, d4T b and boosted PIs</td>
</tr>
</tbody>
</table>

a For adolescents, see section 7.2.4 on first-line ART for children three years and older which includes adolescents infected with HIV (10 years and older).

b Using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used. The duration of therapy with this drug should be limited to the shortest time possible and include close monitoring.

c Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

Background

The 2010 WHO ART guidelines *(2)* recommended that ART in treatment-naive adults should initially consist of an NNRTI (either NVP or EFV) plus two NRTIs, one of which should be 3TC (or FTC) and the other AZT or TDF. The guidelines emphasized the importance of avoiding d4T as a preferred option in first-line regimens because of its well-known mitochondrial toxicity, using regimens that are potentially less toxic and more suitable for most people, preferably as fixed-dose combinations given the clinical, operational and programmatic benefits. The recommended regimens had better toxicity profiles than d4T but were considered comparable in terms of efficacy, since there was no evidence that AZT is virologically superior to d4T, AZT superior to TDF, TDF superior to d4T or ABC, or EFV superior to NVP.
The phasing out of d4T as a preferred option in first-line ART has been variable. Some countries have made rapid and substantial progress, whereas others have taken a gradual approach, such as avoiding d4T only for people starting ART or not using d4T in pregnant women (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

WHO (119,120) promotes a more affordable and efficient approach to treatment, including simpler, single-pill, once-daily ARV regimens. The 2013 guidelines promote further simplification of ART delivery by reducing the number of preferred first-line regimens and focusing on regimens that may be used across a range of populations.

Rationale and supporting evidence

The move to TDF + 3TC (or FTC) + EFV as the preferred first-line option

A systematic review comparing six regimens showed moderate-quality evidence indicating that a once-daily combination of TDF + 3TC (or FTC) + EFV is less frequently associated with severe adverse events and has a better virological and treatment response compared with other once- or twice-daily regimens (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). An additional systematic review showed people receiving NVP are twice as likely as those receiving EFV to discontinue treatment because of adverse events (121).

The Guideline Development Group also reviewed a published meta-analysis and a further updated analysis (122, 123) that showed no increased risk of birth defects with EFV compared with other ARV drugs used during the first trimester of pregnancy (122). 3TC and FTC are pharmacologically comparable (123). TDF + 3TC (or FTC) + EFV offers good potential for harmonizing treatment across different populations: TDF/FTC or TDF/3TC are the preferred NRTI backbone for people coinfected with HIV and HBV and can be used among people coinfected with TB and among pregnant women. EFV is the preferred NNRTI for people with HIV and TB (pharmacological compatibility with TB drugs) and HIV and HBV coinfec tion (less risk of hepatic toxicity) and can be used among pregnant women, including those in the first trimester.

If TDF + 3TC (or FTC) + EFV cannot be used, other once- or twice-daily NNRTI-containing regimens (AZT + 3TC + EFV, AZT + 3TC + NVP, and TDF + 3TC (or FTC) + NVP) can be used as alternative first-line regimens in ART-naive people. Despite being considered equivalent options, they have potential disadvantages compared with preferred regimens. Use of other drugs such as ABC and boosted PIs are acceptable as potential backup options in special situations but are not recommended as preferred alternatives, considering the principles of optimizing ARV drugs.

NVP in pregnant women

There are continued concerns about the higher risk of adverse events with NVP compared with EFV, and about the use of NVP in women with HIV with CD4 cell counts above 250 cells/mm$^3$, with some studies showing an increased relative risk for severe hepatic and skin reactions in pregnant women using NVP at higher CD4 cell counts (124–126). A systematic review (127), updated in 2013 (134) of the risk of NVP-associated toxicity in pregnant women suggests that the frequency of adverse events is elevated but no higher than that observed in the general adult population. The evidence supporting the theory that pregnant women with HIV who have high CD4 counts are at increased risk of adverse events compared with the general population with HIV is weak. The need for lead-in dosing for initial use of NVP and the fact that it is not available as a fixed-dose combination with TDF + 3TC (or FTC) are important considerations. NVP should therefore be used with caution in pregnant women and women who might be pregnant and only after considering the risk and benefits and available alternatives (see section 7.3.2).
Alternatives to NVP, such as ABC and boosted PIs, are acceptable but should only be used when NVP is not available.

**Using alternative regimens and phasing out d4T**

The currently recommended alternative regimens such as AZT instead of TDF or NVP instead of EFV (Table 7.5) are comparable in therapeutic efficacy but have potential clinical and programmatic disadvantages compared with the preferred options. Individuals who are already clinically stable on an alternative regimen with no contraindications can consider continuing that regimen based on national guidance or switch to the preferred options to simplify treatment management, reduce cost, improve tolerability, enhance adherence and promote better regimen sequencing. In special circumstances, ABC and boosted PIs are acceptable but should only be used when other options are not available.

Use of d4T-containing regimens should be discontinued and restricted to cases in which other ARV drugs cannot be used, and the duration of therapy with this drug should be limited to the shortest time possible and include close monitoring. In settings in which d4T regimens are still used as a preferred option for initiating ART, a plan for phasing out d4T should be implemented, preferably towards using TDF-based first-line regimens (2,128,129). Section 10.6 (Box 10.7) further discusses the issue of phasing out d4T.

**TDF toxicity**

A systematic review on TDF toxicity (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) indicates that TDF has a low rate of renal toxicity in the short to medium term, especially among people with pre-existing, or risk factors for, renal disease. Prospective cohort data show that TDF is associated with modest reduction in renal function (measured by the decrease in the estimated glomerular filtration rate) (130,131) and reduction in bone mineral density, but the clinical significance and magnitude of these side effects, especially with prolonged therapy, need to be investigated further. Further research is also needed to determine whether laboratory screening and monitoring of TDF toxicity should be routine or undertaken only in high-risk populations, such as people with hypertension or diabetes or those using boosted PIs. Since TDF renal toxicity is usually tubular, glomerular function tests do not provide a direct measure, and no other simple test can detect renal tubular toxicity. Section 7.4 discusses this issue further.

Evidence suggests that the overall improvement in renal function resulting from ART can offset the risk of TDF toxicity among people with HIV who do not have secondary renal disease.

**HIV-2 infection**

A systematic review of treatment options for individuals with HIV-2 (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) rated the evidence in all observational studies as being of very low quality, with serious risk of bias, inconsistency and imprecision. Since HIV-2 is naturally resistant to NNRTIs, treatment-naive people coinfected with HIV-1 and HIV-2 should be treated with a regimen containing three NRTIs (TDF + 3TC (or FTC) + AZT or AZT + 3TC + ABC) or a ritonavir-boosted PI plus two NRTIs. If a PI-based regimen is used, the preferred option for first-line therapy should be LPV/r, since this will be procured in low-income settings for both second-line treatment for adults and for first-line treatment for children. SQV/r and DRV/r are alternative boosted-PI options, but they are not available as heat-stable fixed-dose combinations.
7.2.2 First-line ART for pregnant and breastfeeding women and ARV drugs for their infants

New recommendations

- A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped (strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants).

- Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding).

Note: For the recommendations on infant prophylaxis, the GRADE ratings and recommendations shown are from the 2010 guidelines and were not reviewed by the Guidelines Development Group for the current guidelines.

Background

The 2010 WHO guidelines on PMTCT (82) recommended a choice of four different regimens for pregnant and breastfeeding women with HIV who required ART for their own health: AZT + 3TC or TDF + 3TC (or FTC) plus either NVP or EFV. Because of concerns about the increased risk of toxicity of NVP among pregnant women with higher CD4 counts (132–134), the recommended regimens for pregnant women who did not require treatment for their own health and who were receiving triple ARV regimens for PMTCT were AZT + 3TC or TDF + 3TC (or FTC) + EFV as the preferred NNRTI regimens. Alternative regimens were AZT + 3TC plus either LPV/r or ABC, rather than NVP. Although TDF and EFV were recommended, there were limited safety data on their use during pregnancy and breastfeeding.

The 2010 WHO guidelines (82) also recommended four to six weeks of infant NVP (or AZT) as post-exposure prophylaxis for all infants born to mothers who were receiving triple ARV regimens for treatment or prevention. Daily NVP infant prophylaxis throughout breastfeeding was recommended if the mother was not receiving a triple ARV regimen.

In clinical trials, infant prophylaxis has been shown to be especially important for PMTCT when the mother has received limited or no antepartum ARV drugs and when virological suppression has not yet been achieved (135–137). This continues to be a recommended component of PMTCT regimens in resource-rich countries as added protection against exposure to HIV during labour, even when mothers receive ART during pregnancy and when the mother is not breastfeeding (138). The data informing this recommendation have not changed since 2010.
7.2 What ARV regimen to start with (first-line ART)

Rationale and supporting evidence

The 2013 guidelines emphasize simplifying and harmonizing first-line therapy. A once-daily fixed-dose combination regimen is recommended, with TDF as the preferred NRTI and EFV as the preferred NNRTI, in combination with 3TC or FTC for all adults – including pregnant and breastfeeding women – as the preferred regimen to improve health outcomes and facilitate adherence and drug procurement (see section 7.2.1 and Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

The ideal first-line regimen for pregnant and breastfeeding women with HIV has low cost; is available as a fixed-dose combination; is safe for both pregnant and breastfeeding women and their infants; is well tolerated; has low monitoring requirements and a low drug-resistance profile; is compatible with other drugs used in clinical care; and is harmonized with the recommendations for non-pregnant adults. The regimen of TDF + 3TC (or FTC) + EFV is available as a once-daily fixed-dose combination and is the recommended first-line regimen for adults because of simplicity, affordability (the cost has declined significantly since 2010) and efficacy against HBV.

Safety is a critical issue for pregnant and breastfeeding women and their infants as well as women who might become pregnant. Although data on EFV and TDF use in pregnant women remain limited, more data have become available since 2010 and provide increased reassurance for recommending TDF + 3TC (or FTC) + EFV as the first-line ARV regimen for pregnant and breastfeeding women (122,139,140). Sections 7.3.1 and 7.5.2 provide more detail on the overall rationale for the recommended first-line regimen, including toxicity and monitoring issues.

Safety of EFV in pregnancy

Early data suggesting birth defects, including anencephaly, microphthalmia and cleft palate among primates with EFV exposure in utero (141) and some isolated case reports and retrospective clinical data on neural tube defects among humans (142) have led to concern about using EFV in the first trimester of pregnancy or in non-pregnant women with childbearing potential. The United States Food and Drug Administration and European Medicines Agency advise against using EFV in the first trimester and in women of childbearing potential unless the potential benefits outweigh the potential risks; however, the British HIV Association recently changed its recommendation to allow EFV to be used in the first trimester (143).

Because the risk of neural tube defects is limited to the first five to six weeks of pregnancy and because pregnancy is rarely recognized this early, especially in resource-limited settings, any potential risk of neural tube defects with the use of EFV would be primarily in women who become pregnant while already receiving EFV. Evaluation of prospectively collected data in humans is reassuring; an updated systematic review and meta-analysis, including the Antiretroviral Pregnancy Registry (47,134), reported outcomes for 1502 live births to women receiving EFV in the first trimester and found no increase in overall birth defects and no elevated signal for EFV compared with other ARV exposure in pregnancy (140). With one identified neural tube defect, the estimated prevalence from the systematic review continues to be about 7 per 10 000 population (0.07%), which is comparable to the estimates of 0.02–0.2% in the general population in the USA (138). Because neural tube defects are relatively rare events and there are limited exposures in the Antiretroviral Pregnancy Registry and in the meta-analyses, current available data are sufficient to rule out a potential increased risk greater than three-fold or up to 0.21% (the more limited data available for the 2010 guidelines were sufficient to rule out a 10-fold increased risk). Although the Guidelines Development Group emphasized that better data on birth defects are needed, it felt confident that this potential low risk should be balanced against the programmatic advantages and the clinical benefit of EFV in preventing HIV infection in infants and for the mother’s health.
Safety of NVP in pregnancy: (see section 7.2.1)

Safety of TDF in pregnancy and during breastfeeding

Potential concerns about the safety of TDF include renal toxicity (see section 7.4.3), adverse birth outcomes and effects on bone density. A systematic review assessed the toxicity of fetal exposure to TDF in pregnancy (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In the Antiretroviral Pregnancy Registry, the prevalence of overall birth defects with exposure to TDF in the first trimester was 2.4% of 1612 live births and did not differ from the background rate in the USA. A limited number of studies showed no difference in fetal growth between infants exposed or not exposed to TDF (144,145). TDF has limited penetration into breast-milk, which would limit potential toxicity for the breastfeeding infant. However, there have been no studies of TDF among lactating women, who normally have bone loss during breastfeeding that stabilizes after lactation. More extensive studies are ongoing of TDF bone and renal safety in pregnancy and breastfeeding for both the mother and child.

The once-daily TDF + 3TC (or FTC) + EFV fixed-dose regimen is simple and convenient, and harmonizing the recommendations for pregnant and non-pregnant women simplifies supply chain management. Based on available data and experience, the Guidelines Development Group felt that the clear benefits of this regimen for pregnant and breastfeeding women (and women of childbearing potential) outweigh the potential risks (see section 7.5.2).

Infant prophylaxis

Table 7.7 Simplified infant prophylaxis dosing recommendations (adapted from (82))

Simplified infant prophylaxis dosing recommendations: NVP

<table>
<thead>
<tr>
<th>Infant age</th>
<th>Daily dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth(^a) to 6 weeks(^b)</td>
<td></td>
</tr>
<tr>
<td>• Birthweight 2000–2499 g</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>• Birthweight ≥2500 g</td>
<td>15 mg once daily</td>
</tr>
<tr>
<td>&gt; 6 weeks to 6 months(^c)</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>&gt; 6 months to 9 months</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>&gt; 9 months until breastfeeding ends</td>
<td>40 mg once daily</td>
</tr>
</tbody>
</table>

\(^a\) Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

\(^b\) Recommended for 6 weeks, but 4 weeks may be considered in settings with replacement feeding.

\(^c\) Dosing beyond 6 weeks of age, with prolonged dosing of up to 12 weeks should be considered in special circumstances. These include the mother having had limited ART and not being likely to be virally suppressed, or where the infant is identified as HIV exposed after birth and is breastfeeding (Table 7.8). This is based on the dosing required to sustain exposure among infants of >100 ng/ml with the least dose changes.
No new data inform any change in the recommendations on infant prophylaxis. For breastfeeding infants, six weeks of infant NVP is recommended; for infants receiving replacement feeding, four to six weeks of infant NVP or AZT continues to be recommended. If toxicity from infant NVP requires discontinuing the drug or if infant NVP is not available, infant 3TC can be substituted. Several studies (146,147) have safely used infant prophylaxis during breastfeeding with 3TC.

Although the Guidelines Development Group did not formally review this, it considered several scenarios in which longer infant prophylaxis might be appropriate. Because several weeks or months are required for maternal ART to achieve virological suppression and a breastfeeding infant may not be protected against postnatal transmission during that period, or when a breastfeeding mother initiates ART very late in pregnancy (such as less than four weeks prior to delivery) during labour or postpartum, increasing the duration of infant NVP prophylaxis to 12 weeks can be considered.

Infant prophylaxis is also important when a breastfeeding mother interrupts ART during breastfeeding, as this places her infant at increased risk of postnatal transmission. In such situations, providing daily infant NVP during the period of maternal ART interruption should be considered, and this could be stopped six weeks after maternal ART is restarted (or one week after breastfeeding ends, whichever comes first). Table 7.8 summarizes the range of scenarios for maternal and infant prophylaxis.

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### Simplified infant prophylaxis dosing recommendations: AZT (only recommended in settings with replacement feeding)

<table>
<thead>
<tr>
<th>Infant age</th>
<th>Daily dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth* to 6 weeks</td>
<td></td>
</tr>
<tr>
<td>• Birthweight 2000−2499 g*</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>• Birthweight ≥2500 g</td>
<td>15 mg twice daily</td>
</tr>
</tbody>
</table>

*Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg twice daily.
### Table 7.8 Summary of maternal and infant ARV prophylaxis for different clinical scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother diagnosed with HIV during pregnancy</strong>&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maternal ARV prophylaxis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infant ARV prophylaxis&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

| **Mother diagnosed with HIV during labour or immediately postpartum and plans to breastfeed** |
| Maternal ARV prophylaxis<sup>a</sup> | Initiate maternal ART | NVP | 6 weeks; consider extending this to 12 weeks |
| Infant ARV prophylaxis<sup>b</sup> | |

| **Mother diagnosed with HIV during labour or immediately postpartum and plans replacement feeding** |
| Maternal ARV prophylaxis<sup>a</sup> | Refer mother for HIV care and evaluation for treatment | NVP<sup>c</sup> | 6 weeks<sup>c</sup> |
| Infant ARV prophylaxis<sup>b</sup> | |

| **Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding** |
| Maternal ARV prophylaxis<sup>a</sup> | Initiate maternal ART | NVP | Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks |
| Infant ARV prophylaxis<sup>b</sup> | |

| **Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is not breastfeeding** |
| Maternal ARV prophylaxis<sup>a</sup> | Refer mother for HIV care and evaluation for treatment | No drug | Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected |
| Infant ARV prophylaxis<sup>b</sup> | |

| **Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)** |
| Maternal ARV prophylaxis<sup>a</sup> | Determine an alternative ARV regimen or solution; counsel regarding continuing ART without interruption | NVP | Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended |
| Infant ARV prophylaxis<sup>b</sup> | |

<sup>a</sup> Ideally, obtain the mother’s CD4 cell count at the time of initiating or soon after initiating ART; country guidelines should be used to determine whether ART is lifelong or is stopped after the risk for transmission has ended.

<sup>b</sup> If infant NVP causes toxicity or NVP is not available, 3TC can be substituted.

<sup>c</sup> If the mother is using replacement feeding, infant AZT can be substituted for infant NVP; if there is documented maternal virological suppression near delivery for a mother receiving ART and using replacement feeding, four weeks of infant ARV prophylaxis may be considered.

<sup>d</sup> If it is known that the mother has initiated ART less than 4 weeks before delivery, consider extending infant NVP for infants who are breastfeeding to 12 weeks.
Alternative regimens: for toxicity, intolerance or lack of availability of recommended regimens

AZT is recommended as the alternative NRTI for non-pregnant women who cannot tolerate or receive TDF. Given the extensive safety and efficacy data on AZT in pregnant and breastfeeding women, AZT is also the recommended alternative NRTI for pregnant and breastfeeding women.

For non-pregnant women who cannot tolerate or receive EFV, the recommended alternative NNRTI is NVP. However, because ART (triple ARV drugs) is now recommended for pregnant and breastfeeding women regardless of CD4 cell count, concerns remain regarding the use of NVP in women with higher CD4 counts. Although the 2010 guidelines (2, 82) stated that the benefit of NVP outweighed the risk for women with CD4 counts of 250 to 350 cells/mm², data on safety in women with CD4 counts ≥350 cells/mm² are limited, and the finding of life-threatening hepatic toxicity when NVP was used for occupational post-exposure prophylaxis in individuals without HIV infection raises concerns regarding its use for individuals with higher CD4 count. However, a recent systematic review of the risk of NVP-associated toxicity in pregnant women (134) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) suggests that the frequency of adverse events is no higher than that in the general adult population. Further, data on the association between NVP toxicity and elevated CD4 cell counts are conflicting, and the risk of significant hepatic toxicity in most studies is about 3% (121). Data suggest that switching to NVP for individuals who have been treated and had virological suppression is not associated with elevated toxicity even where the immune system has reconstituted. Finally, the alternative to substituting NVP for EFV toxicity would be a PI, which is the recommended second-line therapy and is more expensive than NNRTI drugs. On balance, the Guidelines Development Group held that the overall benefit of substituting NVP for pregnant or breastfeeding women in the rare circumstances that EFV is not tolerated outweighs the potential risks.

Clinical considerations

Maintaining the drug supply chain and ensuring uninterrupted delivery of maternal ART and infant ARV drugs during pregnancy and breastfeeding are critical for PMTCT. All antenatal care and maternal and child health sites providing PMTCT services should have the capacity to initiate, support and monitor ongoing maternal ART and infant ARV drugs.

Key research gaps

*Surveillance of ARV drug toxicity.* Research is needed to continue to evaluate both the short- and long-term effects of EFV, TDF and other ARV drugs on pregnant and breastfeeding women, fetuses and children, including monitoring for birth defects and other adverse pregnancy outcomes and evaluating the renal and bone effects of TDF on both the woman and HIV-exposed infant.

*Acceptability of EFV as first-line ART.* The level of intolerance to EFV and whether switching to an alternative first-line regimen is necessary needs to be studied further, as do ways to support alternative first-line regimens in programme settings for pregnant and breastfeeding women.

*Infant prophylaxis.* Better data are needed on the optimal duration of infant prophylaxis when mothers receive ART, especially if the mother starts ART late in pregnancy or during the postpartum period and hence is not virally suppressed at the time of delivery or when breastfeeding begins. NVP formulations that are improved and easier to administer are needed to facilitate drug administration to neonates and infants.

*Optimal management of infants identified as HIV exposed during breastfeeding.* It is important to determine the extent to which perinatal HIV exposure is missed antenatally
and the extent of maternal seroconversion, appropriate strategies for postpartum screening of infants for HIV exposure and optimal testing and prophylaxis strategies.

Stopping NNRTI-based ART (use of a “tail”). Because of the prolonged half-life of EFV (and NVP), suddenly stopping an NNRTI-based regimen risks developing NNRTI resistance. For women who choose to or must stop EFV-based ART because of toxicity or other conditions, more data are needed to determine whether an NRTI “tail” coverage is needed to reduce this risk. Pharmacokinetic modelling reviewed for the guidelines suggests that, if the NRTI backbone included TDF, such a tail may not be needed, but if the NRTI backbone included AZT, a two-week tail is advisable (EFV has a longer half-life than NVP).

7.2.3 First-line ART for children younger than three years of age

New recommendations

- A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with a NVP-based regimen (strong recommendation, moderate-quality evidence).

- Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained (conditional recommendation, low-quality evidence).

Special note: The randomized control trial supporting the use of this approach (148,161) defined virological suppression as a viral load ≤400 copies/mm³, with the goal of identifying the children who are more likely to be able to safely substitute LPV/r with NVP. The use of a higher viral load cut-off for determining virological suppression has not been studied in the context of this strategy.

- For infants and children infected with HIV younger than three years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ARV regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (strong recommendation, moderate-quality evidence).

- For infants and children infected with HIV younger than three years, the NRTI backbone for an ARV regimen should be ABC or AZT + 3TC (strong recommendation, low-quality evidence).

Table 7.9 Summary of first-line ARV regimens for children younger than three years

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>ABC* or AZT + 3TC + LPV/r&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative regimens</td>
<td>ABC* or AZT + 3TC + NVP&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Special circumstances&lt;sup&gt;a&lt;/sup&gt;</td>
<td>d4T&lt;sup&gt;d&lt;/sup&gt; + 3TC + LPV/r</td>
</tr>
<tr>
<td></td>
<td>d4T&lt;sup&gt;d&lt;/sup&gt; + 3TC + NVP</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on the general principle of using non-thymidine analogues in first-line regimens and thymidine analogues in second-line regimens, ABC should be considered as the preferred NRTI whenever possible. The CHAIN working group developed this recommendation. Availability and cost should be carefully considered.

<sup>b</sup> As recommended by the United States Food and Drug Administration, using LPV/r oral liquid should be avoided in premature babies (born one month or more before the expected date of delivery) until 14 days after their due date or in full-term babies younger than...
7. Clinical guidance across the continuum of care: Antiretroviral therapy

7.2 What ARV regimen to start with (first-line ART)

14 days of age. Dosing for children younger than 6 weeks should be calculated based on body surface area (Annex 3).

During the finalization of these guidelines, the United States Food and Drug Administration approved the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg. Due to the limited data to inform the best use of this drug in this age group, the Guidelines Development Group agreed to maintain NVP as the recommended NNRTI for children under 3 years. WHO will provide further guidance as soon as the additional data become available.

Because of the limited options available for children younger than three years, d4T is still included among the recommended NRTIs, but its use should be restricted to the situations in which toxicity to AZT is suspected or confirmed and ABC cannot be used. The duration of therapy with this drug should be limited to the shortest time possible. Box 10.7 provides guidance on phasing out d4T.

Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

Background

Optimizing first-line ART in children younger than three years is critical to achieving effective and rapid control of viral replication in the context of high viral load and rapid infant growth. Considerations that may require alternative therapeutic approaches include the limited availability of drugs in appropriate formulations, the long-term toxicities of ARV drugs, difficulty with adherence and the possibility of pre-existing viral resistance because of ARV drug exposure for PMTCT.

Young children with HIV who are exposed to NNRTIs used for PMTCT may have demonstrable viral resistance (150), which compromises the response to NVP-containing first-line ART (151,152). For this reason, the 2010 WHO guidelines (105) recommended the use of LPV/r-based treatment in children younger than 24 months of age previously exposed to NNRTIs. For young children not exposed to NNRTIs or whose status was unknown, an NVP-based regimen was recommended (105).

New evidence has become available for this age group suggesting the superiority of a LPV/r-based regimen regardless of PMTCT exposure (153,154). Several strategies have also been tested to overcome the challenges of using LPV/r-based regimens or to provide potent alternatives in settings in which using LPV/r is not feasible or is problematic because of the high prevalence of TB. (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

Rationale and supporting evidence

This recommendation is based on evidence of the superiority of a LPV/r-based regimen for young children balanced against feasibility considerations.

Efficacy of a LPV/r-based regimen for infants and young children

A systematic review of two randomized trials (153,154) shows that children younger than 36 months have a reduced risk of discontinuing treatment and virological failure or death if they are started on a LPV/r-based regimen instead of a NVP-based regimen. At 24 weeks, LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In addition, surveillance of drug resistance among children younger than 18 months (149,155) provides further evidence of detectable NNRTI resistance even among children without any history of exposure to ARV drugs for PMTCT or whose exposure status is unknown, suggesting that a history of exposure for PMTCT may not be an accurate marker for identifying children at higher risk of HIV resistance to NNRTI.

LPV/r is known to have a better resistance profile that protects against the selection of NRTI resistance without compromising the use of other PIs in second-line regimens (156,157–159). In addition, a potential advantage is offered by the considerable reduction in the incidence of malaria among children receiving LPV/r-based regimens, as recently demonstrated in a randomized trial comparing the use of LPV/r versus NVP or EFV among children in Uganda receiving an artemether + lumefantrine combination for treating malaria episodes (160).
Feasibility of LPV/r in resource-limited settings

Providing an LPV/r-based regimen to infants and children younger than three years in some resource-limited settings may be challenging. The current LPV/r syrup formulation has cold-chain requirements until the point of dispensing. The syrup is unpalatable, with the potential for suboptimal adherence, as highlighted in the values and preferences survey among health workers, and the risk of metabolic complications among children who initiate LPV/r early in life is unknown. Further, LPV/r is costly and administering this with TB treatment is complex. Alternative approaches are proposed to overcome these challenges.

A recent randomized clinical trial \(^{148,161}\) and an ongoing randomized clinical trial \(^{162}\) have evaluated a strategy in which LPV/r is started and later substituted with an NNRTI (NVP or EFV). Such PI-sparing strategies aim to reduce exposure to LPV/r, offer an easier approach to maintaining treatment and preserve PI-based therapy for second-line ART. This approach has been shown to be safe and effective in the trial setting for children with sustained virological suppression achieved after receiving LPV/r-based first-line therapy, especially in the absence of HIV resistance to NNRTI before initiating ART \(^{148,161}\). However, this approach may also add complexity to treatment programmes and may require access to virological monitoring. This strategy may therefore only be viable in settings in which viral load and/or genotype testing are available.

In settings in which none of these approaches is feasible or affordable, an NVP-based regimen provides an effective alternative, especially given the availability of two- and three-drug fixed-dose combinations. As observed in a recent randomized controlled trial, good virological outcomes (83% had a viral load less than 400 copies per ml for 3.7 years irrespective of age) can be achieved by starting children on ABC, 3TC and an NNRTI \(^{163}\). EFV has not been used in this age group, however during the finalization of these guidelines the United States Food and Drug Administration approved this drug for children 3 months to 3 years old weighing more than 3.5 kg. Dosing for this population is provided in Annex 7 and further guidance on how best to use this drug as an alternative to LPV/r or NVP will be provided when additional data are available.

Choice of NRTIs

The choice of NRTIs should aim to construct a robust and durable backbone that balances minimizing toxicity, minimizing cost and maximizing feasibility. Only limited evidence \(^{164}\) from head-to-head comparisons informs the selection of NRTIs (AZT or ABC) combined with 3TC in a triple ARV regimen. However, the choice of first-line NRTIs affects second-line ART, and failure of AZT is known to result in the accumulation of thymidine analogue mutations, reducing susceptibility to ABC or TDF in a subsequent regimen (if two or more thymidine analogue mutations are present). The risk of this occurring is greater with an NNRTI-based regimen; using AZT in the context of an LPV/r-based regimen may therefore not be as problematic. By contrast, HIV resistance to ABC does not lead to resistance to thymidine analogues and preserves or even increases the susceptibility of HIV to AZT and d4T for second-line use \(^{159}\).

Although ABC may be preferable in the interest of ART sequencing \(^{159,165}\) and harmonizing with the regimens for older children, availability is limited in resource-limited settings. In addition, the cost of ABC may be a significant barrier to adopting it in many countries, especially when combined with LPV/r. Definitive data on the comparative efficacy of ABC and AZT are expected from ongoing studies \(^{166}\).

Since 2010, WHO has recommended that d4T be phased out because of its known long-term toxicity. However, in settings in which using AZT may not be advisable because of the high risk of anaemia (such as malaria-endemic settings) and in which ABC is not available, d4T remains an option within the limited treatment options for this specific age group. d4T also remains
important in the situation in which toxicity to AZT is suspected or confirmed and ABC cannot be used. However, the duration of therapy with this drug should be limited to the shortest time possible. Box 10.7 provides guidance on phasing out d4T.

In developing these recommendations, the Guidelines Development Group emphasized:

- the importance of potent, first-line regimens for which there is evidence of better virological response as indicated by randomized controlled trials in this age group;
- the need to address the increasing evidence of HIV resistance to NNRTI among children younger than 18 months, especially in the context of the recommendation to treat pregnant women with EFV-based regimens for PMTCT;
- the desirability of having one preferred regimen for children younger than three years while providing alternative strategies that remain less costly, preserve second-line options and address feasibility concerns;
- anticipating the availability of new formulations during the next few years (sprinkles or sachets containing LPV/r);
- using non-thymidine analogues in first-line regimens to preserve the response to AZT in second-line regimens and to harmonize the regimens for older children and adults, while also recognizing the additional expense;
- identifying a subset of children who can benefit from alternative strategies to preserve PIs for use in second-line ART as indicated by a randomized trial; and
- identifying a manageable regimen, such as ABC + 3TC + AZT, for use in the context of TB co-treatment that can maintain good clinical and immunological response after virological suppression on standard ART.

### Clinical considerations

Section 10.6 (Implementations considerations for key recommendations, Box 10.6) discusses implementation considerations relevant to programme managers. An important consideration for clinicians and other health care providers relates to the challenges of providing LPV/r for young children. When clinicians anticipate significant difficulties in dealing with storing or administering LPV/r, using NVP (especially an NVP-based fixed-dose combination) can be considered. In addition, using LPV/r oral liquid should be avoided in premature babies or in full-term babies younger than 14 days (167). Dosing for children younger than six weeks should be calculated based on body surface area (Annex 3).

### Key research gaps

The extent to which new approaches to PMTCT influence the resistance pattern of children becoming infected with HIV despite exposure to ARV drugs for PMTCT still needs to be fully explored outside trial settings. In addition, more evidence is needed to inform the optimal choice of NRTIs and to confirm the safety of EFV-containing regimens, as a first-line option or within PI-sparing strategies in the absence of viral load or genotyping. Studies to fully address the long-term metabolic implications of using LPV/r-based regimens for infants and young children are also needed.
7.2.4 **First-line ART for children three years and older (including adolescents)**

**New recommendations**

- For children infected with HIV three years and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (*strong recommendation, low-quality evidence*).

  **Special note:** In determining the choice of NNRTI for first-line therapy, national programmes should consider the dosing characteristics of EFV (once-daily) and NVP (twice-daily) and how this aligns with the NRTI backbone. For example, NVP may be a better choice if the recommended regimen is a twice-daily option using a fixed-dose combination.

- For children infected with HIV three years to less than 10 years old (or adolescents less than 35 kg), the NRTI backbone for an ARV regimen should be one of the following, in preferential order:
  - ABC + 3TC
  - AZT or TDF + 3TC (or FTC)

  (*Conditional recommendation, low-quality evidence*).

  **Special note:** Consideration should be given to the relative merits of ABC versus TDF versus AZT for this population. There is no definitive evidence to make a preferred recommendation, and each option has its respective risks and benefits. ABC can be used once daily, is available across age groups as a fixed-dose combination with 3TC and harmonizes with TDF from a resistance perspective (168). AZT has been widely used and is available as dual and triple fixed-dose combinations with NVP but is dosed twice daily and can cause severe anaemia. TDF has recently been approved for use in children (169), and the advantages include once-daily dosing. However, paediatric TDF formulations are not widely available, experience with TDF in children is limited and there are concerns about the long-term effects of bone toxicity (170,171). Considerations that support the adoption of TDF as the national recommendation include: the national programme uses TDF for adults and pregnant women and a suitable TDF fixed-dose combination formulation for children is available.

- For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ARV regimen should align with that of adults and be one of the following, in preferential order:
  - TDF + 3TC (or FTC)
  - AZT + 3TC
  - ABC + 3TC

  (*Strong recommendation, low-quality evidence*).

  **Special note:** TDF-containing fixed-dose combinations are currently only available in adult, unscored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents. ABC or boosted PIs can be used in special circumstances.
Table 7.10 Summary of recommended first-line ARV regimens for children and adolescents

<table>
<thead>
<tr>
<th></th>
<th>Children 3 years to less than 10 years and adolescents &lt;35 kg</th>
<th>Adolescents (10 to 19 years) ≥35 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>ABC&lt;sup&gt;a&lt;/sup&gt; + 3TC + EFV</td>
<td>TDF + 3TC (or FTC) + EFV&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><strong>Alternatives</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + NVP</td>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV</td>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + EFV</td>
<td>TDF + 3TC (or FTC) + NVP</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + NVP</td>
<td></td>
</tr>
<tr>
<td><strong>Special circumstances&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>d4T&lt;sup&gt;b&lt;/sup&gt; + 3TC + EFV</td>
<td>ABC + 3TC + EFV</td>
</tr>
<tr>
<td></td>
<td>d4T&lt;sup&gt;b&lt;/sup&gt; + 3TC + NVP</td>
<td>ABC + 3TC + NVP</td>
</tr>
</tbody>
</table>

<sup>a</sup> These recommendations apply to children and adolescents who are initiating first-line ART. Children and adolescents who are already taking ABC-containing regimens can safely substitute TDF for ABC, if this is needed for programmatic reasons. Children and adolescents who are on d4T-containing regimens without evidence of treatment failure can safely substitute ABC or TDF for d4T. Despite a lack of direct evidence, consideration can also be given to substituting ABC or TDF for AZT with the goal of simplifying and harmonizing treatment regimens across age groups. Including TDF in initial ARV regimens for children with HBV coinfection offers the potential advantage of reducing the selection of HIV resistance to 3TC that may compromise future options for HBV treatment.

<sup>b</sup> d4T use should be restricted to situations in which toxicity to AZT is suspected or confirmed and access to ABC or TDF is lacking. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

<sup>c</sup> Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

**Background**

Despite increased access to early infant diagnosis and the widespread availability of several child-friendly fixed-dose combinations, ART coverage among children lags significantly behind that of adults. Treatment recommendations for children should be easy to implement at all levels of the health system, including the primary care level, and by all ART service providers, rather than paediatric specialists alone.

The 2010 WHO ART guidelines for children three years and older<sup>105</sup> recommended starting with an NVP- or EFV-containing regimen combined with an NRTI backbone. The recommended NRTI backbones, in preferential order, were 3TC + AZT or 3TC + ABC or 3TC + d4T. For adolescents with HBV, the preferred backbone was TDF + FTC or 3TC. The new recommendations in the 2013 guidelines are based on new evidence on the preferred NRTIs and NNRTIs to use in this group of children.

**Rationale and supporting evidence**

The United States Food and Drug Administration<sup>172</sup> and European Medicines Agency<sup>173</sup> approved using TDF for children older than two years of age, providing an opportunity to offer the same regimen to both adults and children. Harmonizing treatment recommendations with adult regimens could improve children’s access to ART. Other benefits of TDF include the ability to combine it with 3TC and EFV to create a potent once-daily regimen for children<sup>169</sup>. In addition, the fact that HIV resistance to TDF – specifically K65R – can enhance the antiviral effect of AZT may make TDF a good choice for first-line therapy in terms of sequencing NRTIs from first- to second-line regimens<sup>165,174–176</sup>. However, experience with TDF in young children is limited, and although TDF is known to reduce bone mineral density, it is not clear whether this is permanent...
and how it might affect future patterns of growth and fracture risk, as highlighted in the values and preferences survey among health workers. In addition, TDF formulations for younger children are not widely available and to date there are no TDF-containing paediatric fixed-dose combinations. ABC shares many of the benefits of TDF (once-daily dosage and a favourable resistance profile) but, in contrast to TDF, ABC has been more thoroughly studied in children and is generally well tolerated. ABC is also available in paediatric fixed-dose combination formulations but is significantly more costly. Further, among people with HLA-B*5701, it can cause potentially fatal hypersensitivity; although this is very rare among African children, it can affect up to 3–4% of Caucasian and Asian children (177).

A systematic review based on observational data indicates that EFV has a better short-term toxicity profile and is associated with better virological response than NVP (121,178). Most children currently receiving ART are treated with regimens that contain NVP, whereas in adults, EFV is increasingly being selected as the preferred NNRTI. The primary reason for this discrepancy relates to the relative availability of NVP or EFV in fixed-dose combinations for children or adults. Children who are well controlled and stable on NVP-containing regimens do not need to substitute EFV for NVP, but EFV would be a better choice for those initiating ART with other once-daily drugs.

In developing these recommendations, the Guidelines Development Group emphasized:

- using potent first-line regimens;
- the convenience of once-daily dosing and the use of fixed-dose combinations whenever possible;
- using non-thymidine analogues – either ABC or TDF – in first-line regimens to maximize the response to AZT in second-line ART; and
- providing treatment recommendations for older children and adolescents that are aligned with those for adults.

Clinical considerations for scaling up ART for children

Section 10.6 (Implementations considerations for key recommendations, Box 10.6) discusses implementation considerations relevant to programme managers. An important consideration for clinicians and other health care providers relates to whether and how regimen changes can be introduced among children who are clinically stable. As children get older, new fixed-dose combinations become available and programmes transition into different first-line regimens. Modifying the ARV regimens of clinically stable people can be considered to simplify treatment management and harmonize the ARV regimens in use. Table 7.11 summarizes considerations for simplifying and harmonizing ART for children with no history of treatment failure.
Table 7.11 Considerations for simplifying and harmonizing ART for children with no history of treatment failure<sup>a</sup> on any regimen

<table>
<thead>
<tr>
<th>Regimen containing:</th>
<th>Guidance</th>
<th>Individual advantages</th>
<th>Programmatic advantages</th>
</tr>
</thead>
</table>
| d4T                 | Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme | • Reduced risk of d4T-related toxicity  
• May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen) | • Aligned with adult regimens                                  |
| LPV/r               | No need to change, but **consider** substituting NVP or EFV for LPV/r if there is sustained virological response on LPV/r | • May improve adherence as a result of better palatability and use of fixed-dose combinations in more manageable formulations (once-daily scored tablets)  
• Reduced risk of metabolic alterations | • Aligned with adult regimens  
• Preserve PI for second-line ART  
• No cold-chain requirement  
• Reduced drug cost |
| AZT                 | No need to change but **may consider** changing to ABC or TDF | • May improve adherence as a result of once-daily dosing (if on EFV)  
• May reduce the risk of exacerbating anaemia | • Aligned with adult regimens |
| ABC                 | No need to change, but **can consider** changing to TDF, especially for adolescents weighing more than 35 kg | • Fixed-dose combinations can be used (if also on EFV) | • Aligned with adult regimens |
| NVP                 | No need to change, but **may consider** changing to EFV particularly from age 3 years | • May improve adherence as a result of once-daily dosing (if combined with ABC or TDF) | • Aligned with adult regimens |

<sup>a</sup>Defined based on the criteria for treatment failure adopted nationally.
Key research gaps
The long-term efficacy and safety of TDF, ABC and EFV and the recommended combination need further investigation. More data are needed on the bone, growth and renal toxicity profiles of TDF in children and adolescents, especially in the context of malnutrition and stunting. Similarly, adverse events associated with EFV during adolescence, such as central nervous system effects, require investigation to ensure safe harmonization with adult treatment regimens. Toxicity surveillance systems implemented alongside ART at sentinel sites can provide data to better understand the frequency and clinical relevance of these toxicities.

7.2.5 TB co-treatment in children with HIV

TB is one of the most common opportunistic infections affecting children with HIV. Selecting regimens that are compatible with TB therapy is therefore essential. Interactions between rifampicin and LPV/r or NVP mean that co-treatment in children under three years is challenging, but a recent large randomized controlled trial (163) of ART in children has generated preliminary evidence on the efficacy of triple nucleoside therapy which, despite limited data in the context of TB co-treatment, offers a suitable option for children who require TB treatment while already receiving ART (Table 7.12).

The recommended regimens for children diagnosed with TB and starting ART are consistent with the 2010 recommendations and are summarized in Table 7.12, together with broader guidance on choosing regimens for co-treatment of HIV and TB.

Table 7.12 Summary of recommended ARV regimens for children who need TB treatment

| Recommended regimens for children and adolescents initiating ART while on TB treatment
| Younger than 3 years | Two NRTIs + NVP, ensuring that dose is 200 mg/m² or Triple NRTI (AZT + 3TC + ABC)
| 3 years and older | Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)

| Recommended regimen for children and infants initiating TB treatment while receiving ART
| Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP) | Younger than 3 years | Continue NVP, ensuring that dose is 200 mg/m² or Triple NRTI (AZT + 3TC + ABC)
| 3 years and older | If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC)
7. Clinical guidance across the continuum of care: Antiretroviral therapy

7.2 What ARV regimen to start with (first-line ART)

Recommended regimen for children and infants initiating TB treatment while receiving ART

<table>
<thead>
<tr>
<th>Child on standard PI-based regimen (two NRTIs + LPV/r)</th>
<th>Younger than 3 years</th>
<th>3 years and older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triple NRTI (AZT + 3TC + ABC) or Substitute NVP for LPV/r, ensuring that dose is 200 mg/m² or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If the child has no history of failure of an NNRTI-based regimen: Substitute with EFV or Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r consider adding RTV to achieve the full therapeutic dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider consultation with experts for constructing a second-line regimen</td>
<td></td>
</tr>
</tbody>
</table>

* Substitute ARV drugs based on an age-appropriate ARV regimen in line with nationally recommended first-line ART.
* Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI- or NNRTI-based regimen should be restarted when rifampicin-based therapy ends. Based on the findings from the ARROW trial (163), this regimen should be considered as the preferred option for children younger than three years who are receiving a LPV/r-based regimen when starting TB treatment. The United States Food and Drug Administration approval for the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg offers a potential alternative to the triple NRTI approach. An EFV-based regimen in children under 3 years is still not recommended as pharmacokinetics data are needed to ensure that the co-administration of rifampicin does not decrease drug levels below the therapeutic level. Triple NRTI should also be considered as the preferred regimen for children older than 3 years with a history of failure on a NNRTI-based regimen.
* Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.
* Substitution with EFV should be considered as the preferred option (179), and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.
### 7.3 Monitoring response to ART and the diagnosis of treatment failure

#### 7.3.1 Laboratory monitoring before and after initiating ART

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARV drugs. Table 7.13 summarizes recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for coinfections and noncommunicable diseases.

#### Table 7.13 Recommended and desirable laboratory tests at HIV diagnosis and monitoring on ART

<table>
<thead>
<tr>
<th>Phase of HIV management</th>
<th>Recommended</th>
<th>Desirable (if feasible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV diagnosis</td>
<td>HIV serology, CD4 cell count, TB screening</td>
<td>HBV (HBsAg) serology&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCV serology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryptococcus antigen if CD4 count ≤100 cells/mm&lt;sup&gt;3&lt;/sup&gt; &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening for sexually transmitted infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assessment for major noncommunicable chronic diseases and comorbidities&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Follow-up before ART</td>
<td>CD4 cell count (every 6–12 months)</td>
<td>Haemoglobin test for AZT&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>ART initiation</td>
<td>CD4 cell count</td>
<td>Pregnancy test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood pressure measurement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alanine aminotransferase for NVP&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Receiving ART</td>
<td>CD4 cell count (every 6 months)</td>
<td>Urine dipstick for glycosuria and serum creatinine for TDF&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HIV viral load (at 6 months after initiating ART and every 12 months thereafter)</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>CD4 cell count</td>
<td>HBV (HBsAg) serology&lt;sup&gt;a&lt;/sup&gt; (before switching ARV regimen if this testing was not done or if the result was negative at baseline)</td>
</tr>
<tr>
<td></td>
<td>HIV viral load</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> If feasible, HBsAg testing should be performed to identify people with HIV and HBV coinfection and who therefore should initiate TDF-containing ART.

<sup>b</sup> Can be considered only in settings with a high prevalence of cryptococcal antigenaemia (>3%) (180).

<sup>c</sup> Consider assessing the presence of chronic conditions that can influence ART management such as hypertension and other cardiovascular diseases, diabetes and TB.

<sup>d</sup> Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

<sup>e</sup> Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low BMI, diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

<sup>f</sup> Among people with a high risk of adverse events associated with NVP, such as being ART-naive, women with HIV with a CD4 count >250 cells/mm<sup>3</sup> and HCV coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.
7.3.2 Monitoring the response to ART and the diagnosis of treatment failure

**New recommendations**

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (*strong recommendation, low-quality evidence*).
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (*strong recommendation, moderate-quality evidence*).

Special notes: Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a three-month interval, with adherence support between measurements) after at least six months of using ARV drugs. Viral load testing is usually performed in plasma; however, certain technologies that use whole blood as a sample type, such as laboratory-based tests using dried blood spots and point-of-care tests, are unreliable at this lower threshold, and where these are used a higher threshold should be adopted.

Viral load should be tested early after initiating ART (at 6 months) and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm virological failure where possible.

**Background**

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine whether and which ARV regimens should be switched in case of treatment failure. Before 2010, WHO guidelines on ARV recommended using clinical outcomes and CD4 count for routinely monitoring the response to ARV drugs. However, the value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings.

The 2010 WHO guidelines recommended that countries consider phasing in viral load testing to monitor the response to ART and use a viral load threshold above 5000 copies/ml in an adherent person with no other reasons for an elevated viral load (such as drug interactions, poor absorption and intercurrent illness). However, most ARV programmes in resource-limited settings still do not have access to viral load testing and continue to rely on clinical and immunological monitoring. This limited use of viral load monitoring has been identified as a key reason for the lower than expected rates for switching ARV regimens in resource-limited settings.

**Rationale and supporting evidence**

Although evidence from clinical trials for a survival benefit of viral load testing is limited, it can provide an early indication of treatment failure, and the 2013 guidelines strongly recommend using it for detecting virological failure and/or confirming treatment failure among people with evidence of clinical and/or immunological failure (Table 7.14). Since several clinical and epidemiological studies show that the risk of HIV transmission is very low when the viral load is lower than 1000 copies/ml (*181*), the Guidelines Development Group also recommended reducing the viral load threshold for treatment failure from 5000 copies/ml to 1000 copies/ml.
### Table 7.14 WHO definitions of clinical, immunological and virological failure for the decision to switch ARV regimens

<table>
<thead>
<tr>
<th>Failure</th>
<th>Definition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical failure</strong></td>
<td><strong>Adults and adolescents</strong>&lt;br&gt;New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment</td>
<td>The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART</td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong>&lt;br&gt;New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment</td>
<td>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure</td>
</tr>
<tr>
<td><strong>Immunological failure</strong></td>
<td><strong>Adults and adolescents</strong>&lt;br&gt;CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm³</td>
<td>Without concomitant or recent infection to cause a transient decline in the CD4 cell count</td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong>&lt;br&gt;Younger than 5 years Persistent CD4 levels below 200 cells/mm³ or &lt;10% or Older than 5 years Persistent CD4 levels below 100 cells/mm³</td>
<td>A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (182). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure</td>
</tr>
<tr>
<td><strong>Virological failure</strong></td>
<td>Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support</td>
<td>The optimal threshold for defining virological failure and the need for switching ARV regimen has not been determined</td>
</tr>
<tr>
<td></td>
<td></td>
<td>An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assessment of viral load using DBS and point-of-care technologies should use a higher threshold</td>
</tr>
</tbody>
</table>

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*See the list of clinical conditions associated with advanced or severe HIV disease in Annex 1.*  
*Section 6.1 discusses immune reconstitution inflammatory syndrome.*
Virological monitoring (viral load) versus immunological (CD4) and clinical monitoring (WHO clinical staging)

The main rationale for recommending viral load monitoring as the preferred approach compared with immunological and clinical monitoring is to provide an early and more accurate indication of treatment failure and the need to switch to second-line drugs, reducing the accumulation of drug-resistance mutations and improving clinical outcomes. Measuring viral load can also help to discriminate between treatment failure and non-adherence (183) and can serve as a proxy for the risk of transmission at the population level (76).

There is still limited evidence to support any additional survival benefit of viral load monitoring over CD4 and/or clinical monitoring among individuals with HIV receiving ART. A systematic review identified three randomized clinical trials on virological versus immunological and clinical monitoring (184–186) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Compared with immunological and/or clinical monitoring, adding viral load monitoring has not been associated with reduced mortality. In one of these trials (185), no significant difference in the incidence of clinical failure, switching to second-line regimens and resistance mutations was found. One cohort modelling study among adults also found that adding virological monitoring to clinical and/or immunological criteria made no difference in mortality or new AIDS-defining illnesses (187). Although randomized controlled trials have not yet shown that viral load monitoring translates into survival gains, follow-up has been limited (less than five years) and longer follow-up is required to examine the longer-term impact on survival, resistance profile and HIV transmission.

A systematic review provided moderate-quality evidence that current WHO guidelines on immunological and clinical monitoring for treatment failure have poor sensitivity and lower positive predictive value for identifying virological failure in adults (187–200) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). This means that many of the people who are identified with immunological failure in fact have adequate virological suppression and risk being misclassified as having treatment failure and switched unnecessarily to second-line therapy. A further systematic review using data in children also provided moderate-quality evidence that immunological criteria (201–204) have low sensitivity and positive predictive value for identifying children with virological failure.

Immunological monitoring versus clinical monitoring

Where viral load monitoring is unavailable, clinical monitoring and CD4 monitoring are recommended (205). Although a systematic review of two randomized controlled trials (184,206) provide moderate-quality evidence of mortality and morbidity benefits with CD4 and clinical monitoring compared with routine clinical monitoring in adults receiving ART, these trials largely focused on CD4 and clinical monitoring in people who initiated ART at CD4 counts below 200 cells/mm³ (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Existing immunological and clinical criteria may have decreased sensitivity and specificity to detect treatment failure in people who initiate ART at higher CD4 counts, and more accurate immunological criteria for these people remain to be identified.

Routine versus targeted viral load monitoring to detect treatment failure

Viral load should be monitored routinely (every 6–12 months) to enable treatment failure to be detected earlier and more accurately. In settings with limited access to viral load testing, a targeted viral load strategy to confirm failure suspected based on immunological or clinical criteria (Table 7.14) should be used to avoid unnecessary switching to second-line ART. Targeted viral load monitoring is less costly than routine viral load testing, but as with clinical and immunological monitoring, has the potential to delay switching to second-line ART and may subsequently increase the risk of disease progression, selection of ARV drug resistance and HIV transmission.
Threshold for defining virological failure

The optimal threshold for defining virological failure and for switching ARV regimens has not been established. The rationale for the threshold of 1000 copies/ml was based on two main sources of evidence. First, viral blips or intermittent low-level viraemia (50–1000 copies/ml) can occur during effective treatment but have not been associated with an increased risk of treatment failure unless low-level viraemia is sustained (207). Second, clinical and epidemiological studies show that the risk of HIV transmission and disease progression is very low when the viral load is lower than 1000 copies/ml (181, 208, 209).

Most standard blood and plasma viral load platforms available and being developed have good diagnostic accuracy at this lower threshold. However, the sensitivity of dried blood spots for viral load determination at this threshold may be reduced (210, 211). Programmes relying on dried blood spot technology for viral load assessment may therefore consider retaining the higher threshold (3000–5000 copies/ml) until sensitivity at lower thresholds is established (212–214).

Fig. 7.1 Viral load testing strategies to detect or confirm treatment failure and switch ARV regimen in adults, adolescents and children
Special considerations for children

These guidelines aim to harmonize monitoring approaches for children with those recommended for adults. As more children start ART earlier and at higher CD4 counts, viral load monitoring to detect treatment failure and lack of adherence will be increasingly beneficial. In addition, viral load may be instrumental for implementing treatment strategies to preserve second-line options as children age (such as switching from LPV/r to an NNRTI once virological suppression is sustained) (see section 7.2.3).

Evidence from one randomized controlled trial conducted in several countries (including the United States of America, European countries, Brazil and Thailand) PENPACT1 (158), suggests that switching treatment at lower viral load thresholds does not lead to better clinical and virological outcomes but does minimize the development of HIV drug resistance, especially for NRTIs when an NNRTI-based regimen is used. In this context, alignment with the viral load thresholds recommended for adults is advisable. However, viral load results in the first six months after initiating ART should be interpreted carefully, as infants and young children may require longer to achieve virological suppression because of high baseline viral load.

The recommendation to initiate ART for all children younger than five years of age regardless of clinical and immunological criteria means that CD4 cell count testing at baseline is not required for initiating ART. However, where viral load monitoring capacity is limited or unavailable, CD4 monitoring – including baseline measurement and CD4 percentage for children younger than five years of age – will still be important for monitoring treatment response.

As in the case of adults, lack of viral load or CD4 capacity should not prevent children from starting ART. The results from a recently completed trial show that mortality and disease progression are comparable between clinical monitoring and laboratory monitoring, especially in the first year of treatment (163).

Clinical considerations for scaling up viral load testing

Section 10.6 (see section on implementation considerations for key recommendations, Box 10.3) discusses clinical and implementation considerations relevant to programme managers. Additional implementation considerations for clinicians and health workers include the following.

- **Access to ART should be the first priority.** Lack of laboratory tests for monitoring treatment response should not be a barrier to initiating ART.

- **Setting priorities.** If viral load testing is limited, it should be phased in using a targeted approach to confirm treatment failure. This may be especially relevant in populations receiving ARVs to reduce HIV transmission, such as pregnant and breastfeeding women and among serodiscordant couples, for whom sustained viral load suppression is critical to the efficacy of the strategy.
7.4 Monitoring and substitutions for ARV drug toxicities

7.4.1 Guiding principles

- The availability of laboratory monitoring is not required for initiating ART.
- Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

7.4.2 Major types of ARV toxicities

The 2010 WHO ART guidelines recommended a symptom-directed approach to laboratory monitoring of the safety and toxicity of ARV regimens. At the same time, several laboratory tests for monitoring ARV toxicity were advised (but not required) for specific high-risk people using certain drugs. Table 7.15 lists key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment. More data are needed on whether routine or periodic laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all individuals or only people at higher risk.

Table 7.15 Types of toxicities associated with first-, second- and third-line ARV drugs

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Major types of toxicity</th>
<th>Risk factors</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>Hypersensitivity reaction</td>
<td>Presence of HLA-B*5701 gene</td>
<td>If ABC is being used in first-line ART, substitute with TDF or AZT or d4T If ABC is being used in second-line ART, substitute with TDF</td>
</tr>
<tr>
<td>ATV/r</td>
<td>Electrocardiographic abnormalities (PR interval prolongation)</td>
<td>Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval</td>
<td>LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Indirect hyperbilirubinaemia (clinical jaundice)</td>
<td>Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephrolithiasis and risk of prematurity</td>
<td>Risk factors unknown</td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy</td>
<td>Baseline anaemia or neutropaenia CD4 count ≤200 cells/mm³</td>
<td>If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with d4T</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis or severe hepatomegaly with steatosis</td>
<td>BMI &gt;25 (or body weight &gt;75 kg) Prolonged exposure to nucleoside analogues</td>
<td></td>
</tr>
</tbody>
</table>
### Table 7.15 (continued)

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Major types of toxicity</th>
<th>Risk factors</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T</td>
<td>Peripheral neuropathy, lipoatrophy or lipodystrophy</td>
<td>Older age, CD4 count ≤200 cells/mm³, Concomitant use of isoniazid or ddI</td>
<td>If d4T is being used in first-line ART, substitute with TDF or AZT or ABC. If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT.</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis</td>
<td>BMI &gt;25 (or body weight &gt;75 kg), Prolonged exposure to nucleoside analogues</td>
<td></td>
</tr>
<tr>
<td>DRV/r</td>
<td>Hepatotoxicity</td>
<td>Underlying hepatic disease, HBV and HCV coinfection, Concomitant use of hepatotoxic drugs</td>
<td>If DRV/r is being used in second-line ART, substituting with ATV/r or LPV/r can be considered. When it is used in third-line ART, limited options are available.</td>
</tr>
<tr>
<td></td>
<td>Severe skin and hypersensitivity reactions</td>
<td>Sulfonamide allergy</td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion)</td>
<td>Depression or other mental disorder (previous or at baseline), Daytime dosing</td>
<td>NVP. If the person cannot tolerate either NNRTI, use boosted PIs.</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td>Underlying hepatic disease – HBV and HCV coinfection, Concomitant use of hepatotoxic drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Convulsions</td>
<td>History of seizure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reaction, Stevens-Johnson syndrome</td>
<td>Risk factors unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potential risk of neural tube birth defects (very low risk in humans) (122,140)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male gynaecomastia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV</td>
<td>Severe skin and hypersensitivity reactions</td>
<td>Unknown</td>
<td>Limited options are available</td>
</tr>
</tbody>
</table>
### Table 7.15 (continued)

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Major types of toxicity</th>
<th>Risk factors</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPV/r</strong></td>
<td>Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)</td>
<td>People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval</td>
<td>If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years. If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors.</td>
</tr>
<tr>
<td></td>
<td>QT interval prolongation</td>
<td>Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td>Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td>Advanced HIV disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea</td>
<td>Risk factors unknown</td>
<td></td>
</tr>
<tr>
<td><strong>NVP</strong></td>
<td>Hepatotoxicity</td>
<td>Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs CD4 &gt;250 cells/mm$^3$ in women CD4 &gt;400 cells/mm$^3$ for men First month of therapy (if lead-in dose is not used)</td>
<td>EFV. If the person cannot tolerate either NNRTI, use boosted PIs</td>
</tr>
<tr>
<td></td>
<td>Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome)</td>
<td>Risk factors unknown</td>
<td></td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>Rhabdomyolysis, myopathy, myalgia</td>
<td>Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis</td>
<td>Limited options are available</td>
</tr>
</tbody>
</table>
### 7.4.3 Monitoring TDF toxicity

TDF nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease (130).

According to a systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes), no studies have properly compared monitoring strategies for people receiving TDF, such as routine toxicity monitoring versus care with no monitoring or incidental monitoring in case of perceived clinical need. One clinical trial (the DART trial) comparing laboratory with clinical monitoring showed that individuals receiving TDF have an increased risk of reduced estimated glomerular filtration rate but no increased risk of renal failure over a median five years of follow-up (low-quality evidence). A few observational cohort studies reported that using TDF was associated with an increased risk of chronic kidney disease. However, the exposure time to TDF in all these studies was considered too short to indicate a long-term increased risk for renal failure, the occurrence of bone fractures or changes in fat distribution.

The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory to initiate treatment with TDF. However, it is advisable for high-risk people (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. High frequency of glycosuria has also been found in people without diabetes biopsied for TDF nephrotoxicity with increased serum creatinine compared with TDF-treated people with a normal glomerular filtration rate, suggesting that dipstick glycosuria may be a cost-effective screening test for serious TDF-induced kidney injury (215).

### Table 7.15 (continued)

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Major types of toxicity</th>
<th>Risk factors</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF (169)</td>
<td>Tubular renal dysfunction, Fanconi syndrome</td>
<td>Underlying renal disease, Older age, BMI &lt;18.5 (or body weight &lt;50 kg), Untreated diabetes mellitus, Untreated hypertension, Concomitant use of nephrotoxic drugs or a boosted PI</td>
<td>If TDF is being used in first-line ART, substitute with AZT or d4T or ABC. If TDF is being used in second-line ART (after d4T + AZT use in first-line ART), substitute with ABC or ddI.</td>
</tr>
<tr>
<td></td>
<td>Decreases in bone mineral density</td>
<td>History of osteomalacia and pathological fracture, Risk factors for osteoporosis or bone loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis or severe hepatomegaly with steatosis</td>
<td>Prolonged exposure to nucleoside analogues, Obesity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbation of hepatitis B (hepatic flares)</td>
<td>Discontinuation of TDF due to toxicity</td>
<td>Use alternative drug for hepatitis B treatment (such as entecavir).</td>
</tr>
</tbody>
</table>
TDF-related decreases in bone mineral density have been observed in children, although it is unclear how reducing bone mineral density might impact future growth patterns or the risk of bone fracture. In addition, an accurate and feasible method to measure bone mineral density still needs to be identified, and significant uncertainty remains around how best to monitor TDF-related bone toxicity among children. Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while children are receiving treatment with TDF (169).

