Antiretroviral Treatment Update

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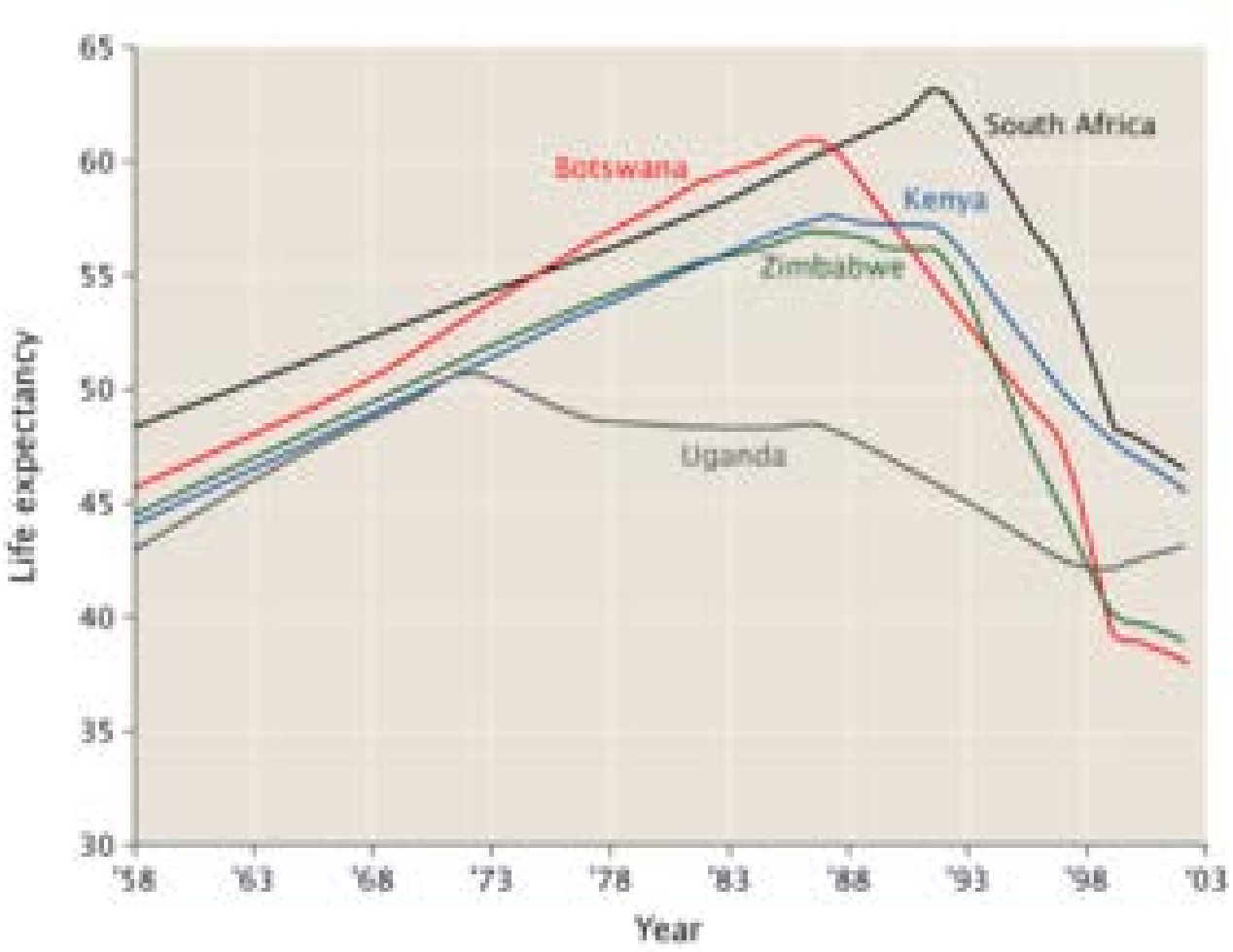
HIV Epidemic in low & middle income countries (LMIC)