**Clinical considerations**

- Laboratory monitoring is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring may be used to assess for hypertension.
- Urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without diabetes using TDF-containing regimens.
- If the creatinine test is routinely available, use the estimated glomerular filtration rate\(^a\) at baseline before initiating TDF regimens.
- Do not initiate TDF when the estimated glomerular filtration rate is <50 ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure.
- Monitor growth in children using TDF.

\(^a\) Using the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) formulas for estimation. An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi.

\[\text{CG formula: } eGFR = (140 – \text{age}) \times (\text{Wt in kg}) \times 0.85 \text{ (if female)/(72 \times \text{Cr in mg%})}.
\]

\[\text{MDRD formula: } eGFR = 175 \times \text{SerumCr}^{–1.154} \times \text{age}^{–0.203} \times 1.212 \text{ (if patient is black)} \times 0.742 \text{ (if female)}.
\]

**Key research gaps**

More data are needed on how to best monitor renal function in people using TDF-containing regimens (whether toxicity monitoring should be routine or targeted in high-risk groups, with alternative drugs for high-risk people). In addition, more data are needed to understand the frequency and clinical relevance of reduced bone mineral density in children. More accurate and affordable methods to monitor bone toxicity should be identified for this specific population.

**7.4.4 Toxicity monitoring for other ARV drugs**

**AZT**

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin is recommended before initiating ART, mainly among adults and children with low body weight, low CD4 counts and advanced HIV disease. People with HIV with severe anaemia at baseline (haemoglobin <7.0 g/dl) should avoid AZT as first-line therapy.

**NVP**

The laboratory measurement of liver enzymes has very low predictive value for NVP-containing regimens. However, monitoring hepatic enzymes is recommended if feasible, especially for women with HIV who have CD4 cell counts >250 cells/mm\(^3\) and individuals with HIV who are coinfected with HBV or HCV. Section 7.2.1 provides more information on the safety of NVP among individuals with high CD4 cell counts.
EFV

The main type of toxicity of EFV is central nervous system side effects, which typically resolve after a few weeks. However, in some cases, they can persist for months or not resolve at all. Despite concerns about the potential risk of teratogenicity associated with using EFV during pregnancy, a recent meta-analysis found no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARV drugs (122). Section 7.3.2 provides more information on the safety of EFV among pregnant women.

7.4.5 Drug substitutions for ARV drug toxicity

Drug regimen or single agent substitutions may be required for drug toxicity and to avoid drug interactions. Section 7.4.3 and 7.4.4 provides guidance on monitoring specific types of ARV drug toxicity.

Clinical considerations

- Delaying substitutions or switches when there are severe adverse drug effects may cause harm and may affect adherence, leading to drug resistance and treatment failure.
- When drug interruptions are required, such as for severe and life-threatening adverse events related to toxicity, it is important to consider the various half-lives of ARV drugs. For example, when a NNRTI needs to be discontinued, a staggered approach should be used by prolonging the use of the NRTI backbone for two to three weeks. Alternatively, the NNRTI could be temporarily substituted with a boosted PI.

7.4.6 Key ARV drug interactions

Providers should be aware of all drugs that people with HIV are taking when ART is initiated and new drugs that are added during treatment maintenance. There are several key drug interactions (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

WHO TB treatment guidelines review key considerations for managing coinfection with TB and HIV (216). A key contraindicated drug combination includes rifampicin and PIs. When people coinfected with TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r and SQV/r can be used for the duration of TB treatment, if the boosting dose of RTV is increased or double the standard dose of LPV/r is used (see section 7.6.1). For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered.

Ribavirin and peginterferon alpha-2a are often used for treating HCV. Administration of these agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfected with HCV and HIV and receiving AZT may need to be switched to TDF.

Itraconazole and ketoconazole are often used to treat fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to subtherapeutic levels. Alternative antifungal agents (such as fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV.

WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria (217). One recommended artemisinin-based combination therapy is artesunate and amodiaquine. EFV increases the concentrations of amodiaquine and has been associated with significant elevations of liver transaminases. Alternative artemisinin-based combination therapies (such as artemether plus lumefantrine, artesunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine) could be used to prevent severe toxicity in people with HIV.
WHO recommends methadone and buprenorphine for treating opioid dependence (218). Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People receiving methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives (219). Limited data suggest potential drug interactions between many ARV drugs (especially some NNRTIs and RTV-boosted PIs) and estrogen-based hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the ARV drug. If women receiving ART decide to initiate or continue using hormonal contraceptives, consistently using condoms and other contraceptive methods is recommended both to prevent HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraception.

Concomitant use of boosted PIs and NNRTI with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratadine and cetirizine.

WHO recommends using statins for people with a 10-year cardiovascular risk exceeding 30% (220). Boosted PIs may lead to increased concentrations of lovastatin and simvastatin. Increased concentrations may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidaemia agents should be used to prevent severe toxicity among people with HIV.

Table 7.16 Key ARV drug interactions and suggested management

<table>
<thead>
<tr>
<th>ARV drug</th>
<th>Key interactions</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Ribavirin and peg-interferon alfa-2a</td>
<td>First-line: substitute AZT with TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second-line: substitute AZT with d4T</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>Substitute rifampicin with rifabutin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjust the PI dose or substitute with three NRTIs (for children)</td>
</tr>
<tr>
<td></td>
<td>Lovastatin and simvastatin</td>
<td>Use an alternative dyslipidaemia agent (for example pravastatin)</td>
</tr>
<tr>
<td></td>
<td>Estrogen-based hormonal contraception</td>
<td>Use alternative or additional contraceptive methods</td>
</tr>
<tr>
<td></td>
<td>Methadone and buprenorphine</td>
<td>Adjust methadone and buprenorphine doses as appropriate</td>
</tr>
<tr>
<td></td>
<td>Astemizole and terfenadine</td>
<td>Use alternative antihistamine agent</td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>EFV</td>
<td>Amodiaquine</td>
<td>Use an alternative antimalarial agent</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>Adjust the methadone dose as appropriate</td>
</tr>
<tr>
<td></td>
<td>Estrogen-based hormonal contraception</td>
<td>Use alternative or additional contraceptive methods</td>
</tr>
<tr>
<td></td>
<td>Astemizole and terfenadine</td>
<td>Use an alternative anti-histamine agent</td>
</tr>
<tr>
<td>NVP</td>
<td>Rifampicin</td>
<td>Substitute NVP with EFV</td>
</tr>
<tr>
<td></td>
<td>Itraconazole and ketoconazole</td>
<td>Use an alternative antifungal agent (for example fluconazole)</td>
</tr>
</tbody>
</table>

*a This table was developed using the University of Liverpool’s drug interaction charts, a resource which can be found online at www.hiv-druginteractions.org. A more comprehensive table of ARV drug interactions is available on the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes).*
WHO commissioned systematic reviews on specific types of toxicities associated with key ARV drugs and laboratory monitoring strategies to consolidate and update technical guidance (140,169). The reviews highlighted remaining evidence gaps in the potential increased risk of toxicity associated with the long-term use of ARV drugs, the use of ARV drugs during pregnancy and in breastfeeding mothers, children and adolescents and populations with associated risk factors and in laboratory monitoring for toxicity.

The available evidence is limited to studies with limited sample size or short duration. It is essential to monitor the use of ARV drugs in resource-limited countries where toxicities may present a different pattern in association with environmental or behavioural factors, the prevalence of other conditions and where ARV drugs are used in association with other medicines. Implementing toxicity surveillance will provide the opportunity to produce evidence on specific types of toxicity, increase confidence in the use of the drugs, identify populations with risk factors and plan preventive strategies.

The Guidelines Development Group encouraged WHO to strengthen toxicity surveillance activities to increase evidence on toxicity in key areas. These areas cover a potential increased risk of toxicity associated with the long-term use of ARV drugs, renal and bone toxicity associated with using TDF among adults and children, the safety of using EFV- and TDF-containing regimens during pregnancy and in breastfeeding mothers and using TDF among children, adolescents and populations with associated risk factors. Developing laboratory markers to monitor renal function among people using TDF is another important area for research.

Several toxicity surveillance activities have already started with WHO support, using standardized approaches at sentinel sites in resource-limited settings. Targeted and systematic surveillance is being conducted in Côte d’Ivoire to monitor renal toxicity associated with TDF in first- and second-line regimens, with an assessment of laboratory monitoring needs in three sentinel sites. A similar approach is being implemented in Viet Nam to assess renal toxicity associated with TDF and central nervous system toxicity associated with EFV in people who use ARV drugs to prevent HIV infection, such as in serodiscordant couples. In the Lao People’s Democratic Republic, anaemia associated with AZT and hypersensitivity associated with NVP are monitored using a targeted and systematic surveillance approach. In Malawi, a surveillance programme will monitor infant growth, following mothers who are breastfeeding and receiving TDF.

The implementation of a pregnancy registry, including a surveillance programme for birth defects, is recommended where feasible to assess the safety of ARV drugs and any other medicines during pregnancy and risk factors for adverse pregnancy outcomes, including maternal health outcomes, premature births, stillbirths, low birth weight and congenital abnormalities. WHO, the United States President’s Emergency Plan for AIDS Relief, the United States Centers for Disease Control and Prevention and the United States National Institutes of Health support the establishment of ARV pregnancy registries and birth defect surveillance in sentinel sites in Malawi, South Africa and Uganda to assess the use of EFV-containing regimens at large scale among pregnant women.

Surveillance of ARV drug toxicity will help to better understand the long-term risk of ART toxicity and optimize the management of ARV drugs for HIV treatment and prevention in all populations.
7.5 What ARV regimen to switch to (second-line ART)

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age (Table 7.17).

Table 7.17 Summary of preferred second-line ARV regimens for adults, adolescents, pregnant women and children

<table>
<thead>
<tr>
<th>Second-line ART</th>
<th>Preferred regimens</th>
<th>Alternative regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (≥10 years), including pregnant and breastfeeding women</td>
<td>AZT + 3TC + LPV/r a</td>
<td>TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td>Adults and adolescents (≥10 years), including pregnant and breastfeeding women</td>
<td>AZT + 3TC + ATV/r a</td>
<td>TDF + 3TC (or FTC) + ATV/r</td>
</tr>
<tr>
<td>Adults and adolescents (≥10 years), including pregnant and breastfeeding women</td>
<td>TDF + 3TC (or FTC) + ATV/r</td>
<td>TDF + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td>Adults and adolescents (≥10 years), including pregnant and breastfeeding women</td>
<td>TDF + 3TC (or FTC) + LPV/r</td>
<td>TDF + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td>Children</td>
<td>If a NNRTI-based first-line regimen was used</td>
<td>ABC + 3TC + LPV/r b</td>
</tr>
<tr>
<td>Children</td>
<td>If a PI-based first-line regimen was used</td>
<td>No change from first-line regimen in use c</td>
</tr>
<tr>
<td>Children</td>
<td>&lt;3 years</td>
<td>AZT (or ABC) + 3TC + EFV</td>
</tr>
<tr>
<td>Children</td>
<td>3 years to less than 10 years</td>
<td>AZT (or ABC) + 3TC + NVP</td>
</tr>
</tbody>
</table>

a DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.

b ATV/r can be used as an alternative to LPV/r for children older than six years.

c Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

7.5.1 Second-line ART for adults and adolescents

New recommendations

- Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).
  - The following sequence of second-line NRTI options is recommended:
  - After failure on a TDF + 3TC (or FTC)–based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.
  - After failure on an AZT or d4T + 3TC–based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
  - Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (strong recommendation, moderate-quality evidence).
- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (strong recommendation, moderate-quality evidence).
Table 7.18 **Summary of preferred second-line ARV regimens for adults and adolescents**

<table>
<thead>
<tr>
<th>Target population</th>
<th>Preferred second-line regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (≥10 years)</td>
<td>If d4T or AZT was used in first-line ART</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + ATV/r or LPV/r</td>
</tr>
<tr>
<td></td>
<td>If TDF was used in first-line ART</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + ATV/r or LPV/r</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Same regimens recommended for adults and adolescents</td>
</tr>
<tr>
<td>HIV and TB coinfection</td>
<td>If rifabutin is available</td>
</tr>
<tr>
<td></td>
<td>Standard PI-containing regimens as recommended for adults and adolescents</td>
</tr>
<tr>
<td>HIV and HBV coinfection</td>
<td>If rifabutin is not available</td>
</tr>
<tr>
<td></td>
<td>Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily)</td>
</tr>
<tr>
<td></td>
<td>AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)</td>
</tr>
</tbody>
</table>

* ABC and ddl can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

**Background**

The 2010 WHO ART guidelines recommended that second-line adult regimens include a boosted-PI plus two NRTIs (determined by the drug used in first-line therapy). Those guidelines placed a high value on using simpler second-line regimens, ideally heat-stable formulations and fixed-dose combinations (once-daily formulations when possible).

Except for the recommendation for people with HIV and TB, the recommendations in 2013 remain unchanged from the 2010 recommendations.

**Rationale and supporting evidence**

**PI options for second-line ART**

Since first-line ART should preferably be based on an NNRTI, PI-based regimens are recommended for second-line therapy. Of the PI options, ATV/r and LPV/r are preferred. DRV/r is an alternative but is currently not available as a fixed-dose combination, although one is in development. The other PIs (FPV/r, IDV/r and SQV/r) are not available as heat-stable fixed-dose combinations and/or are associated with high pill burden and higher frequency of side effects.

The Guidelines Development Group emphasized the importance of simplifying second-line ART by reducing the pill burden and limiting the number of preferred second-line regimens that could be used across populations (adults, adolescents, children, pregnant women and people coinfected with TB, HBV and HCV). The use of less toxic, more convenient and more efficacious heat-stable fixed-dose combinations was also considered critical.

A systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) of data from six clinical trials comparing drugs used for second-line ART (ATV/r, LPV/r and DRV/r) concluded that there was no evidence to support changing the recommendation in the 2010
guidelines (221–226). These studies showed low- to very-low-quality evidence (downgraded in the GRADE evaluation primarily for indirectness and imprecision) for using ATV/r or DRV/r (once-daily) over LPV/r (twice-daily) or vice versa as preferred boosted PI options. ATV/r was considered to be comparable to LPV/r in one trial among ART-experienced individuals (221). In a trial among ART-naive individuals, ATV/r showed a better virological response and better retention in care when compared with LPV/r (224). In two studies, people receiving DRV/r-containing regimens also showed better virological response and retention in care than people receiving LPV/r, both in treatment-naive and experienced people (222,226). DRV/r has been used for second-line therapy in high-income settings. However, two key factors currently preclude DRV/r as a preferred option in these guidelines. These include the high cost and it not being available as a heat-stable fixed-dose combination. Additional research is required to better understand sequencing strategies for PIs in second- and third-line therapy. The different drug toxicity profiles of ATV/r and LPV/r, the contraindication of ATV/r with rifampicin and the lack of WHO approval for the use of ATV/r in children younger than six years provide additional grounds for maintaining both PIs as equal options (Table 7.19). The Guidelines Development Group recommended that DRV/r should be maintained as a preferred third-line drug. However, using it as an alternative option to LPV/r or ATV/r for second-line therapy can be considered, especially when competitively priced fixed-dose combinations are available.

**NRTI backbone**

The Guidelines Development Group maintained the rationale adopted in 2010, recommending drug sequencing consistent with ART-optimizing principles (in particular, availability as fixed-dose combinations and tolerability) and resistance mutation risk, based on the NRTIs used in the first-line regimen. If a thymidine analogue NRTI (AZT or d4T) was used in the failing first-line regimen, TDF should be used in the second-line regimen. If a non-thymidine analogue NRTI was used in first-line ART (that is, TDF), AZT should be used in second-line ART. Other NRTI drugs such as ABC and ddI are acceptable as potential back-up options in special situations but are not recommended as preferred alternatives, since they have no specific advantage and add complexity and cost.

For individuals coinfected with HIV and HBV whose first-line regimen contained TDF + 3TC (or FTC), these NRTIs should be continued in the second-line regimen for the anti-HBV activity and to reduce the risk of hepatic flares, regardless of the selected second-line regimen, which should be AZT + TDF + 3TC (or FTC) + a boosted PI.

For people with active TB disease receiving rifampicin, all boosted PIs in standard doses are contraindicated because of drug interactions and significant reductions in PI plasma concentrations (227–230). In this situation, LPV/r and SQV/r may be used with an adjusted, super-boosted dose of RTV (LPV/r 400 mg/400 mg twice daily or SQV/r 400 mg/400 mg twice daily) or doubling the LPV/r daily dose (LPV/r 800 mg/200 mg twice daily), but this is associated with high levels of toxicity and requires close clinical and laboratory monitoring. The recommendation to use LPV/r 800 mg/200 mg twice daily is based on evidence graded as low-quality, and it is associated with a similar level of toxicity as LPV/r 400 mg/400 mg twice daily (230,231).

However, this option may be less complex and more feasible, since LPV/r is widely available as a single formulation, whereas RTV is not. However, when rifabutin is used in place of rifampicin, all boosted PIs can be concomitantly administered in their standard doses (Table 7.19).

**Clinical considerations**

Clinical and programmatic simplification can be promoted in the sequencing from first- to second-line ART. If AZT- or d4T-based regimens are failing, a second-line regimen with once-daily dosing for boosted PI and NRTI components (such as TDF + 3TC (or FTC) + ATV/r) should be adopted. If a TDF-based regimen is failing, twice-daily dosing for boosted PI and NRTI components (such as AZT + 3TC + LPV/r) should be adopted.
Key research gaps

Several ongoing studies comparing various drugs and ARV classes (232–236) will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches (the results are expected after 2014). Further investigation is needed of the role of DRV in second- and third-line regimens (optimal dosing in adults and children, once versus twice daily, fixed-dose combinations with other boosting agents and integrase inhibitors and sequencing strategies). Several trials are underway that are examining induction and maintenance using PI/r monotherapy in maintenance. The potential of including rifabutin as part of fixed-dose combinations for TB treatment also needs to be explored.

Table 7.19 Comparative analysis: ATV/r versus LPV/r versus DRV/r

<table>
<thead>
<tr>
<th>Major parameters</th>
<th>ATV/r</th>
<th>LPV/r</th>
<th>DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency with paediatric regimens</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of pills per day (standard dose as a fixed-dose combination)</td>
<td>1</td>
<td>4</td>
<td>2 to 4</td>
</tr>
<tr>
<td>Convenience (once- versus twice-daily regimen)</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Safety in pregnancy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gastrointestinal intolerance (diarrhoea)</td>
<td>Not frequent</td>
<td>Common</td>
<td>Not frequent</td>
</tr>
<tr>
<td>Availability of co-formulations (as heat-stable fixed-dose combinations)</td>
<td>Yes</td>
<td>Yes</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Use with a TB treatment regimen that contains rifampicin</td>
<td>No</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Potential for future reduction in cost</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Accessibility in countries (registration status)</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Availability of generic formulations</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup> Approved only for children >6 years old.
<sup>b</sup> Approved only for children >3 years old.
<sup>c</sup> Only if used in higher doses.
<sup>d</sup> A heat stable FDC is currently under development.
7.5.2 Second-line ART for children (including adolescents)

New recommendations

- After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI. *(Strong recommendation, moderate-quality evidence)*

- After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken. *(Conditional recommendation, very-low-quality evidence)*

- After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI. *(Conditional recommendation, low-quality evidence)*

- After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC. *(Strong recommendation, low-quality evidence)*

- After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC). *(Strong recommendation, low-quality evidence)*

Table 7.20 Summary of recommended first- and second-line ARV regimens for children (including adolescents)

<table>
<thead>
<tr>
<th>Children (including adolescents)</th>
<th>First-line ARV regimen</th>
<th>Second-line ARV regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r-based first-line regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 3 years</td>
<td>ABC + 3TC + LPV/r</td>
<td>No change&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + LPV/r</td>
<td></td>
</tr>
<tr>
<td>3 years and older</td>
<td>ABC + 3TC + LPV/r</td>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + LPV/r</td>
<td>ABC or TDF&lt;sup&gt;b&lt;/sup&gt; + 3TC + EFV</td>
</tr>
<tr>
<td>NNRTI-based first-line regimen</td>
<td>All ages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + EFV (or NVP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF&lt;sup&gt;c&lt;/sup&gt; + 3TC (or FTC) + EFV (or NVP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV (or NVP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC or TDF + 3TC&lt;sup&gt;c&lt;/sup&gt; (or FTC) + LPV/r&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> No change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on the recent approval of the use of EFV in children less than 3 years, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

<sup>b</sup> TDF may only be given to children >2 years.

<sup>c</sup> ATV/r can be used as an alternative to LPV/r in children older than 6 years.
Background

Recommendig potent and effective second-line regimens for infants and children is especially difficult because of the current lack of experience in resource-limited settings and the limited formulations available. This highlights the importance of choosing potent and effective first-line regimens and ensuring their durability and effectiveness by optimizing adherence.

The 2010 WHO guidelines recommended a regimen based on a PI boosted with RTV and combined with two NRTIs as the second-line treatment for children who fail a regimen of two NRTIs plus an NNRTI (105). For infants and young children exposed to an NNRTI as part of PMTCT interventions and starting a PI-based regimen in first-line ART, the recommendation for second-line was to use two new NRTIs and an NNRTI, as this was the only new drug class available.

The recommendations are now better informed by paediatric clinical trial data (156,158, 237) and observational data (157). The Guidelines Development Group also considered operational and programmatic issues including the availability of heat-stable formulations and fixed-dose combinations for children.

Rationale and supporting evidence

After reviewing data for adults and children and considering factors such as the availability of a heat-stable fixed-dose combination, optimal daily dose, regimen harmonization with adults, high cost and availability of alternatives, the main recommendations established in the 2010 guidelines were maintained.

For children for whom a LPV/r-based first-line regimen has failed, NNRTIs remain the only new drug class that can be introduced. Randomized data among older children (158) provide indirect evidence supporting the safe use of an NNRTI-based second-line regimen, but concerns remain about this approach for infants and young children. Based on the suboptimal performance of NVP-based regimens (and the limited data available to inform the use of EFV) in children younger than three years (153,154) and the potential rapid re-emergence of archived NNRTI-resistant HIV, second-line NNRTI-based regimens are expected to have limited durability in this age group (238).

Increasing evidence suggests that, in young children for whom LPV/r-based regimens have failed, selection of major mutations to PI is rare and accumulation of thymidine analogue mutations is very limited (156,237,239,240). In this context and in the absence of robust second-line alternatives such as DRV/r-containing regimens, the Guidelines Development Group recommended that children younger than three years of age should be maintained on LPV/r until the age of three years, despite treatment failure. However, a more rapid switch should be considered in situations in which failure results from poor adherence because of the poor palatability of LPV/r or in cases of advanced HIV disease. In such cases, children younger than three years should be switched to a NVP-based regimen, and close monitoring should be provided to ensure adequate adherence.

For children starting first-line ART with an NNRTI-based regimen, PI-based regimens remain the recommended choice for second-line therapy. LPV/r is the preferred option, but ATV/r and DRV/r may be considered if more appropriate formulations become available.

Despite its toxicity profile and limited role in TB and HIV coinfeciton, ATV/r is a promising alternative to LPV/r for children older than six years of age. ATV/r has some advantages over LPV/r, including lower cost and the potential for once-daily dosing. DRV/r is the PI of choice following LPV/r or ATV/r treatment failure and would be valuable as a third-line drug or as second-line therapy in young children for whom first-line ART with LPV/r has
failed. However, ATV/r is currently only licensed for use among children older than six years and DRV/r in children older than three years. Neither ATV/r nor DRV/r is currently available as a co-formulated fixed-dose combination for children. The Paediatric ARVs Working Group identified appropriate doses of both drugs using current WHO weight bands with scaling down from the current adult fixed-dose combination tablets. Validation studies are urgently needed to develop adequate paediatric formulations.

Unboosted PIs (such as fosamprenavir (FPV), DRV and ATV) and other PIs (such as IDV/r, SQV/r, FPV/r and TPV/r) are associated with reduced virological suppression, high pill burden and/or a higher frequency of side effects and are therefore discouraged (241).

Notably, liquid RTV requires cold storage, is unpalatable, has significant gastrointestinal intolerance and is poorly tolerated by infants and children. The heat-stable 100-mg fixed-dose combination tablet formulation of LPV/r for children is better tolerated but cannot be cut or crushed; many children have difficulty in swallowing this tablet whole. Data on whether LPV/r can be given once daily are expected soon from an ongoing randomized trial (242). New heat-stable paediatric sprinkle formulations appear to be a suitable alternative and will be available in the near future (243).

The sequencing of NRTI was determined based on optimizing principles for ARV drugs and the need to maximize antiviral activity despite the selection of resistance mutations. If a thymidine analogue NRTI drug (AZT or d4T) was used in the failing first-line regimen, ABC or TDF should be used in the second-line regimen. If a non-thymidine analogue NRTI drug (ABC or TDF) was used in the failing first-line regimen, AZT should be used in the second-line regimen. The added value of ddI in second-line regimens is unclear; continuing 3TC despite the likely presence of 3TC resistance is the preferred option. HIV harbouring 3TC resistance with the M184V mutation may have reduced viral replication and may also induce some degree of resensitization to AZT or TDF, although this is based on in vitro data (165,244).

**Key research gaps**

More evidence is needed to inform the choice of second-line regimens for young children for whom an LPV/r-based first-line regimen has failed. Validation studies to assess simplified dosing for ATV/r and DRV/r fixed-dose combinations are critical to ensure future effective alternatives. Innovative second-line strategies such as PI + integrase inhibitors or induction and maintenance using PI/r monotherapy among children should also be investigated.
7. Clinical guidance across the continuum of care: Antiretroviral therapy

7.6 Third-line ART

**New recommendations**

- National programmes should develop policies for third-line ART (*conditional recommendation, low-quality evidence*).
- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs (*conditional recommendation, low-quality evidence*).
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (*conditional recommendation, very low-quality evidence*).

**Background**

In 2010, WHO made recommendations on third-line ART in the context of limited evidence to guide third-line strategies. Although there were few studies of newer agents, cohort data showed high mortality among people for whom second-line ART had failed (245).

**Rationale and supporting evidence**

The Guidelines Development Group maintained the recommendations established in the 2010 WHO guidelines. In so doing, the Guidelines Development Group emphasized balancing the need to develop policies for third-line ART with the need to expand access to first-line and second-line ART. It also recognized that many countries have financial constraints that limit the adoption of third-line regimens.

Data from randomized controlled trials are available for DRV/r, etravirine (ETV) and raltegravir (RAL), but most studies have been conducted in well-resourced or middle- to high-income countries. Taken together, these data support the efficacy of these agents in highly ART-experienced patients. In a published pooled subgroup analysis, DRV/r plus an optimized background regimen (OBR) chosen by genotyping and phenotyping was shown to be superior to the control group (boosted PI + OBR where the investigator selected the boosted PI) among highly treatment-experienced individuals (222). DRV/r was also shown to be non-inferior to LPV/r among treatment-experienced people after 96 weeks (223).

Among individuals with limited treatment options, RAL + OBR provided better virological suppression than the OBR alone for at least 96 weeks (246,247). Similarly, ETV + OBR provided better virological suppression and improved immunological response than the optimized background regimen alone after 96 weeks (248). In people with multidrug-resistant HIV who have few remaining treatment options, the combination of RAL, ETV and DRV/r was well tolerated and was associated with a rate of virological suppression similar to that expected among treatment-naive people (249,250).

Evidence from post-marketing reports indicates higher rates of hypersensitivity to ETV than previously reported (251). ETV + RAL is not approved for use in individuals younger than 16 years of age. There are limited data on the use of these newer drugs in infants, children and pregnancy, including very limited pharmacokinetic and safety data.
Special considerations for children

Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used in treating adults such as ETV, DRV and RAL may be possible (for details on using these drugs in children, see Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

Clinical considerations

The criteria for diagnosing the failure of second-line ART are the same as those used for diagnosing the failure of first-line ART. The demand for second- and third-line regimens will increase as access to viral load monitoring improves and first-line ART continues to be scaled up. Although developing a policy on access to third-line ART is desirable, it should not compromise access to initiation of first-line ART. The costs of potential third-line drugs, such as DRV, ETV and RAL, are not well established in resource-limited settings but are expected to be higher than those of first- and second-line regimens.

Key research gaps

Many areas require more information to guide second- and third-line ART for resource-limited settings, including monitoring critical outcomes for people receiving second-line ART, studying once-daily dosing for DRV/r and RAL as an alternative to NRTI-based regimens in second-line ART, and developing heat-stable formulations of DRV/r. Pharmacovigilance research is needed, including studies on the long-term safety and potential drug–drug interactions with TB, malaria, hepatitis and opioid substitution therapy drugs. As the epidemic matures in low- and middle-income countries, pilot studies are urgently needed on implementing third-line ART in settings with limited capacity and resources in the health system.
Goal of this chapter

To provide a summary of selected existing clinical recommendations and relevant resource documents on preventing and managing common coinfections and comorbidities in the context of the broad continuum of HIV care, with a focus on resource and capacity limited settings.
8 CLINICAL GUIDANCE ACROSS THE CONTINUUM OF CARE: MANAGING COMMON COINFECTIONS AND COMORBIDITIES

Introduction

Various coinfections, comorbidities and other health conditions are common among people living with HIV and have implications for their treatment and care, including the timing and choice of ARV drugs. This section provides a brief overview of the most common and important conditions. It summarizes selected key recommendations from already existing WHO guidelines and related materials, focusing on the screening, prophylaxis and timing of ART for these conditions; it does not cover their broader management. Sources and links are provided for relevant guidelines, including the evidence base and rationale supporting different recommendations. The strength of recommendations and quality of evidence is rated using either the GRADE system (strong or conditional recommendations and high, moderate, low and very low quality of evidence) or an alternative grading used prior to 2008 (A (strongly recommended) to C (optional)) and I–IV (level of evidence). In some cases, the sources and web links only are provided. These recommendations were not reviewed or discussed during the 2013 guideline development process, but are included as part of the consolidation of guidance related to HIV care and ARV drugs.

8.1 Prevention, screening and management of common coinfections

8.1.1 Co-trimoxazole preventive therapy

Background

Co-trimoxazole preventive therapy (CPT) should be implemented as an integral component of a package of HIV-related services. Existing recommendations cover initiation of CPT among adults, adolescents, pregnant women and children for prevention of Pneumocystis pneumonia, toxoplasmosis and bacterial infections, as well as benefits for malaria prophylaxis and discontinuation of CPT.

Source for recommendations


These recommendations will be updated in 2014.
Key selected existing recommendations

Table 8.1 shows the recommendations. Refer to the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes) for methodology used in rating the quality of evidence.

Table 8.1 Criteria for initiating, discontinuing and monitoring co-trimoxazole preventive therapy according to the 2006 WHO guidelines

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria for initiation</th>
<th>Criteria for discontinuation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dose of co-trimoxazole</th>
<th>Monitoring approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-exposed infants</td>
<td>In all, starting at 4–6 weeks after birth (A-III)</td>
<td>Until the risk of HIV transmission ends or HIV infection is excluded (A-I)</td>
<td>See Annex 7</td>
<td>Clinical at 3-monthly intervals (A-III)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>In all&lt;sup&gt;b&lt;/sup&gt; (A-II)</td>
<td>Until 5 years of age regardless of CD4% or clinical symptoms&lt;sup&gt;c&lt;/sup&gt; (A-IV) or Never (A-IV)</td>
<td>See Annex 7</td>
<td></td>
</tr>
<tr>
<td>1–5 years</td>
<td>WHO clinical stages 2, 3 and 4 regardless of CD4 % or Any WHO stage and CD4 &lt;25% (A-I) or In all&lt;sup&gt;c&lt;/sup&gt; (C-IV)</td>
<td>Never (A-IV)</td>
<td>See Annex 7</td>
<td>Clinical at 3-monthly intervals (A-III)</td>
</tr>
<tr>
<td>≥5 years, including adults</td>
<td>Any WHO stage and CD4 count &lt;350 cells/mm&lt;sup&gt;3&lt;/sup&gt; (A-III)&lt;sup&gt;d&lt;/sup&gt; or WHO 3 or 4 irrespective of CD4 level (A-I) or In all&lt;sup&gt;c&lt;/sup&gt; (C-III)</td>
<td>Never (A-IV) or when CD4 ≥350 cells/mm&lt;sup&gt;3&lt;/sup&gt; after 6 months of ART&lt;sup&gt;e&lt;/sup&gt; (C-IV) or CD4 ≥200 cells/mm&lt;sup&gt;3&lt;/sup&gt; after 6 months of ART&lt;sup&gt;e&lt;/sup&gt; (B-I)</td>
<td>See Annex 7: for &lt;30 kg, 960 mg daily</td>
<td>Clinical at 3-monthly intervals (A-III)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Discontinue also if the person has Stevens-Johnson syndrome, severe liver disease, severe anaemia, severe pancytopaenia or negative HIV status.

Contraindications to co-trimoxazole preventive therapy: severe allergy to sulfa drugs; severe liver disease, severe renal disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

<sup>b</sup> In all regardless of CD4 percentage or clinical stage in settings with high HIV prevalence, high infant mortality due to infectious diseases and limited health infrastructure.

<sup>c</sup> If initiated primarily for Pneumocystis pneumonia or toxoplasmosis prophylaxis.

<sup>d</sup> Some countries may choose to adopt a CD4 threshold of <200 cells/mm<sup>3</sup>.

<sup>e</sup> In settings with high prevalence of bacterial infections or malaria.
8.1.2 Tuberculosis

**Background**

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. ART should be provided to all people with HIV with active TB disease. HIV care settings should implement the WHO Three I’s strategy: intensified TB case-finding, isoniazid preventive therapy (IPT) and infection control at all clinical encounters.

**Source for recommendations**


**Additional guidance**

Key selected existing recommendations

TB case-finding and antituberculosis treatment

- Adults and adolescents living with HIV should be screened for TB with a clinical algorithm; those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases (Fig. 8.1) (strong recommendation, moderate-quality evidence) (2).

- Children living with HIV who have any of the following symptoms of poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, children should be offered isoniazid preventive therapy regardless of their age (Fig. 8.2) (strong recommendation, low-quality evidence) (2).

- TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least six months of rifampicin treatment regimen (strong recommendation, high-quality evidence).

  The optimal dosing frequency is daily during the intensive and continuation phases (strong recommendation, high-quality evidence) (2).

- Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having HIV-associated TB or multidrug-resistant TB (strong recommendation) (21).
Key selected existing recommendations

Isoniazid preventive therapy (IPT) (2)

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT (strong recommendation, moderate-quality evidence).

- Duration of IPT
  - Adults and adolescents who are living with HIV, have unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women (strong recommendation, high-quality evidence).

  - Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also those on ART, those who have previously been treated for TB and pregnant women (conditional recommendation, moderate-quality evidence).

- A TST is not a requirement for initiating IPT in people living with HIV (strong recommendation, moderate-quality evidence). People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals (strong recommendation, high-quality evidence).

- Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT (strong recommendation, moderate-quality evidence).

- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB (strong recommendation, low-quality evidence).

- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services (strong recommendation, moderate-quality evidence).

- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease (strong recommendation, low-quality evidence).

- All children living with HIV, after successful completion of treatment for TB disease, should receive isoniazid for an additional six months (conditional recommendation, low-quality evidence).
Every adult and adolescent should be evaluated for eligibility to receive antiretroviral therapy. Infection control measures should be given priority to reduce *Mycobacterium tuberculosis* transmission in all settings that provide care.

Chest radiography can be done if available but is not required to classify people into TB and non-TB groups. In settings with high HIV prevalence and a high TB prevalence among people living with HIV (such as exceeding 10%), strong consideration must be given to adding other sensitive investigations.

Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting IPT. Although not a requirement for initiating IPT, tuberculin skin testing may be performed as a part of eligibility screening in some settings.

Investigations for TB should be performed in accordance with existing national guidelines.

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*Fig. 8.1 Algorithm for TB screening among adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings*
Fig. 8.2 Algorithm for TB screening among children older than one year of age and living with HIV

- **Child more than 12 months of age and living with HIV**
  - Screen for TB with any one of the following symptoms:
    - Poor weight gain
    - Fever
    - Current cough
    - Contact history with a TB case
  - **No**
  - **Yes**
  - **Assess for contraindications to IPT**
    - **No**
      - Give IPT
    - **Yes**
      - Defer IPT
  - **Investigate for TB and other diseases**
    - **Other diagnosis**
      - Give appropriate treatment and consider IPT
    - **Not TB**
      - Follow up and consider IPT
    - **TB**
      - Treat for TB

**Screen for TB regularly at each encounter with a health worker or visit to a health facility**

---

- All infants younger than one year should be provided with IPT if they have a history of household contact with a person with TB.
- Poor weight gain is defined as (1) reported weight loss or very low weight (weight for age less than –3 z-score), (2) underweight (weight for age less than –2 z-score), (3) confirmed weight loss (>5%) since the last visit or (4) growth curve flattening.
- Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. A past history of TB should not be a contraindication to starting IPT. Although not a requirement for initiating IPT, tuberculin skin testing may be performed as part of eligibility screening in some settings.
- Investigations for TB must be performed in accordance with existing national guidelines.
Infection control

Background
People living with HIV are at high risk of acquiring TB in health care facilities and congregate settings. National TB programmes and national HIV programmes should provide managerial direction for implementing TB infection control programmes. Each health care facility should have a TB infection control plan for the facility that includes administrative, environmental and personal protection measures to reduce the transmission of TB in health care and congregate settings and surveillance of TB disease among workers (Box 8.1). Health care workers with HIV should be provided with ART and IPT if they are eligible.

Sources for recommendations

<table>
<thead>
<tr>
<th>Box 8.1. Summary of recommendations for key actions for infection control (3)</th>
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</thead>
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<tr>
<td><strong>Administrative (facility-level infection control committee and protocols)</strong></td>
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<tr>
<td>- A triage system to identify people suspected of having TB</td>
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<tr>
<td>- Separate people with suspected or confirmed TB</td>
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<tr>
<td>- Cough etiquette and respiratory hygiene</td>
</tr>
<tr>
<td>- Rapid diagnosis with Xpert MTB/RIF (with prompt treatment of active TB) <em>(strong recommendation, low-quality evidence).</em></td>
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<td><strong>Health workers and carers</strong></td>
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<tr>
<td>- Surveillance and information</td>
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<td>- Package of care for HIV-positive workers (ART and isoniazid preventive therapy)</td>
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<tr>
<td>- Protective equipment (particulate respirator masks that meet or exceed N95 standards)</td>
</tr>
<tr>
<td>- Relocation for health care workers living with HIV to a lower-risk area <em>(strong recommendation, high-quality evidence).</em></td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
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<tr>
<td>- Ventilation (mechanical)</td>
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<td>- Ventilation (natural)</td>
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<tr>
<td>- Upper-room ultraviolet germicidal irradiation <em>(strong recommendation, low-quality evidence).</em></td>
</tr>
<tr>
<td><strong>Personal</strong></td>
</tr>
<tr>
<td>- Spend as much time as possible outside</td>
</tr>
<tr>
<td>- Cough etiquette</td>
</tr>
<tr>
<td>- Sleep alone while smear-positive</td>
</tr>
<tr>
<td>- Avoid congregate settings and public transport while smear-positive <em>(strong recommendation, low-quality evidence).</em></td>
</tr>
</tbody>
</table>
Key selected existing recommendations

Timing of ART for adults and children with TB

- ART should be started in all TB patients, including those with drug-resistant TB, irrespective of the CD4 count (strong recommendation, low-quality evidence) (4).

- Antituberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, moderate-quality evidence). The HIV-positive TB patients with profound immunosuppression (such as CD4 counts less than 50 cells/mm³) should receive ART immediately within the first two weeks of initiating TB treatment (2).

- ART should be started in any child with active TB disease as soon as possible and within eight weeks following the initiation of antituberculosis treatment irrespective of the CD4 count and clinical stage (strong recommendation, low-quality evidence) (5).

- Efavirenz should be used as the preferred NNRTI in patients starting ART while on antituberculosis treatment (strong recommendation, high-quality evidence) (2).

- Section 7.2 provides more detailed information and recommendations on the co-treatment of TB and HIV.

- More detailed information and recommendations on drug interactions between ARV drugs and TB drugs are available in the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes).

Multidrug-resistant TB and HIV

Background

Multidrug-resistant TB (MDR-TB) is defined as TB that is resistant to at least isoniazid and rifampicin. Patients with both HIV and MDR-TB face complicated clinical management, fewer treatment options and poorer treatment outcomes. Limited information is available about the association between HIV and MDR-TB at the population level, especially because only 40% of the people with active TB are tested for HIV (6). Outbreaks of MDR-TB among people with HIV have been documented in hospital and other settings, especially in eastern Europe and in southern African countries with a high HIV prevalence (7).

People with HIV with suspected drug-resistant TB should be tested using Xpert MTB/RIF where possible, since this test is more sensitive for detecting TB among people with HIV and rapidly detects rifampicin resistance, thus greatly shortening the time to diagnosing and treating MDR-TB.

The burden of MDR-TB should be reduced by strengthening HIV prevention, improving infection control and improving collaboration between HIV and TB control activities, with special attention to the groups at the highest risk of MDR-TB and HIV infection, such as people who inject drugs and those exposed in congregate settings.
8. Clinical guidance across the continuum of care: Managing common coinfections and comorbidities

8.1 Prevention, screening and management of common coinfections

8.1.3 Cryptococcal infection

Background
Cryptococcal meningitis is one of the most important opportunistic infections and a major contributor to high mortality before and after ART is initiated. WHO 2011 Rapid Advice covers diagnosis, screening and prevention of cryptococcal infection, induction, consolidation and maintenance regimens, monitoring and managing toxicities, timing of ART and discontinuing maintenance regimens. Full guidelines will be published at the end of 2013.

Source for recommendations

Key selected existing recommendation (4)
- WHO recommends ART for all patients with HIV and drug-resistant TB, requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of anti-tuberculosis treatment (strong recommendation, very-low-quality evidence).

8.1.3 Cryptococcal infection

Screening and prophylaxis (8)
- Use of routine serum or plasma Cryptococcus neoformans antigen (CrAg) screening in ART-naive adults, followed by pre-emptive antifungal therapy if CrAg-positive and asymptomatic, to reduce the development of cryptococcal disease, may be considered prior to ART initiation in patients with a CD4 count of less than 100 cells/mm³ and where this population also has a high prevalence of cryptococcal antigenaemia (conditional recommendation, low-quality evidence).

- Routine use of antifungal primary prophylaxis for cryptococcal disease in people living with HIV with a CD4 count of less than 100 cells/mm³ and who are CrAg-negative or where CrAg status is unknown is not recommended prior to ART initiation (strong recommendation, high-quality evidence).

- The use of routine CrAg screening and pre-emptive antifungal therapy in ART-naive adolescents and children with a CD4 count of less than 100 cells/mm³ prior to ART initiation is not recommended (conditional recommendation, low-quality evidence).
8.1.4 Hepatitis B and C

**Background**

Chronic hepatitis B virus infection affects 5–20% of the 33 million people living with HIV worldwide, and hepatitis C affects 5–15%, although this may be up to 90% among people who inject drugs (9,10). The burden of coinfection is greatest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for hepatitis B. Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, including those on ART. A comprehensive approach includes prevention, hepatitis B and hepatitis C screening, hepatitis B vaccination and treatment and care for people with HIV coinfected with hepatitis B and/or hepatitis C.

**Additional guidance**


**Guidance on timing of ART in hepatitis B and C**

- Hepatitis B: when to start and what to start. See sections 7.1.1 and 7.2.1
- Hepatitis C: when to start and what to start. Initiating ART among people with HIV and hepatitis C should follow the same general principles as for the general population of people living with HIV (section 7.1).

The WHO guidelines for the management of hepatitis C are scheduled to be published in 2014. They will provide detailed guidance on hepatitis C screening, hepatitis C–specific treatment and general hepatitis C care.
8.1 Prevention, screening and management of common coinfections

8.1.5 Malaria

Background

People with HIV with immunosuppression living in malaria-endemic areas are at high risk of complications of malaria, and all infants and children under five years of age and pregnant women are at particular risk of severe malaria and its complications.

Key interventions to control malaria include prompt and effective treatment with artemisinin-based combination therapies and using insecticide-treated nets and indoor residual spraying with insecticide to control the vector mosquitoes. An additional intervention recommended in areas of high transmission for specific high-risk groups is intermittent preventive treatment during pregnancy and seasonal malaria chemoprophylaxis.

People living with HIV who develop malaria should receive prompt, effective antimalarial treatment regimens. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or a rapid diagnostic test.

The drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa- based drugs) and may have clinically important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and PIs). For this reason, people receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions, and people with HIV receiving AZT, or EFV should, if possible, avoid amodiaquine-containing artemisinin-based combination regimens because of increased risk of neutropaenia in combination with AZT, and hepatotoxicity in combination with EFV.

Source for recommendations


Additional guidance


Key selected existing recommendations (11)*

- In areas of stable malaria transmission, people living with HIV (as for the general population) should routinely use insecticide-treated bed-nets or have access to indoor residual spraying to reduce their exposure to malaria infection. (A-I)

- Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to patients with HIV receiving co-trimoxazole prophylaxis. (A-III)

*See the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes) for methodology used in rating quality of evidence.

8.1.6 Sexually transmitted infections and cervical cancer

Background

HIV, other sexually transmitted infections and non-sexually transmitted infections of the reproductive tract frequently coexist. Most of these infections are asymptomatic, especially among women. However, even asymptomatic sexually transmitted infections can cause complications, be transmitted to sexual partners and enhance HIV transmission. Further, HIV infection alters the natural history of sexually transmitted infections. The objectives of diagnosing and managing sexually transmitted infections include identifying the infection and providing appropriate treatment and preventing transmission. Screening, diagnosis and treatment of sexually transmitted infections should be offered routinely as part of comprehensive HIV care among adults and adolescents.

WHO guidelines on treating and managing sexually transmitted infections are scheduled to be updated in 2014. Other recent guidelines cover recommendations on periodic screening and periodic presumptive treatment for asymptomatic sexually transmitted infections in sex workers, and periodic testing for asymptomatic urethral and rectal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections and asymptomatic syphilis infection among female sex workers, men who have sex with men and transgender people.

Cervical cancer is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer. The risk and persistence of human papillomavirus (HPV) infection increases with decreasing CD4 count and increasing HIV viral load. Invasive cervical cancer is a WHO HIV clinical stage 4 condition. Women living with HIV should be followed closely for evidence of pre-cancerous changes in the cervix, regardless of ART status or CD4 count and viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. Thus, all women with HIV should be screened for cervical cancer regardless of age. Immediate management for pre-cancerous and cancerous lesions should be provided. WHO guidance covers HPV vaccination and prevention, screening and treatment and palliative care of cervical cancer. To date, concerns about safety or reduced efficacy among females who may be infected with HIV should not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization.
Additional guidance

Sexually transmitted infections

- WHO guidelines on the syndromic approach to managing people with symptoms of sexually transmitted infections and treating specific sexually transmitted infections are scheduled to be updated in 2014.

Cervical cancer


8.1.7 Vaccines for people living with HIV

Background

People living with HIV should be assessed for eligibility for vaccination at all stages of care. HIV-exposed infants and children and young adults with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules. Those with more severe immunosuppression may be at higher risk of complications from live vaccines. Inactivated vaccines are more effective among people receiving ART and those without immunosuppression, but they are safe and can be used with some efficacy in all groups.
Additional guidance


- For position papers on each vaccine, and statement about use in people living with HIV: (www.who.int/immunization/documents/positionpapers/en/index.html).

### 8.2 Preventing and managing other comorbidities and chronic care for people living with HIV

#### 8.2.1 Screening for and care of noncommunicable diseases

**Background**

People living with HIV are at increased risk of developing a range of noncommunicable diseases (NCDs), including cardiovascular disease, diabetes, chronic lung disease and some types of cancer (12,13). With effective ART, people living with HIV are also living longer and experiencing NCDs associated with ageing. Both HIV and NCDs require health systems that can deliver effective acute and chronic care and support adherence to treatment. Chronic HIV care provides the opportunity for screening, monitoring and managing NCDs, especially through primary care. Integrating interventions such as nutrition assessment, dietary counselling and support, smoking cessation, promoting exercise, monitoring blood pressure and where available cholesterol as part of HIV care provide opportunities for reducing the risks of NCDs among people living with HIV. WHO has defined a package of essential NCDs (WHO PEN) interventions along with recommendations on screening for and treating NCDs. Additional guidance on diagnosis and management of NCDs in people living with HIV is planned for 2014.

**Additional guidance**


8. Clinical guidance across the continuum of care: Managing common coinfections and comorbidities

8.2 Preventing and managing other comorbidities and chronic care for people living with HIV

### 8.2.2 Mental health

**Background**

People living with HIV and their carers may have a wide range of mental health needs. The most common mental health comorbidities among people living with HIV include depression, anxiety, dementia and other cognitive disorders and substance use disorders. HIV care settings provide an opportunity to ensure the detection and management of mental disorders among people living with HIV. Treatment or lack of treatment for these conditions can affect adherence to ARV drugs, retention in care and may involve potential side effects and drug interactions.

WHO has no specific recommendations on screening and treatment for mental disorders among people living with HIV. The Mental Health Gap Action Programme (mhGAP) intervention guide for mental, neurological and substance use disorders in non-specialized health settings makes recommendations related to general mental health that can be relevant to people living with HIV. Additional guidance on management of mental health conditions in people living with HIV is planned for 2014.

**Additional guidance**


### 8.2.3 Drug use and drug use disorders

**Background**

People living with HIV who use drugs may experience a range of disorders related to their drug use, including drug dependence, intoxication, withdrawal and overdose. Injecting drug use is associated with a range of bloodborne and local infections, including viral hepatitis, septicaemia and bacterial endocarditis, in addition to HIV.

WHO has developed guidance for the treatment of opioid dependence and prevention of hepatitis B and C among people who inject drugs.

WHO, UNODC and UNAIDS recommend a comprehensive package of nine interventions for HIV prevention, treatment and care for people who inject drugs, including needle and syringe programmes, opioid substitution therapy, HIV testing and counselling, ART, preventing and treating sexually transmitted infections, condom programmes, targeted behaviour change communication, preventing and treating viral hepatitis and preventing and treating TB.

**Additional guidance**

8.2.4 Nutritional care and support

8.2.4.1 Among adolescents and adults living with HIV

Background

Low energy intake combined with increased energy demands because of HIV infection (14–17) and related infections may lead to HIV-related weight loss and wasting. In addition, an altered metabolism, reduced appetite and higher incidence of diarrhoea may lower nutrient intake and absorption and also lead to nutrient losses. These effects may all be compounded in low income, food insecure contexts. Low body mass index (less than 18.5 kg/m²), weight loss and wasting in children are all independent risk factors for HIV disease progression and mortality (18,19). Nutritional assessment (anthropometry, clinical and dietary assessment), counselling and support should be an integral component of HIV care and conducted at enrolment in care and monitored during all HIV care and treatment. Malnourished HIV patients, especially in food insecure contexts, may require food supplements, in addition to ART, to ensure appropriate foods are consumed to support nutritional recovery. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection or ART should trigger further assessment and appropriate interventions.

WHO is currently revising recommendations for nutritional care and support of adolescents and adults living with HIV, including pregnant and lactating women.

8.2.4.2 Among children living with HIV

Background

Nutritional assessment is essential to identify malnutrition and growth faltering early. Infants and children should undergo initial nutritional assessment (evaluation of nutritional status, diet and symptoms) and then be weighed and have height measured at each visit and monitored with reference to WHO or national growth curves. Growth monitoring should also be integrated into the assessment of ART response (20). If poor growth is identified, then further assessment should be performed to determine the cause, and plan appropriate response. The 2009 guidelines for an integrated approach to the nutritional care of children living with HIV provide details of nutritional interventions.

Additional guidance


vii Body mass index: indicates adequacy of weight in relation to height for older children, adolescents and adults. It is calculated as the weight in kg divided by the height in metres squared. The acceptable range for adults is 18.5 to 24.9, and for children this varies with age.
8.2.5 Palliative care: symptom management and end-of-life care

Background
Throughout all stages of HIV disease, and when receiving treatment, people living with HIV may experience various forms of pain and other discomfort. Care providers should identify and treat the underlying cause when possible, while controlling the pain. Further, effectively managing the side effects of ART is important to support adherence.

Additional guidance

8.2.6 Other relevant general guidance on care

8.2.6.1 Family planning, counselling and contraception

Additional guidance
8.2.6.2 Providing safe water, sanitation and hygiene

Additional guidance


**Goal of this chapter**

To provide guidance on key issues related to operations and service delivery that need to be addressed to strengthen the continuum of HIV care and further integrate the provision of ARV drugs into health systems.
9 GUIDANCE ON OPERATIONS AND SERVICE DELIVERY

9.1 Introduction

ARV drugs and related services need to be delivered as effectively, equitably and efficiently as possible by optimizing available human and financial resources, ensuring appropriate links between care settings and services, supporting adherence to lifelong treatment and maximizing retention of patients across the continuum of care. This chapter provides broad guidance in six operational and service delivery areas in which action is essential to ensure the long-term effectiveness and sustainability of ARV programmes. These areas are:

- adherence to ART;
- retention across the continuum of care;
- service delivery, comprising service integration and linkage and decentralization of HIV care and treatment;
- human resources, including task shifting;
- laboratory and diagnostic services; and
- procurement and supply management systems.

New recommendations, developed through the GRADE process, are found in the sections on adherence and service delivery and human resources and include: text messages to promote adherence; ART integration into and linkage with maternal and child health, TB and opioid substitution therapy services; decentralization of ART; and task shifting.

9.2 Adherence to ART

9.2.1 Barriers to adherence

WHO defines treatment adherence as “the extent to which a person’s behaviour – taking medications, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” [(1)]. For ART, a high level of sustained adherence is necessary to (1) suppress viral replication and improve immunological and clinical outcomes; (2) decrease the risk of developing ARV drug resistance; and (3) reduce the risk of transmitting HIV.

Multiple factors related to health care delivery systems, the medication and the person taking ARV drugs may affect adherence to ART. The individual factors may include forgetting doses; being away from home; changes in daily routines; depression or other illness; a lack of interest or desire to take the medicines; and substance or alcohol use. Medication-related factors may include adverse events; the complexity of dosing regimens; the pill burden; and dietary restrictions. Health system factors may include requiring people with HIV to visit health services frequently to receive care and obtain refills; travelling long distances to reach health services; and bearing the direct and indirect costs of care. Lack of clear information or instruction on medication, limited knowledge on the course of HIV infection and treatment...
and adverse effects can all be barriers to adherence to ART. Moreover, uninterrupted ARV drug supply and continuity of care are essential for people to adhere to their medication. Lack of continuity of care is a strong predictor of non-adherence in the longer term. Adherence to ART may also be challenging in the absence of supportive environments for people living with HIV and due to HIV-related stigma and discrimination (2,3).

Pregnant and postpartum women

The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence. Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Other challenges during this period may include dealing with the diagnosis of HIV infection (many women learn about their HIV infection during routine screening during pregnancy); concerns about how ART affects the health of the fetus; pill burden; the number of clinic visits during pregnancy; fear of disclosure of HIV status to partners; long waiting times at clinics; and lack of follow-up and transfer to other clinics after delivery (4,5).

Adolescents

Adherence challenges faced by adolescents include a potentially large pill burden if they are treatment-experienced; stigma and fear of disclosure; concerns about safety of medications; adverse effects; peer pressure and perceived need to conform; not remembering to take medications; and inconsistent daily routine. The transition from paediatric to adolescent care presents several challenges that may affect treatment adherence in adolescents. These include assuming increased responsibility for their own care (which may lead to treatment interruptions because of forgetfulness); an inability to navigate the health care system; lack of links between adult and paediatric services; lack of health insurance; and inadequately skilled health care providers (6,7). Depression and substance use have also been shown to present challenges in adolescents.

Infants and children

Adherence among children is a special challenge. The limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements, dietary restrictions, loss of primary caregiver, difficulties in swallowing tablets and adverse effects may all affect adherence (3,8,9). Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of children living with HIV may themselves be living with HIV; suboptimal HIV care and treatment for family members could result in suboptimal care for the child.

Mental health disorders

Adherence to ART is known to be complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Studies have linked uncontrolled depressive symptoms with low levels of adherence to ART and poor treatment outcomes. As a result, several treatment strategies target depression and psychosocial stress to improve adherence to ART, ranging from co-counselling for HIV and depression to appropriate medical therapies for individuals with mental disorders (10–13).

Substance use disorders

Individuals with substance use disorders may have poor adherence to ART. Alcohol and other drug use could be associated with forgetfulness, poor organization and diversion of monetary and time priorities (10,14–16).
Most-at-risk populations (including sex workers, men who have sex with men, transgender people and people who inject drugs)

In several settings, most-at-risk populations face multiple challenges to accessing health services. Service delivery approaches to improve longitudinal care and maintain adherence for most-at-risk populations remains a critical gap in many settings. Experience indicates encouraging results with peer-based interventions that include strong social support such as outreach teams, peer educators and health workers providing multidisciplinary, non-judgemental and respectful care.

Incarceration

Incarceration may negatively affect continuity of care, diminish trust and predispose individuals to poor financial and social support both during and after incarceration. Substance use disorders may also be an additional challenge for this population. People who are incarcerated have the additional risk of acquiring TB, resulting in high morbidity and mortality rates in the absence of efficacious HIV and TB treatment (17). However, excellent outcomes can be achieved with adequate support and structured treatment programmes within the prison setting.

9.2.2 Interventions to optimize adherence to ART

No single adherence intervention or package of interventions is effective for all populations and all settings. People’s needs and circumstances may also change over time, and programmes and care providers therefore need to tailor a combination of feasible interventions to maximize adherence to ART based on individual barriers and opportunities.

Programme-level interventions for improving adherence to ART include: (1) avoiding imposing out-of-pocket payments at the point of care, (2) using fixed-dose combination regimens for ART and (3) strengthening drug supply management systems to reliably forecast, procure, and deliver ARV drugs and prevent stock-outs.

The individual-level adherence intervention recommendation in this section relates to the use of mobile phone text messages. There have been simple and robust trials to demonstrate its importance as one of many adherence tools. Adherence interventions, such as text messaging, should clearly be provided as part of a total package of several interventions. Many individual-level adherence interventions are indicated for reasons in addition to improving adherence to ART. For example, nutritional support, peer support, management of depression and substance use disorders and patient education are vital components of routine health and HIV care.

Efforts to support and maximize adherence should begin before ART is initiated. Developing an adherence plan and education are important first steps. Initial patient education should cover basic information about HIV, the ARV drugs themselves, expected adverse effects, preparing for treatment and adherence to ART. Adherence preparation should not delay treatment initiation, when prompt action is necessary.

Patient education and counselling and peer support

Patient education and counselling are essential both when ART is initiated and throughout the course of treatment. Informing and encouraging people receiving ART and their families and peers are essential components of chronic HIV care. Studies show that counselling improves adherence to ART, and in some settings there is an association between peer support and high rates of adherence and retention (18–23).
Substance use and mental health interventions

Studies indicate that improving well-being by treating depression and managing substance use disorders improves HIV treatment outcomes. The systematic review identified very-low-quality evidence from one observational study evaluating opioid substitution therapy for improving adherence. After 12 months, the rates of unsuppressed viral loads were comparable among people who inject drugs using opioid substitution therapy and people who inject drugs without opioid substitution therapy (24). The systematic review also identified very-low-quality evidence from one randomized trial evaluating the treatment of depression for improving adherence. After 12 months, the risk of non-adherence was similar among those who received depression treatment and those who did not (25). WHO recommends co-treatment of depression and substance use disorders irrespective of HIV status, and concurrent treatment should be evaluated in relation to adherence to ART. Other services for people living with HIV who use drugs, such as needle and syringe programmes, drug dependence treatment and peer outreach, provide opportunities for supporting treatment adherence.

Nutritional support

Nutrition assessment, care and support are essential components of HIV care. HIV programmes should ensure that existing national policies on nutritional support are observed when it is necessary and feasible to maximize adherence to ART and achieve optimal health outcomes in food-insecure settings.

Nutritional support could include nutritional counselling, cash transfers and subsidizing food costs and/or food vouchers. ART in conjunction with nutritional support could accelerate recovery. The systematic review identified one study from low- and middle-income countries with low-quality evidence showing that nutritional support provided by community health workers to people receiving ART reduces the risk of non-adherence after one year among food-insecure individuals relative to the standard of care (26).

Financial support

Financial support may include reimbursement for the costs of receiving HIV care (including drugs, diagnostics, clinical services and transport vouchers) and may potentially mitigate the burden of HIV in disadvantaged settings. The systematic review identified very-low-quality evidence that financial support reduces the risk of non-adherence one year post-intervention relative to the standard of care (27). Programmes and care providers should consider a broader programmatic approach for reducing the costs of care for people living with HIV that would include avoiding out-of-pocket payments at the point of care, decentralizing and coordinating care and exploring opportunities to minimize health facility visits. Programmes need to consider ethical implications and equity in providing food and financial support or other similar interventions for people living with HIV and not others. Standardized criteria for supporting people receiving ART may need to be developed based on national poverty levels.

Reminder and engagement tools

New recommendation

- Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions (strong recommendation, moderate-quality evidence).
Background

Forgetfulness and changes in daily routines are often cited as the main reasons for poor adherence to ART in most settings, although the specific reasons for forgetting to take medication could vary. Reminders and communication that engage people in taking ARV drugs could be an important intervention to improve adherence through behavioural change.

The use of mobile text messages for supporting adherence and in health care delivery in general has increased as access to phone technology expands (28). Using this, however, requires adequate national regulations to protect the privacy of the people receiving text messages (29,30). Programmes may explore public-private partnerships to accelerate the scaling up of mobile phone–based interventions.

Rationale and supporting evidence

Mobile phone technology may be a convenient reminder mechanism to engage people living with HIV in care. Moreover, since mobile phones are widely used globally, using them may not require major changes to people’s daily routines. Mobile phone text messaging is also relatively inexpensive or without marginal cost, is a succinct way of sending a message without the need to talk and offers a record of messages.

The systematic review identified five randomized trials and two observational studies on mobile phone text messaging for improving adherence to ART. High-quality evidence from two randomized trials found that text messages contributed to reduced unsuppressed viral loads after one year (31,32). This finding was consistent with high-quality evidence from three randomized trials that found reduced non-adherence levels after one year (31,33,34).

Four observational studies evaluated the use of text messaging for less than one year. Very-low-quality evidence from one observational study found reduced unsuppressed viral loads after nine months (35). Although moderate-quality evidence from two randomized trials showed similar non-adherence levels after 4–6 months (36,37), very-low-quality evidence from two observational studies suggests reduced non-adherence levels after 6–9 months (35,38). Overall, the systematic review supports the use of text message reminders, although the quality of the data was variable and duration of follow-up short (up to one year).

Other patient reminders

Other patient reminder tools include alarms, phone calls, electronic diaries and calendars and are used to send brief reminders about the timing of ARV drugs, drug dosage and appointments. The evidence does not demonstrate that these interventions support treatment adherence better than the standard of care.

The systematic review identified four randomized trials. Moderate-quality evidence from one randomized trial found that the risk of unsuppressed viral loads was similar after 18 months of follow-up using alarms versus the standard of care (19). Low-quality evidence from one randomized trial also found that rates of non-adherence and unsuppressed viral loads were similar after three months using phone calls compared with the standard of care (39). Very-low-quality evidence from one randomized trial further found that the risk of unsuppressed viral load and non-adherence was similar after 15 months using diaries relative to the standard of care (40). Finally, low-quality evidence from one randomized trial found that non-adherence was similar using calendars relative to the standard of care after one year of follow-up (41). Using these interventions requires further exploration among different populations and settings.
9.2.3 Monitoring adherence to ART in routine programme and care settings

Objective monitoring of adherence to ARV drugs is necessary for effective and efficient treatment planning and ongoing support. Each facility visit brings opportunity for assessing and supporting treatment adherence. Effectively monitoring adherence requires a combination of approaches based on human and financial resource capacity, acceptability to people living with HIV and to health workers and the local context.

Viral load monitoring

These guidelines recommend viral load monitoring to diagnose and confirm treatment response and failure. Although treatment failure is often caused by lapses in adherence to ART, it may also result from other factors (such as drug stock-outs, drug interactions or malabsorption). However, viral load monitoring does not provide an opportunity for care providers to monitor non-adherence in real time and prevent progression to treatment failure. Viral load monitoring must therefore be combined with other approaches to monitoring adherence.

Pharmacy refill records

Pharmacy refill records provide information on when people living with HIV pick up their ARV drugs (42,43). When people obtain pharmacy refills at irregular intervals, this may indicate non-adherence to ART; however, in many routine care settings, people may pick up their medications when receiving care irrespective of their adherence level. This behaviour could lead health care providers to overestimate adherence by solely using pharmacy refill records. A recent validation study to assess the usefulness of various adherence monitoring approaches found pharmacy records to be more reliable than self-report (44). In many settings, pharmacy refill records are already a part of national monitoring and evaluation frameworks and can also provide additional information on adherence to ART when used in combination with other tools.

Self-report

Asking people living with HIV or their caregivers how many doses of medication they have missed since the last visit (or within a specified number of days in the past) can help to estimate non-adherence. However, although this method is commonly used, people may not remember missed doses accurately or may not report missed doses because they want to be perceived as being adherent and to avoid criticism. Counselling on the importance of remembering and/or documenting ARV drug doses and an environment that promotes and enables honest reporting of non-adherence are critical components of monitoring adherence to ART in routine care settings (45).

Pill counts

Counting the remaining pills in bottles may help to assess adherence. Pill counts usually take place at routine health care visits. However, some people may throw away tablets prior to health care visits, leading to overestimated adherence (45,46). Although unannounced visits at people’s homes could lead to more accurate estimates, this approach poses financial, logistical and ethical challenges. Counting pills also requires health care personnel to invest significant time and may not be feasible in routine care settings.
9.3 Retention across the continuum of care

9.3.1 Background

Retaining people living with HIV across the continuum of care is essential for optimal health outcomes. Among those who do not have immediate indications for ART, care visits provide opportunities for screening, prevention and treatment of other conditions and comorbid illnesses, including providing co-trimoxazole prophylaxis, PMTCT, isoniazid preventive therapy and regular screening for TB and clinical and laboratory monitoring to allow timely initiation of ART once the indications arise. For people who are eligible for ART at the time they test HIV-positive, rapid linkage to care is critical; delays of days or weeks with people already being ill with TB or other opportunistic infections increases the risk of mortality (47,48). For people living with HIV who are receiving treatment, uninterrupted ART and continual monitoring are essential for sustained viral suppression and optimal treatment outcomes.

Retaining people living with HIV in care, especially people who are not yet eligible for ART and those who are eligible but have not yet initiated treatment, poses a great challenge. Synthesis of available literature from sub-Saharan Africa showed that 54% of those who are not yet eligible for ART were lost to follow-up before becoming eligible, while 32% of the people living with HIV who were eligible for ART were lost before initiating treatment (49,50). Outcomes among those lost to follow-up may vary, as loss to follow-up reported at the health facility level can include people who have self-transferred to another facility, unascertained deaths and true losses to follow-up. People who discontinue care – especially those who are not eligible for ART at initial assessment – frequently return to care only after they become ill with advanced HIV disease, when early mortality after initiating ART is significant (51,52). Data on the proportion of people who remain on ART over time in low- and middle-income countries show that most discontinued care occurs within the first year of starting therapy. In some settings, many people living with HIV who are lost to follow-up in the first months after initiating ART have died (53). In 2011, the average retention rate at 12 months after initiating ART was 81% (92 reporting countries), 75% at 24 months (73 reporting countries) and 67% at 60 months (46 reporting countries) (53).

Multiple factors relating to the health care delivery systems and patients could facilitate or hinder retention in HIV care. Interventions to improve linkage to and retention in HIV care, from diagnosis and across the continuum of care, need to address issues reported by the people receiving care and related to the health system and require a more targeted evaluation in different settings and populations (54–57).

9.3.2 Good practices for retention across the continuum of care

Optimizing retention in HIV care requires interventions at multiple levels of the health care system as well as implementation research. Given the broad array of challenges and heterogeneity of barriers across settings, no single approach is likely to work for everyone in all settings. Improving the understanding of barriers and innovative strategies to address them are important priorities in implementation research and public health.

Studies show that the direct and indirect costs of care affect the ability of people living with HIV to remain in care. They consistently report that the distance from health care facilities is a barrier to retention in diverse settings and along the continuum of HIV care. Related transport costs and loss of income while seeking care serve as disincentives when health facilities are located far from the person’s home. Bringing services closer to
communities, where feasible, reduces the indirect costs of care for the people living with HIV and their families and improves retention.

Waiting times at the facility during consultation are frequently high, especially in settings with a high burden of HIV infection \((58, 59)\). Reorganizing services, such as systems for appointment, triage, separating clinical consultation visits from visits to pick up medicine, integrating and linking services and family-focused care may reduce waiting times at the health facility \((59, 60)\).

Many people living with HIV who are not yet eligible for ART may not attend clinic appointments and may not return to care until they are symptomatic. Regularly following up these individuals is important to ensure continual monitoring and timely initiation of ART. Countries have used approaches and achieved positive outcomes, including providing co-trimoxazole prophylaxis free of user charges, on-site or immediate CD4 testing with same-day results and peer support to improve retention in care \((22, 61, 62)\).

Key populations generally experience more barriers to accessing health services. Interventions harnessing social support have emerged as a promising approach to counteract the structural, economic, service delivery and psychosocial constraints that affect retention in care.

Table 9.1 summarizes the factors related to the health system and people receiving ART influencing retention and adherence and potential interventions.

### Table 9.1 Factors related to the health system and people receiving ART affecting retention and adherence with possible interventions

<table>
<thead>
<tr>
<th>Factors related to the health system</th>
<th>Possible interventions</th>
</tr>
</thead>
</table>
| High direct and indirect costs of receiving care | - ART and related diagnostics and services free of charge at the point of care  
- Decentralize ART where feasible  
- Scheduled facility visits  
- Reduce waiting time at the facility level:  
  - Appointment system  
  - Separate clinical consultation visits from appointments for picking up medicines  
  - Link, integrate and coordinate care  
  - Family-focused care (organizing services around the needs of the family) when appropriate |
<p>| Stock-outs of ARV drugs | Optimize pharmaceutical supply management systems to forecast, procure and deliver ARV drugs. Use fixed-dose combinations to simplify forecasting and supply management systems |
| Lack of a system for monitoring retention in care | Implement systems for patient monitoring across the continuum of care, including cohort analysis and patient tracking systems |</p>
<table>
<thead>
<tr>
<th>Factors related to the health system</th>
<th>Possible interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of a system for transferring people across different points of care</td>
<td>Interlinked patient monitoring system across services for HIV, TB, maternal and child health and PMTCT; system for transitioning from paediatric to adolescent and adult services and from maternal and child health and TB services to chronic HIV care</td>
</tr>
<tr>
<td>Pill burden and complex ARV drug regimens</td>
<td>Use fixed-dose combinations to reduce the pill burden and simplify the regimens</td>
</tr>
<tr>
<td>Lack of accurate information for patients and their families and peer support</td>
<td>Engage and integrate community health workers, volunteers and people living with HIV in peer support, patient education and counselling, and community-level support</td>
</tr>
<tr>
<td>Adherence support</td>
<td>Task shifting for involving community health workers</td>
</tr>
<tr>
<td></td>
<td>Linking with community-level interventions and resources such as peer adherence support</td>
</tr>
<tr>
<td></td>
<td>Using known effect reminder methods (such as text messaging)</td>
</tr>
<tr>
<td></td>
<td>Peer support also provides opportunities for in-person reminders</td>
</tr>
<tr>
<td>Poor relationship between patient and care provider</td>
<td>Train health workers on how to: reduce stigma; improve treatment preparedness, adherence and retention; provide adherence support and care for key populations; and provide simplified approaches for educating patients and their families</td>
</tr>
<tr>
<td>Lack of time for educating people in HIV care</td>
<td>Task shifting and sharing among clinic team members</td>
</tr>
<tr>
<td></td>
<td>People living with HIV as patient experts and peer supporters</td>
</tr>
<tr>
<td></td>
<td>A team approach to care</td>
</tr>
<tr>
<td>Adverse drug effects</td>
<td>Preparedness and knowledge of how and when to self-manage adverse effects and when to return to the clinic</td>
</tr>
<tr>
<td>Factors related to the people receiving HIV care</td>
<td>Possible interventions</td>
</tr>
<tr>
<td>Forgetfulness, life stress, stigma and discrimination</td>
<td>Using text messaging to keep patients engaged</td>
</tr>
<tr>
<td></td>
<td>Peer and family support</td>
</tr>
<tr>
<td></td>
<td>Link to community support group</td>
</tr>
<tr>
<td>Comorbidity, substance and alcohol use disorders and mental health disorders</td>
<td>Manage HIV with mental health disorders, alcohol and other substance use disorders and link with community and social support</td>
</tr>
<tr>
<td>Patient knowledge and beliefs related to HIV infection, its course and treatment</td>
<td>Integrate the education of patients and their families and counselling, broader community literacy and education and community engagement</td>
</tr>
</tbody>
</table>
9.4 Service delivery

9.4.1 Good practices in providing chronic care (63)

In many countries, health services are organized primarily to provide episodic acute care. As HIV begins to become a manageable, chronic condition, programme managers and care providers need to consider how current health delivery systems can be reorganized to provide chronic care.

Once people are diagnosed and enrolled in chronic care, follow-up visits should be scheduled and planned. Waiting until people present with symptoms or preventable complications is costly and inefficient. People living with HIV require care that anticipates their needs at different stages of the care continuum. Compared with the acute care model, planned chronic care models provide opportunities for prevention, early identification of issues and timely intervention.

Chronic care requires broad support for people living with HIV from their communities and health care teams to stay in care, adhere to treatment and cope with stigma. People living with HIV and their families need to be informed about HIV infection and the anticipated side effects of medicines and supported to adhere to treatment. Health care teams play an important role in linking people living with HIV with community-level interventions, resources and support.

A system to keep information on the people receiving care at health facilities is critical for ensuring the continuity of chronic care. A patient registry serves a reminder function for follow-up services. Health care teams can use it to identify people’s needs, to follow-up and plan care, to monitor responses to treatment and to assess outcomes for both individuals and for the overall treatment cohort. Information systems can be paper-based or based on an electronic registry, depending on local context. Programmes should develop a systematic strategy for collecting and aggregating key information that supports better management of the patient and ensures high-quality care. A robust patient information system is also critical for high-quality monitoring and evaluation of programmes and for supply management systems.

When effective operational solutions such as successful service delivery models and processes of care are identified in existing systems, programmes need to consider scaling up such models of care.

9.4.2 Integrating and linking services

Chronic care requires integrating and linking related services to ensure comprehensive and consistent patient management over time, including providing related services in single settings, systems to share information and effective referrals across settings and providers. Integrating and linking services are likely to reduce missed opportunities for initiating ART, enhance long-term adherence support and optimize patient retention in care. Programmes for HIV, sexual and reproductive health, maternal and child health, TB and drug dependence need to collaborate to successfully implement ART and related services at different levels of the health system. Issues to be considered include mobilizing and allocating resources; training, mentoring and supervising health workers; procuring and managing drugs and other medical supplies; and monitoring and evaluation.
9.4.2.1 **Delivering ART in antenatal care and maternal and child health settings**

**New recommendation**

- In generalized epidemic settings, ART should be initiated and maintained in eligible pregnant and postpartum women and in infants at maternal and child health care settings, with linkage and referral to ongoing HIV care and ART, where appropriate *(strong recommendation, very-low-quality evidence)*.

**Background**

In 2011, coverage of effective ARV drug regimens for PMTCT reached 57% in low- and middle-income countries. However, in the same year, only 30% of pregnant women who needed ART for their own health received it, compared with 54% ART coverage for all eligible adults in low- and middle-income countries *(53)*. Ensuring access to ART for pregnant women with HIV who are eligible for treatment continues to be a challenge, as does provision of ARVs for PMTCT among pregnant adolescent girls living with HIV, female sex workers and women who inject drugs.

Because many women living with HIV only access health services at the time of pregnancy, maternal and child health settings provide a key opportunity to expand access to ART for those who need treatment *(56, 57)*. In most generalized epidemic settings, maternal and child health services are provided at the primary care level, where pregnant women and children predominantly access health services. Existing WHO guidance recommends that provider-initiated HIV testing and counselling be implemented in all antenatal and maternal and child health care settings in generalized epidemics and that it should be considered in antenatal and maternal and child health settings for key populations in concentrated and low-level epidemics *(64)*.

These 2013 guidelines recommend that triple-drug ART or ARV prophylaxis be initiated among all pregnant and breastfeeding women living with HIV, regardless of CD4 count, and that countries decide whether to continue this for all pregnant and breastfeeding women or just those who are eligible for treatment for their own health. Therefore, ART should be available in maternal and child health clinics or easily accessible in a linked clinic approach. Countries with generalized epidemics may consider a phased approach to providing ART in maternal and child health settings and effectively transforming such settings into ART sites, giving priority to facilities with the largest burden of HIV and building health systems to ensure uninterrupted ART, adherence and retention.

A challenge is to continue ART beyond the mother-to-child transmission risk period. Not all maternal and child health settings will have capacity to provide long-term HIV care and treatment for women, their partners and infants. These settings will need to assess the best time for referring and linking mothers and their infants to chronic HIV care. This assessment may include the women’s progress in treatment and the capacity and quality of HIV care in the maternal and child health setting as well as the acceptability and proximity of alternative HIV care settings.
Rationale and supporting evidence

The systematic review evaluated the effect of delivering HIV care and treatment in antenatal care and maternal and child health settings on access to ART, mortality, morbidity and retention on ART in generalized epidemic settings. One cluster-randomized trial and three observational studies assessed the impact of delivering ART in antenatal care and maternal and child health settings compared with referring people to HIV care clinics for ART. This positively influenced adherence to ART during pregnancy, enrolment in care and the uptake of ART among women living with HIV. Comparable outcomes were observed for maternal mortality, morbidity, immune response, infant HIV testing uptake, mother-to-child transmission and satisfaction with care. The quality of some of these studies was downgraded because of relatively few events (65–70).

The alternative to providing ART in antenatal care and maternal and child health settings is to refer eligible women and infants to HIV facilities to receive HIV treatment. Referral systems may contribute to the low ART coverage among pregnant and breastfeeding women and infants (57). Referral-based models may further require women and infants to receive care at separate service delivery points that may require pregnant women to travel and wait in queues to receive HIV care and treatment. Studies from Malawi (55), Uganda (56) and Zimbabwe (57) have found that long queues at HIV clinics and the cost of transport from homes to clinics were among the main reasons for loss to follow-up for pregnant and breastfeeding women.

Although HIV programmes may invest to expand access and reduce health facility waiting times, delivering ART in settings where pregnant and breastfeeding women are already receiving care could improve access and provide opportunities for a continuum of care from providing HIV testing to ART at a single site that is also providing antenatal and postnatal care.

In a recent study, women had positive experiences in antenatal care clinics providing ART. They reported that the personnel had “treated them” well and “given them helpful counselling” and that their babies had received “good care” and were free from HIV infection because of this. Other research has explored the operational feasibility of providing ART in maternal and child health care settings and its acceptability to health care personnel in antenatal care clinics. Providers felt that integration increased efficiency, decreased the time people spent in clinics, improved relationships with providers and adherence to ART because of decreased stigma and increased confidentiality. All these factors increased the satisfaction of the people receiving care and may have contributed to improving the quality of care (66,71).
9.4.2.2 Delivering ART in TB treatment settings and TB treatment in HIV care settings

New recommendations

- In settings with a high burden of HIV and TB, ART should be initiated for an individual living with HIV in TB treatment settings, with linkage to ongoing HIV care and ART (strong recommendation, very-low-quality evidence).
- In settings with a high burden of HIV and TB, TB treatment may be provided for an individual living with HIV in HIV care settings where TB diagnosis has also been made (strong recommendation, very-low-quality evidence).

Background

In 2011, 79% and 48% of the people with TB who were known to be living with HIV received co-trimoxazole prophylaxis and ART, respectively (72). The percentage of people with TB with a documented HIV-positive test result who received ART exceeded 75% in only 6 of the 41 countries with the highest burden of HIV and TB, globally.

Since 2010, WHO has recommended ART for everyone with TB who is living with HIV, regardless of their CD4 count. TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of starting TB treatment. Co-trimoxazole prophylaxis is also recommended for all TB patients with HIV. These service delivery recommendations are intended to facilitate expanded ART coverage for people with HIV and TB and to support the early diagnosis and treatment of TB among people living with HIV.

Although the treatment of TB has been decentralized to the community level in most settings, HIV treatment remains difficult to access in many places. Data from a WHO survey indicate that the ratios of the number of health facilities providing TB treatment to the number of health facilities providing ART ranged from 1.3 to 30.2 (72). Moreover, despite a high burden of HIV and TB coinfection, services for HIV and TB treatment may be offered at geographically different sites. Although HIV and TB programmes may invest financial and human resources to improve access and reduce the time associated with receiving care, offering ART and TB treatment at a single point could improve access and adherence to HIV and TB treatment by providing a continuum from HIV testing to HIV and TB co-treatment at a single site.

Implementing TB infection control measures is crucial in HIV care settings to minimize the risk of nosocomial (occurring in a health care setting) transmission of TB. See section 8.1.2 for WHO recommendations on TB infection control in health care settings.

Rationale and supporting evidence

Since people with HIV and TB who do not initiate ART and co-trimoxazole prophylaxis have high mortality and since the combination of ART and co-trimoxazole improves survival (73–75), increasing ART and co-trimoxazole coverage is probably paramount in reducing the large number of people who die from having HIV and TB globally. The systematic review evaluating the effectiveness of delivering ART in TB treatment settings identified 19 observational studies, many of which showed increased ART uptake and timeliness of ART initiation. However, data on mortality and TB treatment success were inconsistent. The systematic review evaluating the effect of delivering TB treatment in HIV care settings identified five observational studies: two studies reported decreased mortality...
and another showed comparable mortality rates. TB treatment success rates and ART uptake were comparable across studies. The quality of evidence was weighed along with programmatic risks and benefits; acceptability; values; preferences; cost implications; feasibility; critical contextual constraints; and contextual relevance. There was consensus that, although the quality of evidence was not high using the GRADE method, there was sufficient rationale to proceed with strong recommendations (76–96).

9.4.2.3 ART in settings providing opioid substitution therapy

**New recommendation**

- ART should be initiated and maintained in eligible people living with HIV at care settings where opioid substitution therapy (OST) is provided *(strong recommendation, very-low-quality evidence).*

**Background**

Data from 49 countries indicate that injecting drug use increases the risk of acquiring HIV infection 22-fold relative to the general population, and in countries in eastern Europe up to 40% of the people acquiring HIV infection are people who inject drugs and their sexual partners (97). Existing WHO guidance states that consideration should be given to recommending HIV testing and counselling to all people attending drug dependence treatment services in generalized, concentrated and low-level epidemics when this is socially acceptable and epidemiologically appropriate. Plans for provider-initiated testing and counselling in such settings should emphasize supportive social, policy and legal frameworks (64).

These guidelines recommend the same criteria for eligibility for ART for all adults regardless of drug use behaviour. Limited global data are available on ART coverage among key populations; however, where data are available, there are often gaps between the coverage among people who inject drugs relative to that of the general population. In 2010, a report including 19 low- and middle-income countries in Europe and central Asia indicated that only 22% of people living with HIV who inject drugs and are eligible for ART received it (53).

For treating opioid dependence, WHO recommends opioid substitution therapy (with methadone or buprenorphine) combined with psychosocial assistance (98). Where there are many opioid-dependent people living with HIV, treatment of opioid dependence should be integrated with and administered in conjunction with HIV treatment. Although ART outcomes improve among people living with HIV who inject drugs and are also accessing opioid substitution therapy, enrolment in settings providing opioid substitution therapy should not be a prerequisite for initiating or maintaining ART for people who use opioids. Nevertheless, providing ART in settings providing opioid substitution therapy may expand access to ART for people who inject drugs.

Common comorbidities such as alcohol use disorders, mental health disorders, TB and viral hepatitis also need to be addressed as part of a comprehensive package of harm reduction interventions, requiring a multi-skilled workforce and close collaboration within the health sector.
Given the high incarceration rates of people who inject drugs, efforts should be made to ensure that ART is available as part of prison health services and continuity of HIV care and ART when people transition from incarceration to the community.

**Rationale and supporting evidence**

In many countries, people who inject drugs are a marginalized population with limited access to and utilization of health care services. Drug overdose and AIDS are leading causes of death in this population (99). Randomized trials found that opioid substitution therapy decreases illicit drug use and increases retention in care relative to placebo (98). Observational studies found that opioid substitution therapy decreases mortality relative to not being in care (100). ART outcomes also improved among people with HIV who inject drugs and are accessing opioid substitution therapy (16). The systematic review found one randomized trial and three observational studies evaluating the effect of delivering ART in settings providing opioid substitution therapy. Most of these studies had small sample sizes that limited the statistical power. Some studies observed trends for improved viral suppression and reduced mortality, whereas others found comparable rates of viral suppression and mortality (101–103).

This recommendation focuses on expanding access to ART by delivering the service in settings providing opioid substitution therapy. Coverage of opioid substitution therapy also remains low in many settings, and policy-makers should evaluate whether providing opioid substitution therapy in settings providing HIV care and treatment is feasible. Where health authorities or the health sector do not manage drug-dependence services, HIV programmes need to collaborate closely with social welfare departments and community and nongovernmental organizations that provide these services.

### 9.4.3 Decentralizing HIV treatment and care

**New recommendations**

The following options should be considered for decentralization of ART initiation and maintenance.

- Initiation of ART in hospitals with maintenance of ART in peripheral health facilities (*strong recommendation, low-quality evidence*).
- Initiation and maintenance of ART in peripheral health facilities (*strong recommendation, low-quality evidence*).
- Initiation of ART at peripheral health facilities with maintenance at the community level (that is outside health facilities in settings such as outreach sites, health posts, home-based services or community-based organizations) between regular clinical visits (*strong recommendation, moderate-quality evidence*).
9. Guidance on operations and service delivery

9.4 Service delivery

Background

Although rapidly scaling up HIV programmes has significantly improved access to ART and increased the health and survival of people living with HIV, it also poses significant challenges to health systems. Decentralizing ART to primary care settings may ease the burden of routine management on other parts of the health system and may improve equity by promoting access to ART in rural areas. In several settings, transport cost is a significant barrier to access and retention in care. In many settings with a high burden of HIV infection, hospitals have long waiting times because of a large flow of patients needing care. Decentralizing HIV care and treatment could reduce the workload for health care personnel, thereby reducing waiting times for people with HIV and people receiving care at hospitals for other conditions and bring HIV services closer to people’s homes. HIV-related services such as TB care and maternal and child health services are decentralized to primary care in several settings. People living with HIV, affected communities and community-based interventions play a pivotal role in providing HIV testing, care and treatment and social support. Decentralizing HIV care and treatment can further strengthen community engagement, linking community-based interventions with health facilities, and may optimize access to services, care-seeking behaviour and retention in care.

Rationale and supporting evidence

The systematic review identified two observational studies evaluating how decentralization of initiating and maintaining ART in peripheral health facilities affects patient attrition (patient death and losses to follow-up). Attrition declined after 12 months, resulting largely from significantly reduced losses to follow-up. The systematic review identified four observational studies evaluating how maintaining ART at peripheral health facilities affected patient attrition. In this further review, attrition declined after 12 months, due to losses to both follow-up and death. The systematic review also identified two cluster-randomized trials evaluating how community-based maintenance of ART affects attrition. Comparable rates of attrition were observed after 12 months (104–115).

When deciding which decentralization option to implement, programme managers may consider (1) the number of people living with HIV likely to attend decentralized settings; (2) whether decentralization brings services closer to people who would otherwise travel long distances to receive ART; and (3) whether decentralizing ART reduces the workload at centralized facilities. This recommendation calls for links to the supply of diagnostics and medicines, services, training and supervision of health workers to maintain the quality of care. In addition, in several settings, decentralizing ART will involve task shifting to ensure an appropriate mix of health care personnel at peripheral facilities.

A WHO operations manual for delivering HIV care and treatment at primary health centres in high-prevalence, resource-limited settings (116) provides additional guidance.

Implementation considerations for decentralizing ART

Box 10.5 discusses implementation considerations relevant to programme managers.
9.5 Human resources

9.5.1 Building human resource capacity

Within the past decade, in the context of the rapid scaling up of HIV care and treatment, in-service training has assumed a key role in rapidly upgrading the competencies of health practitioners.

All health workers, including community health workers, need to be regularly trained, mentored and supervised to ensure high-quality care and the implementation of updated national recommendations. Given the rapidly evolving knowledge on HIV care and treatment, countries need to consider a system for supporting health workers’ continuing education, including clinical mentoring and regular supportive supervision. The use of new technologies such as computer-based self-learning, distance education, online courses and phone-based consultation may supplement classroom in-service training and support the efficient use of health workers’ time and other resources (116,117).

It is, however, equally important to fully embrace and strengthen HIV care and treatment in existing pre-service courses leading to health workers graduating and being certified in various disciplines. Health workers also need to be equipped to manage HIV as a chronic condition, and to work in a team and need to be familiar with the national guidelines and care protocol. In several countries, people living with HIV, other community workers and volunteers are already involved in delivering HIV testing, counselling, care, treatment and social support services. In addition, people living with HIV are involved in training health workers as expert trainers. Involving people living with HIV in both training health workers and delivering HIV services may have the additional benefit of overcoming HIV-related stigma.

Countries should consider long-term reform that could support human resource strategies related to task shifting and introducing new types of health workers (such as for HIV testing or peer counsellors) on a sustainable basis within a comprehensive and nationally endorsed regulatory framework (laws and proclamations, rules and regulations, policies and guidelines). Although volunteers can make a valuable contribution on a short-term or part-time basis, all trained health workers who are providing essential health services, including community health workers, should receive adequate wages and/or other appropriate and commensurate incentives (116).

9.5.2 Task shifting for HIV treatment and care

New recommendations

- Trained non-physician clinicians, midwives and nurses can initiate first-line ART (strong recommendation, moderate-quality evidence).
- Trained non-physician clinicians, midwives and nurses can maintain ART (strong recommendation, moderate-quality evidence).
- Trained and supervised community health workers can dispense ART between regular clinical visits (strong recommendation, moderate-quality evidence).
Background

Reorganizing, integrating and decentralizing HIV treatment and care will require re-examining the roles and tasks of teams of health care providers involved in delivering chronic HIV care. Task shifting involves the rational redistribution of tasks among health workforce teams. With this approach, specific tasks are reassigned, where appropriate, from highly qualified health workers to health workers with shorter training and fewer complementary qualifications to more efficiently and effectively use the available human resources. Task shifting should be implemented alongside other strategies designed to increase the total numbers and capacity of all types of health workers.

Health care personnel remain insufficient in many settings with a high burden of HIV. Although increasing the capacity of countries to train more health care personnel is crucial, clinical tasks need to be shared and shifted to ensure that enough health workers are available to care for people with HIV. Task shifting improves access to ART at sites without physicians (such as rural health facilities, TB services and maternal and child health services). Task shifting also allows physicians to spend more time managing more complex clinical conditions such as coinfection and other comorbidities, toxicity of ART or treatment failure.

WHO guidance in 2008 (118) recommended that nurses and non-physician clinicians may initiate and maintain first-line ART and that community health workers may monitor people receiving ART during long-term follow-up. Since these recommendations were largely based on programme review and good practices, the evidence related to task shifting for ART was reviewed when developing these consolidated guidelines.

In this guideline, initiation of ART includes assessment for ART eligibility (based on clinical and/or immunological criteria); assessment for opportunistic infections; adherence counselling; and the prescribing of first-line ART. Maintenance of ART includes ongoing clinical assessment; monitoring for toxicity, treatment failure (clinical, immunological and virological) and opportunistic and other coinfections; adherence counselling; and the further prescribing of ART. Dispensing ART includes assessment for any new signs and symptoms, adherence monitoring and support and dispensing medication to patients who are already on ART between regular clinic visits.

Rationale and supporting evidence

The systematic review identified three randomized trials and six observational studies addressing task shifting. Overall, the data showed no difference in mortality and losses to care when nurses or non-physician clinicians initiate or maintain people on ART or when community health workers maintain people on ART, relative to physicians providing this care. The quality of care in these studies was ensured by (1) providing training, mentoring, supervision and support for nurses, non-physician clinicians and community health workers; (2) ensuring clear indications for patient referral; (3) implementing referral systems and (4) implementing monitoring and evaluation systems. Patient education could help people and their families understand that care provided by nurses and community health workers is not of lower quality than that provided by physicians (106–108,111,113,114,119–121).

Shifting the initiation and maintenance of ART to adequately trained and supervised nurses and community health workers may enable substantial cost savings through (1) the ability to decentralize care to primary care facilities; (2) lower overhead costs for delivering quality care (with comparable or better outcomes) by nurses, non-physician clinicians and community health workers compared with physicians; and (3) decreased facility and utility costs (if care is being delivered in health facilities complemented with community-level services).
9.6 Laboratory and diagnostic services

9.6.1 Overview

These guideline recommendations support increased access to HIV care and treatment, which will also require increased access to laboratory and diagnostic services. To ensure that testing services are accurate and reliable, relevant quality assurance systems need to be developed and strengthened.

Within a country, a multiplicity of testing settings may exist, such as laboratories, maternal and child health clinics, HIV testing and counselling sites, community-based testing and thus a multipronged and networked approach to selecting diagnostics and laboratory systems should be planned and adopted. Since an increasing number of new diagnostic tests and point-of-care systems is entering the market, the use of only high-quality diagnostics and equipment needs to be ensured. Strategic planning for properly placing and harmonizing testing platforms should be carried out to ensure appropriate use and cost–effectiveness.

9.6.2 Implementation considerations and good practices

This guidance to strengthen laboratory and diagnostic services emphasizes the importance of leadership and governance, high-quality laboratory services, expanding testing services and developing the health workforce:

- to strengthen and expand laboratory and diagnostic services;
- to support a dedicated specimen referral system;
- to increase access to HIV viral load testing;
- to support the expansion of diagnostic services to include testing at the point of care;
- to train and certify health workers who perform the testing; and
- to ensure high-quality diagnostics and plans for implementation, including quality assurance.

9.6.3 Strengthening and expanding laboratory and diagnostic services

The following areas are important to strengthen the network of laboratory and diagnostic services for implementing the guideline recommendations:

- standardizing testing methods to streamline procurement, quality assurance and training;
- incorporating new testing approaches and systems into national laboratory strategic plans and policies;
- evaluating diagnostics for their performance and operational characteristics to validate testing algorithms (with back-up options) before introduction;
- carrying out strategic planning for properly placing and harmonizing testing platforms to ensure appropriate use and cost–effectiveness;
- expanding current laboratory networks to support and monitor the decentralization and integration of testing services or to provide access to testing when diagnostic services are unavailable at service delivery sites; and
- allocating appropriate resources to ensure the availability of testing services, including human and financial resources.
9.6.4 **Supporting a dedicated specimen referral system**

Laboratory referral systems and procedures for collecting and processing specimens need to be strengthened to increase access to viral load testing and other testing (for example, CD4 and early infant diagnosis). Providing for and strengthening a dedicated, efficient, safe and cost-effective specimen referral system requires reliable specimen transport with adequate conditions for whole blood, plasma and dried blood spot (DBS) specimens and rapidly and dependably reporting test results back to the referring site with linkage to care. Rapidly reporting results is essential for timely care.

9.6.5 **Increasing access to HIV viral load testing**

The guidelines call for monitoring the response to treatment and diagnosing and confirming treatment failure with viral load testing. This will require strengthening the existing laboratory services and phased expansion of monitoring services into peripheral facilities and can include:

- strengthening and leveraging existing CD4 and early infant diagnosis networks;
- ensuring that laboratories have adequate infrastructure, technical testing expertise and quality assurance and quality improvement programmes;
- ensuring an appropriate mix of high-volume centralized laboratory testing and testing at the point of care for facilities in remote locations; and
- the use of dried blood spots as a tool to increase access to viral load testing.

9.6.6 **Expanding diagnostic services to point-of-care settings**

Decentralizing laboratory and diagnostic services requires that all aspects of laboratory tests be in place before implementing services, including:

- using only high-quality, evaluated and reliable diagnostic tests;
- supervising and monitoring point-of-care tests for quality and reliability;
- implementing a strategy for managing supply chain and equipment service; and
- establishing data management systems for timely identification of quality issues and regional and national data reporting.
Table 9.2 provides guidance on organizing testing services at various levels of the health care delivery system.

### Table 9.2 Tiered laboratory network at various levels of the health care delivery system

<table>
<thead>
<tr>
<th>Health care delivery level</th>
<th>Laboratory service</th>
<th>Human resources</th>
</tr>
</thead>
</table>
| National                   | Enzyme immunoassays for diagnosis  
                            | Higher throughput CD4  
                            | HIV molecular technologies including  
                            | HIV viral load testing and quantitative and qualitative early infant diagnosis  
                            | HIV resistance testing  |
|                            |                    | Senior laboratory specialists |
| Regional or provincial     | Enzyme immunoassays for diagnosis  
                            | Higher throughput CD4  
                            | HIV molecular technologies including  
                            | HIV viral load testing and quantitative and qualitative early infant diagnosis  |
|                            |                    | Laboratory specialists and senior technicians |
| District                   | Enzyme immunoassays for diagnosis  
                            | Low-throughput CD4  
                            | Chemistry, haematology and microbiology  |
|                            |                    | Laboratory technicians and assistants |
| Primary care               | HIV rapid diagnostic tests and other point-of-care tests  
                            | Collecting DBS  |
|                            |                    | First-level trained health workers such as nurses and clinical officers |
| Community-based            | HIV rapid diagnostic tests  |
|                            |                    | Community health workers |

Source: adapted from: *WHO expert meeting report on short, medium, and longer term product development priorities in HIV-related diagnostics, 6–7 June 2012, Geneva, Switzerland* (122).
9.6.7 Providing guidance for developing health workers’ capacity, including staff training and certification

Countries require guidelines for the qualification of personnel who will perform the laboratory tests. The guidelines should include training requirements for specific tests and the process for certification and recertification. All health workers assigned to perform point-of-care tests must be trained and proficient on the testing procedure, specimen collection and quality assurance before implementing these services.

9.6.8 Implementing comprehensive quality management systems

Developing a comprehensive quality management system including external quality assessment and quality control is essential. The quality management system should:

- be implemented within the laboratory network and all remote testing sites;
- be incorporated into the routine testing procedures and monitored;
- ensure that testing sites undertake quality control, as appropriate;
- ensure that testing sites are enrolled in an external quality assessment scheme (proficiency testing programme);
- ensure the use of standard operating procedures for all processes, including specimen collection and processing, test methods, interpreting results and reporting;
- ensure the use of standardized logbooks or electronic data management and reporting, including identifying errors and potential misclassification; and
- ensure that equipment and facilities are maintained, both preventive and corrective.

9.7 Procurement and supply management systems

9.7.1 Overview

Ensuring adequate and continuous availability of quality and affordable essential medicines, diagnostics and other consumables at service delivery sites is a critical role of procurement and supply management systems. The increasing number of people who need chronic HIV care, especially in settings with a high burden of HIV infection, necessitates an uninterrupted supply of HIV-related health products. This can be achieved only if the procurement and supply management system is strengthened at all levels of the health system. Moreover, ARV drug regimens and formulations and HIV treatment recommendations need to be regularly updated in response to new developments and emerging evidence. This requires a more efficient and dynamic supply management system to prevent waste and shortages.

9.7.2 Rationale and supporting evidence

Successful HIV programmes are only possible if all services providing ART are equipped with an uninterrupted and sustained supply of high-quality ARV drugs, preferably WHO-prequalified products. Other pharmaceuticals that are needed to support ART services include medicines to prevent or treat opportunistic infections, and laboratory reagents, supplies and equipment to diagnose HIV and opportunistic infections, monitor the progression of HIV infection and treatment response and detect adverse drug reactions. Since a single health facility may not carry out the dispensing of all needed pharmaceuticals, in some settings clients would need to be able to access services through a referral system.
9.7.3 Implementation considerations and good practices

Management support is integral to each component of the procurement and supply management cycle: selection, procurement, storage and distribution, use and monitoring. It includes a variety of activities at all levels of the health care delivery system: from the national programme level down to where medicines are dispensed and diagnostics are used. The main activities include managing the information system, ensuring timely information flow between stakeholders at different levels and securing financial and other resources, including the medicines and diagnostics needed for the programme. The following provides broad guidance on key activities at each stage of the supply management cycle.

9.7.3.1 Selecting pharmaceuticals and diagnostics

Countries adapting these guidelines may need to update national medicine lists to include newly recommended ARV drug regimens and formulations. The advantage of using the essential list concept is to enable a health system to limit other more expensive or WHO-delisted medicines and diagnostics from being purchased and accelerating the registration of WHO-prequalified products to facilitate quality-assured procurement (123). If a selected fixed-dose combination or other ARV drug regimen is not on the national list or not registered in the country, HIV programme managers need to coordinate with the national drug regulatory authority and request that these drugs be put on the list and registered.

Detailed national ART guidelines, for example, that provide recommendations for managing toxicity or treatment failure and recommended formulations for weight and age can help to standardize prescribing and dispensing practices and facilitate forecasting for ARV drugs.

Synchronized introduction of new guidelines with forecasting, procurement and distribution planning during the phasing in and phasing out of new and old ARV drug products will minimize the waste of products that are being phased out and shortages of newly recommended products.

In several settings, paediatric formulations are not widely available. The national medicine list should be optimized for paediatric ARV drug formulations, to include fixed-dose combinations, scored or dispersible products that facilitate adherence and supply management. Countries may consider removing less preferred products and aligning paediatric formulations with those of adults, where possible.

Health workers need to be trained at different levels in managing pharmaceuticals and diagnostics, including forecasting, procurement and distribution and ensuring adequate supervision throughout the supply system.

9.7.3.2 Procurement

A uniform and harmonized national procurement system is required for efficiently procuring quality-assured affordable ARV drugs and diagnostics (124,125). Procurement should be based on appropriate selection of products and need-based forecasting, considering consumption, expanding services, phasing in and phasing out formulations and implementing new recommendations. Transparent procedures should be adopted to achieve best-value procurement and a quality assurance system implemented to procure, store and distribute high-quality pharmaceuticals, diagnostics and other health products (124,126).
Procurement systems should:

- procure the most effective, heat-stable, fixed-dose quality-assured ARV drug formulations in the right quantities, at the lowest possible cost and in a timely manner;
- request that the partners supporting the national HIV programme consolidate and harmonize ARV drugs and diagnostics procurement and supply management systems and pool demands for ARV drugs and diagnostics, exploring options for pooling under a common tender system;
- use a publicly accessible database to facilitate access to information about prices and support competition (127–130); and
- follow the principles described in the United Nations interagency guidelines for donated drugs (131).

9.7.3.3 Storage and distribution

Appropriate storage and distribution of HIV medicines, diagnostics and other commodities are important components of the supply management system (Table 9.3). Product integrity and quality need to be maintained during storage and distribution (125,132), and waste from spoilage and expired products should be minimized. Integrated supply systems should be promoted when planning for decentralization, building on what exists and strengthening capacity where required. For example, existing immunization programme infrastructure, including cold chains, could be used to expand the supply of paediatric formulations, such as LPV/r liquid formulations. Facilities should have adequate storage space, trained personnel and the tools to manage supplies effectively. The number of storage levels should be rationalized to reduce the supply pipeline.

Accurate inventory records should be maintained and a system created to track products that enter and leave the supply system. A routine consumption-based reordering cycle at service delivery sites should be established. Flexibility should be introduced in the supply system such as procedures for reporting and redistribution of excess ARV drug supplies, more frequent ordering and filling of non-routine orders to minimize expiry and stock-outs. Pharmaceutical and diagnostic products need to be adequately stored, especially if ART delivery is further decentralized and is dispensed from an increasing number of peripheral health facilities. Measures are required during transport and storage to prevent theft and fraud such as vehicle tracking systems, secured storage areas, audits and labelling of ARV drug products procured by HIV programmes.

9.7.3.4 Use and monitoring

Robust information systems ensure the availability of accurate and timely consumption data on ARV drugs and other information required for effectively monitoring the performance of the entire supply system and for forecasting the ARV drugs and diagnostics needed. Monitoring procurement and supply management through the effective use of early warning indicators prevents stock-outs and overstocks leading to expiry (126).
Table 9.3 Summary checklist of pharmaceutical supply management issues

<table>
<thead>
<tr>
<th>Phase</th>
<th>Activity</th>
<th>Determination</th>
</tr>
</thead>
</table>
| Planning          | Selecting products                            | Updated national HIV guidelines  
Updated national lists to include newly recommended ARV drug regimens and formulations and diagnostics |
|                   | Estimating and quantifying ARV drug requirements |                                                                                                                                             |
| Procurement       | Selecting and locating suppliers             | Open and transparent communication with industry  
Prequalified suppliers  
Implementing review mechanisms |
|                   | Assuring the quality of products and sources  | Criteria for manufacturer prequalification  
Implementing a prequalification system  
Using the WHO certification scheme, inspecting and testing the quality of samples  
Pre-shipment physical inspection with random sampling for laboratory testing  
Systems for records and supply monitoring |
|                   | Arranging for purchasing                      | Ongoing assessment of purchasing options  
Need for special labelling and packing  
Need for reserve or buffer stocks  
Managing purchasing arrangements |
| Distribution, rational use and monitoring | Receiving supplies in the country            | Port clearance, including availability of funds for paying duties and taxes  
Securing appropriate warehousing at all levels needed  
Physical inspection on arrival of each consignment with random sampling for laboratory testing |
|                   | Distributing in the country                   | A logistics system for timely distribution to end-users |
|                   | Rationally using and monitoring pharmaceuticals | Providers adequately trained  
Systems for monitoring and reporting, including monitoring adverse effects feeding into the selection; rational prescription; and forecasting in place  
At the central level, any problem such as theft, recall by the supplier, poor quality and adverse drug reactions should be recorded and reported at different levels to all relevant bodies. This would involve developing problem-reporting forms, indicating to whom they should be sent, and what action should be taken |
Goal of this chapter

To provide programmatic guidance for decision-makers and planners at the national level as they work to adopt and implement the clinical and operational recommendations in these guidelines.
10. GUIDANCE FOR PROGRAMME MANAGERS

10.1 Introduction

The recommendations in these guidelines increase the number of people eligible for ART, promote new first- and second-line regimens and propose changes in approaches and strategies to laboratory monitoring to maximize treatment effectiveness. National stakeholders face several important choices on how to optimally translate these recommendations into national practice. For example, although evidence of clinical efficacy supports the uptake of interventions, issues such as cost and cost–effectiveness, ethical and human rights considerations, the perceptions of various stakeholders and the legal and regulatory environment must also be taken into account (1).

National HIV programme managers play a unique role in managing the process for adapting and implementing the HIV guideline recommendations in their respective countries. First, convening a broad, inclusive and transparent consultative process can help to define what programme changes are relevant and necessary, such as revising national protocols, guidelines and regulations. Second, in parallel, it is necessary to secure the financial resources and political support required to implement the proposed changes. Third, systems are required to ensure broad accountability for implementation from all partners at all levels and adequately document performance to inform programming decisions and maintain political support. Lastly, implementation and operations research should be supported so that innovative approaches can be assessed and taken to scale.

Human rights and ethical principles should guide the revision of national treatment policies to ensure that they are equitable and meet the specific needs of all beneficiaries. New recommendations should inform the HIV programme’s overarching vision, goals and objectives, and existing strategic plans should be adapted accordingly to assure consistency, avoid duplication and leverage potential economies of scale (2).

As HIV programmes mature and increasingly focus on the challenges of long-term prevention, treatment, care and support, national responses need to be considered within the broader health and development contexts. The sustainability and effectiveness of HIV programmes can be greatly enhanced by creating and strengthening linkages with other health and non-health programmes (3).
10.2 Decision-making process

Decisions regarding the implementation of global recommendations should be made through a transparent, open and informed process that recognizes the multisectoral nature of the HIV response. National HIV programmes should consider convening a multidisciplinary working group, if one is not already in place, to advise on the choices and decisions necessary for updating and implementing national guidelines. The role of the guideline group may include (1) reviewing the current context of national HIV and TB epidemics, including the health sector response and the broader policy environment; (2) assessing global and local evidence related to the new recommendations and advising on how to adequately interpret them within the local context; and (3) identifying implementation issues such as estimated costs, human resource and infrastructure requirements and how these should be addressed (4). Sections 10.3 and 10.5 address these topics in greater detail.

Although national programme managers should oversee the decision-making process, it should also be broadly representative. Broad stakeholder engagement in policy design, implementation, monitoring and evaluation will help to ensure that the national adaptation of global guidelines results in HIV programmes that are legitimate, acceptable, effective and equitable and address community needs (1,5).

The composition of the working group may vary over time and depend on the specific recommendations under discussion. For example, when considering how to improve programmes for PMTCT, joint planning with those responsible for maternal and child health should be undertaken. Checklist 10.1 provides a checklist of key elements to consider in implementing a transparent and inclusive decision-making process.

10.3 Data to support decision-making (5)

10.3.1 Overview

Decisions on how to adapt and implement these guidelines should be based on a careful assessment of epidemiological dynamics and programme performance to identify programme strengths and weaknesses and necessary policy changes, consistent with the principles of “know your epidemic, know your response” (Checklist 10.1) (6,7). In some countries, these data may be available from regular monitoring and evaluation activities or from recent programme assessments. Elsewhere, new analyses may be warranted, such as studies of the modes of HIV transmission, to shed light on key epidemiological or response elements. Quantitative and qualitative data should, whenever possible, be disaggregated by gender, age, subnational administrative categories (such as regions and districts) and other relevant stratifications, including key populations, to ensure that new policies address inequities in access and increase the coverage of interventions. The consolidation of health information systems, including patient record registries, into electronic databases is critical to facilitate the management of increasing amounts of data and improve their robustness and availability for programme decision-making (see section 11.5).
10.3.2 National and local HIV epidemiology

An epidemiological analysis should describe the prevalence levels among the general population and in specific key populations, the rate at which HIV infection is acquired and among whom, including infants, young children, pregnant women and serodiscordant couples. Both prevalence and incidence measurements should aim to identify populations at higher risk for HIV infection, including in generalized epidemic settings, and adequate population size estimates for these populations should be available so that results can be interpreted appropriately (9). Data on the prevalence and incidence of key coinfections (such as TB and hepatitis B and C) and other comorbidities should also be gathered to inform decision-making.

10.3.3 Programme performance and response analysis

Determining whether current ARV programmes are adequate to address the needs that have been identified requires understanding who is currently accessing these services. Programmes should assess present ARV coverage levels among the general population as well as key populations, the disease stage at which they access care, how well these groups are retained in care and treatment, the ARV regimens used and the impact of ART on viral load suppression, morbidity and mortality. Programmes that are considering raising the CD4 cell count threshold for ART eligibility should ideally have data on the median CD4 cell counts and the stage of HIV disease of people at the time of their HIV diagnosis and at the time of initiating treatment. Disaggregated data for various groups enable assessment of ARV needs and establishment of priorities for delivering services. Data on adherence, retention and viral load suppression are key to assess the quality of the services provided. Surveillance of transmitted and acquired HIV drug resistance can also be instrumental in informing decisions on optimal regimen choices (Box 11.1). Whenever possible, indicators of impact, such as changes in HIV-related incidence, prevalence, morbidity and mortality, should also be reviewed.

10.3.4 Socioeconomic, policy and legal context

A review of epidemiological and programmatic data is incomplete without a deeper understanding of what drives HIV vulnerability and how various political, social, economic and legal factors affect the ability and willingness of various groups – such as men, women, adolescents, sex workers, men who have sex with men, transgender people and people who inject drugs – to seek and access health services. Stigma, discrimination, poverty, gender inequality, education and migration status are key elements that should be taken into account to inform effective HIV programming. The legal context can also affect access to interventions, such as laws related to intellectual property rights and those that criminalize homosexuality, HIV exposure and/or transmission, drug use and sex work. Such laws should be reviewed and reformed to eliminate discriminatory practices, decrease HIV vulnerability, improve access to health services and protect human rights.

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viii Incidence estimates by modes of transmission have already been developed for some countries and are available from UNAIDS (8).
Checklist 10.1 Process and evidence for decision-making

Process for decision-making \(^{(10,11)}\)

1. **Does the process follow principles for sound and appropriate decision-making?**
   - Publicity: Is the process transparent and open? Are the evidence and rationale for decisions publicly available?
   - Relevance: Do stakeholders affected by these decisions agree that the rationale rests on relevant reasons, principles and evidence?
   - Revisability and appeals: Can decisions be revised and/or appealed in light of new evidence and arguments?
   - Enforcement: Are all stakeholders aware of the means to ensure that these conditions (publicity, relevance and revisability) are met?

2. **Have representatives from all relevant stakeholders been included?**
   - Programme experts and managers, including experts and representatives of sexual and reproductive health, maternal and child health, TB, HIV programmes (ART, HIV testing and counselling and PMTCT), drug dependence and harm reduction
   - Health care providers, including physicians, nurses and counsellors from adult and child HIV clinics, prison health programmes, maternal and child health, TB clinics and harm reduction and drug dependence services in the public and private sectors
   - Civil society, including people living with HIV, women and youth groups, religious leaders, people with disabilities and representatives of key populations, including men who have sex with men, transgender people, sex workers and people who inject drugs
   - Technical specialists, including experts in specific technical areas, such as laboratory services, pharmacy, drug resistance, toxicity management, supply chain and community health
   - Government partners, including representatives of other relevant ministries (such as finance and planning) and decentralized (such as provincial) authorities, international agencies, faith-based groups, other local nongovernmental and community-based organizations and private-sector service providers
   - Finance and budget experts, such as programme budget officers and health economists
   - Academic institutions, including experts in operational research, implementation science, training and supervision
   - Professional associations of different cadres of health workers (such as physicians, nurses and community health workers)

3. **Can all stakeholders participate effectively, be heard and influence decision-making?**
   - Is information accessible to all key stakeholders in written and understandable language?
   - Is the process organized to ensure the meaningful participation of all relevant stakeholders?
   - Have the potential social, cultural, and legal barriers that deter the meaningful participation of historically marginalized stakeholders been identified and addressed?

4. **Transparency regarding the grounds for decisions**
   - Are the decision-making criteria transparent and is the rationale stated explicitly with reference to:
     - Scientific evidence, including effectiveness and risk?
     - Opportunity costs of interventions, including cost–effectiveness?
     - Equity impact (distribution of health benefits and burdens for different groups)?
Evidence for decision-making

1. HIV incidence and prevalence
   - In what population groups are HIV incidence and prevalence highest? Relevant criteria include gender, location (urban versus rural), age, income, general population and pregnant women, and key populations (such as men who have sex with men, people who inject drugs, sex workers and prisoners).
   - What is the HIV seroprevalence among the partners of index cases? What is the incidence of HIV infection in serodiscordant couples?

2. Programme and response analysis
   - Has the decision-making process taken into account:
     - the current coverage of HIV testing and counselling disaggregated by relevant stratifiers?
     - the current coverage of ART disaggregated by relevant stratifiers?
     - the current coverage of ARV drugs for PMTCT and ART among pregnant women living with HIV?
     - the median CD4 cell count and HIV disease stage of people initiating ART?
     - the proportion of people starting ART who are alive and still receiving ART after 12, 24 and 60 months?
     - the prevalence of viral suppression (and % treatment failure) among people receiving ART after 12 months?
     - the prevalence of HIV drug resistance among people starting first-line ART and among those already receiving treatment?

3. Equity in access
   - Based on a review of epidemiological and programme response data, do the recommendations promote greater access to ARV drugs and other services for people with least access or those most in need, including key populations?

4. Alignment between evidence and recommendations
   - Are the recommendations appropriate for the epidemiological setting in which they will be implemented?
   - Are the recommendations aligned with and do they support the implementation of the programme’s overarching vision, goals and objectives?
   - Have the recommendations been informed by local and national evidence?

5. Contextual issues
   - Has the decision-making process taken into account how poverty, gender inequality, education, stigma, discrimination and migration status affect HIV vulnerability and access to services?
   - Are there any punitive laws and practices, at any levels, related to HIV transmission, sex work, drug use or homosexuality?
   - Has it been determined how such barriers will be dealt with and how the responses will affect programme planning?
   - Are there legal or regulatory barriers to adolescents being able to have independent access to HIV testing, counselling, treatment and care?
10.4 Key parameters for decision-making

10.4.1 Ethics, equity and human rights

Multiple legal, social and normative obstacles have resulted in inequitable access to HIV treatment and care. For example, data from 19 countries in Europe and central Asia showed that, although people who inject drugs accounted for 62% of cumulative reported HIV cases with a known transmission route in 2010, they represented only 22% of the people receiving ART in countries surveyed (12,13).

Global and national commitments require providing HIV treatment and prevention to everyone in need, following the human rights principles of non-discrimination, accountability and participation (14–16). National HIV strategies should be planned and implemented from the outset with the ultimate goal of delivering the full package of services and interventions recommended in these guidelines as soon as possible.

Key ethical principles of fairness, equity and urgency should also be observed in the process of reviewing and adapting guidelines. The design of effective and equitable policies implies that strategies should focus comprehensively on addressing barriers to access testing, prevention and treatment services, particularly those faced by key populations. Facility- and community-level reviews may be useful to understand the extent to which services are acceptable and adapted to the specific needs of key populations.

10.4.2 Impact and cost–effectiveness

Realizing positive impact for a population is an important goal of public health programmes and policies. Examples of the impact of HIV programmes include reduced HIV incidence, prevalence, morbidity and mortality and improved quality of life (17). Impact is often a result of a complex set of factors and a combination of diverse inputs and activities or processes, and it is often not attributable to a single intervention or programme (5).

Cost–effectiveness analysis is one of several economic evaluation tools used to measure the value of delivering particular services. Economic evaluation measures the costs and consequences of alternative programmes, which are then compared to assess how the greatest health benefits can be generated. In cost–effectiveness analysis, impact is often measured using indicators related to a change in health status, such as disability-adjusted life-years (DALYs) gained, which includes the estimated number of deaths and infections averted. As the experience of scaling up ART in low- and middle-income countries demonstrates, the cost–effectiveness of health interventions also changes over time, as costs fall because of gains in scale, improvements in technology or the design of more efficient delivery systems.

During the development of these guidelines, a consortium of research groups independently developed and then compared mathematical models to assess the epidemiological and clinical impact as well as cost–effectiveness ratios of various interventions, notably those related to earlier initiation of ART (Box 10.1).

Although evaluating cost–effectiveness and health impact may be useful in systematically comparing various programme interventions, they should be considered in the light of the ethical, equity and human rights implications associated with different courses of action, especially in settings in which not all eligible individuals currently have access to ART.

Investments in critical enabler programmes (such as integrated treatment and rights literacy programmes, legal services, stigma and discrimination reduction programmes, training for health care workers and law enforcement) can play a role in overcoming barriers to accessing treatment and other HIV-related services and keeping people connected to care. As such, these programmes can contribute to overall cost–effectiveness, in addition to achieving other important objectives, such as reducing discrimination (18).
Box 10.1 Estimating the impact and cost–effectiveness of selected recommendations using mathematical models: results from the independent HIV Modelling Consortium

As HIV programme managers work to implement these guidelines, they may face complex choices on how to optimally allocate resources for HIV treatment: for example, determining the relative allocation of resources for scaling up HIV testing and linkage to care and for increasing access to ART based on expanded eligibility criteria.

The HIV Modelling Consortium, an independent group of research institutions (www.hivmodelling.org), used multiple independent mathematical models based on data sets from four countries with different types of epidemics and current ART coverage – India, South Africa, Viet Nam and Zambia – to examine the health benefits, costs and cost–effectiveness of various strategies for expanding eligibility for ART as well as testing and access to HIV care (19) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In each case, a range of potential options was investigated, including various thresholds for ART eligibility (CD4 cell count $\leq 500$ cells/mm$^3$, all people with HIV and specific key populations), assuming current as well as expanded patterns of HIV testing and linkage to care. The costs and both individual and preventive health benefits associated with each intervention were estimated, including changes in HIV incidence, reductions in the loss of healthy life-years and costs over time. These models also considered the relative cost–effectiveness of strategies, highlighting which of them, for a given budget, would be expected to maximize health gains.

Expanding the criterion for ART eligibility to CD4 cell count $\leq 500$ cells/mm$^3$ was found to be highly cost-effective in low- and middle-income settings. However, combining expanded eligibility with a large increase in HIV testing and linkage to care produced the greatest benefits, especially in settings with low ART coverage. Expanding ART eligibility to all adults with HIV (irrespective of CD4 count) was less cost-effective than expanding the criterion to $\leq 500$ cells/mm$^3$ because of less immediate improvements in health as the CD4 threshold for initiating ART is increased.

The modelling results should be interpreted in light of some important limitations. Many of these conclusions could change substantially depending on cost assumptions, especially those related to testing and counselling and to retaining people in pre-ART care. Moreover, the models did not consider how the estimated impact and cost–effectiveness of the various interventions would change if they were combined or only partly implemented. Models also did not address potential trade-offs with non-antiretroviral interventions, and several important issues were not covered, such as treatment of children.

10.4.3 Opportunities and risks

The recommendations in these guidelines have the potential to further reduce HIV-related mortality, improve the quality of life, reduce the number of people acquiring HIV infection and enhance treatment effectiveness. The benefits accrued from implementing them are likely to considerably outweigh the upfront investment needed and have the potential to fundamentally change the course of the epidemic. Nevertheless, domestic factors (such as budget cuts, theft of ARV drugs, attrition of trained health workers and emergence of drug resistance) and external contingencies (such as withdrawal of external financial support, political instability and natural disasters) could negatively affect their implementation. It is essential to design strategies to mitigate such events so that continued service delivery can be assured, especially for those most in need (20).
10.5 Implementation considerations across the health system

As countries consider how to optimally implement these guidelines, the budgetary, human resource requirements and other health system implications should be analysed to identify which inputs and systems are currently available and which areas require additional investment. The six building blocks for health systems identified by WHO provide a useful analytical framework (21). Checklist 10.2 provides a checklist of key critical issues in these areas. Such considerations should not determine whether a particular recommendation is included or excluded from national guidelines but can be used as a tool to understand the impact of a recommendation and how best to adapt it and mobilize resources for its implementation. When the relative budget implications of specific recommendations are considered, it is also important to take into account the costs of inaction in terms of increased mortality, morbidity and HIV transmission. An implementation plan should clearly define the set of activities required in a specified period of time to achieve targeted outcomes, with a clear division of labour among all stakeholders involved in implementing programmes.