Decline in life expectancy



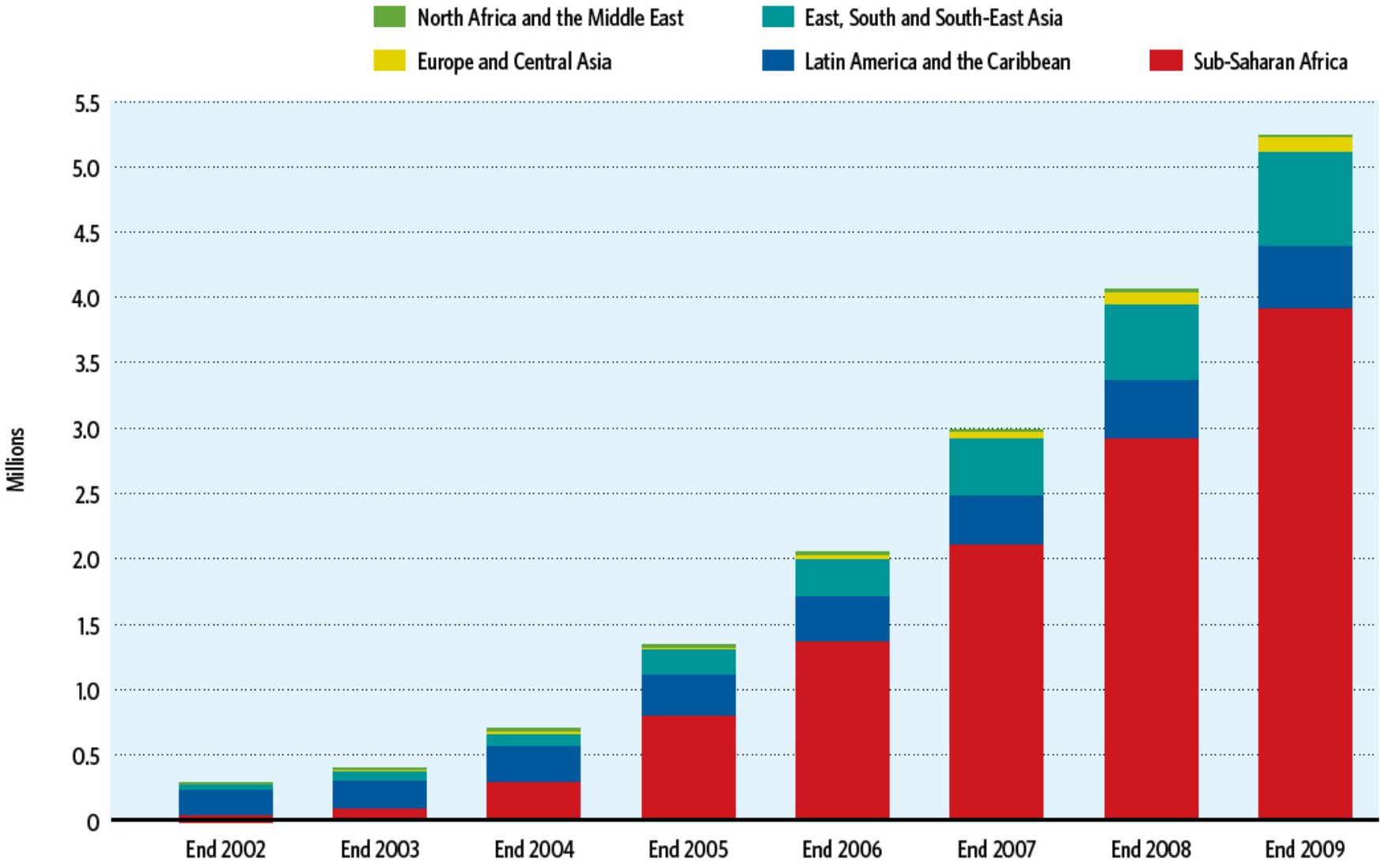
ARV comes to LMIC

Investing in our future

The Global Fund

To Fight AIDS, Tuberculosis and Malaria

Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002–2009



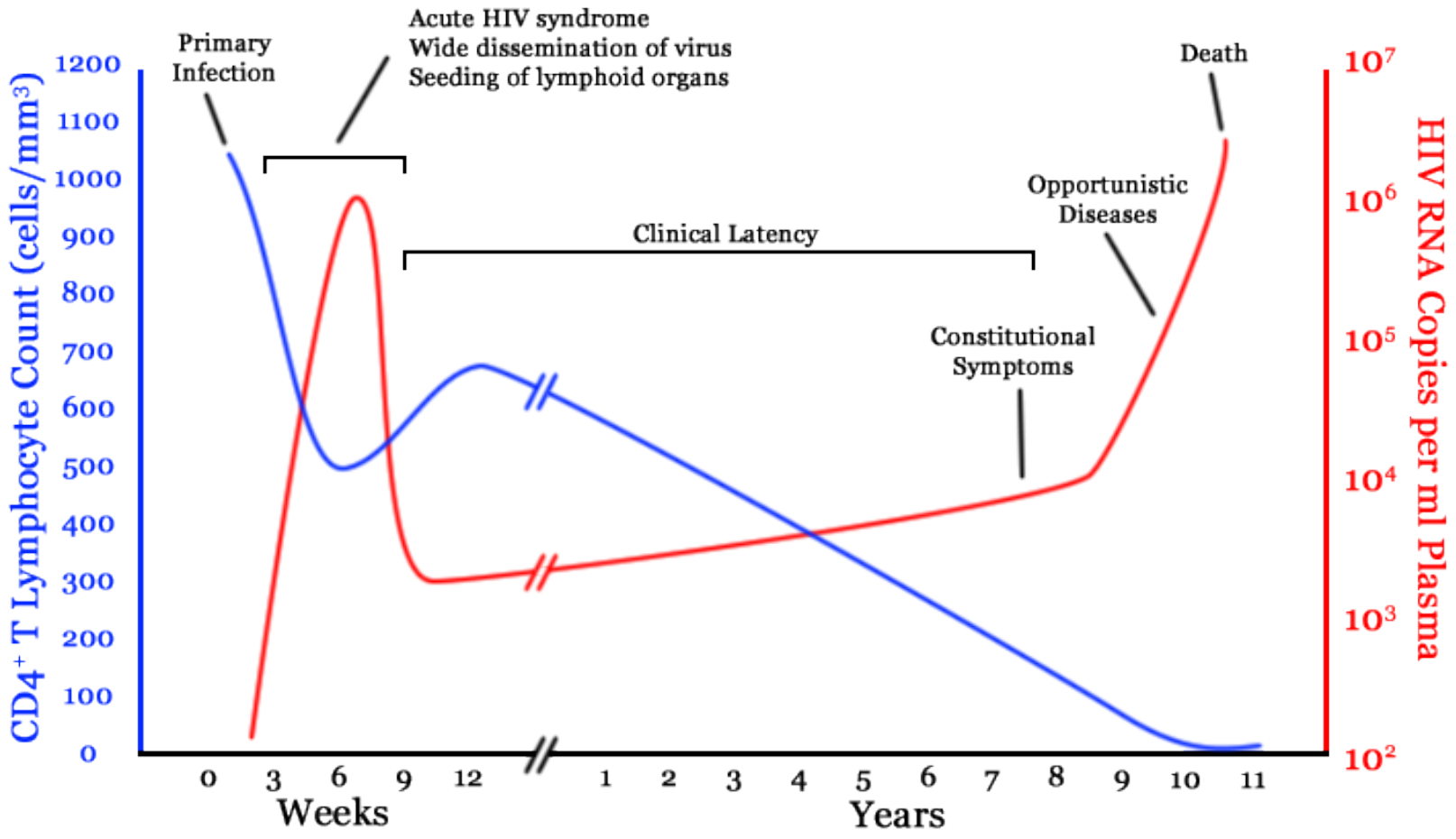
Number of men and women receiving and estimated to need antiretroviral therapy and percentage coverage, December 2009