Robust procurement and supply management systems are needed to ensure the continued availability of all necessary drugs, diagnostics and other commodities across the various levels of the health system. Pooled or joint procurement can be used to secure lower costs through economies of scale, and careful demand forecasting is key to minimizing waste. Fixed-dose combinations and once-daily therapy should be used whenever possible to support adherence and make treatment as convenient as possible for the people receiving therapy and their caregivers. Laboratory capacity must also be reviewed and services should be strengthened to cope with higher demand, and nationally standardized health information systems and patient monitoring tools should be used in all settings. Stronger interventions are also needed to maximize treatment adherence and retention across the continuum of care. Specific interventions may be needed in particular settings, such as postpartum follow-up of mother–infant pairs.

The quality of health care is a critical dimension to consider in the planning and adaptation process. The rapid scale-up observed during the past decade has left gaps in the quality of service delivery at times that have negatively affected, for example, adherence rates, timely enrolment in care or retention on ART. The implementation of new guidelines provides an opportunity to comprehensively review and address such gaps. Critically, this requires effective monitoring and evaluation systems (see Chapter 11). A key component of sound quality assurance mechanisms is a clear delineation of roles and responsibilities for the delivery of the various functions and inputs (such as leadership, financing, supply chain management, human resources, monitoring and evaluation needed for effectively providing services at the national, regional, district, facility and individual clinician levels). A quality assurance and improvement framework developed for HIV testing and counselling may inform broader quality assurance and quality improvement interventions across the continuum of care (22).

Effective HIV programming is multisectoral in nature and goes beyond biomedical interventions. It is essential to assess how HIV interventions can be optimally linked with other health programmes and non-health services to increase coverage and optimize resources. Planning should also take into account the variety of providers involved in health service delivery, including public, private and not-for-profit organizations. Community involvement and peer outreach strategies are key to improve programme design, promote its sustainability and maximize coverage.
Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection

Checklist 10.2 Implementation checklist of key health system issues

The successful implementation of new recommendations depends on several critical decisions in key programme areas.

1. **Communication, leadership and advocacy**
   - Has it been determined who will be responsible for updating currently existing materials, including service delivery guidelines, protocols, clinical and laboratory standard operating procedures, monitoring and evaluation tools, patient monitoring mechanisms or systems, reference manuals, health worker training materials, job aids, supervisory checklists and materials for public information, education and communication?
   - Has it been decided how new recommendations will be communicated to (1) local programme managers, including public, not-for-profit and private institutions; (2) health workers; and (3) other relevant stakeholders, such as people living with HIV?
   - Has it been agreed who will take overall responsibility for advocacy with stakeholders such as political leaders, health personnel and the mass media?

2. **Staffing and human resources**
   - Has it been determined how many additional workers are required to implement new recommendations? Which cadres of health workers (physicians, health officers, nurses, midwives, community health workers and laboratory assistants) are needed and how they can be recruited?
   - Can task shifting and sharing be employed to optimize available human resources and expand service delivery? (see section 9.5.2)

3. **Drugs and supplies**
   - Are any new medicines (such as ARV drugs) needed to implement the new recommendations? In what quantities?
   - Has it been determined what systems are required for forecasting needs and procuring medicines and other commodities at the best possible prices?
   - Has a transition plan been developed to phase out old medicines (such as d4T) and introduce new ones?
   - Do supply management systems – especially at the peripheral level – need to be strengthened to manage increased demand?
   - Is a regulatory process in place to approve and register new medicines and diagnostics in a timely manner?
   - Are laboratory quality control and external quality assurance systems in place and fully functional?
   - Do national laws allow for the purchase and importation of all necessary commodities? Do patent issues exist and can Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities be leveraged to promote access?

4. **System organization**
   - Are linkages and referrals systems adequate?
   - Do services need to be decentralized and/or integrated to support policy implementation?
   - Has the policy been developed in consultation with managers of other relevant programmes (such as TB, maternal and child health and drug dependence services)?

5. **Infrastructure**
   - Has the necessary physical infrastructure (such as warehouses, meeting rooms, consultation space, laboratories, pharmacies, administration areas and equipment) and transport infrastructure (such as vehicles) needed to support implementation been identified? Is it available somewhere in the health system or does it require additional investments from the ARV programme?
   - Is additional communication infrastructure needed, including between health facilities, health workers, laboratories and clients?
10.6 Implementation considerations for key recommendations

Boxes 10.2 to 10.7 discuss implementation considerations for programme managers for six key recommendation areas in these guidelines: (1) changing the CD4 cell count threshold for initiating ART for adults and adolescents from 350 to 500 cells/mm³; (2) scaling up viral load testing; (3) moving to lifelong ART for all pregnant and breastfeeding women; (4) decentralizing ART services; (5) scaling up treatment for children; and (6) phasing out d4T.
Box 10.2 Key implementation considerations for programme managers: raising the CD4 threshold for initiating ART in adults and adolescents from 350 to 500 cells/mm³ (section 7.1.1)

1. **Treat the sickest people first.** Individuals with CD4 cell counts of less than 350 cells/mm³ have a different mortality profile than those with higher CD4 cell counts. What systems will be in place to ensure that the sickest people are adequately given priority, especially in settings with low ART coverage?

2. **Phase out d4T.** Given the long-term toxicity and side effects of d4T, programmes raising the ART initiation threshold to 500 CD4 cells/mm³ should have significantly progressed in phasing out d4T in adult and adolescent regimens to optimize treatment outcomes.

3. **Consider task shifting and decentralization.** Human resource plans should be developed or adjusted to support the policy decision to increase the CD4 eligibility threshold, including through task shifting and training new cadres of health workers (see section 9.5.2).

4. **Reinforce adherence support.** A higher threshold for initiating ART means that more people who feel healthy will become eligible for treatment. What interventions to promote and reinforce adherence will be implemented for these people?

5. **Provide treatment monitoring.** As more people initiate ART earlier and stay on it for longer, monitoring viral suppression becomes increasingly important, as keeping people on failing regimens may lead to higher levels of drug resistance, which might compromise the efficacy of treatment, especially of NNRTIs. How will access to viral load monitoring be scaled up?

Box 10.3 Key implementation considerations for programme managers: scaling up viral load testing (section 7.3.2)

1. **Consider the various diagnostic options.** Several strategies exist to increase access to viral load testing, including the use of dried blood spots (DBS) and, in the near future, point-of-care technologies. Programme managers need to consider the optimal choice in light of multiple factors, such as the availability of existing infrastructure and the number of people receiving services at different levels of care (such as centralized versus peripheral sites).

2. **Review the use of viral load monitoring in the context of alternative patient monitoring strategies.** The relative benefit of CD4 monitoring in a context of greater viral load availability may need to be reassessed considering the different specificity profiles of these technologies as markers of treatment failure, their cost and technical requirements for implementation. For example, programmes may consider reducing the number of CD4 tests done for people whose viral load is being routinely measured. CD4 testing is still required to determine ART eligibility.

3. **Provide adherence support.** An important proportion of people receiving ARV drugs develop detectable viral load because of inadequate adherence to treatment and can return to undetectable levels if adequate counselling is in place, avoiding unnecessary switching to second-line regimens.

4. **Develop treatment literacy on the use of viral load.** As most programmes in low- and middle-income countries have historically relied on CD4 monitoring, people receiving ARV drugs and health care providers may not be familiar with the concept and importance of viral load. Counselling should be provided so that people receiving ARV drugs and health care providers understand the meaning and implications of having a detectable or undetectable viral load and its relation to adherence.
5. Ensure an adequate supply of second-line ARV drugs. People whose viral load remains detectable following adherence support have probably developed drug resistance and may need to switch regimens. Programme managers should be prepared to offer alternative regimens, including second-line ARV combinations, to address these situations.

6. Implement quality assurance strategies. As viral load testing is scaled up, its quality must be assured. Centralized systems should be enrolled in external quality assurance programmes, while new quality assurance approaches are needed for decentralized and point-of-care systems.

Box 10.3 (continued)

Box 10.4 Key implementation considerations for programme managers: moving to lifelong ART for all pregnant and breastfeeding women (option B+) (section 7.1.2 and Annex 6)

1. Consider the appropriate approach to scaling up. The infrastructure and operational implications of providing lifelong ART to all pregnant and breastfeeding women living with HIV must be carefully reviewed. Countries may consider a phased approach with an early learning phase before full scale-up.

2. Assure linkages to care and patient transfer. The location in which ARV drugs are provided to pregnant and breastfeeding women and the provision of long-term ART should be considered and decided before the programme is implemented. Will women continue to receive ART at the site providing ARV drugs for PMTCT or will they be transferred to an existing ART site? What strategies will be put in place to minimize the risk of women being lost to care as they are transferred to various ART service locations?

3. Review human resource requirements. Many staff at PMTCT sites have had limited training in and experience with providing ART, especially in settings in which Option A has been implemented for PMTCT. Capacity-building, task shifting and potential expansion of health personnel may be needed to allow PMTCT sites to successfully take on the additional responsibility of providing lifelong ART.

4. Promote adherence and retention. Adherence to therapy and retention in care of mother–infant pairs may be especially difficult in the postpartum breastfeeding period. What strategies will be put in place to monitor and support adherence and retention and re-engage in care those lost to follow-up, including both the mother and the HIV-exposed children?

5. Consider ethical issues. Initiating lifelong ART for all pregnant and breastfeeding women regardless of CD4 count may result in temporary disparities in access to treatment. For example, a pregnant woman with a high CD4 count may continue to receive ART after delivery, whereas her husband, other family members, neighbours or other women intending to get pregnant with a lower CD4 count may not yet be eligible for treatment. What process and strategies will be put in place at the policy and service delivery levels to address such possible disparities? How can the enrolment of all pregnant and breastfeeding women into lifelong treatment be leveraged to enhance a family approach, including getting partners and other household members tested for HIV and treatment?

6. Assure the quality of HIV testing. Developing quality-assurance programmes, including for HIV rapid testing (which in some settings may be the only test used to determine the initiation of lifelong ART) and appropriate use of testing algorithms, will be important to ensure optimal implementation in all areas of the country.
7. **Assess laboratory monitoring needs.** Although CD4 testing may not be required to initiate ART among pregnant women, toxicity and ART response monitoring, including viral load (which is key for assessing viral suppression), should be available, similar to all people receiving ART. Infant diagnosis is also essential to identify infants infected with HIV and to link them to the necessary treatment and care. Surveillance systems (which can be sentinel sites) should be established to evaluate the impact of ART on birth defects, pregnancy outcomes, safety among infants and young children exposed through breastfeeding as well as transmission outcomes and tolerance of first-line ART.

8. **Implement adequate monitoring and evaluation frameworks.** New strategies are needed to ensure high quality and longitudinal cohort data on the mothers and their HIV-exposed infants across a range of service delivery entry points and across the continuum of care. For breastfeeding mothers and infants, the true effectiveness of a PMTCT programme depends on infant infection status and HIV-free survival at the end of the breastfeeding period and not on early infection status at age six weeks.

9. **Provide infant prophylaxis.** Infant prophylaxis is particularly critical for PMTCT in situations of late HIV diagnosis in the mother, limited or no antepartum maternal ART or if maternal ART is interrupted due to toxicity, intolerance or lack of adherence.

10. **Assure continuous drug supply.** An uninterrupted supply of maternal ART during pregnancy and breastfeeding is critical for PMTCT as well as maternal health. Adequate drug forecasting and drug supply chain is essential.

### Contextual issues to consider for PMTCT options

Although country programmes will define the choice between (1) providing ART to pregnant or breastfeeding women living with HIV for the duration of the risk of mother-to-child transmission or (2) lifelong ART regardless of CD4 cell count based on local circumstances, preferences and values, several contextual features are especially relevant for decision-making.

1. Providing lifelong ART (“Option B+”) to all pregnant and breastfeeding women is particularly relevant in settings with the following characteristics:
   - generalized epidemic;
   - high repeat pregnancy rates and low family planning coverage;
   - low partner testing rates;
   - limited access to CD4 testing;
   - low existing coverage of ART for pregnant women who meet the treatment eligibility criteria for non-pregnant individuals; and
   - long duration of breastfeeding by women living with HIV.

2. Providing ART only during the period of risk of mother-to-child transmission (“Option B”) with continuing lifelong ART only for those women meeting standard eligibility criteria for the treatment of non-pregnant adults is especially relevant in settings with the following characteristics:
   - concentrated epidemics;
   - lower repeat pregnancy rates and higher family planning coverage;
   - high access to CD4 testing;
   - high existing coverage of ART for pregnant women who meet the treatment eligibility criteria for non-pregnant individuals; and
   - formula feeding is recommended, available and safe.

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ii In settings with high fertility rates, it should be a priority to institute family planning programmes to allow women to avoid unplanned pregnancies.
10. Guidance for programme managers

10.6 Implementation considerations for key recommendations

**Box 10.5 Key implementation considerations for programme managers: decentralizing ART services (section 9.4.3)**

1. **Examine the models and options.** Programmes should determine which clinical and laboratory services will be available at what level of the health care delivery system. The optimal model for ART decentralization (partial or full) depends on the local context.

2. **Consider human resources policies and task shifting.** All health workers, including community health workers, need to be trained regularly, mentored and supervised to ensure high-quality care and implementation of updated national recommendations. In many settings, decentralizing ART requires task shifting to ensure an appropriate mix of health workers at peripheral facilities. An appropriate regulatory framework (laws, regulations, policies and guidelines) is needed to allow tasks to be performed by different cadres of health workers, in addition to nationally standardized training, mentoring and supervision for all health workers involved in HIV care.

3. **Implement strategies for retaining staff.** Programme managers should support the development and implementation of policies to create a suitable environment for recruiting, retaining and motivating personnel in rural or remote areas, where health worker turnover and attrition may be considerably higher than in urban settings.

4. **Strengthen linkages and referral systems.** Although community-based treatment programmes provide an important option for decentralizing ART, they should always be linked with regular care at health facilities and with adequate laboratory, diagnostics, monitoring and evaluation and drug and supply management systems.

5. **Agree on a division of labour.** An efficient division of responsibilities among levels of the health system (national, provincial or regional and district) is crucial to minimize duplication and to optimize the use of resources. The role of each level should match its capacity, and the lines of authority and accountability should be clear and well understood by all.

6. **Build partnerships.** National regulatory bodies, professional associations and other stakeholders need to be involved when addressing the scope of practice, roles and responsibilities of health workers.

**Box 10.6 Key implementation considerations for programme managers: scaling up treatment for children – treating all children under 5 years and raising the CD4 threshold in older children from 350 to 500 cells/mm³ (sections 7.1.4 and 7.2.3)**

1. **Expanding ART coverage should be the first priority.** Since all treatment regimen options have been shown to reduce morbidity and mortality, the use of less preferred options is better than leaving children untreated.

2. **Younger children are at greater risk of poor outcomes.** Children younger than two years living with HIV have higher mortality rates and more rapid disease progression than older children. Early diagnosis and prompt initiation of ART are especially critical for infants and young children.

3. **Strengthen links between diagnosis and treatment.** Diagnosis and treatment for children are often performed at different facilities, increasing the risk of their being lost to follow-up. Improving links between early infant diagnosis and ART sites is essential to minimize such losses and improve uptake of ART among children. Family-based approaches to HIV testing and provider-initiated testing and counselling are important approaches to increase HIV diagnosis and treatment among children.

4. **Optimize and improve the choice of ARV formulations available.** It is critical to accelerate regulatory approval of preferred formulations. Scored dispersible fixed-dose combinations for children with dosage based on weight bands can support the scaling up of ART for children in remote areas.
Box 10.7 Key implementation considerations for programme managers: phasing out d4T (section 7.2)

1. **Choose a suitable alternative.** WHO recommends TDF as the preferred alternative to d4T in first-line regimens. TDF is also more likely to be effective than AZT among people who have developed resistance while on d4T.

2. **Design a costed phase-out plan.** The overall operational plan for phasing out d4T should be fully costed and should consider any additional investment in laboratory strengthening and capacity-building that may be required to support implementation.

3. **Identify priorities for implementation.** Because of programme constraints, not all countries may be able to promptly switch everyone receiving d4T to new regimens. Priorities should be clearly defined and agreed with all relevant stakeholders.

4. **Avoid treatment disruption.** Although new d4T orders should be discontinued, adequate and timely forecasting and procurement of the preferred alternative drug are critical to avoid stock-outs and treatment interruption.

5. **Review and compare prices.** Substantial reductions in the price of both TDF and its preferred companion drug EFV have been observed in recent years. Countries are encouraged to ensure they are procuring these drugs at the best possible price. WHO’s Global Price Reporting Mechanism may be a useful source of price information (23).

6. **Manage stockpiles.** Options include reserving stocks for back-up situations for individuals who may require d4T in the absence of alternative choices.

7. **Train and educate both clinic staff and people receiving ART.** Clinic staff should be trained and prepared to carry out the transition and to educate ART patients about their new regimens.

8. **Phase out d4T among children when alternatives are available.** WHO’s recommendation to phase out the use of d4T applies equally to both adults and children. However, considering the limited availability of age-appropriate NRTI formulations, d4T may be used in special circumstances, especially in settings where formulations of ABC for children are not available (see sections 7.2.3. and 7.2.4).
10.7 Implementing recommendations in different contexts

10.7.1 Overview

Although all countries have agreed to provide universal access to HIV prevention, treatment, care and support by 2015, the local context – including epidemiology and current coverage of interventions – will determine their trajectory towards this goal. This section provides a broad outline of possible sequencing approaches to phasing in key recommendations, considering the available scientific evidence, results from mathematical models (Box 10.2) and ethical and human rights issues. It draws on views expressed in the Guidelines Development Group on Programmatic Issues and therefore does not constitute formal recommendations. National stakeholders are responsible for the process of revising and adapting the guidelines, and different approaches may be necessary and equally valid.

10.7.2 Implementing recommendations in different epidemic settings

The guidelines recommend that, in all settings, everyone (adults, adolescents and children) presenting with CD4 cell counts less than 500 cells/mm³ should be offered ART. People with CD4 cell counts of 350 cells/mm³ or less should receive ART as a priority. This is a highly cost-effective intervention that can dramatically reduce HIV-related mortality and morbidity, in addition to HIV incidence. ART should also be initiated in all pregnant and breastfeeding women with HIV, regardless of CD4 count, and be provided to all individuals with active TB and HBV coinfection with severe chronic liver disease and for HIV-positive partners in a serodiscordant couple, irrespective of CD4 count. Coverage of ART among children is also often low, and targeted investment is needed to ensure that all eligible children, including all children younger than five years, have timely access. In addition, the guidelines recommend phasing out d4T and increasing the use of fixed-dose combinations of ARV drugs.

In concentrated epidemic settings with low ART coverage, it is critical to identify opportunities to expand access to HIV treatment and care, including testing and counselling, to most-at-risk populations, such as men who have sex with men, transgender people, sex workers, people who inject drugs and prisoners. This requires addressing any structural barriers that may prevent these populations from seeking and accessing care. Integrating HIV services into drug dependence treatment and harm reduction services and TB clinics can be a highly effective approach to reaching these populations (see section 9.4.2). In these settings, given the relatively limited number of pregnant women living with HIV, phasing out option A for PMTCT and providing ART during pregnancy and breastfeeding to reduce the risk of mother-to-child transmission of HIV (option B) are highly effective and relatively low-cost strategies.

In generalized epidemic settings with low ART coverage, ensuring that all individuals with CD4 counts of less than 350 cells/mm³ are identified and enrolled in care and treatment is a priority and requires greatly increasing HIV testing and counselling rates among the general population. This can be accomplished by scaling up an appropriate mix of approaches to HIV testing and counselling, including provider-initiated HIV testing and counselling for everyone seeking care as well as all pregnant or breastfeeding women, with effective referral systems and links to care and treatment (section 5.1). Identifying individuals with CD4 counts between 350 and 500 cells/mm³ provides an important opportunity to link them into care and initiate ART early. Other strategies to improve the overall levels of access to and uptake of ART include decentralizing HIV services to the primary health care level and integrating HIV services with TB and antenatal care and maternal and child health services (see section 9.4.2), and offering pregnant and breastfeeding women living with HIV the option of receiving lifelong ART, based on national programme decisions. In addition, as in concentrated epidemics, it is important to identify and reach key populations and those with poor access to clinical and community-based services. These may include sex workers, people who inject drugs, men who have sex with
men, transgender people or other groups such as adolescent girls, migrants and other mobile populations, older women and certain high-risk occupational groups.

As coverage of ART increases and programmes mature, expanding access to second-line regimens increasingly becomes a programmatic priority. Scaling up viral load monitoring will be important to adequately identify treatment failure and to avoid switching unnecessarily to second-line regimens. Viral load monitoring is also likely to play a central monitoring role in places in which ART is being broadly expanded to reduce HIV incidence.

As people initiate treatment earlier and stay on it for longer, monitoring the quality of service delivery and strengthening service linkages to improve retention throughout the cascade of care are essential to optimize treatment outcomes and long-term programme performance.

10.8 Useful tools for costing and planning

Estimating the costs associated with implementing new recommendations is a key step in the roll-out process. Several costing tools and resources are available to assist countries in estimating the costing and budgeting of HIV and related interventions and services.

Spectrum is a suite of models and analytical tools to support decision-making. It comprises several software applications including AIM (AIDS Impact Model) and Goals (Cost and Impact of HIV Interventions). The AIM and Resource Needs modules can be used to estimate the impact of key new recommendations on number of deaths averted by ART, the number of infant infections averted by PMTCT and adult, PMTCT and paediatric treatment needs and costs. The key data needed to generate these estimates are demographic projections, HIV incidence trends, historical data on the numbers of people receiving ART, the numbers of pregnant women receiving PMTCT interventions and the unit costs for ART for adults and for PMTCT. All countries already have AIM files prepared as part of their national epidemiological estimates, so both modules can be rapidly applied.

The Goals module can be used to estimate the number of adult HIV infections averted by ART under different eligibility criteria and rates of scale-up. The key inputs required are the distribution of the adult population by risk group (such as serodiscordant stable couples, those with casual partners, female sex workers, male clients of sex workers, men who have sex with men, transgender people and people who inject drugs); sexual behaviour by risk group (numbers of partners per year, acts per partner and condom use) and needle sharing among people who inject drugs. Goals models already exist for about 25 countries, and other countries have compiled these data in the context of modes of transmission studies.

OneHealth is a software tool designed to strengthen health system analysis and costing and to develop financing scenarios at the country level. It is specifically designed to assess health investment needs in low- and middle-income countries and provides planners with a single framework for planning, costing, impact analysis, budgeting and financing of strategies for all major diseases and health system components. OneHealth can also be downloaded free of charge (24).

WHO and collaborating organizations have recently developed a variety of tools to assist with drug quantification and supply management. Several are available for download, with a description of their main purposes and programmatic focus (25). Guidance on the costing of different PMTCT options has also been developed (26). A flexible tool for costing investments in critical enablers (such as integrated treatment and rights literacy programmes, legal services, stigma and discrimination reduction programmes, training for health care workers and law enforcement) has also been developed and can be downloaded for free, along with a user guide (27,28).
MONITORING AND EVALUATION

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Goal of this chapter

To provide programmatic guidance for decision-makers and planners at the national level in tracking the implementation of these guidelines and monitoring their impact on HIV programmes and people receiving ART.
11. MONITORING AND EVALUATION

11.1 Introduction

As countries adapt and implement these guidelines, monitoring and evaluation frameworks and systems need to be adapted to collect and analyse information to track the implementation and impact of new recommendations. Monitoring and evaluation will help programme managers to assess the effectiveness of interventions and linkages between services along the cascade of treatment and care for HIV and associated conditions (Fig. 11.1). Such information is essential to detect and respond to bottlenecks or gaps in programme performance and to adequately characterize and respond to patient attrition. As programmes mature, monitoring individual- and population-level outcomes, including toxicity and adverse events, drug resistance, viral suppression, mortality, survival and incidence, is also essential to assess the impact of programmes.

Fig. 11.1 The HIV treatment and care cascade

Data can be collected in many ways, including routinely reported data from all facilities or sentinel sites; population-based surveys; surveillance data; observations on cohorts of people living with HIV; and periodic evaluation. Programme input and processes can also be monitored through facility surveys or updated lists of service availability; documenting the availability and training of human resources; and monitoring the availability of HIV medicines and diagnostics at various geographical and facility levels. Special studies can be considered where routine monitoring is inappropriate.

In considering how best to collect critical data, efforts should also be made to review monitoring systems, such as better linking the monitoring of services for PMTCT, TB and ART and integrating HIV drug resistance monitoring into routine health information systems. Involving civil society in monitoring and evaluation activities is also critical to better understand successes and failures, especially in assessing the perceptions, values and experiences of people living with HIV, key populations and the broader community in accessing and using services. The community can also play a key role in designing and implementing data collection tools and analysing and interpreting findings.

WHO is developing a consolidated guide on monitoring and evaluation of HIV in the health sector that brings together the various elements of monitoring and evaluation systems for HIV programmes. The guide will consolidate and align existing monitoring and evaluation approaches in relevant programmatic areas (such as HIV testing and counselling, ART, PMTCT and HIV drug resistance) with the recommendations in these guidelines and will also include new guidance in emerging areas for HIV monitoring and evaluation. The publication on three interlinked patient monitoring systems (1) will also be updated to reflect this new monitoring and evaluation guidance.
11.2 Monitoring implications of new recommendations

The monitoring and evaluation strategy should monitor service delivery, including inputs and processes as well as outputs and outcomes, such as the number of people receiving interventions and the impact at the individual and population levels (see section 11.3). The monitoring and evaluation plan should include a framework to track progress in implementing the guidelines to verify whether new policies on ART eligibility and recommendations on and plans for treatment or service delivery are actually implemented. This will enable national programmes to document the effect of the shift in guidelines and can contribute to evaluating the impact of the guidelines.

Table 11.1 lists key areas to review when implementing major new recommendations in these guidelines. For each key area, potential topics to monitor and possible implications for revising monitoring systems are provided. Not all information needs to be captured routinely; data needs and the timing of data collection depend on the local context.

### Table 11.1 Implications for monitoring of the key recommendations in these guidelines

<table>
<thead>
<tr>
<th>Summary of new recommendation areas</th>
<th>Implications for monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing and counselling</td>
<td>Monitor the uptake of community-based HIV testing strategies and testing services for adolescents, including systems for linkages to care</td>
</tr>
<tr>
<td>When to start ART</td>
<td>Monitor the number and percentage of different populations (such as adults, adolescents, children and pregnant and breastfeeding women) who have initiated ART based on the new eligibility criteria. Review the monitoring system to assess what disaggregation is needed for what purpose (such as CD4 counts ≤200 cells/mm³ to routinely monitor late diagnosis or CD4 counts ≤350 cells/mm³ and 350–500 cells/mm³ to periodically assess the distribution of CD4 when ART is initiated) and how to best collect the relevant data, and age disaggregation of children (such as &lt;2 years and &lt;5 years)</td>
</tr>
<tr>
<td>Which ARV regimen to start</td>
<td>Monitor the first- and second-line ARV regimens people are receiving. Monitor the phasing out and/or introduction of specific drugs (such as d4T and TDF). Monitoring tools may need to be adjusted to reflect new regimen options</td>
</tr>
<tr>
<td>Response to ART and diagnosing treatment failure</td>
<td>Monitor the percentage of people receiving ART who had a viral load test and received the results. Monitor the reasons for switching ARV regimen</td>
</tr>
</tbody>
</table>
Summary of new recommendation areas | Implications for monitoring
--- | ---
Service delivery | Monitor retention and adherence among various populations
| Monitor the integration of ART into facilities providing maternal and child health services, TB services and drug dependence services if planned by documenting the facilities providing ART
| Monitor whether the initiation and maintenance of ART has been decentralized as planned at various facilities by documenting the expansion of ART facilities
| Monitor the functionality of linkages from maternal and child health services, TB services and drug dependence services to HIV care and ART and linkages between communities, peripheral facilities and hospitals by documenting transfers
Task shifting | Monitor the number of non-physician clinicians, midwives and nurses who are trained in ART
| Monitor the number of non-physician clinicians, midwives and nurses who are initiating first-line ART and maintaining ART and the number of people they have initiated or maintained on ART
| Monitor the number of community health workers who are trained and are dispensing ART between regular clinical visits, and capture the number of people to whom they dispense ART

11.3 Monitoring the outputs and outcomes of scaling up access to ARV drugs

In addition to monitoring the implementation of new recommendations, health information systems need to be reviewed and adapted to appropriately monitor the outputs and outcomes associated with the new recommendations. Table 11.2 lists areas for gathering data for assessing whether scaling up programmes leads to the anticipated outputs and outcomes at various points along the cascade of HIV treatment and care. Most of the areas have associated indicators in existing WHO guidance (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes provides additional details on indicators and references) and/or form part of internationally agreed core indicators that all countries should track within the framework of the Global AIDS Response Progress Reporting process (2). In some evolving areas (such as links between HIV diagnosis and ART, retention of pregnant women in using ARV drugs and viral load monitoring), indicators are still being reviewed and evaluated. The forthcoming consolidated monitoring and evaluation guide for HIV in the health sector will provide more detailed guidance.
## Table 11.2 Overview of data areas for monitoring and evaluating the HIV treatment cascade

<table>
<thead>
<tr>
<th>Step in the cascade</th>
<th>Indicator areas</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>People living with HIV</td>
<td>Estimated number of people living with HIV in various categories</td>
<td>Estimates the distribution of people living with HIV among the population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estimates the size of relevant populations and need for HIV interventions, to help focus planning</td>
</tr>
<tr>
<td>HIV diagnosis</td>
<td>Percentage of the general population with known HIV test status and within specific populations as well</td>
<td>The level of testing coverage of relevant populations indicates efforts to scale-up HIV testing and counselling, including provider-initiated testing and counselling. Measuring the proportion of population groups aware of their HIV status identifies where more effort may be needed</td>
</tr>
<tr>
<td></td>
<td>Number of people newly diagnosed with HIV infection</td>
<td>Number of people newly diagnosed with HIV infection in a given period indicates the pool of people who should be linked to care</td>
</tr>
<tr>
<td>Linkage and enrolment in HIV care</td>
<td>Percentage of people newly diagnosed with HIV infection enrolled in HIV care</td>
<td>Measures strength of link between diagnosis and enrolment in care. Indicates access to and uptake of HIV care following a positive HIV test</td>
</tr>
<tr>
<td></td>
<td>Profile of people living with HIV initiating HIV care</td>
<td>Identifies who is enrolled in care and whether key populations and priority groups are linked to care</td>
</tr>
<tr>
<td></td>
<td>Retention in care of people living with HIV not yet initiating ART, including HIV-exposed infants</td>
<td>Acts as a proxy measure for maintained linkage to the care of adults and children who may start ART in the future</td>
</tr>
<tr>
<td>Antiretroviral drugs: coverage</td>
<td>Number of people receiving ART (and coverage)</td>
<td>Coverage of ART among eligible people living with HIV, by population groups of interest and regimen:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Indicates trends in the number of people receiving ART, to be used to review programme expansion and plan drug supply</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Helps estimate unmet need for ART and equity in access to ART</td>
</tr>
<tr>
<td></td>
<td>Number of people receiving ARV drugs for PMTCT (and coverage)</td>
<td>Coverage of ARV drugs for PMTCT among pregnant women with HIV:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Estimates unmet need for ARV drugs for PMTCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Input to model the impact of services for PMTCT</td>
</tr>
<tr>
<td>Step in the cascade</td>
<td>Indicator areas</td>
<td>Relevance</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Antiretroviral drugs: drug supply</strong></td>
<td>Percentage of ART facilities with ARV drug stock-outs in a given period</td>
<td>Indicates stock-outs, which could directly affect treatment adherence and clinical outcomes, and may contribute to HIV drug resistance</td>
</tr>
<tr>
<td><strong>Antiretroviral drugs: adherence and retention</strong></td>
<td>Adherence</td>
<td>Indicates the quality of care and the likelihood of viral suppression Adherence acts as an early warning indicator of drug resistance</td>
</tr>
<tr>
<td></td>
<td>Percentage retained on ART and PMTCT</td>
<td>Indicates retention over time and the success of ART programmes Helps to monitor losses and identify where to strengthen engagement in care Low retention acts as an early warning indicator for HIV drug resistance</td>
</tr>
<tr>
<td><strong>Viral suppression</strong></td>
<td>Percentage of viral suppression</td>
<td>Effectiveness of ART programmes in achieving viral suppression</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>Decline in HIV-related deaths and even overall mortality in countries with a high burden of HIV indicates successful HIV programmes</td>
</tr>
<tr>
<td></td>
<td>Incidence and the number of adults and children acquiring HIV infection</td>
<td>Decline in incidence indicates how successful HIV prevention and treatment programmes are in limiting the number of people acquiring HIV infection Identifying who is acquiring HIV infection and where the infection was acquired helps to focus planning Elimination of new HIV infections among children is a measure of the success of PMTCT programmes</td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>Mother-to-child transmission rate</td>
<td>The mother-to-child transmission rate indicates how much vertical transmission occurs</td>
</tr>
<tr>
<td></td>
<td>Survival</td>
<td>Increased survival and extended life-years of people living with HIV receiving ART is a measure of the impact of ART Survival, including HIV-exposed children and children living with HIV, indicates the levels of access to and the quality of health care</td>
</tr>
</tbody>
</table>
11.4 Other monitoring considerations

Programmes are increasingly moving beyond coverage indicators to focus on critical outcomes, such as viral load suppression and immune reconstitution, and on the broader impact of HIV treatment, including HIV-related mortality and HIV incidence. However, programmes also need to measure potential unintended outcomes, such as HIV drug resistance and ARV-related toxicities. Periodic evaluations and implementation research are also central to reviewing programmes.

11.4.1 HIV drug resistance

WHO recommends the use of early warning indicators to help identify deficits in programme performance that favour the emergence of HIV drug resistance (Box 11.1). WHO also recommends that countries undertake surveillance of HIV drug resistance and provides specific guidance on how to do the surveys required.

11.4.2 Sentinel surveillance for ARV toxicity monitoring

Surveillance of the toxicity of ARV drugs is essential to identify and address preventable adverse events. Various approaches have been developed to monitor the toxicity of ARV drugs, including targeted and systematic surveillance reporting on specific types of toxicity and serious adverse events caused by a specific drug in targeted populations, and the pregnancy exposure registry following a cohort of pregnant women exposed to ART, including birth defect surveillance. WHO technical guidance on implementing toxicity monitoring at sentinel sites will become available in 2013.

11.4.3 Evaluation, including impact and programme performance, and implementation research

Routine monitoring should be complemented by systematic evaluations and programme reviews to assess the performance and effects of HIV programmes, either comprehensively or with respect to specific priority areas. Social science and implementation research are important to assess perceptions and values of service recipients and communities along with barriers, facilitators and experiences in delivering and receiving services.

Impact indicators, such as incidence, morbidity and mortality, are often difficult to measure. Guidance on the use of assays for recent infection to estimate HIV incidence at the population level has been recently developed (3), and guidance on monitoring mortality, including the cause of death, will be available in 2013. A short guide summarizing five methods to measure the impact of programmes for PMTCT (4) is already available, and detailed guidance that can be adapted to implement each method will become available in 2013.

Mathematical modelling is often undertaken to project various scenarios for programme planning and evaluating impact. Ensuring the availability of robust data is especially important when estimating the prevention impact of ARV drugs at the population level, as multiple sources of information and uncertainty come into play. Specific data collection efforts and models for particular contexts may provide more accurate estimates.
Box 11.1 Monitoring HIV drug resistance

HIV drug resistance poses a significant threat to the success of national HIV programmes. Drug resistance results in more rapid virological failure among people receiving first-line regimens and increases the need for second-line regimens, which may be associated with greater toxicity, adverse events, poorer adherence and higher costs. Drug resistance may also affect the ability to prevent HIV transmission using ARV-based pre- or post-exposure prophylaxis or topical microbicides.

Surveillance of drug resistance should be an integral component of national HIV programmes. Surveillance data should inform the selection of first- and second-line regimens for ART, as well as ARV drugs for PMTCT, to optimize treatment outcomes within a public health approach.

WHO and its partners have developed a standardized and complementary assessment strategy to be implemented by countries, for both adult and paediatric populations, with the following components.

**Monitoring early warning indicators for HIV drug resistance.** Early warning indicators use existing clinic and pharmacy records to assess the factors associated with the emergence of HIV drug resistance at the level of ART programmes and clinics. These factors include ART prescribing practices; drug supply continuity; adherence to ARV drug regimens measured by on-time pick-up of ARV drugs; retention in care; and viral load suppression, when available. The monitoring of early warning indicators should be integrated into a country’s monitoring and evaluation system and provides the information needed to address practices that may lead to poor outcomes and HIV drug resistance.

**Surveys to monitor acquired HIV drug resistance and associated factors in populations receiving ART.** The WHO generic protocol for monitoring acquired HIV drug resistance uses a standardized survey methodology to assess population-level virological suppression at the national level and the emergence of HIV drug resistance among populations receiving treatment. Performed regularly at representative sites, these surveys provide evidence for action at the programme and clinic level to minimize HIV drug resistance. They also provide evidence to optimize the selection of first- and second-line ARV regimens.

**Surveys to monitor pre-treatment HIV drug resistance.** The WHO generic protocol for surveillance of pre-treatment HIV drug resistance provides a nationally representative estimate of HIV drug resistance in populations initiating therapy. Performed regularly at representative ART clinics, these surveys support national, regional and global decision-making regarding the choice of first-line regimens.

**Surveillance of transmitted HIV drug resistance among individuals recently infected with HIV.** The WHO generic protocol for surveillance of transmitted HIV drug resistance provides estimates of transmitted HIV drug resistance in recently infected populations, and the results should contribute to ART policy decisions, including guidelines on ARV regimens and HIV prophylaxis.

**Surveillance of HIV drug resistance among children under 18 months of age.** The WHO generic protocol for surveillance of HIV drug resistance among children under 18 months of age can provide estimates of national prevalence of HIV drug resistance among infants diagnosed with HIV infection through early infant diagnosis testing. The results assess differences in HIV drug resistance prevalence between populations exposed to ARV drugs for PMTCT and those with unknown exposure to support the selection of optimal first-line ART for this population.

National strategies for assessing HIV drug resistance should be developed and routinely implemented as part of comprehensive HIV treatment programmes.
11.5 Reviewing and strengthening monitoring and evaluation systems

The recommendations in these guidelines may require certain adaptations to the monitoring and evaluation system. Guidance is available on the 12 components of a monitoring and evaluation system and tools to review and strengthen national HIV monitoring and evaluation systems (5). Table 11.3 highlights some specific areas to review to ensure that monitoring and evaluation systems are aligned to the new ARV guidelines.

### Table 11.3 Critical aspects of monitoring and evaluation systems and implications of the new recommendations

<table>
<thead>
<tr>
<th>Selected elements of monitoring and evaluation systems</th>
<th>Key considerations to review with new guidelines</th>
</tr>
</thead>
</table>
| Patient monitoring system                             | • Improving the monitoring of enrolment and retention in HIV care  
• Accurate accounting for transfers and losses  
• Updating data elements required for patient monitoring in line with new guidelines, such as changes in regimen and including viral load (where available)  
• Revisit disaggregation categories and links and synergy for systems for monitoring ARV drugs for PMTCT, TB and ART  
• Move to electronic systems where feasible |
| Data flow and integration                              | • One standardized monitoring and evaluation system, agreed on by all partners and stakeholders, including necessary updates based on evolving ARV drug policies and practices  
• Common country standards and data flow, based on any changes in service delivery  
• Clarify integration of PMTCT and TB programmes with ART programmes and transfers to ART programmes  
• Consider a unique patient identifier  
• Use of mobile phones where proven opportunities exist  
• Functional links between HIV and health management information systems |
| Data generation and quality assurance approach         | • Clear protocols for data generation, standard operating procedures for aggregation, where they do not exist, for any new indicators and for new service delivery scenarios  
• Review available laboratory data as a source of key information  
• Regular assessment of the data quality in facilities and at the subnational level  
• Supportive supervision, including new elements of ARV drug policy and implementation plans  
• Update national reporting forms to capture any new national-level data, including identifying the frequency of data collection necessary for various indicators |
| Data use at various levels and programme reviews       | • Regular review of standardized data at the facility, regional and national levels to identify issues and improve programmes, including a review of early warning indicators for HIV drug resistance  
• Review and update the strategy for using data based on new ARV drug policies and a corresponding monitoring and evaluation framework and plan |
### Table 11.3 (continued)

<table>
<thead>
<tr>
<th>Selected elements of monitoring and evaluation systems</th>
<th>Key considerations to review with new guidelines</th>
</tr>
</thead>
</table>
| **Periodic reporting and data accessibility**          | • Maintaining national and subnational databases, to include new data elements  
• Regular data dissemination and public accessibility of data related to the evolving HIV programme  
• Periodic (sub-) national and international reports to reflect and document the roll-out of new ARV drug policies and their impact |
| **Monitoring and evaluation system capacity**          | • Human and institutional capacity for data generation and analysis at the facility, subnational and national levels, for monitoring and evaluation that is relevant to updated ARV drug guidance and policies  
• Appropriate investment in monitoring and evaluation and reflection in grants (including those from the Global Fund to Fight AIDS, Tuberculosis and Malaria) of the monitoring and evaluation adjustments required to strengthen existing capacity and capture new guidance on ARV drugs |
| **Monitoring and evaluation plan**                     | • A costed national plan with a list of core indicators and planned evaluations, with focus on results and accountability, revisited in light of new guidelines on ARV drugs  
• Regular assessment of the implementation of the monitoring and evaluation plan, based on the updated plan |
| **Evaluation and operational and implementation research** | • Plan and strategy for evaluating impact, considering the rollout of the new guidelines on ARV drugs  
• Agenda and plan for implementation research, considering the rollout of the new guidelines on ARV drugs  
• Review of research results for improving programmes |
| **Monitoring and evaluation partnerships and coordination** | • Coordinating programme monitoring and reporting activities among key stakeholders and partners  
• Alignment with national health strategy, link with other programme strategies (maternal and child health services, TB and key populations) and international initiatives (Commission for Information and Accountability for Women’s and Children’s Health, elimination of mother-to-child transmission of HIV (eMTCT) and Global AIDS Response Progress Reporting (2)) |
Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children 230
Annex 2. Algorithm for the 2013 recommendations for adults and adolescents 232
Annex 3. Algorithms for the 2013 recommendations for pregnant and breastfeeding women 234
Annex 4. Algorithm for the 2013 recommendations for children 236
Annex 5. Algorithm for early infant diagnosis 237
Annex 6. Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women 238
Annex 7. Dosages of recommended antiretroviral drugs 242
# Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children


<table>
<thead>
<tr>
<th>Adults and adolescents*</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical stage 1</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>Persistent generalized lymphadenopathy</td>
</tr>
<tr>
<td><strong>Clinical stage 2</strong></td>
<td></td>
</tr>
<tr>
<td>Moderate unexplained weight loss (&lt;10% of presumed or measured body weight)</td>
<td>Unexplained persistent hepatosplenomegaly</td>
</tr>
<tr>
<td>Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)</td>
<td>Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>Lineal gingival erythema</td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
<td>Recurrent oral ulceration</td>
</tr>
<tr>
<td>Papular pruritic eruption</td>
<td>Papular pruritic eruption</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>Fungal nail infections</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Extensive wart virus infection</td>
</tr>
<tr>
<td></td>
<td>Extensive molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>Unexplained persistent parotid enlargement</td>
</tr>
<tr>
<td><strong>Clinical stage 3</strong></td>
<td></td>
</tr>
<tr>
<td>Unexplained severe weight loss (&gt;10% of presumed or measured body weight)</td>
<td>Unexplained moderate malnutrition* not adequately responding to standard therapy</td>
</tr>
<tr>
<td>Unexplained chronic diarrhoea for longer than 1 month</td>
<td>Unexplained persistent diarrhoea (14 days or more)</td>
</tr>
<tr>
<td>Unexplained persistent fever (intermittent or constant for longer than 1 month)</td>
<td>Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month)</td>
</tr>
<tr>
<td>Persistent oral candidiasis</td>
<td>Persistent oral candidiasis (after first 6 weeks of life)</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>Oral hairy leukoplakia</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>Lymph node tuberculosis</td>
</tr>
<tr>
<td>Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)</td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis</td>
<td>Severe recurrent bacterial pneumonia</td>
</tr>
<tr>
<td>Unexplained anaemia (&lt;8 g/dl), neutropaenia (&lt;0.5 x 10⁹/l) and/or chronic thrombocytopenia (&lt;50 x 10⁹/l)</td>
<td>Acute necrotizing ulcerative gingivitis or periodontitis</td>
</tr>
<tr>
<td></td>
<td>Unexplained anaemia (&lt;8 g/dl), neutropaenia (&lt;0.5 x 10⁹/l) or chronic thrombocytopenia (&lt;50 x 10⁹/l)</td>
</tr>
</tbody>
</table>

*See Annex 1 for additional information about clinical staging of HIV disease in adults, adolescents and children.*
### Annex 1

#### Clinical staging of HIV disease in adults, adolescents and children

<table>
<thead>
<tr>
<th>Adults and adolescents*</th>
<th>Children</th>
</tr>
</thead>
</table>
| **Clinical stage 3** | Symptomatic lymphoid interstitial pneumonitis  
Chronic HIV-associated lung disease, including bronchiectasis |
| **Clinical stage 4c** | Unexplained severe wasting, stunting or severe malnutrition* not responding to standard therapy  
Pneumocystis (jirovecii) pneumonia  
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)  
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month’s duration or visceral at any site)  
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)  
Extrapulmonary tuberculosis  
Kaposi sarcoma  
Cytomegalovirus infection (retinitis or infection of other organs)  
Central nervous system toxoplasmosis  
HIV encephalopathy  
Extrapulmonary cryptococcosis, including meningitis  
Disseminated nontuberculous mycobacterial infection  
Progressive multifocal leukoencephalopathy  
Chronic cryptosporidiosis  
Chronic isosporiasis  
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)  
Lymphoma (cerebral or B-cell non-Hodgkin)  
Symptomatic HIV-associated nephropathy or cardiomyopathy  
Recurrent septicaemia (including nontyphoidal Salmonella)  
Invasive cervical carcinoma  
Atypical disseminated leishmaniasis |

*In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used.

*For children younger than 5 years, moderate malnutrition is defined as weight-for-height < −2 z-score or mid-upper arm circumference ≥115 mm to <125 mm.

*Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

*For children younger than 5 years of age, severe wasting is defined as weight-for-height < −3 z-score; stunting is defined as length-for-age/height-for-age < −2 z-score; and severe acute malnutrition is defined as either weight for height < −3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.
Annex 2. Algorithm for the 2013 recommendations for adults and adolescents

![Algorithm Diagram]

**Initiate one of the following ARV regimens:**
- **Preferred option:** TDF + 3TC (or FTC) + EFV
- **Alternative options:**
  - TDF + 3TC (or FTC) + NVP
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP

**Annex 1** lists the WHO clinical staging for HIV disease.

**ART initiation in individuals with severe or advanced symptomatic disease (WHO clinical stage 3 or 4), regardless of CD4 cell count, or with CD4 count \( \leq 350 \text{ cells/mm}^3 \), regardless of clinical symptoms, should be prioritized.

**Active TB disease** refers to the time when TB breaks out of latency and causes disease. Latent TB infection refers to the period of time when the immune system has been successful in containing the *Mycobacterium tuberculosis* and preventing disease.

**Severe chronic liver disease** includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

**For details on ARVs for pregnant and breastfeeding women with HIV (Option B and Option B+), see Annex 3 and sections 7.1.2, 7.1.3 and 7.2.2.**

**A HIV-serodiscordant couple is a couple in which one of the sexual partners is HIV-positive and one is HIV-negative. Although one partner is currently HIV-negative, this does not mean that this partner is immunized or protected against getting HIV in the future.**

**For adolescents weighing less than 35 kg, refer to the algorithm for children in annex 4 which indicates the appropriate first-line ARV regimen options.**
Annex 2 Algorithm for the 2013 recommendations for adults and adolescents
Annex 3. Algorithms for the 2013 recommendations for pregnant and breastfeeding women

Lifelong ART for all pregnant and breastfeeding women with HIV (Option B+)

- **Initiate lifelong ART:**
  - TDF + 3TC (or FTC) + EFV
  - (Preferred regimen)
  - (assess CD4 baseline where possible)

- **MTCT RISK PERIOD**
  - Breastfeeding
    - Once daily NVP for 6 weeks
  - Replacement feeding
    - 4-6 weeks of once daily NVP or twice-daily AZT

- **CESSATION OF MTCT RISK**
  - Early infant diagnosis
  - Final infant diagnosis

- **LINKAGE TO TREATMENT AND CARE FOR BOTH WOMAN AND INFANT**

---

*See Annex 5. Algorithm for early infant diagnosis*
ART for women with HIV during pregnancy and breastfeeding (Option B)

PREGNANT AND BREASTFEEDING WOMEN WITH HIV

Initiate the following recommended ART: TDF + 3TC (or FTC) + EFV
(assess eligibility (WHO clinical stage 3 or 4 or CD4 ≤500 cells/mm³) for treatment for her own health)

Eligible for treatment for her own health at baseline assessment

Yes

Continue ART

No

Stop ART after 1 week of complete cessation of breastfeeding and refer to care for reassessment

HIV-EXPOSED INFANTS

Breastfeeding
Once daily NVP for 6 weeks

Replacement feeding
4-6 weeks of once NVP or twice-daily AZT

Early infant diagnosis

Final infant diagnosis

LINKAGE TO TREATMENT AND CARE FOR BOTH WOMAN AND INFANT

* See Annex 5. Algorithm for early infant diagnosis
Annex 4. Algorithm for the 2013 recommendations for children

Infants and children infected with HIV

*5 years of age

<5 years of age

Initiate ART

<3 years of age?

>5 years of age

WHO clinical stage 3 or 4 or CD4 ≤500 cells/mm³?

Yes

Initiate ART

< 10 years of age or weighing <35kg

Monitor clinical stage and CD4

No

Yes

Initiate one of the following regimens: *

Preferred option: ABC or AZT + 3TC + LPV/r

Alternative option: ABC or AZT + 3TC + NVP

Initiate one of the following regimens: *

Preferred option: ABC + 3TC + EFV

Alternative options: ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP

Initiate one of the following regimens:

Preferred option: TDF + 3TC (or FTC) + EFV

Alternative options: AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP

* If this recommendation to treat all children between one and under five years of age is not adopted: initiate ART with WHO clinical stage 3 and 4 or with CD4 count ≤750 cells/mm³ or ≤25%, whichever is lower, regardless of WHO clinical stage (105).

* If this recommendation is not adopted, ART should be initiated at WHO HIV clinical stage 3 and 4 or with CD4 count ≤350 cells/mm³ regardless of WHO clinical stage (105, Chapter 7).

Special note: d4T use should be restricted to those situations where there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.
Annex 5. Algorithm for early infant diagnosis


For newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks). See also Table 5.1 on infant diagnosis.

Start ART, if indicated, without delay. At the same time, retest to confirm infection.

The risk of HIV transmission remains as long as breastfeeding continues.
Annex 6. Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women

The 2013 consolidated guidelines recommend that all pregnant and breastfeeding women with HIV should initiate ART and, based on national programme decisions, that either all women continue ART as lifelong treatment or women not eligible for ART for their own health stop after the mother-to-child transmission risk period. Countries planning for this transition, and those working to expand and strengthen their programme, may find it useful to refer to this readiness assessment checklist, which addresses a range of issues from national policy to facility readiness. The checklist (adapted below), as well as a discussion guide, were developed by the United States President’s Emergency Plan for AIDS Relief, and are included as part of the larger Elimination of Mother-to-Child Transmission Inter-Agency Task Team’s Toolkit: Expanding and Simplifying Treatment for Pregnant Women Living with HIV: Managing the Transition to Option B/B+:

- Full Toolkit Link: www.emtct-iatt.org/toolkit

Recommended timing key:

<table>
<thead>
<tr>
<th></th>
<th>Before implementation</th>
<th>Early in implementation</th>
<th>During implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLITICAL COMMITMENT &amp; POLICY ENDORSEMENT</strong></td>
<td>Completed</td>
<td>In Process</td>
<td>Not yet started</td>
</tr>
<tr>
<td>Commitment to Global Plan goals (national and subnational)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time MoH staff responsible for PMTCT (national &amp; possibly subnational)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional technical working group inclusive of stakeholders from MNCH, PMTCT, and HIV treatment, including health care workers and people living with HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National and subnational endorsement of ART for all pregnant and breastfeeding women (Option B or B+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidelines incorporate offering ART to all pregnant and breastfeeding women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FINANCIAL CONSIDERATIONS</strong></td>
<td>Completed</td>
<td>In Process</td>
<td>Not yet started</td>
</tr>
<tr>
<td>Costing of current PMTCT strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costing of ART for all pregnant and breastfeeding women, both short and long term</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conduct resource gap analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased programme funding needs reflected in budget</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstration of national financial commitment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SERVICE DELIVERY MODEL</strong></td>
<td>Completed</td>
<td>In Process</td>
<td>Not yet started</td>
</tr>
<tr>
<td>Defining minimum package of services to provide ART to all pregnant and breastfeeding women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of system capacity (infrastructure, human resources, and commodities) to decentralize ART to MNCH settings, including absorbing women with HIV and their families</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Annex 6 Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women

<table>
<thead>
<tr>
<th>SERVICE DELIVERY MODEL</th>
<th>Completed</th>
<th>In Process</th>
<th>Not yet started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing and location of transition between PMTCT and long-term treatment services has been determined (including consideration of lifelong ART provision within MNCH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic identification of ART clients who become pregnant and linkage to MNCH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing and treating partners and family members within MNCH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral of stable ART clients at current ART facilities to new decentralized ART sites</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HUMAN RESOURCE CAPACITY</th>
<th>Completed</th>
<th>In Process</th>
<th>Not yet started</th>
</tr>
</thead>
<tbody>
<tr>
<td>National endorsement of task shifting/sharing for ART initiation and maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of human resource capacity (nurse, midwife, pharmacy, lab) to support ART scale-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core competencies in HIV management for each health worker cadre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training strategy for ART provision to support rapid scale-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Updating of national in-service and pre-service curricula</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy for retention, retraining, and continuing professional development of health workers, especially those providing in PMTCT/ART</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARV REGIMEN CHOICE</th>
<th>Completed</th>
<th>In Process</th>
<th>Not yet started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplification and harmonization of PMTCT and adult treatment regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plan for alternate regimen for pregnant women not tolerant of 1st-line ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimization of 1st-line regimen for infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establishment of pharmacovigilance system, where appropriate (see discussion guide)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUPPLY CHAIN MANAGEMENT</th>
<th>Completed</th>
<th>In Process</th>
<th>Not yet started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supply chain gap assessment including quantification, distribution and stock management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 month forecast, quantification, and supply plan developed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock management of ART in MNCH settings (training, capacity, and security)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUPPLY CHAIN MANAGEMENT</th>
<th>Completed</th>
<th>In Process</th>
<th>Not yet started</th>
</tr>
</thead>
<tbody>
<tr>
<td>If modifying 1st line regimen, plan to for using ARVs already ordered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revised supply chain management system (consumption, forecasting, and distribution)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MONITORING, EVALUATION, AND DATA USE</strong></td>
<td><strong>In Process</strong></td>
<td><strong>Not yet started</strong></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Antenatal care (ANC) and PMTCT register allows for documentation of initiation versus those already on ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART register allows for documentation of pregnancy and breastfeeding status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tools and registers in MNCH allow for cohort monitoring of maternal ART retention and exposed infant retention in care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant and breastfeeding women initiated on ART in MNCH settings are included in site and national level ART M&amp;E systems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System to track and measure linkages and transition between MNCH and long-term HIV care &amp; treatment for mother and infant (for example, a mother-baby longitudinal registry, unique identifier)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Program evaluation designed to detect early successes and challenges, and to assess longer term maternal and infant outcomes, including mother-to-child transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine data quality assurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harmonization of PMTCT and ART M&amp;E systems and data review processes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized file or card for pregnant and breastfeeding women with HIV and exposed infants</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>SITE SUPERVISION AND QUALITY MANAGEMENT</strong></th>
<th><strong>In Process</strong></th>
<th><strong>Not yet started</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine site supervision and clinical mentoring for quality of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous quality improvement process for the PMTCT program</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HIV TESTING AND COUNSELLING IN PMTCT SETTINGS</strong></th>
<th><strong>In Process</strong></th>
<th><strong>Not yet started</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality assurance measures for rapid HIV testing in all PMTCT sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy decision on treatment of discordant couples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couples HTC and follow-up of discordant couples incorporated into PMTCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy to link or register male partners with HIV in ART program</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>COUNSELLING ON ART INITIATION AND ADHERENCE</strong></th>
<th><strong>In Process</strong></th>
<th><strong>Not yet started</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialized messaging and support services for pregnant and breastfeeding women initiating ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structures to expedite preparation for ART initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative protocols developed for women not in need ART for their own health who decline treatment for life</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>LABORATORY AND CLINICAL MONITORING</strong></th>
<th><strong>In Process</strong></th>
<th><strong>Not yet started</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment monitoring capability for toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Availability of baseline CD4 (point of care or reliable sample transport)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algorithm for CD4 and/or viral load monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFANT DIAGNOSIS AND PEDIATRIC TREATMENT</td>
<td>Completed</td>
<td>In Process</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>EID capacity paralleling PMTCT programme scale-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strengthening of “EID cascade” – early diagnosis, rapid results return, active case finding of infants infected with HIV and initiation of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retention of HIV exposed infants through end of breastfeeding including assuring final diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expand access to pediatric treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RETENTION IN CARE AND TREATMENT</td>
<td>Completed</td>
<td>In Process</td>
</tr>
<tr>
<td>System to ensure that ALL pregnant and postpartum women with HIV are enrolled in ongoing HIV care and/or treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Models of service delivery that consider harmonized mother-infant pair follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility- and community-based services to support adherence and trace defaulters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innovative solutions to improving the accessibility of ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAMILY PLANNING</td>
<td>Completed</td>
<td>In Process</td>
</tr>
<tr>
<td>Assessment of family planning service availability and commodities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access to and uptake of voluntary family planning services in settings providing ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMMUNITY INVOLVEMENT</td>
<td>Completed</td>
<td>In Process</td>
</tr>
<tr>
<td>Women living with HIV are engaged in the planning, implementation and monitoring at national, subnational and community levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community-based activities and services to support PMTCT scale-up and retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community structures to support orphans and vulnerable children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROLL-OUT STRATEGY</td>
<td>Completed</td>
<td>In Process</td>
</tr>
<tr>
<td>Roll-out strategy has been planned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real-time evaluation of implementation in order to inform further scale-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acronyms used: MoH (Ministry of Health); MNCH (maternal, newborn, and child health); M&E (monitoring and evaluation); HTC (HIV testing and counselling); and EID (early infant diagnosis).
### Annex 7. Dosages of recommended antiretroviral drugs

#### Dosages of antiretroviral drugs for adults and adolescents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside reverse-transcriptase inhibitors (NRTIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>300 mg twice daily or 600 mg once daily</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>400 mg once daily (&gt;60 kg) 250 mg once daily (≤60 kg)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>150 mg twice daily or 300 mg once daily</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>250–300 mg twice daily</td>
</tr>
<tr>
<td><strong>Nucleotide reverse-transcriptase inhibitors (NtRTIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>600 mg once daily</td>
</tr>
<tr>
<td>Etravirine (ETV)</td>
<td>200 mg twice daily</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>200 mg once daily for 14 days, followed by 200 mg twice daily</td>
</tr>
<tr>
<td><strong>Proteases inhibitors (PIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir + ritonavir (ATV/r)</td>
<td>300 mg + 100 mg once daily</td>
</tr>
<tr>
<td>Darunavir + ritonavir (DRV/r)</td>
<td>800 mg + 100 mg once daily or 600 mg + 100 mg twice daily</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>400 mg/100 mg twice daily</td>
</tr>
<tr>
<td><strong>Considerations for individuals receiving TB therapy</strong></td>
<td></td>
</tr>
<tr>
<td>In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily) or SQV/r (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase strand transfer inhibitors (INSTIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>400 mg twice daily</td>
</tr>
</tbody>
</table>

*a For adolescents weighing less than 35 kg, see the next page for weight-based dosing for ARV formulations for children.
Weight-based dosing for antiretroviral formulations for children

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on antiretroviral drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing. The work to develop and update simplified guidance on antiretroviral drugs for use in children has been undertaken by WHO through the Paediatric Antiretroviral Working Group. For simplification and ease of implementation, doses are expressed per weight-band rather than per kilogram or per square metre of body surface area. When this simplified weight-band dosing was developed, careful consideration was given to the usual body surface area of children from low- and middle-income countries in that weight band. The primary source of information for the guidance provided is the manufacturer’s package insert. This was supplemented with data from other clinical studies as well as expert paediatric pharmacology consultations. For fixed-dose combinations, a dose-modelling tool (www.who.int/hiv/paediatric/generictool/en/index.html) was used to predict the dose delivered for each component drug against the recommended dosing schedule. In some cases the dose for a component in a particular weight band may be somewhat above or below the target dose recommended by the manufacturer. This is inevitable given the limitations imposed by a fixed-dose combination, but care was taken to ensure that in no case would a child receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. For simplification, Antiretroviral drugs that are no longer considered preferred or alternative options for children such as didanosine and saquinavir are no longer included in the dosing guidance. In addition, dosing for postnatal prophylaxis for HIV-exposed infants is not provided here but can be found in Chapter 7, Table 7.7.