- Number needing ARV 13 million
- Number receiving ARV 4.6 million
- Percentage 35%

Presentation Topics

- How to monitor HIV progression
- When to initiate treatment
- Principles of treatment
- How to monitor on treatment
- The challenge of viral resistance

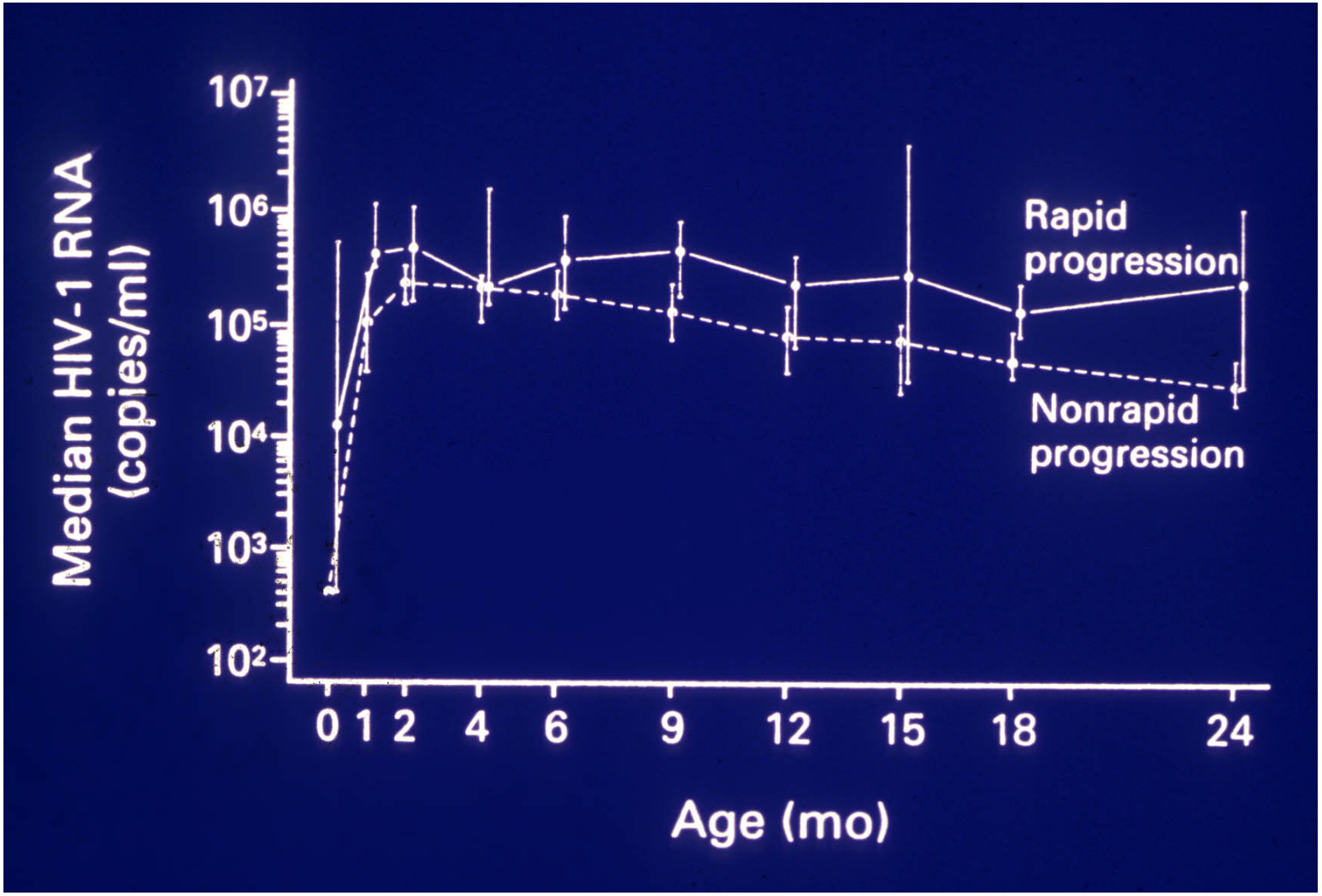
HIV disease course:adult/adol



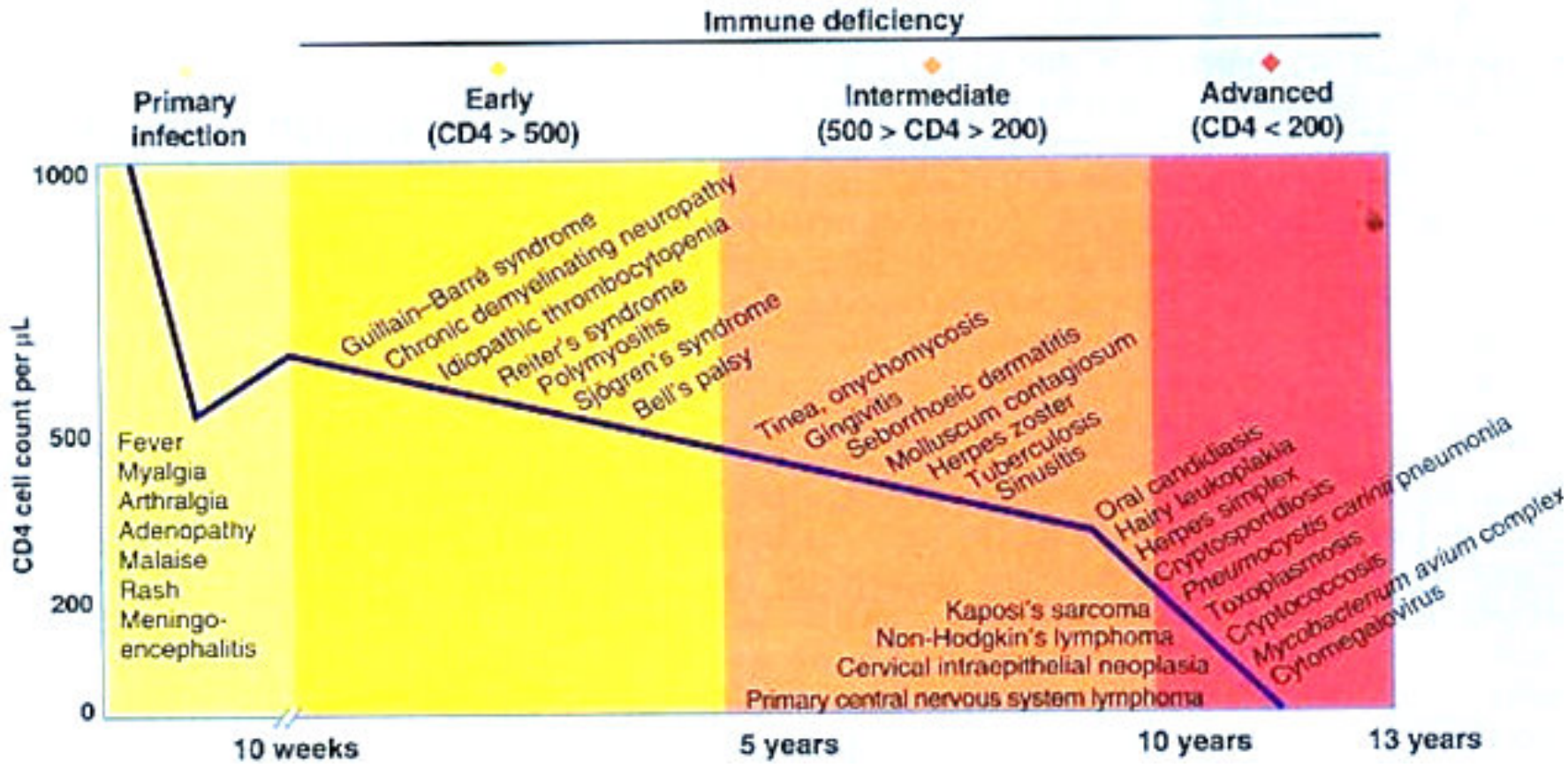
HIV disease course: perinatal

- Rapid progression
- High risk of mortality
- Without treatment
  - 50% of infant die by age 2 yr
  - 80% have CD4 count indication for treatment by age 6 months
- CHER study, many died before they came in to have CD4 count monitored

Viral load for an individual patient may not predict rapid progression in early infancy



Phase of HIV progression



WHO clinical staging criteria

- Stage 1
  - No symptoms
  - Generalized lymphadenopathy

WHO clinical staging criteria

- Stage 2
  - Moderate weight loss
  - Recurrent minor respiratory infections
    - Sinusitis, pharyngitis, otitis media
  - Mild Skin/mucous membrane manifestations
    - Shingles, angular cheilitis, oral ulcers, papular eruptions, dermatitis, fungal nail infections
    - (Peds) Lineal gingival erythema, parotid gland enlargement, extensive warts & molluscum
  - (Peds) Hepatosplenomegaly

WHO clinical staging criteria

- Stage 3
  - Weight loss (more than 10%)
  - More severe oral conditions:
    - Oral Candidaisis, oral leukoplakia, necrotizing stomatitis
  - Pulmonary TB (lymph node TB-peds)
  - Severe bacterial infections
  - Hematologic: anemia, neutopenia, thrombocytopenia
  - Chronic diarrhea
  - Chronic fever
  - Lymphocytic interstitial pneumonitis (Peds)

WHO clinical staging criteria

- Stage 4
  - Wasting,
  - Recurrent bacterial pneumonia
  - Opportunistic infections:
    - Chronic HSV, esophageal candida, disseminated CMV, CNS toxo, disseminated fungal, disseminated MAC
  - Malignancies: KS, lymphoma, cervical CA
  - Organ dysfunction: CNS, heart, PCP

CD4 Lymphocyte monitoring

- T cells
  - CD3/CD4+ cells = helper T cells
  - CD3/CD8+ cells = killer/suppressor T cells
- B cells
  - CD 19 cells = B cells
- Percent and Count
  - Total WBC x % lymphocytes x %CD4 count = Absolute CD4 count