During the finalisation of these Guidelines the United States Food and Drug Administration approval was granted for the use of EFV in children 3 months to 3 years old weighing at least 3.5 kg. While recognizing the opportunity to provide an additional option to children and allow further harmonisation across age groups, the Guideline Development Group highlighted the need for further data prior to recommending EFV as a treatment option in children less than 3 years.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as further data or newer formulations become available, but national programmes are advised to consider the most recent product labelling for up-to-date information. Additional information can also be found in specific drug information sheets in the Web Annex at www.who.int/hiv/pub/guidelines/antiretroviral2013/annexes.

Antiretroviral drugs and formulations are available from several companies, and the dose strengths of tablets, capsules and liquid formulations may vary from the information given here. In addition, the listing of a formulation in this annex does not equate to quality assurance of that formulation. National programme managers should ensure that any product procured for use is approved and of appropriate quality and stability. For guidance on the quality assurance of medicines, see the WHO medicines web site (www.who.int/medicines/areas/quality_safety/quality_assurance/about/en/index.html) and the Access to HIV/AIDS drugs and diagnostics of acceptable quality, which is available and updated at www.who.int/hiv/amds/selection/en/index.html. The current list of WHO prequalified drugs is available at http://apps.who.int/fda/internationalprograms/FDAbeyondbordersforeignoffices/AsiaandAfrica/ucm119231.htm For the policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance, see www.theglobalfund.org/en/procurement/quality/pharmaceutical.

General principles

The principles followed in developing the WHO simplified tables include the following:

- It is preferable to use an age-appropriate fixed dose combination for any regimen if such a formulation is available.

- Oral liquid or syrup formulations should be avoided where possible, especially if volumes are large – such as above 10 ml.

- Dispersible tablets (or tablets for oral solution) are the preferred solid oral dosage forms, since each dispersible tablet can be made into liquid at the point of use.

- In general, young children should be switched to available solid oral dosage forms as soon as they are tolerated.

- Where children have to use adult formulations, care must be taken to avoid underdosing. Adult tablets that are scored are more easily split. For tablets that are not easily split, WHO recommends that this be done in the dispensing pharmacy using appropriate tablet cutters.

- Some tablets such as LPV/r heat-stable tablets are made in a special embedded matrix formulation (a proprietary melt extrusion technology that stabilizes drug molecules that are normally heat labile) and should not be cut, split or crushed, since they lose bioavailability.

- Different dosing between morning and evening doses should be avoided where possible.

- Children have to be weighed at each clinic visit, and dose changes are required as children grow and/or gain weight.
Table 1. Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing among children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of tablets (mg)</th>
<th>Number of tablets by weight band morning and evening</th>
<th>Strength of adult tablet (mg)</th>
<th>Number of tablets by weight band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>Tablet (dispersible) 60 mg/30 mg</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>AZT/3TC/ NVP</td>
<td>Tablet (dispersible) 60 mg/30 mg/50 mg</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>ABC/ AZT/3TC</td>
<td>Tablet (dispersible) 60 mg/60 mg/30 mg</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>Tablet (dispersible) 60 mg/30 mg</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>d4T/3TC</td>
<td>Tablet (dispersible) 6 mg/30 mg</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>d4T/3TC/ NVP</td>
<td>Tablet (dispersible) 6 mg/30 mg/50 mg</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Drug</td>
<td>Strength of tablets (mg)</td>
<td>Number of tablets or capsules by weight band once daily</td>
<td>Strength of tablet (mg)</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-5.9 kg</td>
<td>6-9.9 kg</td>
<td>10-13.9 kg</td>
<td>14-19.9 kg</td>
</tr>
<tr>
<td>EFV</td>
<td>200 mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(scored)</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>EFV</td>
<td>600 mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(double scored)</td>
<td></td>
<td>2/3</td>
<td>1/2</td>
<td>1/3</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>60/30 mg</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Tablet (dispersible)</td>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>600-300 mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*a EFV is not recommended for children younger than 3 years and weighing less than 10 kg. FDA approval for use in children less than 3 years weighing more than 3.5 kg was granted during the finalisation of these guidelines (3.5 kg: two 50 mg capsules; 5-7.5 kg: three 50 mg capsules; 7.5-15 kg: one 200 mg capsule). However, more data are urgently needed to inform recommendations for use of EFV in this age group.

*b The double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling the tablet to be divided into thirds and halves as needed.
### Table 3. Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing

| Drug | Strength of tablets (mg) or oral liquid (mg/ml) | Number of tablets by weight band morning and evening | Strength of adult tablet (mg) | Number of tablets by weight band |
|------|-------------------------------------------------|------------------------------------------------------|-----------------------------|---------------------------------
|      | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| 3–5.9 kg | 6–9.9 kg | 10–13.9 kg | 14–19.9 kg | 20–24.9 kg | 25–34.9 kg |
| **Solid formulations** | | | | | | | | |
| 3TC | Tablet (dispersible) 30 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 150 | 1 | 1 |
| AZT | Tablet (dispersible) 60 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300 | 1 | 1 |
| ABC | Tablet (dispersible) 60 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300 | 1 | 1 |
| NVP<sup>a</sup> | Tablet (dispersible) 50 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 200 | 1 | 1 |
| LPV/r<sup>b</sup> | Tablet (heat stable) 100 mg/25 mg | 2 | 1 | 2 | 2 | 2 | 2 | 100/25 | | | 3 | 3 |
| **Liquid formulations** | | | | | | | | |
| AZT | 10 mg/ml | 6 ml | 6 ml | 9 ml | 9 ml | 12 ml | 12 ml | – | – | – | – | – | – | – | – |
| ABC | 20 mg/ml | 3 ml | 3 ml | 4 ml | 4 ml | 6 ml | 6 ml | – | – | – | – | – | – | – | – |
| 3TC | 10 mg/ml | 3 ml | 3 ml | 4 ml | 4 ml | 6 ml | 6 ml | – | – | – | – | – | – | – | – |
| NVP<sup>a</sup> | 10 mg/ml | 5 ml | 5 ml | 8 ml | 8 ml | 10 ml | 10 ml | – | – | – | – | – | – | – | – |
| LPV/r<sup>b</sup> | 80/20 mg/ml | 1 ml | 1 ml | 1.5 ml | 1.5 ml | 2 ml | 2 ml | 2.5 ml | 2.5 ml | 3 ml | 3 ml | – | – | – | – |

<sup>a</sup> NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the (CHAPAS-I) trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose (Fillekes Q et al. Is nevirapine dose escalation appropriate in young, african, HIV-infected children? AIDS, 2013, ahead of press (http://www.ncbi.nlm.nih.gov/pubmed/23595153, accessed 17 July 2013). doi: 10.1097/QAD.0b013e3283620811) More definitive evidence is expected from an ongoing trial.

<sup>b</sup> LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split or crushed.
**Table 4. Simplified harmonized dosing for currently available TDF formulations for children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Size of powder scoop (mg) or strength of tablet (mg)</th>
<th>Number of scoops or tablets by weight band once daily</th>
<th>Strength of adult tablet (mg)</th>
<th>Number of tablets by weight band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3–5.9 kg</td>
<td>6–9.9 kg</td>
<td>10–13.9 kg</td>
</tr>
<tr>
<td>TDF</td>
<td>Oral powder scoops 40 mg/scoop</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Tablets 150 mg or 200 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

³Target dose: 8 mg/kg or 200 mg/m² (maximum 300 mg). The Paediatric Antiretroviral Working Group developed this guidance to harmonize TDF dosing with WHO weight bands and to reduce the numbers of strengths to be made available. The WHO generic tool was used based on the target dose provided by the manufacturer's package insert. In accordance with the standard Paediatric Antiretroviral Working Group approach, dosing was developed ensuring that a child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

³²00-mg tablets should be used for weight 25–29.9 kg and 300 mg tablets for 30–34.9 kg.

**Table 5. Simplified dosing of isoniazid (INH) and co-trimoxazole (CTX) prophylaxis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of tablet or oral liquid (mg or mg/5 ml)</th>
<th>Number of scoops or tablets by weight band once daily</th>
<th>Strength of adult tablet (mg)</th>
<th>Number of tablets by weight band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3–5.9 kg</td>
<td>6–9.9 kg</td>
<td>10–13.9 kg</td>
<td>14–19.9 kg</td>
</tr>
<tr>
<td>INH</td>
<td>100 mg</td>
<td>–</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>CTX</td>
<td>Suspension 200/40 mg per 5ml</td>
<td>2.5 ml</td>
<td>5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td></td>
<td>Tablets (dispersible) 100/20 mg</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Tablets (scored) 400/80 mg</td>
<td>–</td>
<td>one half</td>
<td>one half</td>
</tr>
<tr>
<td></td>
<td>Tablets (scored) 800/160 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH/CTX/ B6 ⁴</td>
<td>Tablets (scored) 960 mg/300 mg/25 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

⁴This formulation is currently awaiting regulatory approval, and a scored junior tablet (480 mg/150 mg/12.5 mg) is also under development.
The need for new formulations

The work of the Paediatric Antiretroviral Working Group has highlighted the urgent need for formulations, especially fixed-dose combination formulations containing LPV/r in solid forms, suitable for treating younger children, scored tablets of TDF and TDF-based fixed-dose formulations for children. In addition, the availability of ATV/r and DRV/r in heat-stable fixed-dose combination formulations is becoming more critical to facilitate treatment sequencing. Access to a heat-stable formulation containing 30 mg of RTV is also important for “super-boosting” LPV in the setting of rifampicin-based TB treatment. The table below contains some duplication of formulations. for example, a scored adult fixed-dose combination of TDF + 3TC + EFV is not needed if a formulation for children is available. However, the Paediatric Antiretroviral Working Group recognized that, although a child-specific formulation may be ideal, a scored adult formulation may be easier to develop as a first step.

The recent approval of EFV for use in children 3 months to 3 years old has provided an additional option for young children and offers further opportunity for harmonisation. As more data are obtained to inform the best use of this drug in young children, sprinkles formulation should be made available in resource limited settings.

In moving towards the joint UNAIDS/WHO Treatment 2.0 initiative, WHO will continue to work to simplify prescribing, dispensing and dosing guidance and work with the pharmaceutical industry (originator and generic) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate the scaling up of ART for children.

Table 6. Simplified dosing for urgently needed ARV drugs for children recommended by the Paediatric Antiretroviral Working Group

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of tablet or sprinkle sachet or capsule (mg)</th>
<th>No. of tablets or sprinkle capsules/sachets by weight band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3–5.9kg</td>
<td>6–9.9kg</td>
</tr>
<tr>
<td></td>
<td>AM</td>
<td>PM</td>
</tr>
<tr>
<td>ABC/3TC/NVP</td>
<td>60mg/30mg/50mg</td>
<td>1</td>
</tr>
<tr>
<td>LPV/r sprinkles</td>
<td>40mg/10mg</td>
<td>2</td>
</tr>
<tr>
<td>ABC/3TC/ LPV/r</td>
<td>30mg/15mg/ 40mg/10mg</td>
<td>2</td>
</tr>
<tr>
<td>AZT/3 TC/ LPV/r</td>
<td>30mg/15mg/ 40mg/10mg</td>
<td>2</td>
</tr>
<tr>
<td>DRV/r</td>
<td>240/40mg</td>
<td>–</td>
</tr>
<tr>
<td>ATV/r</td>
<td>100/33mg</td>
<td>–</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>120/60mg</td>
<td>1</td>
</tr>
<tr>
<td>TDF/3TC</td>
<td>75mg/75mg</td>
<td>–</td>
</tr>
<tr>
<td>TDF/3TC/ EFV</td>
<td>75mg/75mg/ 150mg</td>
<td>–</td>
</tr>
<tr>
<td>TDF/3TC adult double scoredb</td>
<td>300mg/300mg</td>
<td>–</td>
</tr>
<tr>
<td>TDF/3TC/EFV adult double scoredb</td>
<td>300mg/300mg/ 600mg</td>
<td>–</td>
</tr>
</tbody>
</table>

*a 3 tablets for 25–29.9 kg and 3.5 tablets for 30–34.9 kg.

*b A double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling it to be divided into thirds or halves as needed.
13. References

## Chapter 1


## Chapter 2


## Chapter 3


Chapter 5


Chapter 6

Chapter 7


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Chapter 8


Chapter 9


13. References


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Chapter 10


Chapter 11


13. References
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1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

www.who.int/hiv
GLOBAL UPDATE ON HIV TREATMENT 2013: RESULTS, IMPACT AND OPPORTUNITIES

WHO report in partnership with UNICEF and UNAIDS

JUNE 2013
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ACRONYMS AND ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>lamivudine</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral</td>
</tr>
<tr>
<td>AZT</td>
<td>zidovudine</td>
</tr>
<tr>
<td>d4T</td>
<td>stavudine</td>
</tr>
<tr>
<td>EFV</td>
<td>efavirenz</td>
</tr>
<tr>
<td>eMTCT</td>
<td>elimination of mother-to-child transmission (of HIV)</td>
</tr>
<tr>
<td>FTC</td>
<td>emtricitabine</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>LPV/r</td>
<td>lopinavir/ritonavir</td>
</tr>
<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse-transcriptase inhibitor</td>
</tr>
<tr>
<td>NVP</td>
<td>nevirapine</td>
</tr>
<tr>
<td>PMTCT</td>
<td>prevention of the mother-to-child transmission of HIV</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disproxil fumarate</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
EXECUTIVE SUMMARY

The massive global expansion of access to HIV treatment has transformed not only the HIV epidemic but the entire public health landscape, demonstrating that the right to health can be realized even in the most trying of circumstances.

This publication reports on the progress being made in the global scale-up in the use of antiretroviral (ARV) medicines in low- and middle-income countries, the challenges that are being overcome or that await solutions and the opportunities for building on the achievements of the past decade.1

Chapter 1 provides new data on the latest developments in the global treatment effort, highlighting positive trends as well as aspects that require improvement. It also discusses the key recommendations of the 2013 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, which are designed to take advantage of the multiple benefits of antiretroviral therapy (ART) for treating and preventing HIV infection. Chapter 2 summarizes the impact of the scale-up in reducing AIDS-related mortality and new HIV infections. Chapter 3 examines the sequence of steps in the continuum of care from HIV diagnosis to successful provision of ART services and outlines key supportive innovations. Finally, Chapter 4 discusses the implications and anticipated impact of the new 2013 WHO ARV guidelines.

Promising results

The remarkable increase in access to life-saving ART continued in 2012. Fully 1.6 million more people were receiving ART in low- and middle-income countries at the end of 2012, compared with a year earlier – the largest annual increase ever – with the greatest contribution coming from the WHO African Region. The 300 000 people who were receiving ART in low- and middle-income countries in 2002 increased to 9.7 million in 2012.

In the WHO African Region, which continues to bear the brunt of the HIV epidemic, more than 7.5 million people were receiving treatment at the end of 2012 compared to 50 000 people a decade earlier. There has been progress in every region, including in ones that had been lagging behind. The pace of this global scale-up of treatment is being maintained even in the midst of economic crisis.

These accomplishments reflect the political commitment, community mobilization, technical innovation, domestic and international funding and other forms of support that have catalysed the global scaling up of ART.

Nevertheless, substantial additional effort is needed to enable 15 million people to access ART in 2015, the target agreed to by United Nations Member States in June 2011 at the General Assembly High-Level Meeting on AIDS in New York. The 9.7 million people receiving ART in 2012 represented 65% of that 15 million target, up from 54% at the end of 2011 (Fig. 1).

The overall progress, however, masks some important disparities in access to ART. In most regions, including the WHO African Region, men eligible for ART appear to be less likely to be receiving it than women. Further, the treatment gains are not reaching enough children, adolescents and key populations who face high risk of HIV infection (including sex workers, people who inject drugs, men who have sex with men and transgender people).

The number of children younger than 15 years receiving ART in low- and middle-income countries increased from 566 000 in 2011 to 630 000 in 2012, but the increase was substantially less than for adults. In 2012, over 900 000 pregnant women living with HIV received ARV prophylaxis or treatment for PMTCT

1. At the time this report was prepared (June 2013), country-level HIV programme data for 2012 were available for most but not all countries, and estimates of the number of people eligible for ART were available only for the 22 countries prioritized in the Global Plan. The report therefore focuses on presenting and analysing data on expanding services that are based on programme reports from countries that have submitted data and limits the discussion of service coverage at the end of 2012 to the 22 priority countries in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. References to global and regional coverage estimates are limited to 2011, using 2011 eligibility estimates generated by 2012 country models.
The categorization is based on a linear projection of changes in the number of people receiving and eligible for ART until the end of 2015, based on the most recent year with available data for both ART provision and eligibility, i.e. the year 2012 for the 22 countries included in the Global Plan.

Based on the 2010 WHO treatment eligibility criteria: CD4 count ≤ 350 cells/mm$^3$. (excluding single-dose nevirapine which WHO no longer recommends) – one third more than in 2009. However, many women living with HIV who need ART are missing opportunities to start treatment during pregnancy, including in some countries that have a high burden of HIV infection. Based on current trends in the scaling up of ART programmes, countries can be grouped into three broad categories. In the first group are countries – including some with a high burden of HIV infection – that already are providing treatment to at least 80% of the people who are eligible for it along with several other countries that are poised to emulate them. A second group includes countries that have made considerable progress in scaling up treatment but that need to boost the pace and scope of their efforts significantly if they are to reach the 80% coverage target in 2015. Finally, a third group of countries is far short of the global target and is struggling with serious structural weaknesses in health and governance systems. These countries need major support to boost their treatment efforts.

Regardless of the current status of countries in scaling up ART, renewed efforts are needed everywhere in order to achieve the maximum treatment and prevention benefits.

1. The categorization is based on a linear projection of changes in the number of people receiving and eligible for ART until the end of 2015, based on the most recent year with available data for both ART provision and eligibility, i.e. the year 2012 for the 22 countries included in the Global Plan.
2. Based on the 2010 WHO treatment eligibility criteria: CD4 count ≤ 350 cells/mm$^3$. 

Fig. 1. Actual and projected numbers of people receiving antiretroviral therapy in low-and middle-income countries, and by WHO Region, 2003–2015

An increasingly powerful impact

Expanding access to ART is changing the global HIV epidemic in momentous ways. AIDS-related mortality rates are declining rapidly. The scaling up of ART averted an estimated 4.2 million deaths in low- and middle-income countries in 2002–2012 (Fig. 2). Joint TB and HIV interventions saved the lives of more than 400 000 people in 2011 alone (eight times more than in 2005).

Improved access to ART is resulting in major increases in life expectancy. In South Africa, for example, data from ART programmes in three provinces show that the life expectancy of adults receiving ART is about 80% of the normal life expectancy, provided they do not start treatment late.

The preventive impact of ART is increasingly evident, including in concentrated HIV epidemics and especially when ART is combined with classical prevention efforts. A recent study in rural South Africa, for example, found that the incidence of HIV infection fell by 17% for every 10% increase in the number of people receiving ART.

The scaling up of ART is also contributing significantly to the ongoing drop in annual new HIV infections around the world, including among children. Expanding programmes for PMTCT and the use of more effective ARV regimens helped prevent more than 800 000 children from becoming newly infected between 2005 and the end of 2012. In the 21 African priority countries in the Global Plan, which account for about 90% of all pregnant women living with HIV and new infections among children globally, mother-to-child transmission rates declined overall from an estimated 26% [23-28%] in 2009 to 17% [15-18%] in 2012.

Fig. 2. Annual number of people dying from AIDS-related causes in low- and middle-income countries globally compared with a scenario of no antiretroviral therapy, 1996–2012

The data points for 2012 are projected based on the scaling up of programmes in 2009–2011 and do not represent official estimates of the number of annual AIDS-related deaths.
Maximizing the benefits of ART

Programme coverage is improving in all regions, but significant numbers of adults and children still drop out of care at various points along the treatment cascade, from HIV diagnosis to long-term retention in care. Maximizing the multiple benefits of ART requires improving the uptake of HIV testing and counselling, linking people to care, enabling them to initiate ART early and supporting adherence and retention in care.

In many countries surveyed in sub-Saharan Africa more than half the people estimated to be living with HIV are not aware of their HIV status. In some countries, significant proportions of pregnant women living with HIV either remain undiagnosed or, if diagnosed, do not start on ARV medicines for their own health and to prevent the mother-to-child transmission of HIV. Other studies in sub-Saharan Africa show that close to half the people who test HIV-positive are lost between testing and being assessed for eligibility, and 32% of the people considered eligible for ART are lost between being assessed for eligibility and initiating ART. Numerous efforts are underway to reduce such attrition.

Expanding HIV testing and counselling

HIV testing is the critical first step in linking people living with HIV to the treatment cascade, and it also provides an important opportunity to reinforce HIV prevention. Testing uptake increased impressively in every region, with 118 million people in 124 low- and middle-income countries receiving HIV testing and counselling in 2012.

High coverage of provider-initiated testing and counselling has been achieved in antenatal care and TB clinics (but not in other clinical services), especially in countries with a high burden of HIV infection. Community-based HIV testing and counselling services, including for key populations, and integrating HIV testing with other disease campaigns are proving effective as strategies for effective increasing testing uptake.

However, large proportions of people remain unaware of their serostatus. In all regions, men are less likely than women to take an HIV test, and coverage of HIV testing and counselling is especially low among adolescents and key populations. Structural, operational, logistical
and social barriers – including stigma, discrimination, and punitive laws and policies – continue to hinder access to testing for key populations. Although the early diagnosis of HIV in infants is improving in many countries, in 2011 only 35% [29–41%] of infants born to mothers living with HIV received an HIV test within the first two months of life.

As a consequence, in all regions, large numbers of people test and present late for HIV treatment, usually once their health is failing, which diminishes the benefits of ART.

**Linking patients from testing to care**

Too many patients are being “lost” between taking an HIV test and starting ART. Several approaches for overcoming this challenge are showing promise, including supportive counselling, providing co-trimoxazole prophylaxis free of charge, ensuring shorter waiting times at clinics and using point-of-care CD4 testing.

**Antiretroviral therapy initiation, retention and adherence**

Initiating ART early is vital for successful treatment. The median CD4 count when ART is initiated is rising in all regions but is still too low, and about 1 in 4 people in low-income settings initiate ART late, with CD4 counts <100 cells/mm$^3$.

Once people start ART, the retention rates are initially high and then gradually decline. Data reported in 2013 for 18 countries with cohorts of at least 2000 people on ART indicate that the average retention rates decreased from about 86% at 12 months to 82% at 24 months and 72% at 60 months. Studies confirm that decentralizing ART services improves retention in care, including for children, and various forms of adherence support are also proving effective, including treatment support networks and community adherence clubs, using mobile-phone text reminders, diary cards and food rations.

The goal of ART is to achieve and sustain viral suppression among the people receiving ART. Recent studies show that very good outcomes can be achieved, even in poorly resourced settings. In a large study in Rwanda, for example, 86% of the people receiving ART had viral suppression 18 months after starting ART; in Senegal, about 80% of the people receiving ART were achieving viral suppression after five years. Sustaining such achievements will take special efforts, particularly as there are indications that as ART continues to be scaled up the rates of drug resistance may increase. Systems for monitoring early warning indicators and conducting surveillance of HIV drug resistance must be in place to detect these patterns in a timely manner.

**Implications of the 2013 WHO antiretroviral guidelines**

Current trends in the global scaling up of ART give great cause for optimism. Nevertheless, further improvements are both necessary and possible. To take full advantage of the enormous impact of providing ART for preventing people from dying and from becoming newly infected with HIV, WHO has revised its ARV guidelines to recommend earlier initiation of ART and immediate ART in certain circumstances. The 2013 ARV guidelines recommend initiating ART earlier – at CD4 count ≤500 cells/mm$^3$ – and immediately initiating ART for serodiscordant couples, pregnant women living with HIV, people with TB and HIV, people with HIV and hepatitis B, and children living with HIV who are younger than five years, irrespective of CD cell count.

If fully implemented, the 2013 WHO ARV guidelines could avert at least an additional 3.0 million deaths and prevent close to an additional 3.5 million new infections between 2012 and 2025 in low- and middle-income countries, compared with continuing with the 2010 treatment guidelines (Fig. 4 and 5).

Realizing these benefits could require a 10% increase in total annual investment in the global HIV response in the coming years, which is “very cost effective” according to global criteria. These resource needs are projected to level off over time before declining after 2025, a trend that reflects the accumulated prevention benefits of expanding the provision of ART. Greater access to ART will reduce new HIV infections and thereby eventually reduce the number of people eligible for ART.

The demonstrated benefits of ART in terms of averted deaths and prevented infections exceed many of the expectations that helped launch the global scaling up of ART a decade ago. The 2013 WHO ARV guidelines are designed to extend these benefits more widely and will increase the potential number of people eligible for ART to an estimated 25.9 million (9.2 million more people than were eligible under the previous 2010 WHO treatment guidelines). These changes underscore the need to intensify efforts globally to expand access to ART.
Fig. 4. Projected annual number of people dying from AIDS-related causes in low- and middle-income countries based on the 2010 WHO treatment guidelines and the 2013 WHO ARV guidelines and cumulative deaths averted by switching from 2010 to 2013 guidelines, 2011–2025

Source: special analysis conducted by Futures Institute, 2013.

Maintaining 80% coverage under the WHO 2010 treatment guidelines involves initiating ART at CD4 ≤ 350 cells/mm³ or clinical stages III or IV; maintaining 80% coverage under the WHO 2013 ARV guidelines involves initiating ART at CD4 ≤ 500 cells/mm³, and for serodiscordant couples, pregnant women living with HIV and children living with HIV younger than five years, irrespective of CD4 count.

Fig. 5. Projected annual number of people acquiring HIV infection in low- and middle-income countries based on the 2010 WHO treatment guidelines and on the 2013 WHO ARV guidelines and cumulative number of people avoiding HIV infection by switching from 2010 to 2013 guidelines, 2011–2025

Source: special analysis conducted by Futures Institute, 2013.
1. PROGRESS TOWARDS GLOBAL TARGETS

KEY POINTS

More people than ever received life-saving antiretroviral medicines in 2012

The number of people accessing antiretroviral therapy (ART) globally continues to climb rapidly, and the target of reaching 15 million people with this life-saving treatment is within grasp.

- The number of people receiving HIV treatment has tripled in five years – and reached 9.7 million in low- and middle-income countries in 2012. That total represents 65% of the global target of 15 million people set for 2015, up from 54% at the end of 2011.
- There were about 1.6 million more people on ART at the end of 2012 compared to end-2011, the largest-ever increase in a single year. The remarkable pace of scaling up ART is continuing despite the ongoing global economic crisis.
- If this substantial effort is sustained, the world can reach the global target of 15 million people receiving ART by the end of 2015.
- Most countries with a high burden of HIV infection are potentially on track to achieve universal access (defined as 80% ART coverage, based on the 2010 WHO criteria for treatment eligibility). However, some countries urgently need major support to boost their scaling up of treatment.
- Access to ART has increased in every region. The WHO African Region is leading the scale-up effort and is home to 4 of 5 people who started ART in 2012. The WHO European Region and Eastern Mediterranean Region have seen substantial rates of increase but remain the regions with the lowest estimated treatment coverage among low- and middle-income countries.

The scaling up of antiretroviral (ARV) medicines provided to prevent the mother-to-child transmission (PMTCT) of HIV is progressing well.

- In 2012, over 900 000 women globally were receiving ARV medicines for PMTCT, a third more than the number in 2009, the baseline year for the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive.
- In the 21 African priority countries named in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, 64% [58-70%] of pregnant women living with HIV received ARV medicines for PMTCT in 2012, compared with 59% in 2011 and 49% in 2009.
- Based on current trends, one of the core targets of the Global Plan – providing ARV medicines to 90% of pregnant women living with HIV globally by the end of 2015 – appears to be within reach.

HIV treatment is still not reaching enough children and key populations.

- The number of children younger than 15 years receiving ART rose from 566 000 in 2011 to 630 000 in 2012, but the percentage increase was smaller than for adults (11% versus 21%).
- A huge effort is needed to reach the goal of providing ART to all children eligible for treatment by the end of 2015.
• Certain populations at higher risk of HIV infection are not benefiting equitably from ART, including people who inject drugs, men who have sex with men, transgender people and sex workers.
• Stigma, discrimination and punitive laws are denying these key populations the multiple benefits of ART.
• In some regions, including the WHO African Region, men eligible for ART are less likely than women to receive it.

The 2013 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection aim to boost the impact of ART by broadening the criteria for eligibility for ART.

• The new guidelines reflect evidence indicating the multiple treatment and preventive benefits of initiating ART earlier.
• The CD4 threshold for treatment of adults living with HIV is being raised to 500 cells/mm³, and treatment regardless of CD4 count is recommended for all children living with HIV younger than 5 years, all pregnant women living with HIV, people living with HIV and coinfected with TB or hepatitis B and HIV-positive partners in serodiscordant relationships.
• Applied to the current reality, the new 2013 guidelines would increase the total current number of people eligible for ART in low- and middle-income countries globally from 16.7 million to 25.9 million people. However, the additional prevention benefit of ART means that the total number of people eligible for ART will peak in 2021 and will then decline significantly.

Scaling up antiretroviral therapy: moving to 15 million people receiving antiretroviral therapy – and beyond

The scaling up of life-saving and infection-preventing HIV treatment across the world during the past decade constitutes one of the great public health achievements in recent decades. Its starting-point has been the fundamental principle that everyone has the right to health. The progress thus far demonstrates that this right can be realized, even in settings with extremely limited resources.

When WHO issued its first ART guidelines for resource-limited countries in 2002 (1), about 300,000 people in such settings were receiving HIV treatment, half of them in Brazil. Ten years later, at the end of 2012, about 9.7 million people were receiving ART in low- and middle-income countries (Fig. 1.1).

This rapid expansion of access to ART testifies to the impact of strong political commitment, the mobilization of substantial resources, the tailoring of health systems and service delivery models and the dedication of people around the world, including people living with HIV.

The 9.7 million people receiving ART at the end of 2012 represented 65% of the 15 million target adopted by 189 United Nations Member States in June 2011 at the General Assembly High-Level Meeting on AIDS in New York (2), up from 54% in 2011.
Globally, 1.6 million more people were receiving ART in 2012 compared with 2011, the largest increase ever in one year. If the pace at which ART provision is expanding continues to increase in the coming years, the target of reaching 15 million with ART by the end of 2015 will be within reach (Fig. 1.1).\(^1\)

Importantly, the recent pace of scaling up ART has been sustained in the 22 countries with a high HIV burden that have also been prioritized in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (3) (Table 1.1). Together, this enabled almost 1.4 million more people to be on ART by the end of 2012. In those countries, 63% \([59–66\%]\) of the people eligible for ART were receiving it in 2012, up from 54% \([51–57\%]\) in 2011.

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1. Original data on progress in the AIDS response presented in this document are drawn from the “Global AIDS Response Progress Reporting (GARPR)” mechanism, which is described in detail in the methodological annex. Source data are provided by countries, and are jointly collected and validated by WHO, UNICEF and UNAIDS. Some limitations apply; these are highlighted in the annex.
### Table 1.1. Antiretroviral therapy among adults and children in 22 selected countries with a high burden of HIV infection, 2011 and 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Reported number of people receiving ART, 2011</th>
<th>Estimated number of people eligible for ART, 2011 (range)</th>
<th>Estimated ART coverage, 2011 (range)*</th>
<th>Reported number of people receiving ART, 2012</th>
<th>Estimated number of people eligible for ART, 2012 (range)</th>
<th>Estimated ART coverage, 2012 (range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>35 529</td>
<td>96 000 [80 000–120 000]</td>
<td>37% [31–44%]</td>
<td>42 607</td>
<td>100 000 [87 000–120 000]</td>
<td>42% [35–50%]</td>
</tr>
<tr>
<td>Botswana</td>
<td>178 684</td>
<td>200 000 [190 000–210 000]</td>
<td>89% [87–93%]</td>
<td>212 083</td>
<td>210 000 [200 000–220 000]</td>
<td>&gt;95% [&gt;95–&gt;95%]</td>
</tr>
<tr>
<td>Burundi</td>
<td>26 402</td>
<td>49 000 [43 000–57 000]</td>
<td>54% [47–62%]</td>
<td>29 121</td>
<td>50 000 [44 000–58 000]</td>
<td>58% [50–66%]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>105 653</td>
<td>270 000 [250 000–290 000]</td>
<td>40% [37–43%]</td>
<td>122 783</td>
<td>280 000 [260 000–300 000]</td>
<td>45% [41–48%]</td>
</tr>
<tr>
<td>Chad</td>
<td>32 832</td>
<td>100 000 [87 000–120 000]</td>
<td>33% [27–38%]</td>
<td>40 856</td>
<td>100 000 [89 000–120 000]</td>
<td>40% [33–46%]</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>82 721</td>
<td>230 000 [200 000–250 000]</td>
<td>37% [33–41%]</td>
<td>110 370</td>
<td>230 000 [200 000–260 000]</td>
<td>49% [43–54%]</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>53 554</td>
<td>220 000 [200 000–240 000]</td>
<td>25% [23–27%]</td>
<td>64 219</td>
<td>220 000 [200 000–240 000]</td>
<td>31% [29–34%]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>265 174</td>
<td>480 000 [440 000–530 000]</td>
<td>55% [50–60%]</td>
<td>288 137</td>
<td>470 000 [440 000–510 000]</td>
<td>61% [56–66%]</td>
</tr>
<tr>
<td>Ghana</td>
<td>54 589</td>
<td>120 000 [100 000–130 000]</td>
<td>47% [42–53%]</td>
<td>69 870</td>
<td>120 000 [110 000–140 000]</td>
<td>58% [51–65%]</td>
</tr>
<tr>
<td>India</td>
<td>543 000</td>
<td>1 100 000 [930 000–1 200 000]</td>
<td>50% [45–59%]</td>
<td>604 987</td>
<td>1 100 000 [950 000–1 300 000]</td>
<td>50% [44–58%]</td>
</tr>
<tr>
<td>Kenya</td>
<td>538 983</td>
<td>780 000 [740 000–830 000]</td>
<td>69% [65–73%]</td>
<td>604 027</td>
<td>830 000 [790 000–880 000]</td>
<td>73% [69–77%]</td>
</tr>
<tr>
<td>Lesotho</td>
<td>83 626</td>
<td>160 000 [150 000–170 000]</td>
<td>51% [49–54%]</td>
<td>92 747</td>
<td>170 000 [160 000–180 000]</td>
<td>54% [52–57%]</td>
</tr>
<tr>
<td>Malawi</td>
<td>322 209</td>
<td>550 000 [530 000–590 000]</td>
<td>58% [55–61%]</td>
<td>405 131</td>
<td>580 000 [550 000–620 000]</td>
<td>69% [66–73%]</td>
</tr>
<tr>
<td>Mozambique</td>
<td>273 561</td>
<td>650 000 [600 000–730 000]</td>
<td>42% [37–46%]</td>
<td>309 851</td>
<td>690 000 [630 000–770 000]</td>
<td>45% [40–49%]</td>
</tr>
<tr>
<td>Namibia</td>
<td>104 531</td>
<td>120 000 [110 000–130 000]</td>
<td>86% [79–95%]</td>
<td>116 687</td>
<td>130 000 [120 000–140 000]</td>
<td>90% [82–95%]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>432 285</td>
<td>1 500 000 [1 400 000–1 700 000]</td>
<td>29% [26–32%]</td>
<td>491 021</td>
<td>1 500 000 [1 400 000–1 700 000]</td>
<td>32% [29–35%]</td>
</tr>
<tr>
<td>South Africa</td>
<td>1 702 060</td>
<td>2 500 000 [2 400 000–2 600 000]</td>
<td>69% [65–72%]</td>
<td>2 150 881</td>
<td>2 700 000 [2 600 000–2 900 000]</td>
<td>80% [75–83%]</td>
</tr>
<tr>
<td>Swaziland</td>
<td>72 402</td>
<td>98 000 [94 000–100 000]</td>
<td>74% [70–77%]</td>
<td>87 534</td>
<td>110 000 [100 000–110 000]</td>
<td>82% [78–86%]</td>
</tr>
<tr>
<td>Uganda</td>
<td>313 117</td>
<td>640 000 [580 000–720 000]</td>
<td>49% [43–54%]</td>
<td>438 542</td>
<td>680 000 [620 000–770 000]</td>
<td>64% [57–71%]</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>277 070</td>
<td>690 000 [630 000–760 000]</td>
<td>40% [36–44%]</td>
<td>432 293</td>
<td>710 000 [650 000–780 000]</td>
<td>61% [55–66%]</td>
</tr>
<tr>
<td>Zambia</td>
<td>415 685</td>
<td>570 000 [540 000–600 000]</td>
<td>73% [69–77%]</td>
<td>480 925</td>
<td>610 000 [580 000–640 000]</td>
<td>79% [75–83%]</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>476 321</td>
<td>660 000 [630 000–700 000]</td>
<td>72% [68–76%]</td>
<td>565 675</td>
<td>720 000 [680 000–750 000]</td>
<td>79% [75–83%]</td>
</tr>
<tr>
<td>TOTAL</td>
<td>6 390 000</td>
<td>11 700 000 [11 200 000–12 500 000]</td>
<td>54% [51–57%]</td>
<td>7 760 000</td>
<td>12 300 000 [11 800 000–13 100 000]</td>
<td>63% [59–66%]</td>
</tr>
</tbody>
</table>

Note: some numbers do not add up because of rounding.

* The coverage estimate is based on the estimated unrounded number of people receiving and eligible for ART.

* Based on a numerator from the national Spectrum file which differs in the following countries from the value from the Global AIDS Response Reporting tool printed in the table above: Angola (43,903), Democratic Republic of the Congo (68,970) and India (549,402).

Achieving the full impact of ART requires reaching the 2015 target and continuing further scale-up beyond 2015 (Chapters 2 and 4). The preventive effect of ART on onward HIV transmission has been confirmed in both clinical trials (4) and routine programme settings (5), highlighting the prospect that rapidly scaling up effective combination HIV prevention, including ART, could enable the world eventually to achieve an AIDS-free generation (6).

Confirmation of the major, broader treatment and prevention benefits of ART has led to important revisions in the new 2013 WHO ARV guidelines (7). The changes include recommending earlier initiation of ART for people diagnosed with HIV (at CD4 ≤500 cells/mm³) and immediate ART for serodiscordant couples, pregnant women living with HIV and children living with HIV younger than five years. These recommendations increase the potential number of people eligible for ART to an estimated 25.9 million in 2013 – which amounts to 9.2 million more people than were eligible under the previous 2010 WHO ARV guidelines. These changes underscore the need to intensify efforts globally to expand access to ART.

Expanding effective treatment and prevention interventions would enable countries eventually to reach a “tipping point” beyond which the number of people starting HIV treatment exceeds the number of people acquiring HIV infection. This represents an important milestone in countries’ HIV responses (6). Several countries with high HIV prevalence appear to have passed such a “tipping point” already (for example, Botswana, Ghana, Haiti, Malawi, Namibia, Rwanda, South Africa, Swaziland, United Republic of Tanzania, Zambia and Zimbabwe), and several others are poised to follow their example (Burundi, Ethiopia, Gabon and Uganda).

**Fig. 1.2. Number of people receiving antiretroviral therapy in low- and middle-income countries, by WHO region, 2012**


1. Combination prevention simultaneously uses complementary behavioural, biomedical and structural prevention interventions. They include ART, voluntary medical male circumcision, consistent and correct use of male and female condoms, along with other proven behavioural and structural interventions.

2. Based on the number of new infections, using the 2011 Spectrum estimates, and the number of people on ART, according to the 2012 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).
The extent of ART provision differs considerably between regions, as Fig. 1.2 shows. In 2012, ART continued to be rolled out at a remarkable pace in the African Region, which bears a disproportionately large share of the global HIV burden. Home to only 12% of the world’s population, the region accounts for 69% [65–73%] (23.4 million, range 22.0–24.7 million) of all people living with HIV. In 2011, an estimated 10.9 million [10.3–11.6 million] people in this region needed ART (according to the 2010 WHO treatment guidelines (8)), of whom 6.2 million were receiving it. The number of people on ART increased by one fifth to more than 7.5 million at the end of 2012.

As Fig. 1.3 shows, the expansion of access to ART has been particularly impressive in Eastern and Southern Africa, a region that accounts for about 50% of all people living with HIV and where almost 6.4 million people were receiving ART in 2012. South Africa’s ART programme is the largest in the world, with about 2.2 million people on HIV treatment in 2012 — almost 450 000 more than in 2011. An additional 90 000 people in Zimbabwe and 65 000 in Kenya were receiving ART in 2012 compared with 2011.

Access to ART increased also in Western and Central Africa, where the number of people receiving ART increased by more than one fifth in Algeria, Benin, Cape Verde, Chad, Congo, Côte d’Ivoire, Gambia and Ghana. Nevertheless, in most countries in this part of Africa, less than half the people eligible for ART (according to the 2010 WHO treatment guidelines (8)) were receiving it in 2012 (see Fig. 1.3).

**Fig. 1.3. Adults and children eligible for and receiving antiretroviral therapy, in low- and middle-income countries in eastern and southern Africa and in western and central Africa, 2003–2012**

![Graph showing ART provision in Eastern and Southern Africa and Western and Central Africa from 2003 to 2012](image)


1. The WHO African Region includes Algeria but does not include Somalia, Sudan or South Sudan.
2. In Fig. 1.3 to 1.11, the number of people receiving ART is available up to end of 2012, while the number of people eligible for ART in 2012 has not yet been established and therefore is shown up to the end of 2011.
The scaling up of treatment has also expanded significantly in other regions. In the WHO South-East Asia Region, 938 000 people were receiving ART at the end of 2012, about 100 000 more than in 2011 (Fig. 1.4). This increase was largely driven by rapid programme expansion in India and by the consolidation of high ART coverage in Thailand. Together, those two countries account for about 87% of the estimated number of people eligible for ART in this region. India and Thailand were the only countries in this region in which more than half the people eligible for ART in accordance with the 2010 WHO treatment criteria were receiving it in 2012.

**Fig. 1.4. Adults and children eligible for and receiving antiretroviral therapy, in low- and middle-income income countries in the WHO South-East Asia Region, 2003–2012**

![Graph showing the number of adults and children eligible for and receiving antiretroviral therapy from 2003 to 2012 in the WHO South-East Asia Region.](image)


In the Western Pacific Region, the number of people receiving ART reached 308 000 at the end of 2012 (Fig. 1.5). The scaling up of ART is proceeding at a fast pace, largely because of increases in China, where the number of people receiving ART rose from 126 000 to 154 000 between 2011 and 2012. In Cambodia, which had already exceeded 80% ART coverage in 2011, almost 50 000 people were receiving ART by the end of 2012. Other countries in this region, including Papua New Guinea and Viet Nam, also stepped up the provision of ART in 2012.

In the WHO Region of the Americas, 722 000 people were receiving ART in 2012, about 65 000 more than the 657 000 in 2011 (Fig. 1.6). Five countries (Brazil, Cuba, the Dominican Republic, Guyana and Mexico) had already reached the 80% coverage target in 2011, and Argentina and the Bolivarian Republic of Venezuela were very close to reaching that target.

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1. The low- and middle-income countries in this region are Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste.

2. The low- and middle-income countries in this region are Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People’s Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu and Viet Nam.
**Fig. 1.5.** Adults and children eligible for and receiving antiretroviral therapy in low- and middle-income countries in the WHO Western Pacific Region, 2003–2012

![Graph showing the number of people receiving treatment and eligible for treatment in the WHO Western Pacific Region from 2003 to 2012.](image)


**Fig. 1.6.** Adults and children eligible for and receiving antiretroviral therapy in low- and middle-income countries in the WHO Region of the Americas, 2003–2012

![Graph showing the number of people receiving treatment and eligible for treatment in the WHO Region of the Americas from 2003 to 2012.](image)

The number of people receiving ART in the countries of the WHO Eastern Mediterranean Region also continued to rise (Fig. 1.7) and reached 25,100 in 2012, up from 20,300 in 2011. ART coverage, however, has remained very low, with less than one in eight people eligible for ART receiving it, including in the four countries that account for about 80% of the people needing ART in the region (Iran (Islamic Republic of), Pakistan, South Sudan and Sudan).

Fig. 1.7. Adults and children eligible for and receiving antiretroviral therapy in low- and middle-income countries in the WHO Eastern Mediterranean Region, 2003–2012

In the European Region, 199,000 people were receiving ART in 2012, 45% more than the 137,000 people in 2011 (Fig. 1.8). Access to ART expanded substantially in Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Lithuania, the Republic of Moldova, the Russian Federation, Tajikistan, Turkey, Ukraine and Uzbekistan. However, the region’s scale-up efforts are not keeping pace with the annual increases in the number of people acquiring HIV infection. The HIV burden in this region is large among people who inject drugs, sex workers and men who have sex with men, but access to ART for these key populations appears to be lower than for the wider population.

In the 50 high-income countries globally, an estimated 875,000 people were receiving ART in 2012.

1. The low- and middle-income countries in this region are Afghanistan, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Lebanon, Libya, Morocco, Pakistan, Somalia, South Sudan, Sudan, Syrian Arab Republic, Tunisia and Yemen.

2. Gauging progress towards achieving 80% coverage of ART depends on the accuracy of estimations of how many people are eligible for ART. Such estimations can be challenging, especially in countries with epidemics that are concentrated among key populations and in which HIV surveillance is based on case reporting (as in most of the European Region) rather than on sentinel surveillance in key populations. In addition, HIV data and ART are limited for the Russian Federation, which is estimated to be home to more than half the people eligible for ART in Eastern Europe and Central Asia.
Increasing numbers of antiretroviral therapy sites and greater decentralization of services

A key factor associated with the increase in access to ART in recent years is the steep rise in the number of facilities providing ART services in low- and middle-income countries. The latest available data indicate that almost 30,000 facilities were offering ART in the 132 countries that reported these data. The number of sites providing ART services increased by 14% between 2010-2011 and 2012 in the 108 countries that reported data for both periods, and by 21% in the WHO African Region.

The increase in the number of facilities that provide ART in the WHO African Region has resulted mainly from extensive efforts to improve access to ART beyond cities and referral hospitals by decentralizing ART services to primary health care facilities. Each of the facilities providing ART in this region serves large numbers of ART patients — an average of 498 people per facility compared with 388 in the WHO South-East Region and about 151 in the WHO Americas Region, for example.

HIV care and treatment for children is also being decentralized to primary health care facilities in several countries in the WHO African Region. One recent study reported a three-fold increase between 2008 and 2010 in the number of primary health care facilities providing HIV care and treatment for children in Kenya, Lesotho, Mozambique, Rwanda and the United Republic of Tanzania. However, the comparatively small numbers of people being treated at these facilities mean that this did not translate into large gains in the numbers of children receiving treatment (9).

1. This approach, which is supported by the 2013 WHO ARV guidelines (6), is also becoming more widely adopted in other regions.
Providing antiretroviral therapy for children

Most HIV infections in children occur during the perinatal period, and result from mother-to-child transmission of HIV. Effective, established approaches to prevent mother-to-child transmission have the potential to prevent many children from acquiring HIV infections and dying from AIDS-related causes, and early HIV diagnosis and timely care and treatment can prevent many AIDS-related deaths among children living with HIV. The 2013 WHO ARV guidelines now recommend initiating ART immediately for all children younger than five years of age who are diagnosed with HIV, irrespective of CD4 count.

More children receiving antiretroviral therapy

The number of children younger than 15 years receiving ART in low- and middle-income countries rose to 630,000 at the end of 2012, up from 566,000 in 2011. However, the percentage increase was lower than for adults: 11% versus 21% between 2011 and 2012 (Fig. 1.9 and 1.10).

Fig. 1.9. Number of children eligible for and receiving antiretroviral therapy in low- and middle-income countries, 2005–2012

A global estimate of the number of children eligible for ART in 2012 is not yet available. However, the 22 priority countries identified in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive account for nearly 90% of the pregnant women living with HIV and for a similar percentage of the children living with HIV. In these 22 countries, the number of children eligible for ART (based on the 2010 WHO treatment guidelines) fell by 60,000, from 1.72 million [1.59 – 2.03 million] in 2011 to 1.66 million [1.53 – 1.95 million] in 2012.

1. The Global Plan has 22 priority countries, all but one of which (India) are in the African region. The Global Plan priority countries are: Angola, Botswana, Burundi, Cameroon, Chad, Côte d’Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

2. Launched in mid-2011, the Global Plan features two high-level targets: reduce the number of children newly infected with HIV by 90% and reduce the number of mothers dying from AIDS-related causes by 50%.
Some countries (such as Ethiopia, Malawi, Mozambique, Uganda and Zimbabwe) achieved a strong increase in PMTCT provision in 2012 that lead to a considerable impact in reducing the number of children acquiring HIV infection (and therefore also the number of children eligible for ART). Other countries (such as Namibia, South Africa and Zambia) already had high coverage of services for PMTCT in 2011 and therefore experienced a more moderate decrease in the number of children acquiring HIV infection. Only in India did the population of children eligible for ART increase significantly between 2011 and 2012 (Table 1.2).

**Antiretroviral therapy for children is lagging behind**

A stronger focus on expanding ART for children remains essential, especially in the 22 priority countries. As Table 1.2 shows, ART coverage in these countries increased from 29% [26–31%] in 2011 to 33% [27–33%] in 2012 – much lower than the Global Plan 2015 target of providing ART to all children in need.

**Fig. 1.10. Number of children (0-14 years old) receiving antiretroviral therapy in low- and middle-income countries, by WHO region, 2012**

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Table 1.2. Children (0–14 years old) eligible for and receiving antiretroviral therapy, and antiretroviral therapy coverage in the 22 priority countries in the Global Plan, 2011 and 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of children receiving ART, December 2011</th>
<th>Estimated number of children eligible for ART, 2011 (range)</th>
<th>ART coverage among children, December 2011 (range)*</th>
<th>Number of children receiving ART, December 2012</th>
<th>Estimated number of children eligible for ART, 2012 (range)</th>
<th>ART coverage among children, December 2012 (range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>2 397</td>
<td>19 000 [15 000–24 000]</td>
<td>13% [10–16%]</td>
<td>2 903</td>
<td>19 000 [15 000–24 000]</td>
<td>15% [12–19%]</td>
</tr>
<tr>
<td>Botswana</td>
<td>9 702</td>
<td>10 000 [9 900–10 000]</td>
<td>&gt;95% [93–95%]</td>
<td>10 261</td>
<td>10 000 [9 900–10 400]</td>
<td>&gt;95% [95–95%]</td>
</tr>
<tr>
<td>Burundi</td>
<td>1 927</td>
<td>10 000 [8 500–13 000]</td>
<td>18% [15–23%]</td>
<td>2 023</td>
<td>9 700 [7 800–12 000]</td>
<td>21% [17–26%]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>4 440</td>
<td>34 000 [30 000–39 000]</td>
<td>13% [11–15%]</td>
<td>4 992</td>
<td>33 000 [29 000–38 000]</td>
<td>15% [13–17%]</td>
</tr>
<tr>
<td>Chad</td>
<td>1 531</td>
<td>20 000 [17 000–26 000]</td>
<td>8% [6–9%]</td>
<td>5 842</td>
<td>20 000 [17 000–25 000]</td>
<td>29% [23–35%]</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>5 190</td>
<td>37 000 [31 000–44 000]</td>
<td>14% [12–17%]</td>
<td>5 620</td>
<td>35 000 [29 000–41 000]</td>
<td>16% [14–19%]</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>6 238</td>
<td>54 000 [48 000–61 000]</td>
<td>12% [10–13%]</td>
<td>4 751</td>
<td>53 000 [47 000–61 000]</td>
<td>9% [8–10%]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>16 000</td>
<td>86 000 [74 000–100 000]</td>
<td>19% [16–22%]</td>
<td>17 677</td>
<td>73 000 [63 000–84 000]</td>
<td>24% [21–28%]</td>
</tr>
<tr>
<td>Ghana</td>
<td>2 480</td>
<td>16 000 [13 000–19 000]</td>
<td>16% [13–19%]</td>
<td>3 504</td>
<td>14 000 [12 000–17 000]</td>
<td>25% [20–29%]</td>
</tr>
<tr>
<td>India</td>
<td>22 896</td>
<td>81 000 [65 000–100 000]</td>
<td>28% [23–35%]</td>
<td>34 367</td>
<td>86 000 [70 000–110 000]</td>
<td>37% [30–46%]*</td>
</tr>
<tr>
<td>Kenya</td>
<td>48 546</td>
<td>160 000 [140 000–180 000]</td>
<td>31% [27–36%]</td>
<td>55 439</td>
<td>150 000 [130 000–170 000]</td>
<td>38% [33–44%]</td>
</tr>
<tr>
<td>Lesotho</td>
<td>6 095</td>
<td>22 000 [20 000–25 000]</td>
<td>27% [25–31%]</td>
<td>5 395</td>
<td>22 000 [19 000–24 000]</td>
<td>25% [22–28%]</td>
</tr>
<tr>
<td>Malawi</td>
<td>28 722</td>
<td>110 000 [94 000–120 000]</td>
<td>27% [24–30%]</td>
<td>36 441</td>
<td>100 000 [90 000–110 000]</td>
<td>36% [33–41%]</td>
</tr>
<tr>
<td>Mozambique</td>
<td>23 053</td>
<td>110 000 [91 000–130 000]</td>
<td>22% [18–25%]</td>
<td>27 164</td>
<td>100 000 [88 000–120 000]</td>
<td>27% [22–31%]</td>
</tr>
<tr>
<td>Namibia</td>
<td>10 284</td>
<td>13 000 [12 000–15 000]</td>
<td>80% [69–89%]</td>
<td>11 340</td>
<td>13 000 [12 000–15 000]</td>
<td>88% [77–95%]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>36 716</td>
<td>260 000 [220 000–300 000]</td>
<td>14% [12–16%]</td>
<td>31 556</td>
<td>260 000 [220 000–290 000]</td>
<td>12% [11–14%]</td>
</tr>
<tr>
<td>South Africa</td>
<td>230 000</td>
<td>230 000 [210 000–250 000]</td>
<td>67% [60–74%]</td>
<td>140 541</td>
<td>220 000 [210 000–250 000]</td>
<td>63% [57–69%]</td>
</tr>
<tr>
<td>Swaziland</td>
<td>6 567</td>
<td>14 000 [12 000–15 000]</td>
<td>48% [44–53%]</td>
<td>7 431</td>
<td>14 000 [12 000–15 000]</td>
<td>54% [49–60%]</td>
</tr>
<tr>
<td>Uganda</td>
<td>24 735</td>
<td>120 000 [99 000–140 000]</td>
<td>21% [18–25%]</td>
<td>35 453</td>
<td>110 000 [88 000–130 000]</td>
<td>33% [27–40%]</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>18 298</td>
<td>130 000 [110 000–160 000]</td>
<td>14% [12–16%]</td>
<td>32 407</td>
<td>130 000 [110 000–150 000]</td>
<td>26% [22–30%]</td>
</tr>
<tr>
<td>Zambia</td>
<td>30 187</td>
<td>94 000 [85 000–100 000]</td>
<td>32% [29–36%]</td>
<td>34 084</td>
<td>89 000 [80 000–99 000]</td>
<td>38% [34–42%]</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>40 140</td>
<td>110 000 [100 000–120 000]</td>
<td>36% [32–40%]</td>
<td>46 874</td>
<td>100 000 [94 000–120 000]</td>
<td>45% [40–50%]</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>498 000</strong></td>
<td><strong>1 730 000 [1 590 000–1 930 000]</strong></td>
<td><strong>29% [26–31%]</strong></td>
<td><strong>553 000</strong></td>
<td><strong>1 550 000 [1 530 000–1 860 000]</strong></td>
<td><strong>33% [27–33%]</strong></td>
</tr>
</tbody>
</table>

Note: some numbers do not add up because of rounding.

* The coverage estimate is based on the estimated unrounded number of children receiving and eligible for ART.

b Based on a numerator from the national Spectrum file which differs from the value from the Global AIDS Response Reporting tool printed in the table above: India (32,243).

Two of the Global Plan priority countries (Botswana and Namibia) have already achieved universal access (with at least 80% of the children eligible for ART receiving it), and several others have shown encouraging increases in coverage. However, the very low coverage in Angola, Cameroon, Côte d’Ivoire, the Democratic Republic of the Congo and Nigeria is a serious concern.

Fig. 1.11 depicts the regional trends in the numbers of children eligible for ART and receiving it. In the WHO African Region overall, 544 000 children were receiving ART in 2012, a 10% increase since 2011. Besides the priority countries in the region (see above), ART access for children increased encouragingly in Gambia, Guinea, Guinea Bissau, Niger and Senegal in that same period.

Fig. 1.11. Children (0–14 years old) eligible for antiretroviral therapy in low- and middle-income countries (2005–2011) and receiving it (2005–2012), by WHO region

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1. Estimating the number of children eligible for ART is particularly challenging in low-level and concentrated HIV epidemics, and yields wider ranges of uncertainty.
Access to ART also increased in the WHO South-East Asia Region. In India, the country with the largest burden of HIV infection among children in this region, the number of children receiving ART rose from 22,896 in 2011 to 34,367 in 2012.

In the WHO Region of the Americas, overall ART coverage for children remains below 50%. However, Chile, El Salvador, Guyana, Jamaica, Mexico and Paraguay all exceeded the universal access target. In the WHO Western Pacific Region, where the number of children eligible for ART is comparatively small (an estimated 23,000 children, range 20,000 – 27,000 in 2011), the number of children receiving ART also increased. Even smaller numbers of children are eligible for ART in the WHO European Region, where the number of children receiving ART increased from 8200 in 2011 to 8500 in 2012. Integrating HIV testing and ART provision into maternal and child health programmes has been an important factor in that progress. In the WHO Eastern Mediterranean Region, ART access for children increased marginally between 2011 and 2012 but remains very low.

Several improvements are needed to scale up ART for children more rapidly. Approaches to identify greater numbers of children who have acquired HIV need to be improved – for example, during routine immunization visits and during delivery by mothers who did not receive antenatal care. Stronger links between antenatal care, child health services, immunization clinics and HIV testing, care and treatment services are needed for both mothers and their children. Family-focused HIV care services should expand, while task shifting can be applied more widely. Approaches for providing HIV services (including ART) in adolescent-friendly ways are also becoming increasingly important.

Expanding the provision of antiretroviral medicines to prevent mother-to-child transmission

The Global Plan (3) includes three targets for ARV prophylaxis and therapy: 90% of pregnant women living with HIV receive perinatal ART or prophylaxis; 90% of pregnant women living with HIV eligible for ART for their own health receive lifelong ART; and 90% of breastfeeding mother–infant pairs (either mother or baby) receive ART or prophylaxis (10).

The scaling up of services for PMTCT progressed well in 2012, with over 900,000 women in low- and middle-income countries receiving ARV medicines (either ART or prophylaxis, but excluding single-dose nevirapine prophylaxis regimen no longer recommended by WHO). This was a third more than the number in 2009, the baseline year for the Global Plan. While the total need for PMTCT in low- and middle-income countries at the end of 2012 was not yet determined at the time of compiling this report, a comparison of trends among women needing for and receiving ARVs for PMTCT during 2005-2011 indicates that encouraging progress is being made towards meeting one of the core targets of the Global Plan – providing ARV medicines to 90% of the pregnant women living with HIV by the end of 2015 (Figure 1.12).

Regional differences in scaling up services for preventing mother-to-child transmission

The number of pregnant women living with HIV and who receive ART or ARV prophylaxis has expanded enormously in all regions since the early 2000s, when programmes for PMTCT were still beginning and comprised mainly pilot projects in a few facilities (Fig. 1.13).