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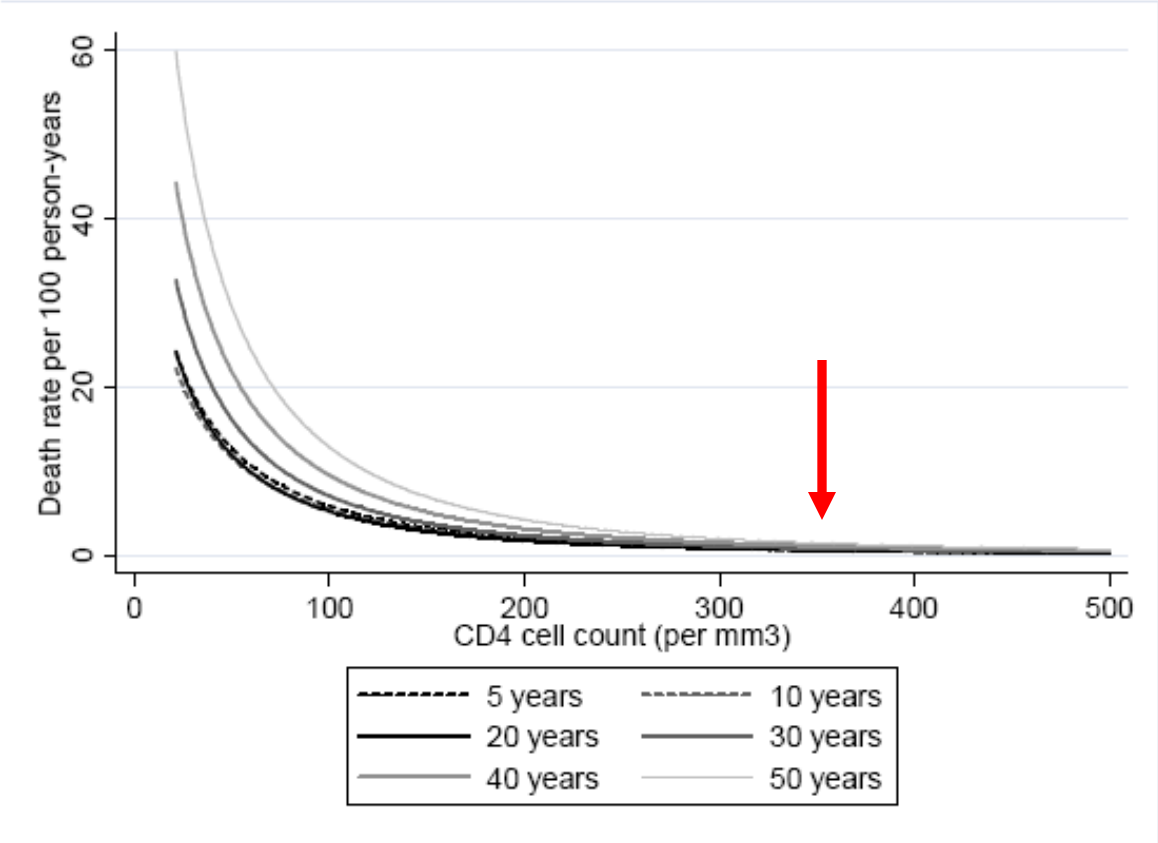
CD4 count cutoff for starting ARV

• Adults • Adolescents • Children > age 5yr	• CD4 count < 350 cells/m^3
• Children > age 2-5yr	• CD4 count < 750 cells/m^3 or CD4% <25%
• Children <2yr	• Any CD4 count or %