The WHO European Region, for example, has achieved and maintained very high estimated coverage of 95% through 2011. Nevertheless, there are still pregnant women living with HIV in the Region who do not access antenatal care or who present late – especially women who inject drugs, trafficked women, sex workers, ethnic minorities, migrant women, refugees and prisoners. In some countries in the Region, substantial proportions of pregnant women living with HIV report that their sexual partners are at high risk of HIV infection. Up to 60% have partners who inject drugs and about 40% have partners with a history of imprisonment (11). In central Asia, an emerging risk factor for women acquiring HIV is having a sexual partner who is a migrant labourer (11,12).
**Fig. 1.12.** Number of pregnant women living with HIV needing and receiving antiretrovirals for preventing mother-to-child transmission of HIV (2005–2011)

![Graph showing the number of pregnant women living with HIV receiving ARV medicines for PMTCT from 2005 to 2011.](image)

- Number of pregnant women living with HIV receiving any ARV medicine for PMTCT
- Number of pregnant women living with HIV needing ARV medicines for PMTCT

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**Fig. 1.13.** Percentage of pregnant women living with HIV receiving antiretroviral medicines for preventing the mother-to-child transmission of HIV in low- and middle-income countries by region, 2005, 2010 and 2011

![Bar chart showing the percentage of pregnant women receiving ARV medicines for PMTCT by region and year.](image)

- Coverage is based on need estimates generated by the 2012 version of country Spectrum models
- The data for 2005 include single-dose nevirapine, no longer recommended

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Coverage of the most effective ARV regimens for PMTCT reached 70% in the WHO Region of the Americas in 2011, up from 57% in 2010. In the WHO Western Pacific Region, coverage also improved, from 6% in 2005 to 38% in 2011. Coverage has remained fairly stagnant in the South-East Asia Region, where it was 16% in 2011 (13). Nevertheless, some countries in that region (Malaysia and Thailand, for example) have achieved high coverage. In the WHO Eastern Mediterranean Region, coverage was lower, at only 6% in 2011. The WHO African Region has shown tremendous progress, with coverage increasing from 13% in 2005 to 59% in 2011. There are sub-regional differences between eastern and southern Africa (71%) and western and central Africa (26%). Overall progress in low- and middle-income countries overall mirrors the progress observed in the WHO African Region, which accounts for most of the PMTCT burden globally.

**Progress in the 21 African priority countries of the Global Plan**

Global progress in expanding access to services for PMTCT is being determined mainly by the scale-up of services in the 22 priority countries in the Global Plan, which are home to about 90% of pregnant women with HIV globally. Steady progress has been made with PMTCT ARV coverage increasing to 64% in 2012, compared to 59% in 2011 (Fig. 1.14). In the 21 Global Plan countries in Africa, six countries (the Democratic Republic of the Congo, Ethiopia, Kenya, Malawi, Nigeria and Uganda) account for 80% of the remaining gap in reaching 90% ARV coverage for PMTCT in 2012.

Four of the priority countries (Botswana, Ghana, Namibia and Zambia) are estimated to have achieved the Global Plan target of very high coverage of ARV medicines for PMTCT – over 90% in 2012. However, the estimated national ARV coverage for PMTCT was less than 20% in four other priority countries: Angola, Chad, the Democratic Republic of the Congo and Nigeria (Fig. 1.15; Table 1.3). Overall, 16 of the priority countries are potentially on track to reach the Global Plan target of 90% coverage in 2015.

**Fig. 1.14. Pregnant women needing and receiving antiretroviral medicines for the prevention of mother-to-child transmission in 21 African priority countries of the Global Plan, 2009-2012**

Note: Numbers from 2009 include single-dose nevirapine. Numbers from 2010-2012 exclude single-dose nevirapine.

Table 1.3. Pregnant women living with HIV needing and receiving antiretroviral medicines for PMTCT and PMTCT antiretroviral coverage\(^a\) among eligible pregnant women in the 21 African priority countries in the Global Plan, 2011 and 2012.

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of pregnant women living with HIV receiving antiretroviral medicines(^a) for PMTCT, 2011</th>
<th>Estimated number of pregnant women living with HIV needing antiretroviral medicines for PMTCT, 2011</th>
<th>Antiretroviral coverage among pregnant women living with HIV, 2011</th>
<th>Number of pregnant women living with HIV receiving antiretroviral medicines(^a) for PMTCT, 2012</th>
<th>Estimated number of pregnant women living with HIV needing antiretroviral medicines for PMTCT, 2012</th>
<th>Antiretroviral coverage among pregnant women living with HIV, 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>2 584</td>
<td>15 000 [12 000–19 000]</td>
<td>17% [14–22%]</td>
<td>2 656</td>
<td>15 000 [12 000–19 000]</td>
<td>17% [14–22%]</td>
</tr>
<tr>
<td>Botswana</td>
<td>12 738</td>
<td>13 000 [12 000–14 000]</td>
<td>&gt;95% [88–95%]</td>
<td>12 207</td>
<td>13 000 [11 000–14 000]</td>
<td>&gt;95% [87–95%]</td>
</tr>
<tr>
<td>Burundi</td>
<td>2 670</td>
<td>5 200 [4 100–6 600]</td>
<td>51% [41–65%]</td>
<td>2 742</td>
<td>5 100 [3 900–6 500]</td>
<td>54% [42–70%]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>15 190</td>
<td>28 000 [24 000–31 000]</td>
<td>55% [48–63%]</td>
<td>17 362</td>
<td>27 000 [23 000–31 000]</td>
<td>64% [56–74%]</td>
</tr>
<tr>
<td>Chad</td>
<td>1 611</td>
<td>13 000 [10 000–17 000]</td>
<td>13% [10–15%]</td>
<td>1 680</td>
<td>12 000 [10 000–16 000]</td>
<td>14% [10–17%]</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>10 875</td>
<td>20 000 [17 000–25 000]</td>
<td>53% [44–65%]</td>
<td>13 294</td>
<td>20 000 [16 000–24 000]</td>
<td>68% [55–84%]</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>2 098</td>
<td>33 000 [29 000–38 000]</td>
<td>6% [6–7%]</td>
<td>4 176</td>
<td>32 000 [28 000–37 000]</td>
<td>13% [11–15%]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>10 103</td>
<td>43 000 [36 000–51 000]</td>
<td>24% [20–28%]</td>
<td>15 828</td>
<td>38 000 [32 000–46 000]</td>
<td>41% [35–49%]</td>
</tr>
<tr>
<td>Ghana</td>
<td>8 057</td>
<td>10 000 [8 300–12 000]</td>
<td>80% [67–95%]</td>
<td>8 957</td>
<td>9 500 [7 800–11 000]</td>
<td>95% [79–95%]</td>
</tr>
<tr>
<td>Kenya</td>
<td>57 644</td>
<td>87 000 [77 000–98 000]</td>
<td>66% [59–75%]</td>
<td>45 397</td>
<td>86 000 [76 000–97 000]</td>
<td>53% [47–59%]</td>
</tr>
<tr>
<td>Lesotho</td>
<td>10 105</td>
<td>16 000 [14 000–17 000]</td>
<td>64% [58–71%]</td>
<td>9 153</td>
<td>16 000 [14 000–17 000]</td>
<td>58% [53–65%]</td>
</tr>
<tr>
<td>Malawi</td>
<td>33 557</td>
<td>68 000 [61 000–76 000]</td>
<td>48% [44–55%]</td>
<td>40 770</td>
<td>68 000 [61 000–75 000]</td>
<td>60% [54–67%]</td>
</tr>
<tr>
<td>Mozambique</td>
<td>50 554</td>
<td>95 000 [83 000–113 000]</td>
<td>53% [45–61%]</td>
<td>80 779</td>
<td>94 000 [81 000–110 000]</td>
<td>86% [72–95%]</td>
</tr>
<tr>
<td>Namibia</td>
<td>7 868</td>
<td>8 400 [7 000–9 900]</td>
<td>94% [79–95%]</td>
<td>7 619</td>
<td>8 100 [6 700–9 700]</td>
<td>94% [79–95%]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>40 517</td>
<td>202 000 [174 000–232 000]</td>
<td>20% [17–23%]</td>
<td>33 323</td>
<td>200 000 [170 000–230 000]</td>
<td>17% [15–20%]</td>
</tr>
<tr>
<td>South Africa</td>
<td>260 073</td>
<td>287 000 [261 000–310 000]</td>
<td>91% [84–95%]</td>
<td>234 952</td>
<td>280 000 [260 000–310 000]</td>
<td>83% [77–91%]</td>
</tr>
<tr>
<td>Swaziland</td>
<td>10 641</td>
<td>12 000 [11 000–13 000]</td>
<td>87% [79–95%]</td>
<td>10 167</td>
<td>12 000 [11 000–13 000]</td>
<td>83% [75–93%]</td>
</tr>
<tr>
<td>Uganda</td>
<td>47 965</td>
<td>99 000 [85 000–117 000]</td>
<td>49% [41–56%]</td>
<td>73 870</td>
<td>100 000 [88 000–120 000]</td>
<td>72% [61–84%]</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>71 041</td>
<td>97 000 [83 000–112 000]</td>
<td>73% [64–85%]</td>
<td>73 855</td>
<td>97 000 [83 000–110 000]</td>
<td>77% [66–89%]</td>
</tr>
<tr>
<td>Zambia</td>
<td>71 429</td>
<td>80 000 [72 000–89 000]</td>
<td>90% [81–95%]</td>
<td>76 963</td>
<td>79 000 [71 000–88 000]</td>
<td>&gt; 95% [87–95%]</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>35 948</td>
<td>68 000 [61 000–76 000]</td>
<td>53% [47–59%]</td>
<td>55 849</td>
<td>68 000 [60 000–76 000]</td>
<td>82% [73–92%]</td>
</tr>
<tr>
<td>Total</td>
<td>760 000</td>
<td>1 300 000 [1 200 000–1 430 000]</td>
<td>59% [53–64%]</td>
<td>820 000</td>
<td>1 280 000 [1 180 000–1 410 000]</td>
<td>64% [58–70%]</td>
</tr>
</tbody>
</table>

\(^a\) The coverage estimate is based on the estimated unrounded number of pregnant women needing and receiving ARVs.

\(^b\) Excluding single-dose nevirapine regimen, which is no longer recommended

Note: some numbers do not add up because of rounding.
Antiretroviral prophylaxis and treatment for women’s own health

In 2012, 19 of the 21 Global Plan priority countries in WHO African region reported disaggregated data for both ARV prophylaxis for PMTCT and lifelong ART for women’s own health. Reporting accurate data on pregnant women receiving lifelong ART is still challenging in some countries but data has become increasingly available. On average 59% [53-64%] of the pregnant women living with HIV estimated to be eligible for ART based on CD4<350 received lifelong ART in 2012 – a marked improvement over recent years and a level of coverage approaching the overall ART coverage in the general population.

However, many pregnant women living with HIV who are eligible for ART are still missing opportunities to start treatment during pregnancy: ART coverage among eligible pregnant women was estimated to be below 40% in Chad, Côte d’Ivoire, the Democratic Republic of the Congo, Ethiopia, Mozambique and Nigeria in 2012. Among the difficulties encountered are a lack of programme support and trained personnel to initiate ART in maternal and child health clinics, incomplete links and referrals to ART sites and limited access to prompt CD4 testing to determine eligibility for ART. Given these challenges, the 2013 WHO ARV guidelines (7) streamline and simplify the delivery of ARV medicines to pregnant women living with HIV.

Adequate coverage of services for PMTCT requires improving health systems and addressing community-level factors so that more pregnant women living with HIV are identified and access to lifelong ART is enhanced. As overall ART coverage increases, further analysis is needed to assess the impact of that coverage, as reflected in the estimated rates of mother-to-child transmission and the estimated numbers of children acquiring HIV infection (see Chapter 2).

Access to antiretroviral therapy for adolescents

The enormous success in preventing the vertical transmission of HIV has resulted in a decline in new HIV infections among infants. However, there remains a significant burden of HIV among older children and adolescents. This diverse cohort comprises infants who have newly acquired HIV from their mothers, surviving children who acquired HIV in that manner, as well as surviving adolescents and adolescents who acquired HIV through sexual intercourse, injecting drug use or nosocomial (hospital-acquired) transmission. All of them need treatment.

There are insufficient data currently to accurately determine the numbers of adolescents who need and receive ART. The best available estimate is that about 2.2 million (6.5%) of the estimated 34 million

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1. The United Nations defines adolescents as people aged 10–19 years. However, most countries with high burdens of HIV lack programmatic data on the size and characteristics of the HIV epidemic in this age group. The HIV data for adolescents are often reported in other age ranges (such as 0–14 and 15–19 years).
people living with HIV globally in 2011 were 10–19 years old. Adolescents in some countries with a high burden of HIV infection have been reported to have a very high HIV prevalence. A study in urban South Africa, for example, found an HIV prevalence of 16% among adolescents 12–17 years old (15).

Inequities in access to antiretroviral therapy for key populations

Improving epidemiological surveillance has demonstrated that the HIV epidemic disproportionately affects certain populations, especially sex workers, men who have sex with men, transgender people and people who inject drugs. In some regions and countries, prison populations, refugee populations, migrants and mobile workers are also at higher risk of HIV infection. However, data detailing the access to ART of these populations remain extremely limited. One reason is that classifying people receiving ART as members of key populations can have serious human rights and legal complications in countries in which the behaviour associated with a key population is stigmatized and/or criminalized.

These key populations are known to encounter many barriers to accessing health services generally and HIV services specifically. In many parts of the world, they are likely to face systematic exclusion along with both social and institutionalized stigma, discrimination and harassment. In addition, sex work, injecting drug use and sex between men are criminalized in many countries, which introduces additional barriers to accessing HIV prevention and treatment services, as country-based studies have confirmed (16,17).

**People who inject drugs**

The prevalence of HIV infection among people who inject drugs is at least 22 times higher than for the population as a whole, according to data from 49 countries (18). Nevertheless, the limited available data indicate significant inequities in access to ART for people who inject drugs and who are living with HIV. For example, only an estimated 4% [2–18%] of the people living with HIV who inject drugs worldwide were receiving ART in 2009, when overall ART coverage among people living with HIV globally was estimated at 18% [17–20%] (19).

More recent global data are not available. However, among the 19 countries in the WHO European Region that reported data for 2011, an average 21% of people receiving ART reported that they acquired HIV through injecting drug use (Fig. 1.16). Although this figure is prone to underreporting, it is strikingly smaller than the estimated 59% of people who were eligible for ART and who had reported injecting drug use.

**Fig. 1.16. People who inject drugs as a proportion of all people living with HIV with a known transmission route and the proportion of people who inject drugs who received antiretroviral therapy in reporting countries, WHO European Region, 2002–2011**

- **Diagnosed people who acquired HIV through injecting drug use** (% among all people diagnosed with HIV infection with a known transmission mode)

  - 2002: 71%
  - 2006: 77%
  - 2011*: 59%

- **People who acquired HIV through injecting drug use who were receiving ART** (% among all people receiving ART with a known transmission route)

  - 2002: 20%
  - 2006: 26%
  - 2011*: 21%

*a Preliminary 2011 ART data and 2010 HIV surveillance (case reporting) data.

Sources: European Centre for Disease Prevention and Control and WHO Regional Office for Europe (21,22); HIV/AIDS surveillance in Europe. End-year report 2006 (23); HIV/AIDS in Europe: moving from death sentence to chronic disease management (24); Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).
Such disproportionately poor access to ART is likely to be even more pronounced in specific subgroups, such as people living with HIV who inject drugs and who are pregnant. For example, a prospective cohort study in Ukraine among pregnant women with HIV showed that the mother-to-child transmission rates of HIV were almost twice as high among women who injected drugs than among women who did not. Women who injected drugs and were eligible for treatment were less likely to receive ART compared with their counterparts who did not inject drugs (20).

Access to ART among people who inject drugs has been improving in some countries in Asia. In Viet Nam, for example, substantial proportions of people receiving ART report a history of injecting drug use – as many as 73% in a study in Ho Chi Minh City (25). Evidence indicates that their treatment outcomes match those of non-drug-injecting populations. At two clinics in Ho Chi Minh City, the increase in median CD4 count over 24 months after initiating ART was the same for both treatment populations (25).

Generally, however, many obstacles still prevent people who inject drugs from accessing and maintaining HIV care and treatment – including stigma, discrimination and punitive policies in both health care settings and wider communities. Even in countries in which large proportions of the people acquiring HIV infection are people who inject drugs, few HIV counselling and testing services are tailored for them. The people who may need ART are often unaware that they have acquired HIV. As a consequence, late HIV diagnoses are common (26), and many people who inject drugs and test HIV-positive start ART with very low CD4 counts (27,28). In addition, some countries resist providing ART before people have undergone drug detoxification, thus delaying access to treatment (29).

A recent meta-analysis of studies done in North America, Europe and Asia found that providing opioid substitution therapy to people who inject opioids is a critical facilitator for adherence to ART – and was also associated with a 54% reduction in the risk of acquiring HIV infection among people who inject drugs (30).

However, global coverage of opioid substitution therapy among people who inject opioids appears to be very low, and was estimated at 8% in 2010 (19), far below the recommended target of 40% of opioid-dependent people receiving such therapy (31). As many as half the countries worldwide that report HIV cases among people who inject drugs are not providing opioid substitution services. Some countries are expanding access to opioid substitution therapy, but the programmes remain small in size and limited in scope in many others, and weak links between opioid substitution therapy services and HIV testing, care and treatment services hinder progress (32).

**Sex workers**

Globally, female sex workers are on average 14 times more likely to be living with HIV than women overall (33). A recent systematic review (33) has shown that the average HIV prevalence among female sex workers was 37% in sub-Saharan Africa, 11% in Eastern Europe, 6% in Latin America and the Caribbean, 5% in Asia and 2% in the Middle East and North Africa. Exceptionally high HIV prevalence has been found among female sex workers in urban settings in some countries: 57% in Kisumu, Kenya (34), 32% in Mauritius (according to UNGASS country reports) and 20% in Bangkok, Thailand (35), for example. Migrant sex workers in low-income settings appear to be at especially high risk for acquiring HIV infection (36). Transgender sex workers also have an especially high HIV prevalence, especially in low-income settings (37).

Male, female and transgender sex workers face many challenges in accessing HIV care and treatment, including a fear of adverse consequences if their HIV status is disclosed, along with negative experiences in health care settings (38). The few studies that have examined AIDS-related mortality rates among female sex workers with HIV indicate that they tend to be less likely than other women with HIV to receive timely and adequate HIV treatment and care. In a study in a rural part of southern India, the AIDS-related mortality rate for sex workers with HIV was 10 times higher than the national mortality rate among women of a similar age (39). Nevertheless, when sex workers are able to access ART, their treatment outcomes are generally good, and the available evidence disproves concerns about possible increases in high-risk sexual behaviour (40).

Given the pervasiveness of sex work globally and the very high HIV prevalence among sex workers in many countries, the scaling up of ART has to include
much stronger efforts to support access to treatment and care for sex workers. ART services specifically designed for sex workers continue to be an exception, including in regions with very high HIV prevalence in this population group. A recent literature review of interventions for sex workers in sub-Saharan Africa (41), for example, failed to identify any published studies specifically aimed at improving sex workers’ access to ART. Major opportunities are being missed — not only for preventing morbidity and mortality but also for averting onward HIV transmission. For example, expanding ART access to female sex workers in Kenya could reduce the number of female sex workers acquiring HIV infection by an estimated 25% (42).

Men who have sex with men

Men who have sex with men continue to be at considerably higher risk of acquiring HIV infection worldwide than men overall. A variety of studies have found the HIV prevalence among men who have sex with men in capital cities to be an average 13 times higher than in the country’s general population (43).

However, there is limited information about the access of men who have sex with men to HIV prevention and treatment services. A biennial online survey conducted by the Global Forum on MSM and HIV is filling some of these data gaps. About 1000 men living with HIV around the world participated in the most recent self-administered survey, which indicated that access to HIV treatment is limited for men who have sex with men in low- and middle-income countries (Fig. 1.17).

The availability of more general HIV prevention interventions that engage men who have sex with men varies widely from region to region and may mirror trends in access to ART. Despite evidence indicating high HIV prevalence among men who have sex with men in sub-Saharan Africa (45), focused interventions are rare in that region. Moreover, the legal and policy environment remains hostile for this key population in many countries across the world.

Fig. 1.17. Percentage of men who have sex with men reporting that condoms, lubricants, HIV testing and HIV treatment are easily accessible, by income level, 2012

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1. While this study provides useful insights, it was not designed to be representative of men who have sex with men in the many countries that do not have extensive access to the Internet, or who are not reached by networks of men who have sex with men.
Transgender people
Gender disaggregation in routine ART reporting currently does not take account of transgender people, but evidence indicates that this key population experiences an exceptionally high prevalence of HIV infection and need for ART. A recent meta-analysis of 39 studies performed between 2000 and 2011 in 15 countries found that transgender women were 49 times more likely to be living with HIV than the overall adult population. The aggregate HIV prevalence among transgender women was 18% in low- and middle-income countries and 22% in high-income countries (37). HIV prevention services for transgender people are inadequate, and the available evidence indicates that they have poor access to ART — as shown in a recent study from India (46). Research also suggests that transgender women who do start ART are less likely to have positive interactions with health care providers than other women, with lower treatment adherence rates and poorer outcomes (47).

The gender gap in access to antiretroviral therapy
In most regions of the world, and especially in settings with a high burden of HIV infection, women are more likely than men to be accessing ART. This pattern has been noted especially in the WHO African Region. By end-2011, 109 countries had reported sex-disaggregated data for people receiving ART, with the data showing a total female-male ratio of 59% to 41% (Fig. 1.18).

As Fig. 1.18 shows, in the WHO African Region, men comprised only 36% of the people receiving ART but accounted for 44% of the people eligible for ART. Similar disparities have been documented at the country level in Kenya (48), Malawi (49), South Africa (50,51) and Zambia (52). HIV testing rates are also consistently lower among men than women, and men tend to have lower CD4 cell counts when accessing treatment. AIDS-related mortality rates also appear to be higher among men than women in the WHO African Region, a pattern that is partly explained by the fact that they often present late for care (49,53–56). All other regions have a similar pattern except the Americas, which has achieved gender parity in access to ART, although this is largely because of high ART coverage among men in a few countries with comparatively large HIV burdens, notably Brazil, the Dominican Republic and the Bolivarian Republic of Venezuela.

Fig. 1.18. Disparities in antiretroviral therapy access: women and men as percentages of all people eligible for and receiving antiretroviral therapy, by WHO Region, 2011
There are several possible explanations for men being underrepresented among people receiving ART (50). High rates of HIV testing within antenatal care facilities may partly explain the greater access of women to ART. Men generally also tend to have poorer health-seeking behaviour than women (57,58), and in settings where men are more likely than women to have paid work, the opportunity costs of visiting treatment facilities may discourage some men from starting or continuing on ART (59).

**Providing care for people living with HIV who have TB**

Tuberculosis (TB) remains a leading cause of HIV-related morbidity and mortality worldwide. Recent autopsy studies confirm that, even in a setting with significant scaling up of ART, TB is responsible for the single-largest share of deaths among people living with HIV: 21–52%, depending on the study (60–62). WHO has developed guidelines to promote collaborative TB and HIV activities along with a framework for recommended actions (63). The latest full data for the scaling up of these activities will be available in the 2013 *Global tuberculosis report*.

**Preventing TB among people living with HIV**

WHO recommends that everyone living with HIV be screened for symptoms of TB, using a simple algorithm at each clinical encounter. The available data suggest that many countries are routinely screening increasing numbers of people living with HIV for TB, and these data are being reported through national systems. Provisional data from 62 countries showed that more than 3.5 million people attending HIV care services were screened for TB in 2012. However, additional efforts are needed to scale up these valuable interventions nationally and to improve the accuracy and completeness of reporting. Persons without signs of TB are eligible for isoniazid preventive therapy to prevent TB disease. Isoniazid preventive therapy is recommended for at least 6 months. In addition, ART has been shown to reduce the incidence of TB. According to preliminary data, more than 40 countries provided isoniazid preventive therapy to over half a million people living with HIV in 2012. Fourteen of these countries have high TB/HIV burdens, and 11 of them reported providing isoniazid preventive therapy for the first time. However, data on the overall coverage of isoniazid preventive therapy globally are not yet available, and progress towards achieving the target of 100% coverage among those in need by 2015 is difficult to assess.

**Reducing deaths from TB among people living with HIV**

Everyone with TB should be routinely offered HIV testing to identify those who need HIV-related services. WHO recommends that everyone with TB and HIV receive co-trimoxazole preventive therapy and immediately initiate ART, regardless of CD4 count. Early initiation of ART among people living with HIV who have active TB reduces mortality by up to 56% compared with deferring ART until after TB treatment has been completed (64).

Globally, HIV testing for people with TB has improved and is particularly high in the WHO African Region. Initial data reported for 2012 suggest that HIV testing rates continued to rise in that region and elsewhere. Among the countries with a high burden of HIV infection reporting these data, Myanmar quadrupled the number of people with TB tested for HIV (compared with 2011), while the number doubled in Angola and increased by almost 50% in China and Ethiopia and by 20% in India.

To date, coverage of ART among people with TB has remained significantly below the overall ART coverage rate among people who need ART, although more than 80% of reporting countries said they had a policy of providing ART to people with TB irrespective of CD4 count (Fig. 1.19). Urgent efforts are needed to ensure universal access to ART among all people with TB to reduce preventable deaths from TB.
Fig. 1.19. Number of people with TB and HIV receiving antiretroviral therapy in 41 countries with a high burden of TB and HIV, 2004–2012

The data for 2012 are provisional, as reported by 17 June 2013.

Note: The numbers in parentheses refer to the number of countries reporting data.

Three scenarios for scaling up towards 2015 and beyond

As the 2015 deadline approaches, countries still urgently need to strengthen and safeguard their efforts to scale up treatment. An extrapolation of future ART coverage based on the assumption of continued linear growth in the number of people on ART reveals differences in countries’ progress towards reaching the 2015 universal access target.¹ Based on this analysis, it is possible to discern the following scale-up patterns and to highlight noteworthy successes and challenges.

Strong progress: universal access reached or within grasp

By the end of 2011, 13 countries were providing ART to at least 80% of the people estimated to be eligible for HIV treatment, based on the 2010 WHO eligibility criteria (8):² Botswana, Brazil, Cambodia, Cuba, Dominican Republic, Fiji, Guyana, Mexico, Namibia, Rwanda, Sao Tome and Principe, Swaziland and Zambia.

Strikingly, that list includes four countries with very high HIV prevalence (although comparatively small total population sizes), and the others have lower overall HIV prevalence and epidemics that are largely concentrated among certain key populations.

Many other countries with a high burden of HIV infection³ achieved universal access to ART in 2012 or are on track to do so (based on the 2010

¹ The categorization is based on a linear projection of changes in the number of people eligible for and receiving ART until the end of 2015, based on the most recent year with available data for both ART provision and eligibility, i.e. the year 2012 for the 22 countries included in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, and the year 2011 for other countries.
² This threshold became equated with universal access to ART: 80% of people eligible for ART based on the 2010 WHO treatment guidelines (8).
³ Countries that ranked among the 50 countries with the largest numbers of people eligible for ART at the end of 2011.
WHO guidelines (8)) by 2015 if they sustain the recent pace of scaling up ART. Some have large, generalized or mixed HIV epidemics (for example, Benin, Burundi, Congo, Côte d’Ivoire, Haiti, Ghana, Kenya, Malawi, South Africa, Uganda and Zimbabwe), whereas others have concentrated epidemics (for example, Argentina, Brazil, Peru, Thailand, the Bolivarian Republic of Venezuela and Viet Nam).

Although scaling up treatment involves distinct challenges in different settings, these achievements have shared certain features. Strong political support, robust funding from both domestic and external sources, solid planning and technical guidance, adapting service delivery systems (especially decentralized delivery) and meaningfully involving community structures and networks have all been central elements in rolling out treatment in these countries.

In South Africa, for example, strong political commitment in the past few years has been backed by major domestic funding for the HIV response: US$ 1.9 billion from public resources in 2011 alone (65). All the African countries in the list are successfully decentralizing their ART services, and some are targeting specific groups of people who need ART with new policies. For example, Malawi’s policy of initiating ART among all pregnant women living with HIV and maintaining this led to a seven-fold increase in ART uptake in that group in one year (see Chapter 3) (66).

Many countries in this group have initiated a policy dialogue on expanding access to ART beyond the groups defined in the 2010 WHO treatment guidelines (8) to take greater advantage of the therapeutic and prevention benefits of ART. Hence, several have anticipated some of the changes to the eligibility criteria for ART detailed in the 2013 WHO ARV guidelines (7).

**Boost needed: universal access is in reach, but only with stronger efforts**

Several other countries also significantly expanded ART access in recent years. However, they will need to step up the pace of expanding treatment if they are to reach the 80% coverage target in 2015. Countries with a high burden of HIV infection in this group include some with generalized or mixed epidemics (such as Angola, Burkina Faso, Chad, Ethiopia, Mali, Mozambique, Niger and Togo) and many countries with concentrated HIV epidemics (including China.

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1. In Fig. 1.20 to 1.22, the number of people eligible for ART in 2012 in some countries has not yet been established and therefore is shown up to the end of 2011.

---

**Fig. 1.20. Number of people eligible for and receiving antiretroviral therapy in selected countries1, 2003–2012**

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Colombia, India, Indonesia, Myanmar, and Ukraine).

Critical factors holding back the scaling up of ART in many countries include insufficient funding from domestic and international sources, limited numbers of health workers, limitations of their current service delivery models, and difficulties in identifying,
enrolling and maintaining people eligible for ART in ART programmes. In some countries, progress in expanding ART has been limited despite good enrolment rates because of high levels of attrition and loss to follow-up among people who have been diagnosed and enrolled (see Chapter 3).

Many of the countries in this group are taking special steps to enhance their efforts to scale up treatment. India, for example, is strengthening community support for retaining people on ART and is introducing reminder calls for CD4 testing, as well as a smart card system. In the WHO European Region, the Russian Federation and Kazakhstan have assumed complete responsibility for funding their ART programmes after grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria ended. In Ukraine, the Government has assumed strong leadership in ART provision, a programme initially driven by civil society with Global Fund support. Indonesia has launched a major effort to boost ART access, with a particular focus on key populations.

**Behind schedule: major support needed to reach the universal access goal**

Finally, several countries have managed to increase the number of people receiving ART by small margins in the past few years but are struggling to achieve high ART coverage. This group includes countries with generalized or mixed HIV epidemics (such as the Central African Republic, the Democratic Republic of the Congo, Nigeria and South Sudan) and countries with comparatively small concentrated epidemics (including Bolivia (Plurinational State of), Iran (Islamic Republic of), Uzbekistan and Yemen). The group also includes several countries in the WHO Eastern Mediterranean Region (including Afghanistan, Djibouti, Egypt, Pakistan, Somalia and Sudan).

Based on the current pace of their ART scale-ups, none of these countries is likely to reach 80% ART coverage in 2015 (using the 2010 WHO treatment eligibility criteria) (7). Diverse factors are holding them back, including political instability and conflict, a lack of resources and weak and poorly functioning health systems (for example, weak infrastructure, supply chains and diagnostic capacity) and inadequate numbers of trained health workers.

Other reasons for their faltering progress include inadequate methods of identifying and enrolling people who need ART and retaining them on treatment, as well as persistent stigma and discrimination (including in health facilities). In Sudan, for example, it is estimated that less than one fifth of the people living with HIV are aware of their HIV status. Some of these countries are investing special efforts to enhance access more quickly.
How will the new WHO guidelines affect eligibility for antiretroviral therapy?

In recent years, most countries’ ART programmes have followed the treatment eligibility guidelines issued by WHO in 2010 (8) that recommend treatment for everyone who tests HIV-positive and has CD4 cell counts ≤350 cells/mm³ or who is coinfected with active TB or hepatitis B.

A series of recent breakthrough scientific findings has prompted WHO to revise these guidelines in 2013. WHO’s new HIV ARV guidelines (7) recommend earlier initiation of ART – at CD4 ≤500 cells/mm³. In addition, they recommend immediately initiating ART for serodiscordant couples, pregnant women living with HIV, people with both HIV and TB, people with both HIV and hepatitis B and children living with HIV younger than 5 years – irrespective of CD cell count. Table 1.4 summarizes the new recommendations.

Table 1.4. Summary comparison of WHO antiretroviral guidelines: immunological criteria for initiating antiretroviral therapy, 2010 and 2013

<table>
<thead>
<tr>
<th>Category</th>
<th>2010 guidelines (8)</th>
<th>2013 guidelines (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents living with HIV</td>
<td>≤350 CD4 cells/mm³</td>
<td>≤500 CD4 cells/mm³</td>
</tr>
<tr>
<td>Children living with HIV</td>
<td>&lt;24 months old: all</td>
<td>&lt;5 years old: all</td>
</tr>
<tr>
<td></td>
<td>2–5 years old: ≤750 CD4 cells/mm³ or 25%</td>
<td></td>
</tr>
<tr>
<td>Pregnant women living with HIVa</td>
<td>No specific provision</td>
<td>All</td>
</tr>
<tr>
<td>People coinfected with TB and HIV</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>People coinfected with HIV and hepatitis B</td>
<td>All with chronic active hepatitis</td>
<td>All with chronic severe liver disease</td>
</tr>
<tr>
<td>Serodiscordant couples</td>
<td>No specific provision</td>
<td>All</td>
</tr>
</tbody>
</table>

a For their own health, excluding other options with the primary purpose of preventing the mother-to-child transmission of HIV.
If applied globally, the new ARV guidelines would increase the total number of people living with HIV who are eligible for treatment in low- and middle-income countries from 16.7 million to 25.8 million, based on end-of-2012 epidemic estimates (Fig. 1.23).¹

Fig. 1.23. Numbers of people eligible for antiretroviral therapy in low- and middle-income countries under WHO 2010 and WHO 2013 antiretroviral guidelines, based on the epidemic and response status at the end of 2012

The change in eligibility criteria will affect adults and children, people with co-infections, pregnant women and people with HIV who live in partnerships with people who are not HIV-positive. The changes will increase the numbers of people eligible for ART as follows.

- Currently, an estimated 5.1 million adults with CD4 counts ≤350 cells/mm³ have no access to ART. By moving the CD4 threshold to ≤500 cells/mm³, that number will increase to 9.3 million.

- The current number of children younger than 15 years eligible for ART who are not receiving ART, based on the 2010 ARV guidelines, is estimated to be 1.2 million. That number will increase to 2.6 million once the expanded criteria apply to all children living with HIV younger than five years, regardless of CD4 count.

- The 2013 guidelines recommend providing ART to all pregnant women living with HIV regardless of CD4 count, which will add 0.7 million women to the current pool of people requiring ART (in addition to the women who would be eligible for ART because they have CD counts ≤500 cells/mm³).

- The 2013 guidelines also recommend ART for all HIV-positive partners in serodiscordant couples. This means an estimated 3.2 million additional people become eligible for ART: those living in serodiscordant relationships who are HIV-positive but have CD4 counts >500 cells/mm³.

- The 2010 ARV guidelines recommend providing ART to people with HIV and active co-infection with TB or hepatitis B, regardless of CD4 count. The 2013 guidelines again include this category of people living with HIV. A large percentage of them will be eligible for ART, also because of the elevated adult CD4 threshold of ≤500 CD4 cells/mm³.

¹. This is based on modelling undertaken by Futures Institute, using Spectrum (a standard tool developed by UNAIDS/WHO for national, regional and global HIV estimates) and the “Goals” model (used to model the impact of specific interventions). The end-of-2012 estimate is based on an extrapolation of previous global trends, and does not represent the official 2012 epidemic estimate, which will become available later in 2013.
The increased number of people receiving ART will have an important effect in preventing HIV transmission, which in turn will contribute to reducing the number of people eligible for ART in the long term.

Thus, modelling of future ART provision under the 2013 WHO ARV guidelines indicates that scaling up ART to 80% coverage will result in a peak of close to 24.5 million people receiving ART in 2021. This number would then gradually decrease due to a decline in the number of people eligible for ART. Such an outlook contrasts with the constant increase in the absolute numbers of people receiving ART in a scenario in which coverage rates are maintained at current levels, resulting in a similar or even higher number of people on ART in the long term.

The impact of these changes in the eligibility criteria will differ from country to country. Specific tools have been developed to help countries in modelling the effects and how increasing ART access is likely to affect AIDS-related mortality and HIV incidence, along with the associated costs and benefits.¹

¹ The tools used to model these various scenarios can be found at http://www.futuresinstitute.org/software.aspx
2. MAKING AN IMPACT: THE STRATEGIC USE OF ANTIRETROVIRAL DRUGS TO TREAT AND PREVENT HIV

KEY POINTS

Expanding access to antiretroviral therapy is changing the global HIV epidemic in momentous ways

AIDS-related mortality rates are declining rapidly, including in countries with a very high burden of HIV infection.

- The annual number of people dying from AIDS-related causes globally fell from a peak of 2.3 million in 2005 to 1.7 million in 2011.
- In Eastern and Southern Africa, AIDS claimed 38% fewer lives in 2011 than in 2005, when ART began to be scaled up in that region.
- The life expectancy for people receiving ART now approaches normal life expectancy, including in countries with a high burden of HIV infection.
- The global scale-up of treatment has saved 4.2 million lives in 2002–2012 in low- and middle-income countries.

Scaling up ART is a major factor in recent HIV prevention successes and is driving down the incidence and mortality of TB.

- The number of people acquiring HIV infection globally declined by 20% between 2001 and 2011.
- The scaling up of PMTCT services prevented more than 800 000 children from acquiring HIV infection between 2005 and the end of 2012.
- Joint TB and HIV interventions saved more than 400 000 lives in 2011 alone (8 times more than in 2005).

Widening access to ART is bringing momentous changes to the global HIV epidemic. AIDS-related mortality rates are declining rapidly, including in countries with a very high burden of HIV infection. The average life expectancy of people living with HIV who adhere to effective treatment now approaches the life expectancy in the general population (1).

The preventive benefits of ART are also firmly established and widely recognized, following the results of the nine-country HPTN 052 study in 2011 and recent findings from programme settings (2,3). The evidence has focused greater attention on the long-standing concept of treatment as prevention.¹ These developments have informed the 2013 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (4) (see Chapter 1). As eligibility for ART expands, the distinction between ART for treatment and ART for prevention is becoming less relevant.

¹. Treatment as prevention is a term used to describe HIV prevention methods in which people living with HIV use ART, independent of CD4 cell count, to decrease the chance of onward HIV transmission.
Clinical benefits of antiretroviral therapy

The life-saving benefits of ART are vividly evident. Before ART, about 80% of the people presenting at clinics with AIDS-defining illnesses died within two years (5), but even the most severely ill people living with HIV today have at least an 80% chance of survival after two years of ART (6). In Brazil, for example, mortality rates from AIDS-related causes have declined dramatically – from 9.2 deaths per 100 person-years in 1986–1991 to 1.4 deaths per 100 person–years in 2007–2009;1 in contrast, mortality rates from non-AIDS-related causes showed no change over time (Fig. 2.1) (7). Meanwhile in China, mortality rates fell from 45.7 per 100 person-years in 2002 to 9.2 per 100 person-years in 2011 – a 78% decrease – as treatment coverage increased from almost zero to 63% (Fig. 2.2) (8).

Fig. 2.1. Mortality rates in Brazil for AIDS-related, non-AIDS-related and unknown causes of death, 1986–2009

Source: Grinsztejn et al. (7). Changing mortality profile among HIV-infected patients in Rio de Janeiro, Brazil: Shifting from AIDS to non-AIDS related conditions in the HAART era. PLoS One, 2013, 8:e59768 doi:10.1371/journal.pone.0059768. Licensed under the Creative Commons Attribution license (CC-BY 2.5) http://creativecommons.org/licenses/by/2.5/legalcode

Fig. 2.2. Mortality declines in China among people living with HIV meeting the eligibility criteria for antiretroviral therapy based on the 2010 WHO guidelines (9), 2002–2011

Source: National Center for AIDS Control and Prevention (NCAIDS), China: updated from a presentation at the National HIV and STI Programme Managers Meeting of Asian Countries in the Western Pacific Region, Kunming, February 2013.

1. AIDS-related deaths are defined in this report as all deaths related to HIV infection, including those among people with HIV who do not meet the clinical definition of having “AIDS”.
Much wider access to ART and the steady decline in the incidence of HIV infection during the past 15 years have led to significant decreases in the number of people dying from AIDS-related causes globally. The number of annual AIDS-related deaths around the world declined from a peak of 2.3 million [2.1-2.6 million] in 2005 to less than 1.7 million [1.5-1.9 million] in 2011 (10). By the end of 2012, the scaling up of ART had averted an estimated 4.2 million deaths in low- and middle-income countries in the previous decade (Fig. 2.3) (10).

Fig. 2.3. Annual number of people dying from AIDS-related causes in low- and middle-income countries globally compared with a scenario of no antiretroviral therapy, 1996–2012

The drop in AIDS-related mortality is especially apparent in the regions with the greatest burden of HIV infection. In 2011, an estimated 800 000 [730 000–890 000] people died from AIDS-related causes in Eastern and Southern Africa, 38% fewer than the 1.3 million [1.2 million–1.4 million] dying in 2005. Several other regions have had significant declines, including in the Caribbean, where the number of people dying from AIDS-related causes decreased by 48% between 2005 and 2011. During the same period, more modest declines occurred in Latin America (10%) and Asia (4%). Two other regions, however, experienced significant increases in mortality from AIDS: Eastern Europe and Central Asia (21%) and the Middle East and North Africa (17%) (11).

Antiretroviral therapy increases life expectancy

Once people living with HIV are stable on ART, they have considerably increased life expectancy. Recent studies confirm that gains in life expectancy among people living with HIV receiving ART in low- and middle-income countries are as impressive as those previously documented in the high-income countries of Europe and North America (12,13). In South Africa, for example, data from six HIV treatment programmes in three provinces show that adults starting ART have a life expectancy of about 80% of normal if they start treatment before their CD4 count drops below 200 cells/mm³ (14). In Uganda, a 20-year-old person living with HIV and receiving ART can expect to live an additional 27 years: about two thirds as long as a 20-year-old in the overall population could expect to live (15,16).

Between 2005 and 2011 in South Africa as a whole, the average life expectancy at birth increased from 54 to 60 years, a gain largely attributed to the rollout of ART and programmes for preventing the mother-to-child transmission of HIV (17). In one rural South African setting, overall adult life expectancy rose by more than 11 years between 2003 (the year before ART became widely available in the public health system) and 2011 – from 49.2 years to 60.5 years (Fig. 2.4) (18).
Fig. 2.4. Average adult life expectancy, rural South Africa, 2000–2011

Box 2.1. TB remains a leading cause of death among people living with HIV

Although AIDS-related mortality is declining, it is still unacceptably high. Large numbers of people do not yet know that they are living with HIV, and many of them are eligible for ART. Among those who do seek care, many present for treatment only once their health has seriously deteriorated, often after having acquired opportunistic infections. Opportunistic infections therefore continue to be the major driver of HIV-associated morbidity and mortality (20,21). In sub-Saharan Africa, for example, TB remains the leading cause of death among people with HIV. A review of autopsy studies done between 1993 and 2010 in 12 African countries (22) identified TB as the cause of death in 32–45% of cases. In more recent studies, TB has remained the dominant cause of death in sub-Saharan Africa (23) and in certain countries in other regions, such as the Russian Federation (24). Globally, an estimated 400 000 people died from HIV-associated TB in 2011 (25).

In high-income settings many of the recent deaths appear not to be related to AIDS (26), while among the infectious cause of death viral hepatitis is a leading cause of mortality (27).

Generally, life expectancy studies have found that the risk of mortality is greater and that life expectancy is correspondingly lower among people who initiate ART late in disease progression (CD4 ≤200 cells/mm³). Similar to the general population, among people receiving ART, life expectancy is lower for men than for women (see Chapter 1) (19).

An important contributing factor in the reduction of the number of people dying from AIDS-related causes has been co-trimoxazole use among people living with HIV who receive ART. A recent systematic review (28) estimated that co-trimoxazole prophylaxis can reduce mortality by 40–70% in the first year of ART, although the benefits over longer periods are not yet clear.

Several studies show that scaling up treatment is also yielding increases in labour productivity. Studies in South Africa, for example, show that people were almost as likely to be employed four years after initiating treatment as they had been 3–5 years before starting ART and began to fall ill (29). In Cambodia, the proportion of patients with full-time employment doubled in less than 3 years after starting on ART (30). There is mounting evidence of improved work performance associated with ART access (31): in Kenya, for example, people were...
found to be working at least 30% more after starting ART (32). In Uganda, a decrease in food insecurity in households was also observed once people living with HIV began receiving ART (33). These positive results were underscored in a systematic review of economic and quality of life outcomes of ART in low- and middle-income countries which found evidence of improved physical, emotional and mental health and daily function, increased work performance and decreased absenteeism (34).

**Antiretroviral drugs reduce TB and other infections**

ART is also associated with significant declines in the incidence of many opportunistic infections. A recent systematic review of how ART affects 15 major HIV-related opportunistic infections and conditions among adults in low- and middle-income countries (35) found that the rates of most opportunistic infections fell to levels comparable to those observed in many high-income countries. During the first year of ART, the reduction in risk ranged from 61% to 98% and was greatest for oral candidiasis, toxoplasmosis, shingles, Kaposi’s sarcoma and *Pneumocystis jirovecii* pneumonia and for both pulmonary and extrapulmonary TB. Some of the reduction in incident risk probably resulted from the concomitant increased use of chemoprophylaxis for protozoal and fungal infections (35).

TB control is especially challenging in countries with a high prevalence of HIV infection, since HIV increases the risk of progression to active TB. However, studies from resource-limited settings have confirmed that ART is strongly associated with a reduction in the incidence of TB.

A recent meta-analysis (36) reviewed observational studies from low- and middle-income countries and found that ART reduced the risk of TB by up to 65%. The preventive benefit occurred even among people with high CD4 cell counts, which suggests that earlier initiation of ART may be a key strategy for reducing HIV-associated TB. At the national level, studies from Malawi (37) and South Africa (38) indicate that, when ART coverage in a population reaches a high level of coverage, TB notification rates decrease (Fig. 2.5).

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**Fig. 2.5. Notification of new cases of TB in relation to the scaling up of antiretroviral therapy in Thyolo District, Malawi, 2002–2009**

The estimated number of lives saved annually with collaborative TB and HIV activities rose from fewer than 50,000 in 2005 to more than 400,000 globally in 2011 (Fig. 2.6) (25). Overall, scaling up of TB and HIV collaborative activities, as recommended by WHO, saved an estimated 1.3 million [1.2 million–1.5 million] lives between 2005 and 2011 (25,39,40). These activities include providing ART during TB treatment, co-trimoxazole prophylaxis during TB treatment, isoniazid preventive therapy for people living with HIV and diagnosing TB early by systematically screening people living with HIV. Studies have demonstrated that a six-month (or longer) course of isoniazid preventive therapy can reduce the risk of active TB. Isoniazid preventive therapy is therefore recommended as a key intervention in HIV care settings (41).

In Eastern and Southern Africa, which has an exceptionally large burden of both TB and HIV, deaths from TB among people living with HIV declined by about 30% between 2004–2006 (when they peaked at an estimated 330,000 deaths per year) and 2011 (42). Nevertheless, TB remains the leading cause of AIDS-related deaths in many resource-limited settings (Box 2.1).

Except for TB, however, the incidence of opportunistic infections and the impact of ART on these infections among adults and children in resource-limited settings are not well documented. The reasons include the absence of national reporting systems for AIDS diagnoses and the fact that standard country-level monitoring does not include opportunistic infections. Nevertheless, a recent modelling study suggests that ART might have averted as many as 900,000 cases of opportunistic infections globally in 2012, with annual cost savings of US$ 32.7 million (35).

The changing epidemiology of opportunistic infections since ART was introduced has been well documented in high-income countries, where dramatic reductions in the occurrence of AIDS-defining illnesses among adults living with HIV have been reported (43,44). At the same time, high-income countries are witnessing a progressive shift in the pattern of comorbid conditions, with an increasing contribution of chronic liver disease caused by hepatitis C and B (Box 2.2), cardiovascular disease and non-AIDS cancer (45,46). A similar impact of ART on the incidence and prevalence of opportunistic infections has been reported among children living with HIV in high-income countries (47).
Box 2.2. HIV and viral hepatitis: challenges and opportunities

Globally, about 400 million people are infected with hepatitis B virus (HBV), and 180 million are infected with hepatitis C virus (HCV). These two infections account for 60% of cirrhosis and 80% of hepatocellular carcinoma and cause 1 million deaths worldwide each year, mostly in low- and middle-income countries (48).

Because of common routes of transmission, people are frequently coinfected with viral hepatitis and HIV: an estimated 5–25% of people living with HIV are also infected with either HBV (2–4 million) and/or HCV (4–5 million). Low- and middle-income countries have the greatest burden of coinfection. A recent study from Rwanda found that 5.2% of people living with HIV were antibody-positive for HBV, as were 5.7% for HCV. An estimated 3–11% of the people living with HIV in South-East Asia are coinfected with either or both HBV and HCV (49). Ongoing surveys suggest that the rates of HCV coinfection among people living with HIV who inject drugs may exceed 70% in all regions.

HIV infection has been shown to significantly affect the progression of chronic HBV and HCV, with a higher risk of cirrhosis and hepatocellular carcinoma. In high-income countries, coinfection has emerged as a major cause of morbidity and mortality in recent years, and the incidence of cirrhosis and its complications, including hepatocellular carcinoma, has increased considerably.

Treatment of HBV among people living with HIV is simplified by the fact that the WHO-recommended first-line ARV drugs for treating HIV (TDF, 3TC and FTC) are also active against HBV. Treatment for HCV is more challenging. Pegylated interferon and ribavirin still constitute the standard of care for most people infected with HCV worldwide. People coinfected with HIV and HCV genotypes 2 or 3 can achieve satisfactory treatment success using these drugs; genotypes 1 or 4, however, have very low rates of treatment success (50).

Important innovations are anticipated. New treatments for HCV are being developed, including directly acting antiviral agents that show very high rates of treatment success over a shorter time period compared with existing treatment and with minimal side effects. These drugs are likely to become the standard of care in most high-income countries in the near future. The simplicity and efficacy of these new drugs makes them especially suited for use in resource-limited settings, and assuring access to the preferred treatments for people infected with HCV living in those settings should be a priority.

The first set of WHO global guidelines for managing viral hepatitis is scheduled for release in early 2014.

Antiretroviral drugs prevent HIV transmission and reduce incidence

Since the potential benefit of ART for preventing the transmission of HIV was first modelled two decades ago (51), numerous studies have confirmed the preventive impact of ART (2,52,53), including in concentrated epidemics (54) and especially when ART is combined with classical prevention efforts. The estimated 2.5 million people acquiring HIV infection around the world in 2011 were 700 000 fewer than the 3.2 million in 2001. The rate of people acquiring HIV infection fell by 50% or more in 25 low- and middle-income countries – more than half of them in the WHO African Region – during that same period (10).

A 2011 modeling study estimated that a combination of classical HIV prevention interventions and ART coverage of 80% (based on the 2010 WHO ARV guidelines (9)) could reduce the number of people acquiring HIV infection globally from more than 3 million per year to 1.2 million by 2025 (55). Such a combination prevention approach would involve the simultaneous use of complementary behavioural, biomedical and structural prevention interventions, including promoting voluntary medical male circumcision, encouraging people to use male and female condoms consistently and correctly, along with other proven behavioural and structural interventions.
Large randomized trials and studies in programme settings have confirmed the modelled effects of scaling up ART on the incidence of HIV infection.

- The HPTN 052 trial among serodiscordant couples showed a 96% reduction in transmission among couples who initiated ART early compared with those who waited until the CD4 count of the HIV-positive partner dropped (2).

- A prospective cohort analysis among African couples documented a 92% reduction in HIV transmission among couples who initiated ART at CD4 counts >250 cells/mm$^3$ compared with those who did not initiate ART with CD4 counts in the region of 250 cells/mm$^3$ (56).

- Data from a cohort in China of almost 39 000 serodiscordant couples showed that the incidence of HIV infection was 1.3 per 100 person-years among individuals whose HIV-positive partners had initiated ART for their own health (and had done so late, with median CD4 <200 cells/mm$^3$) versus 2.6 per 100 person-years among individuals whose partners were not receiving ART (57).

The findings of such studies are supported by ecological associations between increased coverage of ART, reduced community viral load (an indicator that is being considered as an aggregate measure of viral load in a particular geographical location or community (58)\(^1\)) and lower risk of acquiring HIV.

A recent assessment of a large population-based cohort in rural South Africa found that the incidence of HIV infection was significantly lower in areas with high ART coverage (>30% of people living with HIV were receiving ART) than in areas with low coverage (<10%). For every 10% increase in the number of people receiving ART, the incidence of HIV infection fell by 17% (59). Another study, also from South Africa, reported a substantial decline in community viral load as ART was scaled up. Analysis of data from all viral loads assessed in two cities between 2004 and 2011 found that the proportion of people with suppressed viral load (defined as <1000 copies/mm$^3$) had doubled from less than 40% to about 80% during that period (60).

**Impact of scaling up programmes to prevent the mother-to-child transmission of HIV**

Because of rapidly expanding PMTCT programmes and more efficacious ARV regimens, the number of children acquiring HIV infection globally has been declining rapidly (Fig. 2.7). Between 2005 and the end of 2012, an estimated 890 000 children were prevented from acquiring HIV infection. The number of children acquiring HIV infection globally declined by 35% between 2009 — the baseline year of the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (61) — and the end of 2012. This positive trend appeared to continue in 2012, with the number of children acquiring HIV infection decreasing by a further 37% in the 21 African priority countries defined in the Global Plan.

The Global Plan includes the target of reducing mother-to-child transmission of HIV to less than 5% in breastfeeding populations and to less than 2% in non-breastfeeding populations. Without any interventions, between 15% and 45% of infants born to mothers living with HIV will acquire HIV infection: 5–10% during pregnancy, 10–20% during labour and delivery and 5–20% through breastfeeding (62).

In the 21 African priority countries of the Global Plan, which account for about 90% of all pregnant women living with HIV and new HIV infections in children in low- and middle-income countries, mother-to-child transmission rates declined overall from an estimated 33% [30–36%] in 2005 to 26% [23-28%] in 2009 and 17% [15-18%] in 2012.

In addition to preventing children from acquiring HIV infection, providing lifelong ART to pregnant and breastfeeding women living with HIV improves the mother’s health and prevents onward transmission to sexual partners who do not have HIV.

The impact on the number of sexual partners who can avoid acquiring HIV infection and the impact on the population-level HIV incidence will vary depending on several factors, including population size, HIV prevalence (and specifically the prevalence among pregnant women), the percentage of partnerships that are serodiscordant and the percentage of serodiscordant partnerships in which women are the infected partner (and are receiving ART) (63).

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1. The mean community viral load for a period of time (such as a year) is defined as the average of the most recent viral load values reported for all people living with HIV in a specific population during that period of time.
Rounded to the nearest 10,000

a Compared with the background rate, assuming no ARV interventions.
b Includes infections averted in the 21 African priority Global Plan countries in all previous years.
c Baseline year for the Global Plan.

db based on no ARV medicines for PMTCT

db based on current coverage of ARV medicines for PMTCT

Fig. 2.7. Number of children acquiring HIV infection in low- and middle-income countries, 1996–2012

![Graph showing the number of children acquiring HIV infection from 1996 to 2012.]

Table 2.1. Overview of the impact of services to prevent the mother-to-child transmission of HIV in the 21 African priority countries of the Global Plan

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated number of pregnant women living with HIV needing PMTCT ARVs [range]</th>
<th>Estimated mother-to-child transmission rate [range]</th>
<th>Estimated number of children acquiring HIV infection [range]</th>
<th>Estimated cumulative number of infections averted by PMTCT [range] a, b</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>1 390 000 [1 280 000–1 520 000]</td>
<td>33% [30-36%]</td>
<td>460 000 [420 000–510 000]</td>
<td>32 000 [29 000–35 000]</td>
</tr>
<tr>
<td>2006</td>
<td>1 370 000 [1 270 000–1 500 000]</td>
<td>32% [29-35%]</td>
<td>440 000 [410 000–490 000]</td>
<td>58 000 [54 000–65 000]</td>
</tr>
<tr>
<td>2007</td>
<td>1 360 000 [1 250 000–1 480 000]</td>
<td>30% [28-33%]</td>
<td>410 000 [380 000–460 000]</td>
<td>110 000 [100 000–120 000]</td>
</tr>
<tr>
<td>2008</td>
<td>1 340 000 [1 240 000–1 470 000]</td>
<td>29% [26-31%]</td>
<td>390 000 [350 000–440 000]</td>
<td>170 000 [160 000–190 000]</td>
</tr>
<tr>
<td>2009</td>
<td>1 330 000 [1 230 000–1 460 000]</td>
<td>26% [23-28%]</td>
<td>340 000 [310 000–390 000]</td>
<td>280 000 [250 000–310 000]</td>
</tr>
<tr>
<td>2010</td>
<td>1 320 000 [1 220 000–1 440 000]</td>
<td>23% [21-25%]</td>
<td>310 000 [280 000–350 000]</td>
<td>410 000 [370 000–470 000]</td>
</tr>
<tr>
<td>2011</td>
<td>1 300 000 [1 200 000–1 430 000]</td>
<td>20% [18-22%]</td>
<td>260 000 [240 000–310 000]</td>
<td>580 000 [520 000–670 000]</td>
</tr>
<tr>
<td>2012</td>
<td>1 280 000 [1 180 000–1 410 000]</td>
<td>17% [15-18%]</td>
<td>210 000 [190 000–260 000]</td>
<td>770 000 [670 000–930 000]</td>
</tr>
</tbody>
</table>

a The data points for 2012 are projected based on the scaling up of programmes in 2009–2011 and do not represent official estimates of the number of annual child HIV infections.

Rounded to the nearest 10,000

a Compared with the background rate, assuming no ARV interventions.
b Includes infections averted in the 21 African priority Global Plan countries in all previous years.
c Baseline year for the Global Plan.
Estimates of the percentage of pregnant and breastfeeding women living with HIV who have serodiscordant partners globally range from 10% to 40% (64,65). According to a 2010 meta-analysis of data from sub-Saharan Africa (66), women were the HIV-positive partners in almost half (47%) of all discordant partnerships. This highlights the important opportunities that exist to reduce HIV transmission by providing lifelong ART to all pregnant and breastfeeding women living with HIV, as recommended in the 2013 WHO ARV guidelines (4).

Many analyses of the national impact of PMTCT programmes are based on modelled data. They therefore are influenced by various assumptions (such as high adherence and retention) and are based on extrapolating available data from specific research settings to larger and sometimes different populations. However, data for measuring the impact of PMTCT programmes are increasingly available at the district or national levels. For example, a national study of the effectiveness of PMTCT services in South Africa estimated that population-level early transmission at 4–8 weeks was less than 4% (67). Similar studies are either planned or in progress in several other countries, including Malawi, Namibia, Swaziland, Zambia and Zimbabwe.

A recent prospective study in one province in Viet Nam (Thai Nguyen) (68) found that the rate of mother-to-child transmission of HIV had declined from 27% in 2009 to 8% in 2012. HIV-free survival at 12 months was estimated to be 77% for infants with unknown HIV status or HIV-positive status. In a study in Kazakhstan’s five most severely affected regions (69), the rate of mother-to-child transmission of HIV declined from 11% to 4% between 2007 and 2010.

Routinely measuring the rates of mother-to-child transmission of HIV (including final transmission rates) and the number of children acquiring HIV infection would help to improve the empirical data that are needed to support the evaluation of the impact of PMTCT services (70).

Pre-exposure prophylaxis for HIV infection

The efficacy of pre-exposure prophylaxis has been assessed in four randomized controlled trials among men who have sex with men (iPrEx (71)), serodiscordant couples (Partners PrEP (72)), sexually active young adults (TDF2 (73)) and injecting drug users (the Bangkok Tenofovir Study (74)). In each of these trials, the efficacy was closely linked to adherence. When adherence was high, the reduction in HIV incidence exceeded 90% (75). Pre-exposure prophylaxis works best when the regimen is followed as indicated. However, some trials have failed to attract participants who are willing or able to use the drugs as directed. The FemPrEP trial, for example, was halted for “futility” (76), and the VOICE trial completed only one arm after two others had been stopped (77). In both these trials, adherence was very poor and little or no protective benefit was observed. A major issue is how best to implement pre-exposure prophylaxis to reach the levels of adherence that are needed to realize its full potential benefit.

Moving from an intervention with some proven level of efficacy, as demonstrated in carefully controlled trials, to an intervention that can be scaled up safely and effectively is always a challenge. Pre-exposure prophylaxis involves the challenge of identifying the populations that most need additional prevention support and that have sufficient familiarity with pre-exposure prophylaxis and are willing and able to use it. WHO is encouraging countries that have both the need and the capacity to undertake demonstration projects to explore these key implementation questions (78). In July 2012, the United States Federal Drug Administration endorsed the use of daily oral TDF + FTC for preventing the sexual transmission of HIV. The United States Centers for Disease Control and Prevention developed guidance to assist clinicians in prescribing daily oral pre-exposure prophylaxis. Outside the United States of America, as of June 2013, no country has included pre-exposure prophylaxis in its HIV prevention portfolio, although there is growing interest in undertaking demonstration projects. If the implementation challenges can be overcome and sufficient levels of adherence can be attained, pre-exposure prophylaxis may slot in alongside other prevention methods as part of the combination prevention approach.

1. The study used the almost universally attended six-week immunization visits for infants as an entry point. A follow-up study is in progress to determine the final mother-to-child transmission rate, including during the breastfeeding period.
3. CHALLENGES AND OPPORTUNITIES IN STRENGTHENING THE TREATMENT CASCADE

KEY POINTS

The main steps in the treatment cascade involve diagnosing HIV infection, linking people who take an HIV test to treatment and prevention services, enrolling and retaining people in pre-antiretroviral therapy (ART) care, initiating ART, ensuring long-term adherence and ultimately achieving and maintaining viral load suppression.

- Programme coverage is improving in all regions, but significant proportions of people still drop out of care at each step of the treatment cascade.
- Programmes are identifying new opportunities to improve uptake of testing, reduce the time elapsing before eligibility is assessed and treatment is initiated, and support adherence and retention in care.
- The Treatment 2.0 framework provides a lens for identifying opportunities for improvement at every step, with a focus on adapting service delivery, optimizing treatment regimens and diagnostics, reducing costs and mobilizing communities.

To maximize the multiple benefits of ART, people living with HIV should be diagnosed as early as possible after acquiring HIV infection (1,2), and they should be offered appropriate prevention and care services as well as being assessed for ART eligibility. Once they start HIV treatment, support is needed to ensure long-term adherence to ART and viral suppression. Together, these elements comprise what has become known as the treatment cascade (Fig. 3.1).

**Fig. 3.1. The treatment cascade**

The treatment cascade provides a framework for assessing programme implementation and improving programme management so that the optimum outcomes can be achieved at each step, from HIV testing to achieving and maintaining viral load suppression, as shown in Fig. 3.1. Attrition at each step undermines the success of the overall treatment programme. It is therefore critically important to understand whether and why people are not progressing from one step to the next in
the cascade and how ART programmes can minimize losses by strengthening the weak links.

The available evidence points to high rates of attrition at each step of the treatment cascade. In most countries surveyed in Demographic and Health Surveys in the WHO African Region, for example, more than 50% of people living with HIV are not aware of their HIV status (3). A systematic review of treatment cohorts in sub-Saharan Africa (2) shows that 41–54% of people are lost between testing and the assessment of eligibility for treatment, and 32% of those considered eligible for ART are lost between the assessment of eligibility and initiating ART. Once they start ART, about one quarter of the people temporarily interrupt treatment (4) and another quarter are lost within three years (5). Among those lost, up to half (46%) may have died (6).

Note that these estimates are not cumulative, because the treatment cascade is not a simple, linear process. People who do not complete one step in the pathway may re-enter it later and may ultimately receive successful long-term ART (7). Nevertheless, cohort studies in the WHO African Region indicate that only about one quarter of the people who test HIV-positive actually initiate ART (Fig. 3.2).

Fig. 3.2. Percentage of people testing positive for HIV infection in the WHO African Region completing different stages between testing positive and starting ART

<table>
<thead>
<tr>
<th>Tested HIV+</th>
<th>CD4 measurement</th>
<th>Eligible for ART</th>
<th>Start of ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>72% (95% CI 60–84)</td>
<td>40% (95% CI 26–55)</td>
<td>25% (95% CI 13–37)</td>
</tr>
</tbody>
</table>


Similar to adults, large numbers of children are being lost along the treatment cascade. A recent systematic review of eight studies from sub-Saharan Africa and two studies from Asia found that 3–22% of the children diagnosed HIV-positive did not have their CD4 cell count or percentage measured, and 1–60% of the children eligible for treatment did not start treatment. Two studies provided data on pre–ART mortality and found rates of 6 and 13 per 100 person-years, respectively. The fact that the large majority of children (63–91%) were eligible for ART (in accordance with WHO guidelines) at first presentation highlights the general need for health systems to improve the diagnosis HIV infection among children and enrol children in HIV care early in the course of the disease (9).

Similarly, for the cascade for preventing the mother-to-child transmission of HIV (PMTCT) national-level data show that, in some countries, significant proportions of pregnant women living with HIV either remain undiagnosed or, if diagnosed, do not start on ARV medicines (including lifelong treatment for their own health). Follow-up of HIV-exposed children is also noticeably weak along the cascade of PMTCT interventions (Fig. 3.3) and there is a dearth of data on the final outcomes of all HIV-exposed children. A recent systematic review and meta-analysis of 44 studies from 15 countries found that the HIV testing coverage at antenatal care facilities was 94% when offered as an opt-out option but only 58% when offered as an opt-in option. The coverage of ARV prophylaxis was 70%, while 62% of eligible pregnant women living with HIV received ART for their own health. Among HIV-exposed infants, 64% received an early diagnosis and 55% were tested for HIV once they were 12–18 months old (10).
Fig. 3.3. Selected components of the cascade of preventing mother-to-child transmission in five countries

The Treatment 2.0 initiative for enhancing HIV treatment

Increased concern about how to maximize retention along the treatment cascade has prompted many efforts to identify the factors that either block or facilitate linking people to ART care and that enable them to maintain treatment (11). This has improved understanding of the kinds of interventions that are needed, both in health facilities and surrounding communities, to enrol and retain people in care.

Drawing on this knowledge, the WHO/UNAIDS Treatment 2.0 framework identifies the tools and strategies that can make HIV care and treatment more accessible and affordable (12,13). Treatment 2.0 focuses on five dimensions in which potential improvements can be made at each step of the cascade:

- optimize drug regimens;
- provide point-of-care and other simplified diagnostic and monitoring tools;
- reduce costs;
- adapt service delivery; and
- mobilize communities.

For example, access to HIV testing can be increased through community and self-testing approaches, and identifying people who need ART can be made easier by using point-of-care CD4 tests (Box 3.8). Prescriptions for ARV medicines can be simplified, and the use of fixed-dose combinations can support treatment adherence (Box 3.10), while service delivery approaches can be improved when services are integrated and decentralized. Rationalizing the number of medicines in use can reduce costs, and communities can be involved more systematically in supporting ART services. Many countries and regions have been using the Treatment 2.0 framework to identify opportunities for resolving challenges in the treatment cascade (14).
1 HIV testing and linkage to care

**KEY POINTS**

**Early HIV testing is the first step in the pathway to successful HIV care**

- Globally, about 118 million people aged 15 years and older in 124 low- and middle-income countries received HIV testing and counselling in 2012.

- In most low- and middle-income countries surveyed, most men and women living with HIV have never been tested for HIV, and therefore are not in the position to know their status.

- In all regions, women are more likely than men to have had an HIV test.

- Large numbers of people test and present late for HIV treatment, usually once their health is failing.

- Coverage of HIV testing and counselling is especially low among adolescents and key populations in most parts of the world.

- Globally, about 40% of pregnant women in low- and middle-income countries received HIV testing and counselling in 2012, up from 26% in 2009.

- Early infant diagnosis is being scaled up in many countries, but in 2011 only 35% [29–41%] of the infants born to mothers living with HIV received an HIV test within the first two months of life.

- The coverage of early infant diagnosis is less than 10% in five of the Global Plan priority countries.

- The number of people in HIV care globally who were screened for TB increased by 46% between 2010 and 2012, from 2.4 million to 3.5 million.

HIV testing is the critical first step in linking people living with HIV to the treatment cascade, and it provides an important opportunity to reinforce HIV prevention.

Globally, about 118 million people aged 15 years and older in 124 low- and middle-income countries received HIV testing and counselling in 2012. There was an 8% increase in the numbers of people taking HIV tests in a subset of 75 countries which provided data in both 2011 and 2012 (Table 3.1). All regions reported increases, with the biggest percentage increase occurring in the WHO Eastern Mediterranean Region.
Table 3.1. HIV testing and counselling in low- and middle-income countries reporting for both 2011 and 2012, by WHO region

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of people 15 years and older who received HIV testing and counselling*</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African Region</strong></td>
<td></td>
<td>41 725 000</td>
<td>45 556 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td><strong>Region of the Americas</strong></td>
<td></td>
<td>4 256 000</td>
<td>4 304 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>South-East Asia Region</strong></td>
<td></td>
<td>19 572 000</td>
<td>20 750 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>European Region</strong></td>
<td></td>
<td>1 215 000</td>
<td>1 299 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean Region</strong></td>
<td></td>
<td>244 000</td>
<td>436 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
<td></td>
<td>3 673 000</td>
<td>3 824 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>70 685 000</td>
<td>76 169 000</td>
</tr>
<tr>
<td>Number of countries reporting</td>
<td></td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>


* Rounded to nearest 1000. Based on the numbers of people tested, as reported by countries but without correcting for the fraction of people who are tested more than once.

**Significant regional variation**

In the WHO African Region, HIV testing and counselling services have expanded substantially, as Fig. 3.4 illustrates. This is a remarkable achievement given the human resource and other constraints in many countries in the region.

Increasing availability and access to testing, however, only addresses one of several factors that determine whether or not people take an HIV test and receive the results. A recent systematic review of studies in sub-Saharan Africa indicates that some of the main factors facilitating the uptake of HIV testing are personal and may include deteriorating physical health and/or the death of a sexual partner or child (15). Other factors that appear to increase a willingness to test include decreasing stigma and discrimination, free services, the availability of ART and social network support. Barriers include people’s perceptions that they have a low risk of acquiring HIV infection, concerns about confidentiality, fear of HIV-related stigma, discrimination and criminalization, the anticipated emotional burden of living with HIV and the financial costs of accessing HIV testing (15).

In the WHO European Region, HIV testing services are often available routinely in clinical settings such as antenatal care services, blood donation stations, sexually transmitted infection clinics, TB clinics, drug dependence treatment facilities and prison settings. Many tests are performed annually in many countries, but this does not necessarily mean that the testing efforts focus strategically on the populations that are at highest risk for HIV, including hard-to-reach populations such as people who inject drugs.

**Awareness of serostatus among people living with HIV**

Expanding testing throughout clinical services and supporting the testing of partners and family members of people with HIV has increased the number of people who know their serostatus. The 25 Demographic and Health Surveys carried out in the WHO African Region since 2003 found
that individuals living with HIV were more likely to have been tested for HIV than individuals who had not acquired HIV. Overall, however, coverage has remained low: in 16 of 25 countries for which data were available between 2003 and 2010, most men and women living with HIV had never been tested for HIV, and therefore were not in the position to know their status (3).

Late testing

Among people who are diagnosed with HIV, significant proportions in all regions test late in their HIV infection. Many of them present for HIV treatment once they already have advanced disease, and often when they are very ill. Such late diagnosis leads to initiating ART late, which undermines its prevention and treatment benefits.

Box 3.1. Understanding the reasons for late HIV diagnosis in Georgia

A WHO study of HIV diagnoses in Georgia in 2009–2011 found that 64% of new HIV diagnoses could be considered “late”, i.e. eligible for ART, and 47% had an AIDS-defining illness at the time of diagnosis. Late presenters were more likely to have a history of injecting drug use, to be male and to be older. The study concluded that the reasons for the high rates of late diagnosis included a lack of access to acceptable HIV testing and counselling services. The actions taken by the National HIV/AIDS Programme to overcome these challenges include increasing HIV testing uptake among key populations at higher risk, expanding provider-initiated HIV testing and counselling, introducing guided testing for people considered clinically to potentially have HIV and introducing continual surveillance of late HIV diagnoses to monitor progress and inform further public health actions.
Sex differences in HIV testing and counselling

In all countries, women are more likely than men to take an HIV test. This probably reflects women’s more frequent contact with health services, especially with reproductive and child and maternal health services, at which HIV testing and counselling is often routinely available. Recent data from Kenya, for example, show that HIV testing rates were significantly higher among women of reproductive age (15–49 years) (49%) than among men in the same age group (29%) (16). This highlights the need to develop strategies that can increase men’s uptake of HIV testing and counselling, including providing testing in settings that are more accessible and acceptable to men (17) and revising ways to encourage more men to test with their partners in clinical settings (18).

Testing for adolescents

In countries with a high burden of HIV infection, adolescents have less access to HIV testing and counselling than adults do. Restrictions related to the age of consent for testing can hinder adolescents’ access to HIV and other health services. Depending on the country, the age of consent for HIV testing ranges from 12 years to 18 years. New WHO guidelines on HIV testing and counselling for adolescents (19) recommend that health ministries revisit those provisions given the need to uphold adolescents’ rights to make decisions about their own health and well-being. Survey data from 2005 to 2010 in the WHO African Region indicate that, on average, fewer than 1 in 5 women and men 15–24 years old were aware of their HIV status. Access and coverage, however, varied considerably between countries (20). Although data are scarce, ART coverage among adolescents also appears to be low (21).

Low testing coverage for key populations

HIV testing and counselling services are not accessible enough to key populations that are at high risk of HIV infection. Structural, operational, logistical and social barriers – including stigma, discrimination, punitive laws and policies and vulnerable socioeconomic status – continue to hinder access to existing testing and counselling services for key populations in many countries (including in the African Region) and need to be addressed.

Mandatory and coerced testing of key populations (including prisoners (22), migrants (23,24) and ethnic minorities) occurs in some settings, including in clinical settings (25). Some countries acknowledge that substantial proportions of the HIV tests are performed either before employment or travel, or are done in another non-voluntary manner. In November 2012, WHO reiterated its opposition to mandatory testing (26) and emphasized that all forms of HIV testing and counselling should be voluntary and should adhere to the “five C’s”: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention.

Box 3.2. Increasing testing uptake in Viet Nam

Injecting drug use is the main driver of Viet Nam’s HIV epidemic. Testing uptake among people who inject drugs, however, is low. Many people living with HIV, especially people who inject drugs, initiate ART late, with most starting ART with CD4 counts <100 cells/mm³. In 2012, the Ministry of Health started a pilot Treatment 2.0 programme in Dien Bien and Can Tho provinces in which HIV testing, counselling and treatment follow-up services were decentralized to commune health stations. This enabled the communes to reach people who inject drugs but who previously had been unable or reluctant to use district-level services. The new decentralized model, combined with outreach services, appears to be effective in some geographical areas in promoting HIV testing and counselling and in increasing ART uptake in key populations such as people who inject drugs. However, people who inject drugs still face stigma, discrimination and various structural barriers when seeking to use HIV services.
services (27). Because of social vulnerabilities and the need for confidentiality, peer-led testing approaches are more likely to be suitable for some populations.

Testing for preventing the mother-to-child transmission of HIV

HIV testing and counselling for pregnant women is the first step toward enrolling mothers living with HIV in the cascade of PMTCT interventions. Globally, around 40% of pregnant women in low- and middle-income countries received HIV testing and counselling in 2012, up from 26% in 2009. As Fig. 3.5 and Table 3.2 show, however, the global coverage estimate masks differences between countries and regions. Some countries with large populations and low national HIV prevalence have low HIV testing rates. Countries with higher HIV prevalence tend to have much higher coverage of HIV testing among pregnant women, although this could be improved further.

Among the priority countries in the Global Plan (28), four countries (Botswana, Mozambique, South Africa and Zambia) exceeded 95% testing coverage in 2012, but the coverage was less than 25% in three others (Chad, the Democratic Republic of the Congo and Nigeria) (Table 3.2). In the WHO African Region, 45% of pregnant women were tested for HIV, but coverage varies at 70% in eastern and southern Africa and 32% in western and central Africa.

### Table 3.2. HIV testing and counselling coverage among pregnant women in the Global Plan priority countries, 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Testing coverage among pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>34%</td>
</tr>
<tr>
<td>Botswana</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Burundi</td>
<td>51%</td>
</tr>
<tr>
<td>Cameroon</td>
<td>42%</td>
</tr>
<tr>
<td>Chad</td>
<td>7%</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>75%</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>9%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>39%</td>
</tr>
<tr>
<td>Ghana</td>
<td>66%</td>
</tr>
<tr>
<td>India</td>
<td>31%</td>
</tr>
<tr>
<td>Kenya</td>
<td>85%</td>
</tr>
<tr>
<td>Lesotho</td>
<td>48%</td>
</tr>
<tr>
<td>Malawi</td>
<td>72%</td>
</tr>
<tr>
<td>Mozambique</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Namibia</td>
<td>91%</td>
</tr>
<tr>
<td>Nigeria</td>
<td>19%</td>
</tr>
<tr>
<td>South Africa</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Swaziland</td>
<td>81%</td>
</tr>
<tr>
<td>Uganda</td>
<td>65%</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>68%</td>
</tr>
<tr>
<td>Zambia</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>90%</td>
</tr>
</tbody>
</table>


The number of pregnant women was proxied using the estimated live births from the United Nations Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision.

Fig. 3.5. Estimated HIV testing and counselling coverage among pregnant women, low- and middle-income countries overall and by WHO region, 2005 and 2009–2012

Infant diagnosis

Early testing of infants who have been exposed to HIV is essential for identifying infants who may be living with HIV and for starting them on early, life-saving treatment. In the absence of these interventions, one third of infants living with HIV die before their first birthday. Early testing can also provide important information on early HIV transmission rates and on the effectiveness of perinatal PMTCT interventions.

WHO recommends that infants exposed to HIV be tested at 4–6 weeks of age, using a virological test (29). Dried blood spot to polymerase chain reaction testing or point-of-care technologies are highly suitable for decentralizing and expanding testing, and ART should be started as soon as the infants are found to be HIV-positive, regardless of clinical and immune status. Some countries are considering earlier testing, at birth, especially for children born to mothers who have not received PMTCT services.

Testing rates for infants are low, however. Globally in 2011, only 35% [29–41%] of the infants born to mothers living with HIV received an HIV test within their first two months of life. Among the Global Plan priority countries in the WHO Africa Region 2012, only South Africa and Swaziland were providing early infant diagnosis for more than 80% of infants in need, while only Namibia and Zambia had achieved early infant diagnosis coverage of 50–80% for HIV-exposed infants (Table 3.3).

Such generally low coverage of early infant diagnosis is mirrored by low HIV care coverage for infants. Currently, only about 30% of infants who are diagnosed through virological testing are promptly referred to treatment facilities to initiate ART. The coverage of early infant diagnosis is less than 10% in five of the priority countries in the Global Plan: Angola, Chad, the Democratic Republic of the Congo, Malawi and Nigeria.

Based on countries that reported data, the WHO European Region had the highest early infant diagnosis coverage of any region in 2011 (>95%, ranging from 69% to >95%), followed by the WHO Region of the Americas (46%, range 25–76%), the WHO South-East Asia Region (40%, range 30–59%), the WHO African Region (34%, range 29–40%), the WHO Western Pacific Region (23%, range 16–34%) and the WHO Eastern Mediterranean Region (2%, range 1–3%). However, within sub-saharan Africa, the average coverage of early infant diagnosis was extremely low, at 7% [6–9%] in west and central Africa, compared with 46% [40–53%] in eastern and southern Africa.

When systems exist to improve the turn-around time of test results, the numbers of children initiating ART tend to increase and mortality rates decrease. This was shown, for example, in a study in Lesotho, in which the use of mobile phone messages to communicate results reduced the waiting time for results to less than two weeks (30). A study in Zambia found that a similar method shortened the average time between collecting samples and notifying the relevant health facilities and caregivers of the results from 44 days to 28 days (31).

Table 3.3. Proportion of infants receiving a timely virological test in the 21 African priority Global Plan countries in 2012, as reported by countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Early infant diagnosis coverage [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>85% [78–94%]</td>
</tr>
<tr>
<td>Swaziland</td>
<td>81% [73–90%]</td>
</tr>
<tr>
<td>Namibia</td>
<td>74% [62–89%]</td>
</tr>
<tr>
<td>Lesotho*</td>
<td>69% [63–76%]</td>
</tr>
<tr>
<td>Zambia</td>
<td>61% [54–68%]</td>
</tr>
<tr>
<td>Kenya</td>
<td>39% [35–44%]</td>
</tr>
<tr>
<td>Botswana</td>
<td>38% [35–42%]</td>
</tr>
<tr>
<td>Mozambique</td>
<td>37% [31–42%]</td>
</tr>
<tr>
<td>Cameroon</td>
<td>35% [31–41%]</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>34% [30–38%]</td>
</tr>
<tr>
<td>Uganda*</td>
<td>30% [26–35%]</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>28% [24–32%]</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>27% [22–34%]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>19% [16–22%]</td>
</tr>
<tr>
<td>Ghana</td>
<td>18% [15–22%]</td>
</tr>
<tr>
<td>Burundi</td>
<td>11% [8–14%]</td>
</tr>
<tr>
<td>Angola</td>
<td>7% [5–8%]</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>6% [5–7%]</td>
</tr>
<tr>
<td>Malawi</td>
<td>4% [4–5%]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>4% [4–5%]</td>
</tr>
<tr>
<td>Chad</td>
<td>4% [3–4%]</td>
</tr>
</tbody>
</table>

* In some countries, the estimated coverage for early infant diagnosis may be significantly affected by underreporting of performed diagnosis.

* Lesotho and Uganda did not report 2012 data, thus 2011 estimates are presented.

Box 3.3. Expanding access to early infant diagnosis in Kenya

Kenya’s national ART guidelines recommend the use of molecular testing for early infant diagnosis. Before 2007, however, funding, laboratory testing infrastructure and challenges in transporting samples limited the provision of early infant diagnosis in Kenya. Testing was performed on whole blood samples, which required cold-chain processing that was only available in central locations. Consequently, fewer than 10 000 tests (less than 10% of those needed) were conducted per year. To address these issues, the Ministry of Health collaborated with partners and other stakeholders to strengthen and standardize the scaling up of early infant diagnosis. The best practices from other countries were adopted, including establishing high-throughput laboratories and an efficient system for transporting samples. This resulted in adopting dried blood spots as the preferred sample type for early infant diagnosis, increasing testing capacity (four molecular laboratories were established) and reorganizing the national system for transporting samples. Restructuring early infant diagnosis in Kenya led to rapid scale-up, with coverage increasing from less than 10% in 2007 to about 40% by the end of 2012.

Combination testing approaches

Most countries have widely accepted provider-initiated testing and counselling in health settings (Table 3.4) (32). High coverage has been achieved in antenatal care and TB clinics, especially in countries with a great burden of HIV infection. A recent review of HIV testing in antenatal care reported testing uptake exceeding 80% in Botswana, Ethiopia, Malawi, Uganda and Zimbabwe (33). High rates of testing can also be achieved in other clinical settings: data from 36 outpatient departments in South Africa, Uganda and the United Republic of Tanzania showed that more than 90% of the people who were referred to on-site testing and counselling services took an HIV test (34).

Table 3.4. Policies and practices related to HIV testing and counselling

<table>
<thead>
<tr>
<th>Does the national policy promote provider-initiated testing and counselling?</th>
<th>Does the policy require health providers to offer testing and counselling in all patient encounters? (countries with generalized epidemics)</th>
<th>Does the country use community-based testing approaches?</th>
<th>Does the country have policies that support HIV point-of-care rapid testing by lay health workers?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>80</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Countries reporting</td>
<td>83</td>
<td>41</td>
<td>85</td>
</tr>
</tbody>
</table>

By the end of 2012, 95% of 102 countries surveyed in the Global AIDS Response Progress Reporting process reported that they had explicit policies for provider-initiated testing and counselling in their health facilities. Among them, 49 countries with generalized HIV epidemics reported that they had policies to offer HIV testing in all patient encounters, regardless of presenting symptoms or facility type. Other countries were targeting HIV testing at specific facilities or in relation to specific symptoms. Overall, 90% of the surveyed countries confirmed that their policies note the non-mandatory nature of HIV testing and counselling.

WHO recommends that facility-based testing be complemented with a range of community-based testing approaches. Depending on the country context, multiple testing approaches are needed to increase people’s awareness of HIV serostatus. They may combine various forms of stand-alone sites, home-based testing, mobile outreach (including index partner testing, testing in workplaces, schools and universities and accessible and safe venues for key populations), special testing events and testing campaigns. These approaches should include effective methods for linking people who are diagnosed with HIV to care and treatment services.

Box 3.4. South Africa’s massive HIV testing and counselling campaign (35)

South Africa staged an intensive HIV testing and counselling campaign between April 2010 and June 2011, which urged everyone 12–60 years old to take a test. All sites providing HIV testing and counselling services were linked to referral facilities that provide CD4 testing, ART, care and support. Testing and counselling was carried out at health facilities, workplaces and community outreach sites. By the end of the campaign, it was reported that:

- more than 13 million HIV tests had been performed, with approximately 2.2 million people testing HIV-positive (of whom 52% had CD4 counts <350 cells/mm³);
- more than 400 000 people initiated ART, including 57 000 pregnant women;
- more than 8 million people were screened for TB;
- 185 million male condoms and 524 000 female condoms were distributed;
- 237 000 males were medically circumcised, exceeding the campaign target of 100 000; and
- 3686 health facilities (80% of the total) were delivering ART, supported by task shifting and training 10 542 nurses.

Box 3.5. National testing days in El Salvador

Every June, El Salvador stages a National HIV Testing Day. Featuring parades and other entertainment, this health sector-wide campaign offers HIV testing and counselling countrywide using mobile units, health clinics, nongovernmental organization centres and various public venues. In June 2012, 117 000 people were tested in one day, of whom 0.2% were diagnosed with HIV. The campaign accounted for 28% of all HIV tests performed and yielded 20% of all HIV-positive diagnoses in 2012. The national testing day has helped to normalize HIV testing, increase knowledge and reduce stigma towards HIV.
Partner and couples testing (including in antenatal care settings) (36)

Data from Demographic and Health Surveys suggest that in at least two thirds of couples in which one partner is HIV-positive, the other partner is HIV-negative (37). Evidence from eastern and southern Africa, for example, indicates that 50–65% of the people who acquire HIV infection in Swaziland, 35–62% in Lesotho and 44% in Kenya are within marital or cohabiting relationships (38). WHO has recommended couples testing and counselling in antenatal care settings since 2006 and, in 2012, WHO recommended that all HIV-positive partners in serodiscordant relationships be offered ART regardless of their CD4 count (39).

By the end of 2012, at least 14 countries had already adopted policies for couples testing and treatment of the HIV-positive partners (Table 3.5). Encouragingly, a recent randomized trial in Cameroon, the Dominican Republic, Georgia and India showed that providing couples-oriented, post-test HIV counselling increased partner testing rates in all sites — and by as much as 30-fold in one site in Georgia — compared with standard counselling (40).

Country experiences in scaling up HIV testing and counselling for couples have shown that the approach can be acceptable, feasible and effective. In Uganda, peer sensitization and establishing male-friendly spaces in antenatal care facilities increased male partner testing in antenatal care from 5.9% in 2002 to 76% in 2011 (41). In Rwanda, more than 80% of pregnant women now undergo HIV tests with their partners (42). In South Africa, couples-based HIV testing has also been found to be highly acceptable among men who have sex with men.

Nevertheless, these are exceptions. Available data indicate that few countries have achieved couple HIV testing and counselling rates exceeding 20% in antenatal care settings. Hindrances include male partners’ perception that antenatal clinics are not male-friendly, a sense that services focus too narrowly on HIV testing and counselling rather than on general health (43) and strong beliefs about gender roles and hierarchies (44). Couples HIV testing and counselling can bring enormous benefits, including disclosure of HIV status to partners, stronger uptake of and adherence to ART and PMTCT interventions; however, couples HIV testing and counselling should be non-coercive, and health care workers should be sensitive to supporting women to test alone without their partners if they fear gender-based violence (45).

Expanding HIV testing and counselling into communities

Community-level HIV testing and counselling may help to improve access and reduce the stigma and discrimination that is often associated with clinic-based testing (46). According to the Global AIDS Response Progress Reporting system, 73 of 82 countries are using community-based (outside clinics) testing approaches, and 53 of 73 countries allow lay workers to perform HIV rapid testing.

A recent systematic review of 21 studies conducted in Kenya, Malawi, South Africa, Uganda and Zambia (47) found that home-based HIV testing and counselling was highly acceptable, with 83% of people accepting testing when offered. People living with HIV were linked to care in slightly more than half the studies included in the review. As with all HIV testing and counselling, home-based HIV testing and counselling needs to include effective procedures for referral and linkage to care and other HIV and health services (48).

In some settings, community-based testing for key populations is proving to be highly acceptable and effective in reaching large populations of first-time testers and in diagnosing people living with HIV soon after seroconversion (49). For these reasons, the 2013 WHO ARV guidelines (50) recommend that community-based testing approaches complement provider-initiated testing.

Self-testing – a potentially useful new approach to increase access to HIV screening

HIV self-testing offers an additional possible approach for enhancing testing access. Rapid diagnostic testing has been approved for self-testing in the United States of America (51), and other countries are investigating the feasibility of including self-testing in their national AIDS strategies. While experience remains limited, self-testing appears to be highly acceptable. In a formal programme of self-testing for health workers in Kenya, where self-testing is included in the national HIV testing and counselling guidelines, 85% of the people who attended an information session used a self-test kit, and 64% of those with partners reported that their partners also used the kits (52). Similarly high uptake and acceptability of this emerging approach has been reported recently in Malawi (Box 3.6).
Box 3.6. Supervised self-testing in Malawi (53)

A supervised self-testing programme in Malawi is using trained resident volunteers to offer HIV self-testing with counselling to their neighbours in neighbourhoods in the city of Blantyre. The initial results of the programme, which started in February 2012, show strong uptake but indicate a need for proactive interventions to link people testing HIV-positive to care.

- Of the 16,660 adults older than 15 years who participated in the programme, 81% took self-tests and 89% returned the kits after use to their counsellors.
- Among the self-testers, 42% were men, and 21% were younger than 20 years.
- 98% of the participants said they would recommend a self-test to friends and family.
- More than three times as many adults who were eligible for ART in the home-based arm of the programme started ART compared with those in the facility-care arm (46% versus 15%).

Further studies will assess cost–effectiveness, adherence to ART and retention in care.

WHO is examining the legal, ethical, gender, human rights and public health implications of scaling up HIV self-testing. A forthcoming WHO and UNAIDS policy brief (54) will outline the possible application of supervised and non-supervised HIV self-testing, associated concerns and the recommended conditions and requirements for self-testing.

Testing people with TB for HIV infection

Worldwide, the number of people with TB tested for HIV has increased consistently each year. The WHO African Region, which accounts for almost 80% of the people who are HIV-positive globally (55), has made particularly strong progress. Provisional data from 43 countries in the African Region show that an average 75% of people notified as having TB had a documented HIV test result in 2012 compared to only 11% in 2005; more than 40% of the people tested were HIV-positive. The final data will be available in the WHO Global tuberculosis report 2013.

Some countries (such as Kenya) are implementing national policies to offer HIV testing to everyone with presumptive TB. Available data indicate that a large proportion of people with presumptive TB test HIV-positive in settings with a high burden of HIV (56). Data from Zimbabwe (57) and India (58) show that the prevalence of HIV among people with presumptive TB is as high as among people with diagnosed TB, with the prevalence varying according to the epidemiological context. In a study in Zimbabwe, 63% of the people with presumptive TB were diagnosed with HIV (57). WHO recommends HIV testing among people with presumptive TB, but the practice is not yet routine (59).

Linking people from testing to care

It is vital that people diagnosed with HIV be linked promptly to care. The reasons for poor linkage to care after testing HIV-positive are diverse and include clinical, structural and personal barriers (60,61). A recent survey in sub-Saharan Africa (62) suggests that stigma, poor referral systems and poor post-test counselling are important deterrents. Transport and opportunity costs such as loss of income or threat of losing a job for taking time off work to seek care also act as disincentives, especially when health facilities are located far from patients’ homes or workplaces (63). Decentralizing treatment and care services is therefore crucial for strengthening the treatment cascade.

Linking key populations to care

Linking key affected populations to HIV care poses particular challenges, especially for people who inject drugs. The criminalization of injecting drug use and the requirement in some countries that drug users formally register with government services act as major deterrents to seeking care. In the WHO European Region, for example, low coverage of opioid substitution therapy and a lack of integration of HIV, TB and opioid substitution therapy services are barriers to HIV care (Box 3.7).
Box 3.7. Integrating TB, HIV and opioid substitution in Belarus

TB, HIV and drug dependence services in Belarus used to be delivered via separate programmes, each with its own administration, financing and staff. This hindered uptake of ART by people who were diagnosed in TB settings, many of whom injected drugs. Belarus responded by allowing ART to be initiated in TB clinics; however, people were still not able to start opioid substitution therapy while in TB hospitals. That changed when a national consultative process in early 2012 recommended that opioid substitution therapy be able to be initiated in TB clinics, with financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria and the Belarus Ministry of Health.

Some TB clinics have created positions for narcologists or made arrangements for consultancy services. One TB hospital plans to operate a permanent distribution site for opioid substitution therapy, which would facilitate stronger integration of services. The new approach is spurring the expansion of the opioid substitution therapy programme in Belarus, which currently reaches 920 people, of whom 35% are living with HIV and 20% are receiving ART.
Historically, whereas efforts have been made to expand testing and the initiation of ART, providing routine pre-ART HIV care for people not yet eligible for treatment has been neglected (64). A 2010 audit of 122 public primary-care facilities offering HIV testing and counselling in Cape Town, South Africa, found that 78% of people who tested HIV-positive received a CD4 count and only 47% were clinically staged. Overall, less than half (47%) of the people found to be eligible for ART were referred to an ART facility.

Data on the outcomes among people waiting for ART are limited but suggest that outcomes are poor. A study from the Free State Province in South Africa analysing data from 2004–2007 (65) found that 23% of the people eligible for ART had died before starting ART and that men were less likely to start ART and more likely to die than women.

Several interventions have been shown to improve outcomes for people receiving pre-ART HIV care, including high-quality counselling, providing co-trimoxazole prophylaxis, various methods to encourage regular visits (such as transport allowances) and approaches that shorten the pre-ART period such as using point-of-care CD4 testing (Box 3.8) (1).
Box 3.8. Point-of-care CD4 testing

Several recent studies have highlighted the benefits of point-of-care CD4 testing as a way to improve linkage between HIV testing and HIV care and to reduce the time before eligible people initiate ART. In South Africa, receipt of a CD4 count at the time of HIV testing was found to increase ART initiation rates (72). In neighbouring Mozambique, using the technology in primary care clinics almost halved the loss to follow-up before initiating ART, from 64% to 33% (73).

A recent systematic review of data from 18 studies (74) found that people using point-of-care testing were more likely to both receive a CD4 result and start ART compared to those relying on laboratory-based methods. Point-of-care CD4 testing significantly reduced both the median time between HIV diagnosis and having a CD4 test and between HIV diagnosis and receiving the test result. The use of this technology was predicted to be cost-effective and to result in more life-years saved than current methods (74).

The uptake of point-of-care CD4 testing has been rapid: more than 2500 machines were in use in 41 low- and middle-income countries at the end of 2012.

CD4 testing

CD4 testing can be a key method for assessing whether people are eligible for ART. In order to avoid that lack of CD4 testing becomes a barrier to treatment initiation, WHO guidelines do not insist on a CD4 test before initiating ART, but for clinical reasons it is considered desirable at the start of treatment. However, access to CD4 testing remains limited. Indeed, some countries with a high burden of HIV infection (such as Malawi) have successfully scaled up ART without making CD4 testing mandatory (66). Nevertheless, even in settings in which CD4 testing is routinely available, it is not routinely performed.

- A recent study from China reporting on data from 83,000 people in the Yunnan and Guangxi provinces found that only 37% of those who tested HIV-positive received a CD4 count within six months (67).
- A study from Kenya, Uganda and the United Republic of Tanzania reported that even in a research setting in which efforts were made to reduce missing data, pre-ART CD4 counts were missing for 15% of the people living with HIV (68).
- In Johannesburg, South Africa, among 437 people who had recently been diagnosed with HIV, only 19% had a CD4 test within 6 weeks, and 29% had one within 6–12 weeks of testing HIV-positive (69).
- A report from a nationally representative sample of 100 clinics in the United Republic of Tanzania showed that the proportion of people with missing CD4 counts did not improve between 2004 and 2009, with one in five people lacking a CD4 count throughout that period. Mortality rates were significantly higher among the people lacking a CD4 count than among those with a recorded CD4 count (10).

According to the WHO 2012 diagnostics survey (71), 3781 CD4 count machines were operating in 69 low- and middle-income countries in 2011. However, even where tests are available, access may be limited because of user charges for laboratory tests, malfunctioning machines or a lack of reagents. Data from 47 countries included in the WHO 2012 diagnostics survey (71) found that the average CD4 count machine was used to perform about four tests per day, whereas cost-effective deployment requires testing between 20 and 100 samples per day.
One encouraging development that can increase access to CD4 is the recent and rapid deployment of point-of-care CD4 testing technology (Box 3.8). This technology can speed up the assessment of eligibility for ART and reduce losses to care before initiating ART. However, effectively using point-of-care CD4 technology requires solving several challenges, according to the WHO survey (71), including shortages of reagents, non-installation, inadequate training and — especially — poor or no maintenance. These issues highlight the need for a national strategic plan for purchasing and deploying laboratory technologies.

Retention in pre-antiretroviral therapy

A systematic review of 28 studies in sub-Saharan Africa showed that 32% of the people considered eligible for ART are lost between their eligibility being assessed and ART being initiated (2). Retaining people in pre-ART over extended periods of time poses significant challenges, many of them distinct from the factors that affect whether people are retained in ART.

Losses between HIV diagnosis and initiating ART also pose challenges for care for children, although a recent meta-analysis of studies involving more than 10 000 children living with HIV (9) found that linkage to care after diagnosis was better than for adults: depending on the specific study, between 40% and 99% of children diagnosed with HIV and deemed eligible for ART actually started ART.

Lack of CD4 testing or delays in receiving CD4 results (see above), long waiting times at clinics, concerns about possible drug side effects, a lack of confidence in the effectiveness of the treatment and drug stock-outs1 can all contribute to attrition before initiating ART (62). Many of the reasons are similar to those that cause people to be lost to care after initiating ART; these are discussed in the next section.

1. A stock-out occurs when the demand or need for an item cannot be met from the current inventory.
3 Antiretroviral therapy: initiation, retention and adherence

**KEY POINTS**

**Initiating treatment early is vital for success**
- As of 2012, most countries globally allowed ART to be initiated at CD4 $\leq 350$ cells/mm$^3$, and a few have already moved to a higher initiation threshold of CD4 $\leq 500$ cells/mm$^3$.
- Median CD4 when initiating ART is rising in all regions but is still too low: about 1 in 4 people in low-income settings initiate ART late, with CD4 counts $< 100$ cells/mm$^3$.
- Option B+ for preventing the mother-to-child transmission of HIV is being rapidly adopted as a way to increase the coverage of ART for pregnant women living with HIV.
- Decentralizing HIV care improves access and retention, and an increasing number of countries have piloted or are rolling out ART delivery at the community level.

**Improving retention in ART care is a key challenge for programmes**
- The latest data from 23 countries indicate that the average retention rates for people on ART decreases over time, from about 86% at 12 months to 82% at 24 months and 72% at 60 months, with considerable variation between countries.

Most countries in 2012 allowed for initiation of ART at CD4 $\leq 350$ cells/mm$^3$, in accordance with the 2010 WHO treatment guidelines (75). A few countries (including in low-income settings in the WHO Region of the Americas and in the WHO African Region) have already moved to the higher initiation threshold for ART now recommended by WHO: CD4 $\leq 500$ cells/mm$^3$ (76).

An increasing number of countries are also implementing or considering policies of initiating lifelong ART earlier for specific groups. At least 14 countries have adopted a policy of providing ART to the HIV-positive partners in serodiscordant relationships, regardless of their immune status, and at least five countries are providing ART to people with a CD4 count $\leq 500$ cells/mm$^3$. As of early 2013, at least 28 countries had a policy for implementing lifelong ART for pregnant women living with HIV (Option B+) (77).

**Timing of initiation**
Increased HIV testing, policy shifts towards initiating ART earlier and expanded ART coverage have led to steady increases in all regions in the average CD4 count at which people initiate ART. As shown in Fig. 3.6, the increases have been most notable among women, especially in low- and middle-income countries. The fact that people on average are starting ART in better health, along with the massive increases in the coverage of ART in recent years, is reducing AIDS-related mortality and increasing the life expectancy of people living with HIV (see Chapter 2).
However, in all regions the average CD4 cell count when initiating ART remains far lower than the recommended threshold currently used in most countries and considerably lower in low- and middle-income countries. Significant proportions of people still present with advanced immunosuppression (CD4 cell counts \( \leq 100 \) cells/mm\(^3\)). According to cohort data, about one quarter of the people in low- and middle-income settings start ART with a CD4 count \( <100 \) cells/mm\(^3\). This is a major reason for the high mortality rates observed during the first months of ART (6,79). Generally, men are more likely than women to begin treatment late (Fig. 3.7) (78). A solid understanding of such persistent late presentation is urgently needed. Although the policy evolution towards initiating ART earlier is important for reducing HIV incidence and mortality, these data highlight the need to remain focused on identifying the people who most urgently need ART.
Fig. 3.7. Proportions of men and women starting antiretroviral therapy with CD4 <100 cells/mm³ in low- and middle-income countries, 2002–2010

![Graph showing proportions of men and women starting antiretroviral therapy with CD4 <100 cells/mm³ in low- and middle-income countries, 2002–2010.](image)

Source: Mugglin et al. (78) with additional data provided by the authors.

Initiating treatment among children living with HIV

Country data on the ages at which children initiate ART remain limited. In 2012, UNICEF and WHO supported rapid assessments of care for children in Swaziland, the United Republic of Tanzania and Zimbabwe. In Zimbabwe, the median age when initiating ART was 7 years; most children were referred from hospitals, which indicates that they had already presented with AIDS-related conditions or they “progressed slowly”. In the United Republic of Tanzania, the median age at initiation was 4.3 years, and only 15% of children initiating ART were referred from the PMTCT programme. In Swaziland, the median age when initiating ART was 4.9 years in 2010 and 3.4 years in 2011 (80). Fig. 3.8 depicts the main entry points through which children initiate ART.

The late initiation of treatment reflects several weaknesses in the treatment cascade, ranging from inadequate identification of children living with HIV to weak linkage to care (9).

Fig. 3.8. Entry points for initiating antiretroviral therapy among children 0–14 years old, 2010

![Diagram showing entry points for initiating antiretroviral therapy among children 0–14 years old, 2010.](image)

Source: A rapid assessment of paediatric care and treatment in four countries: Swaziland, Tanzania, Uganda and Zimbabwe (80).
Initiating treatment among pregnant women living with HIV

Providing ART to treatment-eligible women in PMTCT programmes has been a longstanding challenge, since it involves accessing CD4 testing and ART at decentralized maternal and child health clinics. According to the 2010 WHO treatment guidelines (75), all pregnant women living with HIV should be assessed for eligibility for ART and should receive ART if they are eligible (CD4 ≤350 cells/mm³ or Stage 3 or 4 clinical disease). Using these criteria, an estimated 40% of the pregnant women living with HIV would be eligible for treatment.

Among low- and middle-income countries, 64% of pregnant women with HIV-positive test results were subsequently assessed for eligibility for ART in 2012, up from 57% in 2011. Despite this improvement, the fact that one third of the pregnant women diagnosed with HIV had not been assessed for eligibility for ART constitutes a major missed opportunity for initiating ART and ensuring that appropriate ARV regimens for PMTCT are provided. Among women who were assessed in 2012, around 75% were assessed by CD4 count and the rest were assessed by clinical staging only. Regions and countries vary widely, however. The largest increases in ART eligibility assessment were reported in the WHO African Region and the WHO European Region.

WHO issued a technical update in 2012 detailing the advantages of Option B and Option B+ (which involve starting all pregnant women living with HIV on triple ARV medicines) (81,82). Since then, many of the Global Plan priority countries have begun or are planning to provide ART to all pregnant women diagnosed with HIV, regardless of their immune status (Table 3.6) (81,82).

The 2013 WHO ARV guidelines (50) recommend that all pregnant women living with HIV initiate ART and that, in most settings, women should continue with lifelong treatment. For the women who are not eligible for ART for their own health, countries will decide their own national policies on the need to continue treatment versus stopping ART after the labour, delivery and breastfeeding risk periods for HIV transmission have ended.

Table 3.6. Regimen policy for preventing the mother-to-child transmission of HIV among pregnant women living with HIV in the 22 priority countries of the Global Plan, as of May 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>PMTCT regimen policy after WHO 2010 ARV guidelines</th>
<th>Current PMTCT regimen policy as of May 2013</th>
<th>Implementation status of ART for all pregnant and breastfeeding women living with HIV (Option B or B+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>B</td>
<td>B+</td>
<td>Select regions</td>
</tr>
<tr>
<td>Botswana</td>
<td>B</td>
<td>B</td>
<td>National</td>
</tr>
<tr>
<td>Burundi</td>
<td>B</td>
<td>B</td>
<td>National</td>
</tr>
<tr>
<td>Cameroon</td>
<td>A</td>
<td>B+</td>
<td>Planned</td>
</tr>
<tr>
<td>Chad</td>
<td>B</td>
<td>B</td>
<td>National</td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>B</td>
<td>B</td>
<td>National</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>A</td>
<td>B+</td>
<td>Planned</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>A</td>
<td>B+</td>
<td>Select regions</td>
</tr>
<tr>
<td>Ghana</td>
<td>A</td>
<td>B</td>
<td>National</td>
</tr>
<tr>
<td>India</td>
<td>A</td>
<td>B</td>
<td>Select regions</td>
</tr>
<tr>
<td>Kenya</td>
<td>A</td>
<td>A/B</td>
<td>Select regions, planning to move to B+</td>
</tr>
<tr>
<td>Lesotho</td>
<td>A</td>
<td>B+</td>
<td>National</td>
</tr>
<tr>
<td>Malawi</td>
<td>B+</td>
<td>B+</td>
<td>National</td>
</tr>
<tr>
<td>Mozambique</td>
<td>A</td>
<td>B+</td>
<td>Select regions</td>
</tr>
<tr>
<td>Namibia</td>
<td>A</td>
<td>B+</td>
<td>Planned</td>
</tr>
<tr>
<td>Nigeria</td>
<td>A/B</td>
<td>A/B</td>
<td>Select regions</td>
</tr>
<tr>
<td>South Africa</td>
<td>A</td>
<td>B</td>
<td>National</td>
</tr>
<tr>
<td>Swaziland</td>
<td>A</td>
<td>A</td>
<td>Piloting B+ in select regions</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>A</td>
<td>B+</td>
<td>Planned</td>
</tr>
<tr>
<td>Uganda</td>
<td>A</td>
<td>B+</td>
<td>National</td>
</tr>
<tr>
<td>Zambia</td>
<td>A</td>
<td>B+</td>
<td>Planned</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>A</td>
<td>B+</td>
<td>Planned</td>
</tr>
</tbody>
</table>

Option A (maternal AZT); Option B (initiation of ART to all pregnant women living with HIV, lifelong if treatment-eligible, or through end of the mother-to-child transmission risk period if not eligible for treatment); Option B+ (initiation of lifelong ART for all HIV-positive pregnant and breast-feeding women).

Implementation of new regimen (either Option B or B+) in select regions or nationally where implementation is defined as: 1) sites selected; 2) staff training completed; 3) ART regimens available at site and supply chain management system in place.

Source: unpublished reports from IATT Country Focal Points, IATT Secretariat (www.emtct-iatt.org), WHO

1. For Option B, this entails discontinuing treatment after the delivery and breastfeeding mother-to-child transmission risk period, whereas for Option B+ it involves lifelong ART.
Box 3.9. Implementing Option B+ in Malawi

In mid-2011, Malawi began implementing a policy of universal lifelong ART for all pregnant and breastfeeding women living with HIV, regardless of their CD4 count or WHO clinical stage. This approach has become known as Option B+.

Fig. 3.9. Transition from prophylactic antiretroviral regimens for preventing mother-to-child transmission to Option B+ in Malawi

Monitoring and evaluation had revealed significant difficulties affecting access to the previous ARV regimens for PMTCT and to ART for pregnant women. Most pregnant women living with HIV access care at peripheral health centres in Malawi, and delivering uninterrupted, quality-controlled CD4 count testing at more than 570 antenatal clinic sites was considered unrealistic. In addition, stopping ART after breastfeeding ended for a subset of women would have confused the public health messages about the need to continue ART for life. It also would have led to a start-stop-start approach to treatment, because of the lengthy average duration of breastfeeding (24 months), high fertility (six births per woman) and short birth intervals (83).

Malawi selected TDF + 3TC + EFV for Option B+ because of the low risk of side effects and because this regimen is available as a daily fixed-dose combination tablet. The rollout of Option B+ was completed within nine months and involved retraining more than 4500 health workers and decentralizing ART services from 303 to more than 650 facilities.

Option B+ has effectively merged Malawi’s PMTCT and ART programmes; all maternal and child health sites have become ART sites. This had led to simplified protocols and integrated clinical HIV guidelines for pregnant women, children and adults. Other improvements include an
More details on Malawi's ART programmes and PMTCT programmes are available at www.hivunitmohmw.org/Main/AntiretroviralTherapy, including a current set of data on access and retention on Option B+.

During an 18-month period in 2011–2012, almost 57 000 women started ART under Option B+, of whom 64% started in pregnancy and 36% while breastfeeding. Option B+ is expected to result in a rapid increase of coverage of ART among women of reproductive age living with HIV, offering optimal protection for subsequent pregnancies regardless of the timing of the first antenatal care visit. Data on the number of women who were already receiving ART when they became pregnant have been collected since July 2012. Between October and December 2012, 39% of the almost 11 000 women who were receiving ART during pregnancy had initiated ART before becoming pregnant.

The early data on retention rates are encouraging. In the first 18 months of implementing Option B+, 83% of women were retained on ART 6 months after ART initiation and 78% after 12 months. This is similar to the retention rates in the general ART cohort. Retention on Option B+ is expected to increase as sites gain experience with optimal patient education, preparation and follow-up.

Phasing out single-dose nevirapine prophylaxis for preventing mother-to-child transmission

Significant progress has been made in phasing out single-dose nevirapine (NVP) prophylaxis for PMTCT (which WHO has not recommended for use since 2006). In the Global Plan priority countries, the percentage of women receiving only a single-dose of NVP decreased from 17% to 4% between 2011 and 2012.

**Fig. 3.10. Percentage distribution of various antiretroviral regimens provided to pregnant women in 21 African priority Global Plan countries**

<table>
<thead>
<tr>
<th>Year</th>
<th>Effective Prophylactic Regimen</th>
<th>ART</th>
<th>Single-dose Nevirapine</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>46%</td>
<td>37%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>54%</td>
<td>41%</td>
<td>4%</td>
<td>1%</td>
</tr>
</tbody>
</table>


1. More details on Malawi’s ART programmes and PMTCT programmes are available at www.hivunitmohmw.org/Main/AntiretroviralTherapy, including a current set of data on access and retention on Option B+.
Choosing optimal regimens

Successive WHO guidelines for ART during the past decade have sought to simplify treatment by reducing the number of recommended drugs, harmonizing regimens across different populations and age groups and promoting once-daily, fixed-dose combinations to simplify drug management and improve adherence (84).

Fixed-dose combinations have been shown to provide significant benefits compared with separate tablets, including improved adherence and treatment outcomes (85) and reduced risk of treatment interruptions during stock-outs (86). There are also indications that they are more cost-effective than separate tablets (87). In line with the Treatment 2.0 framework, the 2013 WHO ARV guidelines recommend a single, preferred regimen of TDF + 3TC or FTC + EFV (50), which is available as a once-daily fixed-dose combination and can be used for most people. As countries shift toward TDF-based regimens, the use of fixed-dose combinations should continue to be given priority.

Recent surveys show that many countries still have room for improvement. According to data from 80 countries that responded to WHO’s 2012 annual survey on the use of ARV medicines, the number of first-line ART regimens per country ranged from a minimum of 4 to a maximum of 38 with a median of 10 (Fig. 3.11) (77). A 2011 Pan-American Health Organization study found that countries in the Americas were using an average of 12 first-line regimens and 15 second-line regimens for adults, including several drugs that were no longer recommended for use because of high toxicity (such as d4T) or low efficacy (such as nelfinavir) (14). Countries are advised to reduce the number of first-line regimens they use to reduce market segmentation, simplify prescribing and make procurement more efficient.

In the next 2–5 years, there is potential for further improving the alignment and sequencing of first- and second-line regimens for adults living with HIV, pregnant women living with HIV, people with TB and HIV and children older than three years living with HIV. Dolutegravir and darunavir are among the drugs considered to have the potential to improve treatment outcomes in the short term. In the longer term, current first- and second-line ART regimens are expected to be improved further as new drugs and innovative strategies (such as induction maintenance, long-acting formulations, anti-latency drugs and gene therapy) become available (88).

Fig. 3.11. Number of first-line antiretroviral regimens used in selected countries, 2012

Source: Use of ARV medicines by December 2011 based on the WHO survey in low- and middle-income countries (77).
Box 3.10. South Africa adopts fixed-dose combinations

South Africa adopted a fixed-dose combination formulation of TDF + FTC + EFV as preferred first-line ART in April 2013 after successfully negotiating a price of about US$ 113 per person per year. Health workers and civil society groups have applauded the decision as an important step towards simplifying treatment from the perspective of both the people receiving ART and providers. Fixed-dose combinations are promoted in other infectious disease areas, notably malaria and TB, to limit the emergence of drug resistance. In HIV, fixed-dose combinations have been shown to offer multiple advantages over separate pills, including reduced risk of stock-outs (86), improved user-reported quality of life (89) and improved adherence, notably among groups considered at to be at higher risk of non-adherence (85). For these reasons, the WHO 2013 ARV guidelines (50) give preference to fixed-dose combinations.

Phasing out d4T

In 2010, WHO recommended that countries shift away from using d4T because of commonly reported toxicity issues and instead opt for AZT and TDF. In Lesotho, for example, people receiving d4T were almost six times more likely to experience a toxicity-driven regimen switch compared with people receiving TDF (90), while in Cambodia, more than 90% of the people receiving ART had switched from d4T within six years of initiation because of toxicity (91). These concerns have led to a progressive decline in the use of d4T globally over the past five years (Fig. 3.12).

However, as Fig. 3.13 shows, the shift has been uneven, since some countries with a high burden of HIV infection have not yet phased out d4T. In 2011, about 1.1 million people were still being newly initiated on d4T-based first-line regimens, the vast majority in resource-limited settings with a high burden of HIV infection in the WHO African Region. Elsewhere, a few countries with significant HIV epidemics have been slow to phase out d4T. The latest WHO ARV survey (77) shows that, at the end of 2011, 31% of the people receiving ART globally were taking d4T-based regimens, and only 7% were taking the preferred first-line regimen of TDF + 3TC (or FTC) + EFV. Renewed efforts are needed to replace d4T, preferably with a TDF-based regimen in line with the 2013 WHO ARV guidelines (Box 3.11.) (50).

Fig. 3.12. Trends in d4T, AZT and TDF use in first-line antiretroviral therapy regimens for adults in low- and middle-income countries, 2006–2011

![Graph showing trends in d4T, AZT, and TDF use](source: Use of antiretroviral medicines by December 2011 based on the WHO survey in low- and middle-income countries (77).)
Fig. 3.13. Varied progress in phasing out d4T in selected countries in the WHO African Region at the end of 2011

Box 3.11. Funding support for phasing out d4T

At the end of 2012, the Global Fund to Fight AIDS, Tuberculosis and Malaria was supporting the provision of ART to 4.2 million people, up from 1.4 million five years earlier. A review to assess countries’ progress in implementing the 2010 WHO treatment guidelines found that the majority of 85 countries receiving Global Fund support to deliver ART had made a policy shift away from regimens containing d4T by the end of 2012. Progress had initially been slow in some countries, but the Global Fund, working with technical partners and countries, accelerated the transition by supporting reprogramming within current grants and by providing new funding as part of a shift to a new funding model. The Global Fund continues to work with technical partners, especially WHO, to complete the shift away from d4T-based regimens.

In June 2013, UNITAID announced a proposal for a strategic collaboration with the Global Fund and WHO to accelerate phase out of d4T in favour of the preferred TDF-based first line. The collaboration, which will be confirmed in the third quarter of 2013, would support accelerated phase out by providing up to US$ 77 million to subsidize the cost of switching, negotiate lower prices with manufacturers and ensure timely supplies.

Source: Use of ARV medicines by December 2011 based on the WHO survey in low- and middle-income countries (77).
Optimizing antiretroviral therapy for children

Treatment recommendations for children should be relatively straightforward to implement at all levels of the health system, including the primary care level. However, this has not always been the case. Child-friendly drug formulations such as liquids, sprinkles, scored tablets and palatable tastes, co-formulations and fixed-dose combinations are often unavailable, creating difficulty in optimizing drugs and simplifying regimens.

Many infants who have acquired HIV infection perinatally and who have been exposed to NVP via maternal treatment, prophylaxis or treatment after prophylaxis for PMTCT have acquired viral resistance. Surveillance data have shown a prevalence of NVP resistance of up to 60% among children younger than 18 months who underwent virological testing (92). The scaling up of ART in children therefore should promote the regimens that are most likely to be effective. For infants and children younger than three years of age, the preferred treatment regimen is an LPV/r-based regimen. However, the current lack of availability of appropriate formulations remains a challenge. New formulations and fixed-dose combinations are needed.

The WHO 2013 ARV guidelines (50) aim to further reduce barriers to children initiating treatment and to simplify programme management by recommending ART for all children living with HIV younger than five years, irrespective of immune status.

Co-trimoxazole prophylaxis for children

Co-trimoxazole is critically important for increasing survival among HIV-exposed and HIV-infected children (93). It has also been shown to reduce overall infection rates (especially malaria and sepsis episodes), including among children living with HIV who are clinically stable on ART and who have achieved successful immune recovery (94).

Although co-trimoxazole has been recommended since 2006 (95) as an essential component of the HIV care package, only 31% [26–37%] of HIV-exposed infants in the low- and middle-income countries (based on 2011 estimates) that reported those data received co-trimoxazole in 2011. Nevertheless, this did mark an increase from the 26% [22–30%] coverage reported in 2010. The increase largely resulted from progress made in countries in eastern and southern Africa, where coverage improved from 31% [29–35%] in 2010 to 42% [37–49%] in 2011. Preliminary data from 2012 show that coverage continued to expand, with 6 of the 22 priority countries in the Global Plan achieving at least 50% coverage. Overall access to co-trimoxazole remains too low, however.

Expanding access to co-trimoxazole prophylaxis requires a set of interrelated interventions, including strengthening links between HIV testing and treatment and establishing mechanisms to identify and follow up HIV-exposed infants at and after birth. Integrating co-trimoxazole provision with immunization services that are provided as part of routine maternal and child health clinic activities may help to improve co-trimoxazole coverage.

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Box 3.12. Policy changes towards the rational use of co-trimoxazole in resource-limited settings (96)

Co-trimoxazole is a broad-spectrum antimicrobial agent that targets a range of bacteria, fungi and protozoa. Co-trimoxazole is on the essential medicines list of most countries. Providing co-trimoxazole has been part of the standard of care for preventing Pneumocystis jiroveci pneumonia and toxoplasmosis since the early 1990s. A survey of 81 guidelines from 50 resource-limited settings has shown a significant increase in the number of countries that have issued policy directives for using co-trimoxazole since WHO issued its 2006 guidelines recommending such an approach.
Antiretroviral therapy for older populations

HIV infection among people older than 50 years has attracted attention in high-income countries but less so in resource-limited settings, in which it has previously been assumed that people living with HIV do not live long enough for this to be a major concern. However, as life expectancy among people receiving ART improves, there is growing realization that HIV among older people is an important issue. A recent report from ART programmes in 9 countries in the WHO African Region indicated that more than 1 in 10 people initiating ART were aged 50 years and older and that the mortality of those receiving ART was higher compared with the rest of the adult cohort (97). Cardiovascular disease, diseases of the nervous system, mental disorders, cancer and musculoskeletal disorders appear to be more pronounced in older individuals living with HIV (98).

Supporting adherence and retention in care

Retaining people receiving ART in care and ensuring good treatment adherence are critical determinants of successful ART outcomes. Data reported in 2013 for 23 countries with cohorts of at least 2000 people on ART indicate that the average retention rates tend to decrease over time, from about 86% at 12 months to 82% at 24 months and 72% at 60 months. However, as Fig. 3.14 shows, retention rates at 60 months appear to vary considerably between countries.

Fig. 3.14. Antiretroviral therapy retention rates (%) at 12, 24 and 60 months reported by selected low- and middle-income countries, 2012

Estimates for retention in care are often based on health facility reports, which do not always describe the outcomes of the people who are not retained in care. One systematic review has indicated that 33–48% of the people who are lost to follow-up after initiating ART had in fact died, and a further 12–54% of those lost to follow-up were “self-transfers” and were accessing care elsewhere (6); more recent data from South Africa show that 13% of the people initiating ART transferred out within 2.5 years (99). These findings highlight the complexity of ascribing treatment outcomes to people who appear to be lost to care and underline the need for information systems that can ascertain the vital status of people who move in and out of the health care system.

As ART programmes mature in resource-limited settings, more positive long-term outcomes are being observed. For example, programme data from South Africa showed that over 50% of the people initiating ART in 2001 were still in care at the end of 2011 (Fig. 3.15). However, the rates of loss to follow-up appear to be higher in the most recent years, possibly reflecting mounting health system challenges in managing larger cohorts of people (100).

Comparable retention rates have been reported in generalized epidemics and among key populations in some concentrated HIV epidemics. A recent evaluation of the first five years of ART provision among people who inject drugs in Viet Nam found high retention at 12 months among both the people who injected drugs (82%) and those who did not inject drugs (84%) (101). An earlier study in Guangxi, China reported an 87% retention rate at 12 months among people who inject drugs (102).

People may disengage from care because of conflicting priorities, such as unexpected family obligations or competing work schedules. Some research indicates that intentional reasons for disengagement from care also include dissatisfaction with the quality of services and care received at HIV clinics (103).

On the other hand, several studies in the WHO African Region have shown that decentralizing ART services improves retention in care. In a study from South Africa comparing outcomes from 47 primary health care facilities, 9 district hospitals and 3 regional hospitals, 80% were retained on

**Fig. 3.15. Proportion of people remaining in care in Khayelitsha, South Africa, according to the duration of antiretroviral therapy**

Source: Data courtesy of the Western Cape Provincial Department of Health, South Africa.
ART at primary health clinics compared with 69% at the regional hospitals (104). Data from more than 4000 ART recipients in Thyolo, Malawi, showed that those accessing ART at the hospital were more likely to be lost to follow-up than those using the “lower-level” health centres (105). Positive outcomes were also observed for nurse-managed treatment at the primary health care level in Lesotho (106). The findings have informed the recommendation in the WHO 2013 ARV guidelines (50) for decentralizing ART to primary health care services. Although interventions to improve linkage to care require more rigorous evaluation, these and other studies indicate several potential ways to reduce attrition (11,107,108). Table 3.7 summarizes some of the main issues related to health systems, providers and recipients that influence retention and adherence to ART along with potential remedies.

Table 3.7. Barriers to and solutions for improving access and retention in care

<table>
<thead>
<tr>
<th>Factors related to the health system</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>High direct and indirect cost of care to users</td>
<td>Antiretroviral therapy free of charge at the point of care</td>
</tr>
<tr>
<td>Facility visits modified according to clinical need</td>
<td>Decentralizing and integrating ART</td>
</tr>
<tr>
<td>• patient appointment system;</td>
<td>Reduce waiting time at the facility level:</td>
</tr>
<tr>
<td>• separate clinical consultation visits from drug refill appointments;</td>
<td>• link, integrate and coordinate care; and</td>
</tr>
<tr>
<td>• family-focused care (organizing services around the need of the family), as appropriate.</td>
<td></td>
</tr>
<tr>
<td>Limited patient and family education and counselling, and peer support in HIV care</td>
<td>Engage community health workers, volunteers and people living with HIV for peer support, patient education and community-level support.</td>
</tr>
<tr>
<td>Inadequate adherence support</td>
<td>Task shifting for involving community health workers</td>
</tr>
<tr>
<td>Linkage with community-level interventions such as peer adherence support</td>
<td>Patient reminders (including text messaging)</td>
</tr>
<tr>
<td>Lack of systems for monitoring retention in care</td>
<td>Systems for patient monitoring across the care cascade, including cohort analysis</td>
</tr>
<tr>
<td>Lack of systems for transitioning people across different points of care</td>
<td>Interlinked patient monitoring systems across HIV, TB, maternal and child health and PMTCT services; systems for transitioning from paediatric to adult services</td>
</tr>
</tbody>
</table>

**Provider-related factors**

| Patient–provider relationships | Training health workers in treatment preparedness, adherence, retention and providing adherence support |
| Prevent stigma in the health sector |
| Poor patient communication | Simplified approach for patient and family education |
| Lack of time for patient education | Task shifting and sharing of tasks among clinic team members, team approach to care and consider patient triage |

**Patient-related factors**

| Comorbid conditions, alcohol or drug use, mental health disorder | Co-manage HIV with mental health, substance and alcohol use disorders, social support, community support |
| Patient knowledge and beliefs related to HIV infection, disease progression and treatment | Integrate patient and family education and counselling, broader community literacy and education and mobilization |
Antiretroviral medicines for mothers and infants

The substantial disparity between the uptake of ARV medicines for infants and for mothers, respectively, highlights the urgent need to address retention along the continuum of care for PMTCT, especially for its components related to infants. Strategies to reduce the early loss to follow-up of the mother-infant pair are also needed (Fig. 3.16).

Among the estimated 1.47 million infants born to mothers living with HIV globally in 2011, 41% (range of country values 34–49%) received infant ARV prophylaxis. Coverage was similar (43%, range of country values 36–51%) in 2010. The global coverage is primarily limited because of very low coverage in western Africa (about 10%) and low coverage in the WHO South-East Asia Region (36%) and in eastern and southern Africa (53%). In contrast, coverage exceeded 95% in the WHO European Region (which has a relatively small total number of mothers and children affected) and in some countries in the WHO Region of the Americas (including Argentina, Cuba, Guyana and Suriname), while coverage was 87% in Brazil.

Retention in care among children

Improving retention in care for children on ART is critically important. A recent multi-site evaluation assessing ART outcomes among more than 13 000 children found that the risk of loss to follow-up within 18 months of starting ART was 4% in Asia, 9% in southern Africa, 14% in eastern Africa and 22% in western Africa (110).

Recent studies also show that decentralizing care for children can achieve similar or better outcomes than tertiary settings. A five-country study from the WHO African Region (Kenya, Lesotho, Mozambique, Rwanda and the United Republic of Tanzania) reported that children receiving ART were 45% less likely to be lost to follow-up if they accessed it at primary care facilities rather than hospitals (111). The WHO 2013 ARV guidelines (50) therefore propose that HIV care for children be decentralized to increase access and strengthen retention in care.

Training and mentorship for health care workers is also needed to facilitate task shifting and allow

Fig. 3.16. Percentage of pregnant women living with HIV and their infants who received antiretroviral medicines for preventing mother-to-child transmission, low- and middle-income countries, 2007-2011"
ART coverage to be expanded to primary health facilities. In addition, alternative models for providing care, such as family-based models, could facilitate the further expansion of ART coverage and integration of services (112). Increased attention should also be paid to integrating the delivery of HIV services for children with maternal and child health services.

Community-based HIV care and treatment: innovations and opportunities

The combination of decentralizing services and task shifting has accompanied the rapid scaling up of treatment in settings with a high burden of HIV infection including Malawi (113), South Africa (114), Kenya, Mozambique and Swaziland (115). Evidence suggests that task shifting can save time, can increase access to ART and can be cost-effective. Studies in South Africa (115,116) have shown that the quality of care generally matches that provided at hospital-based ART clinics and treatment costs are lower in some cases.

Several pilot programmes have reported that involving community-based groups in providing ART has dramatically improved retention (Box 3.13). In addition, a recent systematic review of two randomized trials from Uganda and Kenya and a prospective cohort study in Uganda found that community-based delivery of ART produced good outcomes (117). Dispensing ARV medicines in communities, rather than only at clinics and hospitals, also appears to improve treatment adherence and seems especially effective in keeping men in treatment according to a study conducted in Uganda, the United Republic of Tanzania and Zambia (118). The 2013 WHO ARV guidelines (50) therefore recommend community-supported ART delivery as a strategy to expand care for people receiving ART who are clinically stable.

Community-based interventions that involve peers can address multiple barriers simultaneously and can be used effectively in a wide range of settings. In a cluster-randomized trial in rural Uganda, 15 clinics were randomized to host community-based, peer worker support interventions in which peer health workers received brief HIV training and basic remuneration. The intervention reduced viral failure by 50% at 96 weeks (119).

Some studies suggest that such models, by engaging community workers and peer supporters in the delivery of HIV services, may also contribute to reducing stigma (120,121) and to enhancing coverage and access to HIV care and treatment services (122,123).

Box 3.13. Community groups strengthen the delivery of and retention on antiretroviral therapy in Mozambique (124)

In partnership with Médecins Sans Frontières, Mozambique’s Ministry of Health in 2008 launched an out-of-clinic model for distributing ART, monitoring adherence and promoting support by community ART groups (125). Groups of people receiving ART were formed, with individuals taking turns to collect and deliver ART for their groups, while each group member attended the clinic at least once every six months. Other roles included providing community-based adherence support, monitoring treatment outcomes and establishing a community-based treatment social support network. At the end of 2012, fully 97% of the more than 4000 people enrolled in the community ART groups remained in care. Staff at health facilities reported that the community ART groups facilitated an almost four-fold reduction in formal consultations among people who received community group-based ART care. Mozambique’s experience with this approach suggests that it can also reduce the transport and opportunity costs associated with the uptake of ART.

Studies from Uganda (126) and Kenya (127) provide further evidence of the feasibility of the out-of-clinic approach to providing care and managing ART for people receiving ART who are clinically stable. The approach is also being piloted in several other countries, including the Democratic Republic of the Congo, Malawi and South Africa (125) as well as in countries with concentrated epidemics, such as Cambodia. Longer-term evaluation is needed to confirm the effectiveness and sustainability of this approach as a large-scale model for delivering services.
Box 3.14. Community-based scaling up of treatment in Cambodia

Cambodia, which already has achieved “universal access” to ART, has been using a community-based model for scaling up the coverage of ART. The approach involves establishing community linkage so that home-based care teams or self-help groups encourage the people who are at high risk of HIV infection to access HIV testing and counselling. Those who test HIV-positive are then linked to early care and treatment at district-level hospitals. Once these people are enrolled in pre-ART care (with the help of peer volunteers at the hospitals), they are referred back to home-based care teams or self-help groups to be supported in their own communities.

Integrating services for HIV and TB

TB remains a leading cause of death among people living with HIV (128). Reducing the number of people dying from AIDS-related causes therefore requires timely case-finding for both HIV and TB, prompt treatment of both diseases and improved efforts to estimate and monitor progress. The 2013 WHO ARV guidelines (50) recommend integrating the delivery of ART into maternal and child health, antenatal care, TB and opioid substitution services.

Efforts to integrate services for people with TB and HIV are underway in many countries. In 2012, 41 of 86 reporting countries indicated that TB clinics provide ART, and 55 of 83 reporting countries indicated that ART clinics provide TB medication. In many cases, different personnel in the same facilities attend to patients, or people with TB are required to attend separate facilities for their HIV care and medicine refills. Effective integration involves overcoming challenges such as these, but the benefits can be huge.

Although the treatment of TB has been decentralized to the community level in most settings, people still have difficulty in accessing HIV treatment in some places with a high burden of HIV infection. Data from the Global tuberculosis report 2012 (55) indicate that TB facilities still tend to outnumber ART facilities, even in countries with a very high burden of both diseases. In addition, services for HIV and TB treatment are still sometimes offered at geographically separated sites.

WHO’s policy guidance on collaborative TB/HIV activities was updated in 2012 (129) and includes initiating ART earlier along with the “three I’s” for HIV and TB (isoniazid preventive treatment, infection control for TB and intensified case finding for TB) as key interventions to prevent TB among people living with HIV. ART is recommended for all people with TB and HIV, irrespective of their CD4 count. These recommendations are supported by systematic reviews that show evidence of increased ART uptake and timeliness of initiating ART when it is delivered in TB treatment settings (130–133). Evidence also indicates decreased mortality at sites that deliver ART in TB treatment settings (131,134,135).
Box 3.15. Decentralizing and integrating antiretroviral therapy services for people with TB in India

India has the greatest TB burden and the second-greatest burdens of HIV and of TB and HIV co-infection globally. Although TB is endemic across India, the HIV epidemic is concentrated mainly in six states (Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland and Tamil Nadu). More than 75% of all HIV-infected TB cases notified in 2012 occurred in those states.

India began TB and HIV collaborative activities in 2003. Its 2007 joint national TB and HIV policy framework has guided the establishment of coordinating mechanisms at various levels. Under the current policy, people with TB who are living with HIV receive ART at the same facility as other individuals living with HIV. In accordance with WHO policy, all people living with HIV who have active TB initiate ART irrespective of their immune status. The number of people with TB who are diagnosed with HIV and initiate ART has increased steadily recently; by the end of 2011, about three quarters of the people with both TB and HIV were receiving ART (Fig. 3.17).

Fig. 3.17. Detection of HIV infection among people with TB and linking them to ART in India, 2009–2011

Despite this progress, the case fatality among people with both HIV infection and TB cases in India is four times higher than that among people with TB who are HIV-negative. Timely ART is the most critical intervention for reducing that rate; currently, the median duration for initiating ART after starting TB treatment is more than 40 days, and about 15% initiate ART late (after eight weeks). Recognizing the importance of initiating ART early, India’s National AIDS Control Programme is now requiring treatment sites to report on the number of people who have initiated ART within two weeks after starting TB treatment. Linking to ART facilities early and promptly initiating ART will be an important focus of the programme in the years ahead.
Integrating services can increase access to antiretroviral therapy for key populations

Lack of integration of services for people who inject drugs is recognized as a challenge in many parts of the world. Qualitative research in the Russian Federation, for example, has identified the need to integrate HIV, TB and drug treatment services to improve access to ART (136). Some countries are making progress on this front. Viet Nam began expanding the provision of methadone maintenance therapy for people who inject drugs in 2008. Four years later, it was providing methadone maintenance therapy to more 12 000 people at 60 sites in 14 provinces. Increasingly, methadone maintenance therapy is being provided at integrated facilities that also deliver HIV testing and counselling and ART services. People who inject drugs are offered on-site voluntary HIV testing and counselling, and those who test HIV-positive are then linked to HIV treatment and care services. The preliminary results show that men receiving methadone maintenance therapy tend to start ART at significantly higher CD4 counts compared with the overall population of men receiving ART.

Box 3.16. Reaching men who have sex with men, sex workers and transgender populations in Peru

Peru has a concentrated HIV epidemic with a national adult HIV prevalence of 0.4% but much higher prevalence among men who have sex with men (10%) and transgender women (29%). These populations experience severe stigma, discrimination and even violence. Many men who have sex with men and transgender women are highly reluctant to access the HIV and sexually and reproductive health services they need for their health. With support from the International AIDS Alliance, the local nongovernmental organization Via Libre runs clinics that provide ART to men who have sex with men and to transgender sex workers as well as screening for and treatment of sexually transmitted infections, family planning counselling and HIV testing. People enrolled in this programme represent 5–6% of the people receiving ART in Peru.

To create an environment that respects the rights of men who have sex with men and of transgender sex workers, the Alliance has developed a model focused on small working groups in various localities. The groups include Ministry of Health service providers and community-based educators, some of who are former sex workers. The groups strive to sensitize communities and reduce homophobia, stigma and discrimination. They also gather high-quality data on access to health and other services for men who have sex with men and transgender women and on rights violations. In 2012, less than 10 of the 1008 people receiving ART were lost to follow-up or transferred to other treatment centres – indicating the strength of this approach.

Support for adherence

A recent review of 26 studies of adherence interventions in sub-Saharan Africa (137) indicates that treatment supporters, diary cards, food rations and mobile-phone text messages are potentially effective ways to improve adherence. Access to communication technology has increased exponentially in low- and middle-income countries, with more than 600 million new mobile phone subscriptions in 2011, totalling 78 subscriptions per 100 inhabitants (138). The potential of mobile phone technology to serve as an adherence support tool is gaining attention, especially after positive trial results from Kenya that showed that adherence to ART improved significantly among people who received text-message reminders (139). Supporting adherence through adherence clubs led by people receiving ART is another approach that is being adopted in countries with a high burden of HIV infection (Box 3.17).
**Box 3.17. Scaling up antiretroviral therapy in Morocco**

In Morocco a considerable number of people needing ART belong to hard-to-reach key populations, including people who inject drugs, sex workers and men who have sex with men. Nevertheless, within less than a decade, the country increased the number of people receiving ART 20-fold, and coverage is one of the highest in the Eastern Mediterranean region.

- In 2012, Morocco conducted 222,000 HIV tests, which led to a 30% increase in the number of people receiving ART. Through public and nongovernmental organization involvement, numerous HIV testing and counselling approaches are used, including fixed-site voluntary counselling and testing, provider-initiated testing across various secondary and tertiary health services, mobile testing services and HIV testing campaigns.

- HIV care and treatment services are decentralized, bringing ART closer to people who are eligible. The country’s 15 ART sites cover most of its regions.

- The costs of ARVs have been lowered due to tax exemptions, price negotiations with pharmaceutical companies, the use of generic products, and improved forecasting, procurement and supply systems.

- Domestic funding for ARV and related commodities has increased.

- A national psychosocial support programme was set up with the involvement of a nongovernmental organization to support ART patients with therapeutic education and various forms of social assistance. A medical assistance scheme that fully subsidizes health care services for people living with HIV is being set up.

- Community-support groups provide adherence support, and treatment retention at 12 months is high, at 90%.

**Supply of antiretroviral medicines**

Stock-outs of ARV medicines are a concern in many low- and middle-income countries. According to a WHO survey (71), the proportion of low- and middle-income countries reporting stock-outs declined from 35% in 2011 (38 of 108 countries) to 30% in 2012 (30 of 98 countries). Several ways of avoiding or overcoming stock-outs have proved successful in recent years. In some countries, people switched temporarily to a different ART regimen (for example, Cameroon, Guatemala and Thailand). In other cases, neighbouring health facilities or regions transferred ARV medicines to enable people to remain on the same ART combinations (for example, in Malawi, Mexico and Nigeria). Other remedial strategies included providing people a three-month supply of ARV medicines (for example, in the Maldives) or purchasing emergency supplies from neighbouring countries (for example, in Benin).

Countries considered to be at high risk of stock-outs may face financial constraints that lead to interrupted supplies of ARV medicines and other health commodities. In 2012, supported by the Clinton Health Access Initiative, UNITAID provided funds for children’s and second-line ARV medicines to 21 countries in 2012. The HIV/AIDS Emergency Commodity Fund of the United States President’s Emergency Plan for AIDS Relief has also helped preventing stock-outs. In 2012, the Fund supported four countries in averting stock-outs of ARV and opportunistic infection medicines by funding the supply of 1.2 million ARV tablets, 97,000 test kits and 2,500 opportunistic infection tablets.

More work is needed to improve drug forecasting, planning several years ahead, ensuring adequate funding and ensuring sufficient buffer stocks at the health facility and central levels.

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1. Benin, Botswana, Burkina Faso, Burundi, Cameroon, China, Côte d’Ivoire, Democratic Republic of the Congo, Haiti, India, Malawi, Mali, Mozambique, Nigeria, Senegal, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.
Box 3.18. Treatment adherence clubs in South Africa

In Khayelitsha township, in South Africa’s Western Cape Province, more than 25 000 people had started ART by early 2012. As the number of people receiving ART increased, the proportion of those lost to follow-up also began to rise, as clinics became overburdened. In response, Médecins Sans Frontières and the provincial health authorities set up out-of-clinic adherence clubs to support treatment adherence. The clubs meet every two months, either at the facility or at a community venue. Participation is voluntary and open to all adults who have been receiving ART for at least 12 months and who are considered clinically stable (CD4 count >200 cells/mm³ and with two consecutive undetectable viral load tests).

Lay health workers support the groups by performing essential tasks such as measuring their weight and conducting basic symptom check-ups. The facilitator prepackages medicines for each participant, brings them to the group and refers anyone with symptoms, ill health or weight loss for further health care attention. A nurse at the facility supports the club and is available after each group session to attend to referred club members. All club members receive annual blood tests and annual clinical consultations. They also get repeat prescriptions of ART.

An evaluation of the pilot project involving the first 20 clubs found that retention in clinic care after 40 months was 97% for club members versus 85% for people who qualified for the clubs but were managed at the clinic without participating in the clubs. Participants in the clubs were 67% less likely to experience viral rebound, which indicates better adherence in clubs than in mainstream care (140).

The adherence clubs began as a local solution to a local problem, but the approach is being scaled up. In early 2011, the Western Cape health department adopted the ART club model for a phased roll out starting in the greater Cape Town area. By December 2012, more than 600 adherence clubs were operating in and around the city.

Box 3.19. Antiretroviral toxicity and the need for surveillance

In 2012, WHO commissioned several reviews of ARV toxicity. For TDF, data on the risk of clinical events such as mortality, renal failure and bone fractures were limited and showed no difference between TDF and comparison drugs. In one clinical trial, less than 1% of the people taking TDF had severe renal disease that could be ascribed to TDF among the nearly 2500 adults taking this drug. The trial also showed a very low rate of chronic kidney disease (<6% five years after initiating ART) (141).

A review of NVP and EFV found that patients on NVP were more than twice as likely as those receiving EFV to discontinue treatment because of adverse events. Among pregnant women, adverse events associated with NVP are no more frequent than observed in the general adult population, and although pregnant women with a high CD4 count may be at increased risk of adverse events, the evidence supporting this association is weak (142).

Finally, a review of the safety of EFV in the first trimester of pregnancy found no evidence of increased risk of birth defects, in line with the findings of previous systematic reviews and technical guidance (143,144).

WHO, the United States President’s Emergency Plan for AIDS Relief, the United States Centers for Disease Control and Prevention and the United States National Institutes of Health are supporting the establishment of ARV pregnancy registries and birth defect surveillance programmes in Malawi, South Africa and Uganda. Other surveillance programmes have been established in Côte d’Ivoire (to monitor TDF use), Kenya (to monitor overall drug toxicities in adults and children living with HIV), Viet Nam (to monitor EFV and TDF toxicity among people who use ARV medicines mainly to prevent HIV infection, such as in serodiscordant couples) and the Lao People’s Democratic Republic (focusing on AZT and NVP). Data from these and other initiatives will help to support improvements in the quality of care and help guide future drug regimen choices.
4 Suppressing viral load

KEY POINTS

Retaining people receiving antiretroviral therapy in care and ensuring good treatment adherence are critical determinants of successful long-term viral load suppression.

- Data from Rwanda showed that 86% of the people receiving ART had viral suppression 18 months after starting treatment. In Senegal, about 80% of the people receiving first-line therapy were achieving viral success after five years on treatment.
- Access to viral load testing remains limited but is increasing rapidly in some countries. For example, Kenya has increased its viral load testing capacity 40-fold, from fewer than 10 000 tests in 2011 to a projected 400 000 tests in 2013.

Viral load testing

In 2010, WHO recommended that countries begin to phase in viral load testing as the preferred approach to treatment monitoring. Few countries with a high burden of HIV infection have the capacity to offer viral load testing routinely to everyone receiving ART, although the ability to test viral load is becoming increasingly available. The 2012 WHO diagnostics survey (71), carried out in 83 low- and middle-income countries, found that about 576 viral load platforms (for either viral load or early infant diagnosis or both) were available in country at the end of 2011. Various approaches have been taken to increase access, including viral load pooling, using dried blood spots and reducing the frequency of testing (Box 3.20) (150). Access to viral load testing is expected to improve significantly in the next few years as point-of-care viral load technologies become available; several such tests are in the final stages of development and are expected to become available in 2013 (151).

Viral suppression among adolescents

Data from both high-income (152) and low- and middle-income settings (153,154) suggest that ART outcomes for adolescents tend to be worse than for adults. Disclosure of HIV status appears to be one key factor affecting ART outcomes for adolescents, according to recent data from western Africa (155). Other factors include the ease with which the transition from child to adult services is managed and access to appropriate adherence counselling and support.
Box 3.20. Increasing access to viral load testing in Kenya, Malawi and the United Republic of Tanzania

Kenya’s national ART guidelines have recommended the use of targeted viral load testing for monitoring treatment failure since 2005. However, funding and sample stability concerns have limited the expansion of viral load testing nationwide. To address these issues, the Ministry of Health convened partners and stakeholders to adopt best practices from the early infant diagnosis programme and to leverage existing national systems. The changes included standardizing viral load testing platforms, introducing national pricing for test reagents and using dried blood spots as the primary sample type which allowed viral load testing to be carried out in remote areas. By standardizing testing platforms, Kenya consolidated test volumes and funding and negotiated favourable reagent pricing. Consequently, Kenya is increasing its viral load testing capacity 40-fold, from fewer than 10,000 tests in 2011 to a projected 400,000 tests in 2013.

Malawi’s Ministry of Health established a national programme for viral load testing in 2011, which it has funded with the support of the Global Fund and the United States President’s Emergency Plan for AIDS Relief. The Ministry also coordinates the provision of technical assistance from partners. This coordinated effort has leveraged existing molecular laboratory testing capacity from the early infant diagnosis programme, enabling the Ministry to perform 100,000 viral load tests per year. Viral load testing volume is expected to grow from less than 1,000 tests in 2012 to a projected 10,000 tests in 2013.

The United Republic of Tanzania has been providing early infant diagnosis services for several years. Four high-throughput automated instruments were deployed in public facilities, with a combined output of close to 160,000 tests per year. However, the early infant diagnosis programme was using only 25% of that capacity. This prompted the Ministry of Health and Social Welfare to roll out viral load testing by using the excess early infant diagnosis capacity. This has led to some equipment being upgraded for both early infant diagnosis services and viral load testing platforms, or relocated, making a total of six viral load testing sites, to improve access and ease the transport of samples. The move enabled the United Republic of Tanzania to perform many more viral load tests than would have been possible if the dedicated budget had been used solely for early infant diagnosis services.

Second-line treatment

The proportions of people receiving first- and second-line regimens vary substantially between regions, according to the latest WHO survey data (77). The variation can be explained by differences in the maturity of the ART cohorts, the availability of viral load testing to diagnose treatment failure and the availability of second-line ART.

In low- and middle-income countries in Latin America and the Caribbean in 2011, 77% of adults on ART were receiving first-line regimens and 21% second-line regimens. In the other regions overall, however, 96% of the adults were receiving first-line drugs and 4% second-line regimens. Notably, in the WHO African Region viral load testing capacity for detecting treatment failure early is not commonly in place, leading to delays in the diagnosis of treatment failure.

Market segmentation remains an important factor affecting the availability of second-line ARVs. While LPV/r remains the predominant protease inhibitor (and is used globally by 86% of those receiving a second-line regimen), 12% of people receiving second-line ART used regimens that are not recommended by WHO, including regimens containing non–protease inhibitors (77). Cost is another limiting factor, as second-line regimens tend to be more widely patented than first-line regimens, and standard second-line regimens tend to cost considerably more than first-line regimens in low- and middle-income countries, and third-line treatment is even more expensive (see Chapter 4).

Drug resistance

WHO and partners have been monitoring the emergence of HIV drug resistance since 2004 using standardized protocols to support the identification of optimal first- and second-line treatment regimen choices and to select the most effective approaches for PMTCT and for pre- and post-exposure prophylaxis. The 2012 WHO HIV drug resistance report (156) recently published the data collected between 2004 and 2010.

Data from 82 surveys found evidence of increasing levels of transmitted drug resistance to NNRTIs,
particularly in the areas surveyed in the WHO African Region, where the prevalence of resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTI) reached 3.4% (range of country values 1.8–5.2%) in 2009. Greater coverage of ART was associated with a higher prevalence of resistance to NNRTIs (Fig. 3.18), although this association remained modest in most of the areas surveyed.

**Fig. 3.18. Relationship between transmitted resistance to non-nucleoside reverse-transcriptase inhibitor drugs and coverage of antiretroviral therapy**

Further data from 36 WHO surveys of acquired HIV drug resistance in low- and middle-income countries show that the prevalence of resistance to any drug among people starting ART increased from 4.8% [range of country values 3.8–6.0%] in 2007 to 6.8% [range of country values 4.8–9.0%] in 2010 (156). Among people failing first-line therapy after 12 months in 40 WHO surveys, almost 30% failed with no resistance detected and potentially could have been switched unnecessarily to costlier second-line regimens. Among those with detected HIV drug resistance, the resistance patterns observed suggest that, if they were switched to second-line regimens soon after viral suppression fails, standard second-line therapies consisting of two nucleoside analogues and a boosted protease inhibitor would still be effective in achieving viral load suppression in most cases.

Monitoring HIV drug resistance early warning indicators is an important component of global and national strategies to minimize the emergence of preventable HIV drug resistance. Such clinic-level indicators can identify weaknesses in ART programmes, which may result in suboptimal treatment or treatment interruption, and potentially can lead to the emergence of HIV drug resistance. Monitoring of early warning indicators in 50 countries has highlighted the existence of important gaps in service delivery and programme performance, especially in procurement and supply systems, adherence and clinical retention.

As ART continues to be scaled up, the rates of drug resistance may increase, and robust systems for monitoring early warning indicators and surveillance of HIV drug resistance, integrated into national monitoring and evaluation frameworks, must be in place to detect these patterns in a timely manner. National programmes are encouraged to perform routine surveillance of HIV drug resistance to enhance programme planning and management and to inform ART policies.

WHO, through its partner network of collaborating institutions, is committed to monitoring HIV drug resistance globally and to advocate for expanded routine surveillance, using standardized methods and increased mobilization of national and international funds to support HIV drug resistance surveillance.
4. LOOKING FORWARD: EARLIER ANTIRETROVIRAL TREATMENT TOWARDS CONTROLLING THE EPIDEMIC

KEY POINTS

Implementing the 2013 WHO guidelines on the use of antiretroviral medicines for HIV treatment and prevention can prevent considerably more people from dying from AIDS-related causes and acquiring HIV infection

- Fully implementing the 2013 WHO ARV guidelines could reduce the number of people dying annually from AIDS-related causes from 1.7 million in 2011 to about 800,000 in 2025, compared to an anticipated reduction to 1.3 million if the 2010 treatment guidelines were fully implemented.
- Between 2013 and 2025, the total number of AIDS-related deaths averted could increase from 9 to 12 million if the 2013 WHO ARV guidelines are fully implemented.
- Fully implementing the 2013 ARV guidelines could reduce the annual number of people newly acquiring HIV infection in low- and middle-income countries from 2.4 million in 2011 to 800,000 in 2025, compared to an anticipated decrease to 1.25 million if the 2010 treatment guidelines were fully implemented.
- Between 2013 and 2025, the total number of HIV infections averted could increase from 15.5 to 19 million if the 2013 ARV guidelines are fully implemented.
- Achieving this additional impact would require increasing the total annual investment in the HIV response in low- and middle-income countries over the coming years by approximately 10% above the US$ 22-24 billion target included in the Political Declaration on HIV and AIDS in 2011. This additional investment can be deemed “very cost effective” according to global criteria.

Current trends in the global scaling up of ART give great cause for optimism. HIV testing and ART delivery for treatment and for PMTCT are increasing in most countries and regions with a high burden of HIV infection. The global target of reaching 15 million people with ART by 2015 appears to be attainable.

Significant improvement is still needed, however, in some regions and countries and for some key populations that are at high risk of HIV infection. As the analysis of the treatment cascade in the previous chapter shows, certain critical steps in the care pathway need to be reinforced to ensure that the maximum number of people benefit from timely HIV treatment and care interventions.

Nevertheless, the past decade has shown that enormous progress can be achieved with sufficient political commitment, funding, technical innovation and community mobilization. Clinical and implementation science continues to devise new tools and methods to support the further scaling up of testing and treatment.

These achievements and the powerful evidence of the life-saving and preventive effects of ART...
have informed the 2013 WHO ARV guidelines (1). If implemented, these guidelines are expected to have a major positive impact on the HIV epidemic in the coming years.

Projected impact of the 2013 WHO antiretroviral guidelines on AIDS-related mortality

It is estimated that expanding ART access to more then 80% of people eligible for treatment under the 2010 WHO treatment guidelines could avert 9 million deaths between 2013 and 2025. Initiating ART earlier, as recommended in the 2013 WHO ARV guidelines (1), could increase the number of averted deaths between 2013 and 2025 to more than 12 million, thus preventing an additional 3 million people from dying (Fig. 4.1).

If the 2013 WHO ARV guidelines are implemented, the annual number of people dying from AIDS-related causes in low- and middle-income countries could fall from 1.7 million in 2011 to 800 000 in 2025, compared with a projected 1.3 million if the 2010 eligibility criteria continued to be applied.

Impact of the 2013 WHO antiretroviral guidelines on HIV incidence

Full implementation of the 2010 treatment guidelines could help avert 15.5 million HIV infections between 2013 and 2025, compared with maintaining current ART coverage levels. Full implementation of the 2013 WHO ARV guidelines could help avert 19 million HIV infections between 2013 and 2025 (Fig. 4.2).

The annual number of people acquiring HIV infection could decline from 2.4 million in 2011 to close to 800 000 globally by 2025, compared with a projected 1.25 million per year if the 2010 eligibility criteria continued to be applied.

Further reductions in the number of people acquiring HIV infection depend on the scale and effectiveness of the existing array of prevention interventions, the use of new interventions such as pre-exposure prophylaxis of HIV and the potential development of effective microbicides and/or an HIV vaccine.

Fig. 4.1. Projected annual number of people dying from AIDS-related causes in low- and middle-income countries based on the 2010 WHO treatment guidelines and the 2013 WHO ARV guidelines and cumulative deaths averted by switching from 2010 to 2013 guidelines, 2011–2025

Achieving 80% coverage under the WHO 2010 treatment guidelines implies initiating ART at CD4 ≤350 cells/mm$^3$ or clinical stages III or IV; achieving 80% coverage under the WHO 2013 ARV guidelines implies initiating ART at CD4 ≤500 cells/mm$^3$, and for serodiscordant couples, pregnant women living with HIV and children living with HIV younger than five years, initiating ART irrespective of CD4 count.

Source: special analysis conducted by Futures Institute, 2013.
**Box 4.1. Impact of the new antiretroviral therapy guidelines on Zambia's epidemic**

Zambia is currently assessing the impact of implementing new policies on initiating ART. Preliminary analysis suggests that shifting towards initiating ART at CD4 $\leq 500$ cells/mm$^3$ in Zambia would lead to a small (5%) increase in the number of people eligible for ART – from about 733,000 in 2013 to 763,000 in 2015, with the number then levelling off until 2020. Implementing the 2013 WHO ARV guidelines would yield rapid gains, according to modelling studies.

Adopting the new eligibility criteria would reduce the projected prevalence of HIV infection among adults from 12.4% in 2013 to 11.8% in 2015 and to 10% in 2020. That decrease implies significantly fewer people acquiring HIV infection. Projections indicate that the total annual number of people acquiring HIV infection would drop from 59,600 in 2013 to 45,000 in 2015. The number of children (0–14 years old) acquiring HIV infection would decrease from 11,500 in 2013 to 3,130 in 2015 (Fig. 4.3). In contrast, maintaining the current policy of initiating treatment at CD4 $\leq 350$ cells/mm$^3$ would reduce the total number of people acquiring HIV infection from a projected 73,700 in 2013 to 61,900 in 2015.

Overall, estimates indicate that implementing the new eligibility threshold would slightly reduce the number of adults dying from AIDS-related causes: from 24,400 in 2013 to 22,400 by 2015. However, the number of children (0–14 years old) dying from AIDS-related causes would almost halve from 7,230 deaths in 2013 to 4,260 deaths in 2015.
Costs and cost-effectiveness

Estimates from 2011 indicated that an effective global HIV response (including providing treatment based on the 2010 WHO treatment guidelines (2) would cost US$ 22 billion to US$ 24 billion annually in 2015 (3).

Countries’ abilities to fund their ART programmes vary enormously and depend on the size of their overall budgets, the proportions of those budgets that are allocated to the health sector in general and to HIV programmes in particular, the structure of countries’ health systems and the extent of external aid and other forms of assistance that are available. Low- and middle-income countries have increased their own investment in HIV responses in recent years – by an estimated 15% between 2010 and 2011 alone (4). Nevertheless, many low-income countries will only be able to increase their domestic contributions to a limited extent, and many countries will continue to require additional external support. Countries and their external partners have a joint responsibility to fill the treatment investment gap together, by investing their respective fair shares.

Fully implementing the 2013 WHO ARV guidelines (1) would expand the pool of people eligible for ART globally to a potential 25.9 million people, compared with close to 16.7 million under the 2010 guidelines. Progressively scaling up of ART to achieve high coverage for this larger group of eligible people will require increased funding but will also generate substantially greater returns.

**Fig. 4.3.** Projected numbers of adults and children acquiring HIV infection and dying from AIDS-related causes in 2013 and 2015 in Zambia based on the 2013 WHO ARV guidelines
Assuming that ART coverage increases gradually to about 80% of the total number of people eligible for treatment, total annual investment in the HIV response in low- and middle-income countries would increase by approximately 10% above the target of US$ 22-24 billion included in the Political Declaration on HIV and AIDS by the United Nations General Assembly in 2011 (5). This increase is based on the assumption that the basic approach in the HIV response and costs for delivering services would not change significantly over the next few years. This assumption may be affected by various factors that could offset the additional investments for treatment, such as efficiency savings in some aspects of the response. Over time, these additional resource needs are projected to level off and then decline, reflecting the accumulated prevention benefits of expanding ART provision. Greater access to ART will reduce the number of people acquiring HIV infection and thereby eventually reduce the number of people eligible for ART.

The modelling estimates are based on constant costs for HIV treatment. However, future unit costs may decrease. For example, further efficiency gains can be achieved if facilities serve more people, visits and check-ups become less frequent and task shifting and the decentralization of ART activities to community-based services expand. These adjustments would save costs and provide simpler, improved and more accessible services. In addition, improving access to durable and affordable point-of-care diagnostics, along with less expensive and quicker laboratory tests, might save costs in both diagnosis and monitoring. There are also potential cost savings on commodities, including medicines (Box 4.2), as intellectual property hindrances are removed or overcome, as economies of scale increase and as treatment optimization reduces the doses of active pharmaceutical ingredients used in ARV medicines.

Efficiencies in the HIV response may also be achieved by more closely focusing all relevant HIV services. With significant decreases in new infections following the strategic scale-up of basic programme components, the pool of people living with HIV will start to shrink over the coming decade and the majority of those living with HIV will be receiving effective ART. These factors may well offset additional treatment investments, including those based on the new guidelines and eligibility criteria.

Recent experiences confirm the potential for further gains. Exploiting existing opportunities for cost efficiency has more than halved the average cost per person receiving ART in programmes supported by the United States President’s Emergency Plan for AIDS Relief, from more than US$ 1000 to less than US$ 400 per year between 2004 and 2011 (Fig. 4.4). Whether such drastic efficiency savings can be achieved in programmes at their current levels of maturity is uncertain.

However, significant cost drivers must also be acknowledged. Reaching rural and marginalized populations who currently do not access ART may be more difficult and expensive. Testing and retesting services will have to be greatly expanded, additional investment in strengthening health infrastructure might be needed, and the ratio of first- to second- and third-line treatment might shift towards more costly regimens. Instead of commodity prices falling, prices might increase because of patent restrictions and if there is a weakening in the generic competition that has helped to drive down the prices of first-generation ARV medicines.

In all scenarios, the substantial return in people averting HIV infection and life-years saved will justify investment in expanding ART. Compared with maintaining current levels of ART provision, each additional quality-adjusted life-year (QALY) gained globally by implementing the 2013 WHO ARV guidelines would cost approximately US$ 630, and each additional person avoiding acquiring infection would cost less than US$ 6000 – assuming that the unit costs remain stable. Since the cost per QALY gained is substantially lower than the annual per capita gross domestic product in all regions, providing ART in accordance with the 2013 ARV guidelines (1) is regarded as being very cost-effective (7). Similarly, recent comparative modelling of the cost-efficiency of shifting from Option A for preventing mother-to-child transmission (ART only for pregnant women with CD4 counts \(\leq 350\) cells/mm\(^3\)) to Option B (ART for all pregnant women regardless of CD4 count) and Option B+ (continuing ART for life after delivery) in Kenya, South Africa, Viet Nam and Zambia indicated that Option B+ is the most cost-efficient scenario in all four countries (8).
The implications of applying the 2013 WHO ARV guidelines (1) will vary between countries (Boxes 4.2 and 4.3). Countries will have to adopt a strategic approach in scaling up their ART programmes by combining increased HIV testing of appropriate populations, broadened treatment eligibility criteria and stronger systems for linking people diagnosed with HIV infection into care.

Countries’ strategic choices will depend largely on country-specific costs and their capacity for diagnosing more people living with HIV, enrolling these individuals in ART programmes and providing eligible individuals with life-long ART (see Chapter 3). These factors can significantly influence the overall cost-effectiveness of an ART programme (11). However, the return in investment for specific approaches will always remain one among the many factors that are appraised in building a national consensus for expanding HIV treatment.

The demonstrated benefits of ART in terms of preventing people from dying and from acquiring HIV infection exceed many of the expectations that helped launch the global scale-up of ART a decade ago. Current evidence also confirms the enormous potential for further progress. The 2013 WHO ARV guidelines (1) reflect this evidence and aim to extend the multiple benefits of initiating ART earlier for both prevention and treatment and boosting the overall impact of ART in all regions. The past decade has shown that combining firm political commitment, adequate funding and resourcing, strong community mobilization, and technical and logistical innovation can save millions of lives. The new ARV guidelines hold the potential for expanding these achievements much further.
Box 4.2. Antiretroviral drug prices in low- and middle-income countries

Declining prices for ARV medicines in recent years have made expanding treatment programmes more affordable. Prices have declined despite the wider adoption of more expensive TDF-based regimens, which can be attributed to the continued scaling up of treatment programmes (leading to larger transaction volumes), greater predictability of demand and increased competition among manufacturers. Prices can be reduced further. For example, the cost of the fixed-dose combination of the WHO-recommended first-line regimen of TDF + FTC + EFV was US$ 186 per person per year in 2012, whereas a two-pill regimen using the same drugs costs only US$ 112 (Fig. 4.5).

Fig. 4.5. Median prices per person per year in US dollars for first- and second-line antiretroviral therapy regimens in low-, lower-middle- and upper-middle-income countries, 2008–2012

Source: Global Price Reporting Mechanism of the AIDS Medicines and Diagnostics Service. The median prices might obscure price outliers; the Global Price Reporting Mechanism has limited coverage.
However, the costs can be much higher in middle-income countries: Brazil and the Russian Federation, for example, pay more than US$ 1000 per person per year for the WHO-recommended first-line TDF + [3TC or FTC] + EFV.

The prices of second-line regimens also declined substantially between 2010 and 2012, but the median prices remained higher than for first-line regimens. In 2012, the median reported cost of the most commonly used second-line regimen (3TC + AZT + LPV/r) was US$ 453 per person per year in low-income countries, US$ 451 per person per year in lower-middle-income countries and US$ 442 in upper-middle-income countries. These prices vary widely from country to country, however (9). Several factors have contributed to the price trend for second-line regimens since the mid-2000s. They include decreases in the prices of abacavir, LPV/r and TDF and the prequalification of generic versions of LPV/r. Greater economies of scale, new pricing policies by research-based pharmaceutical companies and efforts to expand the market for second-line regimens also contributed. Although these developments are encouraging, addressing the relatively higher cost of second-line regimens is an important priority.

Options beyond second-line treatment remain extremely costly. There are no WHO-prequalified generic versions of raltegravir, etravirine or darunavir, and prices remain extremely high. The lowest possible price for a third-line regimen containing raltegravir, etravirine or boosted darunavir is around US$ 2000 in low-income countries, almost 18 times more than the lowest price for first-line regimens. Some middle-income countries are paying much higher prices. In 2012, Georgia paid US$ 13 225 per person per year for raltegravir, Paraguay paid US$ 7782 per person per year for etravirine, while Armenia paid US$ 8468 and Thailand paid US$ 4760 per person per year for darunavir (10).
ANNEX: METHODS OF DATA COLLECTION AND VALIDATION

Methods of data collection and validation

Most of the health sector response data presented in this report were collected by WHO, UNICEF and UNAIDS through the joint Global AIDS Response Progress Reporting and Health Sector Reporting processes (1), unless stated otherwise. Country data were submitted based on guidance to national AIDS programmes and partners on the use of core indicators for measuring and reporting on national HIV responses. Countries submitted data between March and April 2013, using the joint online reporting system. A data validation process followed the country submission.

The country offices of WHO, UNICEF and UNAIDS worked jointly with national counterparts and partner agencies to validate data in a single collaborative consultation process. When discrepancies or inconsistencies were identified in the reported data, national authorities were asked to clarify or resolve them.

Number of people 15 years and older who received HIV testing and counselling and know the results

The number of adults who received HIV testing and counselling in the past 12 months and know the results in a given country is collected from routine reports from all service points, including voluntary counselling and testing sites, clinics, hospitals and nongovernmental organization outreach points. The data are compiled at the district or local level and then finally at the national level. A total of 97 low- and middle-income countries reported data for 2012 while data from 27 countries were imputed from the latest available year in the period 2009 to 2011. If countries did not have a system to remove double-counting, these data are not corrected for the fraction of people who have been tested more than once in the year.

Regional data are presented on the availability of HIV testing and counselling services at the national level for adults in 75 low- and middle-income countries for 2011 and 2012.

Number of people receiving and eligible for antiretroviral therapy

For December 2012, 107 of the 144 low- and middle-income countries had provided data on access to ART. These 107 countries accounted for 94% of the people receiving treatment at the end of 2012. An additional three countries (Botswana, Islamic Republic of Iran and Thailand) submitted data for cut-off points between September and November 2012. Together, these 110 countries represent more than 98% of the total estimated number of people receiving ART at the end of 2012 in low- and middle-income countries. Fourteen countries submitted data for cut-off points between January and March 2012. Only 20 countries, all with relatively small HIV epidemics, did not report these data for 2012.

Estimating the number of people receiving ART involves some uncertainty for countries that have not yet established regular reporting systems for capturing accurate data on people who initiate treatment for the first time, people who discontinue treatment, and people who are lost to follow-up which may include people who have self-transferred (i.e. still in care), died or have been truly lost to follow up.

Uncertainty may also arise because of difficulties in measuring the extent of ART provided in the for-profit and not-for-profit private sectors. Some people receive treatment through nongovernmental organizations and/or private clinics that do not report through official channels in some countries. Private companies may have programmes to support the provision of ART to workers with advanced HIV disease, but do not necessarily report those data to the public health
Estimating treatment eligibility and coverage
Standard methods were used for estimating the size and course of the HIV epidemic, number of people living with HIV, number of people newly infected, mortality attributable to AIDS and eligibility for treatment (2,3). Eligibility for treatment is estimated using statistical modelling methods that include all people who meet the criteria for initiating ART, whether or not these people know their HIV status and their eligibility for ART. At the time this report was prepared, the eligibility for 2012 had been estimated for 22 priority countries only.1 Estimates of ART coverage were calculated by dividing the number of people receiving ART at the end of 2012 by the estimated number of people who were eligible for treatment in 2012. The ranges around the levels of coverage are based on the uncertainty ranges around the estimates of eligibility (4). Some countries have developed their own methods for estimating treatment eligibility, which could differ from the estimates derived using WHO/UNICEF/UNAIDS methods and tools. The report uses standardized estimates of treatment eligibility calculated using WHO/UNAIDS methods.

Chapter 1 provides data on access to ART disaggregated by sex and by age (adults – 15 years and older; children – younger than 15 years) for low- and middle-income countries. Disaggregated data on the number of children and adults receiving ART are available for 139 low- and middle-income countries of which 124 countries reported breakdowns for 2012. Data disaggregated by sex that were used in this report were available for 109 countries by end of 2011.

The 2010 WHO treatment guidelines (3) recommend that all children younger than 24 months living with HIV be provided with ART regardless of CD4 counts.

The estimates of ART coverage for children in the 22 priority countries were calculated by dividing the number of children receiving ART at the end of 2012 by the estimated number of children who were eligible for treatment in 2012 (based on WHO/UNAIDS methods). The ranges around the levels of coverage are based on the uncertainty ranges around the estimates of eligibility (4).

As changes in recommendations for ART eligibility came into effect in 2009, (8) i.e. initiation of ART for adults living with HIV at or below CD4 350 cells/mm3 instead of CD4 200 cells/mm3, all ART line-charts in this report depicting trends in ART eligibility for adults and children (combined) will show increases as of 2009.

Similarly, changes in age-specific eligibility criteria for children living with HIV – from younger than 12 months of age to younger than 24 months of age -- took effect in 2010 in accordance with the revised WHO treatment guidelines for infants and children (2010). Hence, all ART line-charts in this report depicting trends in ART eligibility for children will show increases as of 2010.

Prevention of mother-to-child transmission

Number of pregnant women living with HIV receiving antiretroviral medicine for preventing mother-to-child transmission
The number of pregnant women living with HIV and who are receiving antiretroviral (ARV) medicine for preventing mother-to-child transmission (PMTCT) is based on national programme data that are aggregated from facilities or other service delivery sites, as reported by countries.

A total of 129 countries reported these data for 2012; together, they account for nearly all of the estimated pregnant women living with HIV in low- and middle-income countries. This report focuses on the 21 African priority countries of the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (5). Among these countries, 19 submitted disaggregated data indicating whether ARV regimens were provided as prophylaxis or as lifelong treatment in 2012.

The estimated coverage of ARV medicine for PMTCT includes only the most effective regimens (ART and combination regimens) and excludes single-dose nevirapine, which WHO no longer recommends.

Estimating the number of pregnant women living with HIV who are eligible for antiretroviral medicine for preventing mother-to-child transmission
The number of pregnant women living with HIV who are eligible for ARV medicine for PMTCT is estimated using standardized statistical modelling. This is based on UNAIDS/WHO methods that consider various epidemic and demographic parameters, such as the

1. The 22 priority countries are Angola, Botswana, Burundi, Cameroon, Chad, Côte d’Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.
HIV prevalence among women of reproductive age and the effect of HIV on fertility (2). Regular scientific updates have been provided on these tools (6).

Coverage of pregnant women living with HIV receiving antiretroviral medicine for preventing mother-to-child transmission
The coverage of ARV medicine for PMTCT is calculated for the 22 priority countries by dividing the number of pregnant women living with HIV who received ARV medicine for PMTCT in 2012 by the estimated number of pregnant women living with HIV needing ARV medicine for PMTCT in a given country (PMTCT need).

The ranges around the levels of coverage are based on the uncertainty ranges around the estimates of PMTCT need.

Classification of countries

Classification by income
Unless stated otherwise, all data analysis in this report is based on data from the 144 countries the World Bank classifies as low- and middle-income countries as of July 2012 (7). The economies are classified as low, middle or high income according to the gross national income per capita, calculated using the World Bank Atlas method (to reduce the effect of exchange-rate fluctuation). The groups are:

- low-income, US$ 1025 or less;
- lower-middle-income, US$ 1026 to US$ 4035, and upper-middle-income, US$ 4036 to US$ 12 475; and
- high-income, US$ 12 476 or more.

Classification by HIV epidemic level
HIV epidemics are categorized as low-level, concentrated and generalized based on the following principles.

Low-level epidemic
Although HIV infection may have existed for many years, it has never spread to significant levels in any subpopulation. Recorded infection is largely confined to individuals with high-risk behaviour, such as sex workers, people who inject drugs and men who have sex with men. This epidemic state suggests that networks of risk are rather diffuse (with low levels of partner exchange or sharing of drug-injecting equipment) or that the virus has been introduced very recently.

Concentrated epidemic
In concentrated epidemics, HIV has spread rapidly in a defined subpopulation but is not well established in the general population. This epidemic state suggests active networks of risk within the subpopulation. The frequency and nature of links between highly infected subpopulations and the general population determines the future course of the epidemic.

Generalized epidemic
In generalized epidemics, HIV is firmly established in the general population. Although populations at higher risk may continue to contribute disproportionately to the transmission of HIV, sexual networking in the general population is sufficient to sustain an epidemic independent of populations at higher risk of infection and transmission.

Classification of Member States by WHO region
This report presents data on low- and middle-income countries classified by WHO region. WHO has 194 Member States grouped in six regions, and 144 of these are low-and middle-income countries: WHO African Region (n = 45); WHO Region of the Americas (n = 29); WHO Eastern Mediterranean Region (n = 16); WHO European Region (n = 22); WHO South-East Asia Region (n = 11); and WHO Western Pacific Region (n = 21). There are 50 high-income countries.

Explanatory notes on the analysis performed by Futures Institute
The special analysis conducted by Futures Institute to model the implications of switching from the 2010 WHO treatment guidelines (8) to the 2013 WHO ARV guidelines (9) is based on applying the Goals model (10), which is part of the Spectrum software package, to model the potential impact of various interventions in 24 countries that together account for 85% of the people newly infected with HIV in low- and middle-income countries.

The model estimates the annual number of adults newly infected with HIV by sex and risk group (sex workers and clients, men who have sex with men, people who inject drugs, heterosexual couples in stable relationships and men and women with casual partners), as a function of behaviour (number of sexual partners, acts per partner, condom use, age at first sex, rates of behaviour change and needle-sharing) and according to the characteristics of partners (stage of infection, presence of other
sexually transmitted infections, male circumcision and use of ART).

The population living with HIV is tracked by CD4 count, and mortality is determined by CD4 count category and ART status. The number of children newly infected with HIV by mother-to-child transmission is estimated, and the children are tracked as they progress to eligibility for treatment and death. The parameter values for progression and mortality rates have been published previously (6,11). The data inputs for each country were drawn from national surveys (Demographic and Health Surveys and AIDS Indicator Surveys) and national progress reports (available on the UNAIDS web site) and were adjusted to match the prevalence trends from national estimates as reported to UNAIDS (12). The results were adjusted for countries that were not explicitly modelled to represent the totals for all low- and middle-income countries.

Futures Institute used the model to estimate eligibility for ART and the cost and impact of providing ART between 2013 and 2025 under the 2010 WHO treatment guidelines (8) and the 2013 WHO ARV guidelines (9). The work builds on previous modelling on costs and the impact of the overall HIV response, which was published as the Investment Framework for HIV in 2011 (13). For both the 2010 and 2013 WHO guideline scenarios, the same pattern for scaling up and costing for a basic package of prevention and structural interventions was assumed. These included scaling up to universal access for all “basic programmes” (PMTCT, voluntary male medical circumcision, outreach to most-at-risk populations, condom promotion and behaviour change) as well as a package of “critical enablers” (including counselling and testing, community mobilization and mass media).

The differences between the two scenarios were limited to assumptions about the scaling up of ART. The 2010 guidelines scenario assumed reaching at least 80% coverage of ART for adults (that is, CD count <350 cells/mm$^3$), 100% coverage of ART for children and 90% coverage for PMTCT in 2015, with the coverage subsequently maintained over time. For the 2013 guidelines scenario, it was assumed that treatment coverage would be 80% for adults (CD4 count <500 cells/mm$^3$ plus all serodiscordant couples, all people living with HIV who have active TB and all people with HIV and hepatitis B virus with active liver disease) and 100% coverage for children in 2020. Table 1 provides details.

For the impact analysis, it was assumed that ART reduces the rate of transmission from virally suppressed people living with HIV by 80% for all levels of CD4 counts and in all scenarios if ART is provided through high-quality programmes.

Futures Institute used a cost per person per year of treatment of US$ 515 based on a weighted average median price in 2011 of US$ 145 for first- and second-line ARV medicines (14), US$ 222 for average costs of service delivery and monitoring (15) plus an additional 40% for costs above the facility level for administration, logistics, training, planning etc. Sensitivity analysis was performed for a 20% cost increase or decrease by 2025.

### Table 1. Assumptions about antiretroviral coverage

<table>
<thead>
<tr>
<th>Population</th>
<th>2010 WHO guidelines</th>
<th>2013 WHO guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2015</td>
<td>2020</td>
</tr>
<tr>
<td>People living with HIV by CD4 count (cells/mm$^3$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>200–250</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>250–350</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>350–500</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;500</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Total adults</td>
<td>50%</td>
<td>65%</td>
</tr>
<tr>
<td>Total children in need</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Special populations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women living with HIV</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Serodiscordant couples</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>People with HIV and TB</td>
<td>0%</td>
<td>80%</td>
</tr>
<tr>
<td>People with HIV and HBV</td>
<td>0%</td>
<td>80%</td>
</tr>
</tbody>
</table>
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CHAPTER 2 REFERENCES


CHAPTER 3 REFERENCES


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REFERENCES FOR EXPLANATORY NOTES


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A progress report on the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive

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Director,
Global Plan Secretariat
www.zero-hiv.org

Mid term Review meeting
Nairobi 6-7th December 2012
The Creation of the Global Plan

- Global Plan launched at UN High Level Meeting on AIDS in July 2011 as part of Political Declaration on AIDS
- Global Task Team co-chaired by Michel Sidibé and Ambassador Eric Goosby
- Membership of 40 countries, 30 civil society and private sector organizations, and 15 international and regional bodies/organizations
There are 22 priority countries for the Global Plan

1. Angola
2. Botswana
3. Burundi
4. Cameroon
5. Chad
6. Côte d’Ivoire
7. DR Congo
8. Ethiopia
9. Ghana
10. India
11. Kenya
12. Lesotho
13. Malawi
14. Mozambique
15. Namibia
16. Nigeria
17. South Africa
18. Swaziland
19. Tanzania
20. Uganda
21. Zambia
22. Zimbabwe

These countries accounted for 89% of all HIV-positive pregnant women in low- and middle-income countries in 2011.
The gap in treatment and prophylaxis coverage is uneven among low- and middle-income countries.

The share of each low- and middle-income country in the total shortfall in providing antiretroviral medication to HIV-positive pregnant women to prevent new HIV infections among children.

Source: UNAIDS 2012
2- Specific targets for 2015

Reduce the number of new HIV infections among children by 90% from a baseline of 2009.
A four-pronged approach is required to prevent new HIV infections among children and keep mothers alive

1. Prevent HIV among women of reproductive age
2. Prevent unintended pregnancies among women living with HIV
3. Prevent HIV transmission through antiretroviral treatment during pregnancy and breastfeeding
4. Treatment, care and support for mothers living with HIV, their children, partners and families

DO IT
Number of new child infections, 21 priority countries

Source: UNAIDS Estimates 2012
## New HIV infections among children, 2009–2011

<table>
<thead>
<tr>
<th>Rapid decline</th>
<th>Moderate decline</th>
<th>Slow or no decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will reach the target if the 2009–2011 decline of more than 30% continues through 2015.</td>
<td>Can reach the target if the decline in 2009–2011 of 20–30% is accelerated.</td>
<td>In danger of not reaching the target, with a decline in 2009–2011 of less than 20%.</td>
</tr>
<tr>
<td>31% Ethiopia</td>
<td>22% Botswana</td>
<td>0% Angola</td>
</tr>
<tr>
<td>31% Ghana</td>
<td>30% Burundi</td>
<td>4% Chad</td>
</tr>
<tr>
<td>43% Kenya</td>
<td>24% Cameroon</td>
<td>– Democratic Republic of the Congo</td>
</tr>
<tr>
<td>60% Namibia</td>
<td>20% Côte d’Ivoire</td>
<td>5% Mozambique</td>
</tr>
<tr>
<td>49% South Africa</td>
<td>21% Lesotho</td>
<td>2% Nigeria</td>
</tr>
<tr>
<td>39% Swaziland</td>
<td>26% Malawi</td>
<td>19% United Republic of Tanzania</td>
</tr>
<tr>
<td>55% Zambia</td>
<td>24% Uganda</td>
<td>– India</td>
</tr>
<tr>
<td>45% Zimbabwe</td>
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<td></td>
</tr>
</tbody>
</table>

**Note:** The baseline year for the Global Plan is 2009. Some countries had already made important progress in reducing the number of new HIV infections among children in the years before 2009, notably Botswana which by 2009 already had 92% coverage of antiretroviral regimens among pregnant women and a transmission rate of 5% (see table pp122–123). In countries with high coverage, further declines are much harder to achieve.

**Source:** UNAIDS Estimates 2012
New child HIV infections =

\[
\text{Number of HIV+ pregnant women} \times \text{Mother to child transmission rate}
\]

- Reducing new infections among reproductive age women (prong 1)
- Eliminating unmet need for family planning (prong 2)
- Reducing the transmission rate (prong 3)
- Increasing coverage of PMTCT services
- Improving effectiveness of regimens
Slight decline in new HIV infections among women 15-49, 21 priority countries

Source: UNAIDS Estimates 2012
Reduction in unmet need for family planning is slow, countries with available data

Source: Demographic and Health Surveys 2000-2011
... As a result the number of women in need of PMTCT services remains flat.
New child HIV infections  =

\[
\text{Number of HIV+ pregnant women} \times \text{Mother to child transmission rate}
\]

- Reducing new infections among reproductive age women \text{(prong 1)}
- Eliminating unmet need for family planning \text{(prong 2)}
- Reducing the transmission rate \text{(prong 3)}
- Increasing coverage of PMTCT services
- Improving effectiveness of regimens
New child HIV infections and PMTCT coverage, 21 priority countries

Source: UNAIDS Estimates 2012
### PMTCT coverage, 21 priority countries

<table>
<thead>
<tr>
<th>High coverage 66+ %</th>
<th>Medium coverage 33-65%</th>
<th>Low coverage &lt;33%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>Burundi</td>
<td>Angola</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>Cameroon</td>
<td>Chad</td>
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<tr>
<td>Ghana</td>
<td>Lesotho</td>
<td>DR Congo</td>
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<td>Kenya</td>
<td>Malawi</td>
<td>Ethiopia</td>
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<td>Namibia</td>
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<td>Nigeria</td>
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<td>Swaziland</td>
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<td>South Africa</td>
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Source: UNAIDS Estimates 2012
Prophylaxis coverage: the other half of the picture

Number of women/infant pairs receiving prophylaxis, 2011, 21 priority countries

Source: UNAIDS Estimates 2012
As a result … MTCT transmission rates are still high

Source: UNAIDS Estimates 2012
Prong 4: Care and treatment for the family
Early Infant diagnosis is still unacceptably low: 35% in 21 countries

<table>
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<tr>
<th>High coverage (66+ %)</th>
<th>Medium coverage (33-65%)</th>
<th>Low coverage (&lt;33%)</th>
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Source: Global AIDS Progress Reporting 2012
Maternal survival is important for child growth and development.
Increasing ART results in substantial declines in pregnancy-related deaths

Percent change in pregnancy-related deaths to women living with HIV between 2005 and 2010

TOGETHER WE WILL END AIDS
Actions needed to reach zero

• Strengthen efforts to reduce unmet need for family planning
  • Limited data on unmet need among women living with HIV

• Increase coverage of prophylaxis during breastfeeding

• Ensure eligible children receive ART
  • Increasing early infant diagnosis from 35% to higher levels will improve ART uptake
Outstanding questions:

• Why are pregnant women less likely to be on ART than all adults when they are more likely to have interaction with health system?

• There is still significant uncertainty in how HIV interacts with pregnancy. Estimates are uncertain. Reducing AIDS deaths around the time of pregnancy will allow countries to reach the 50% reduction goal.
Thank you