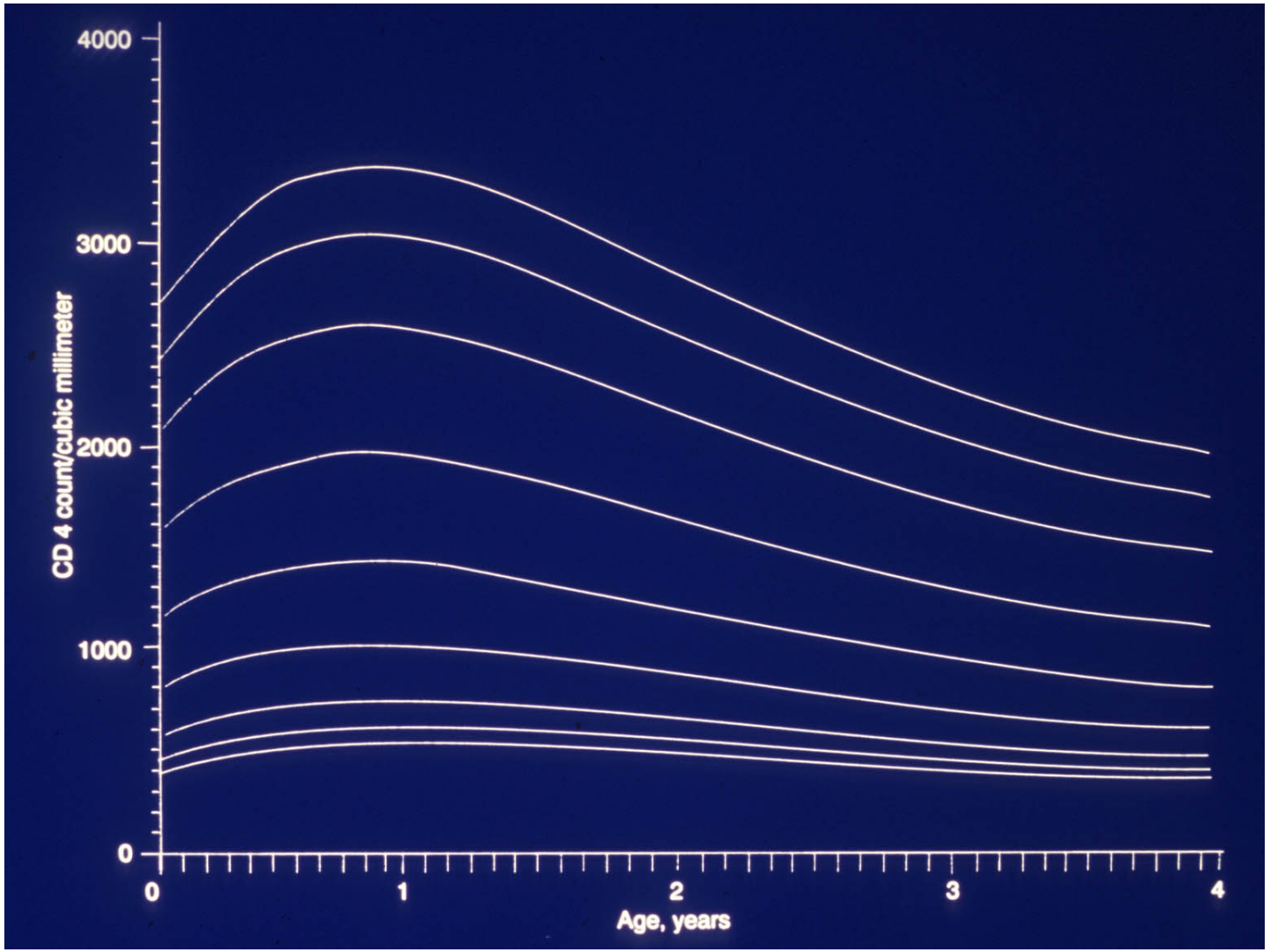
HIV progression by CD4 count

Figure 3: Death Rate per 100 Person-Years in HIV-Infected Children Age 5 Years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study* **(Updated February 28, 2008)**



* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. J Infect Dis 2008 in press.

CD4 counts vary with age until age 5 yr



- Infant CD4 percentages do not change much by age
- CD4 >25% considered no evidence of immunosuppression

When to initiate treatment--adults

- WHO clinical stage 3 and 4
- Active TB
- Hepatitis requiring treatment
- WHO clinical stage 1 and 2 if CD4 counts of ≤350 cells/mm^3
  - Estimated that 50% of WHO clinical stage 2 have a CD4 count of ≤350 cells/mm3

When to initiate treatment: children

- WHO Stage 3 or 4
- Age <2yr
- For age 2-5 yr, CD4 <25% or 750 cells/m^3
- For age 5yr, CD4 <350 cells/m^3

HIV Medication Chart

Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTI)

Emtriva* (emtricitabine, FTC)

Epivir* (lamivudine, 3TC)

Retrovir* (zidovudine, AZT, ZDV)

Videx EC (didanosine, ddl)

Viread (tenofovir, TDF)*

Zerit* (stavudine, d4T)

Ziagen* (abacavir, ABC)

Protease Inhibitors (PI)

Aptivus (tipranavir, TPV)

Crixivan (indinavir, IDV)

Invirase (saquinavir hard gel capsules, SQV)

Kaletra* (lopinavir/ritonavir, LPV/r)

Lexiva (fosamprenavir, FPV)

Norvir* (ritonavir, RTV)

Prezista (darunavir, DRV)

Reyataz (atazanavir, ATV)

Viracept (nelfinavir, NFV)

Fixed Dose Combinations

Atripla (TDF+FTC+EFV)

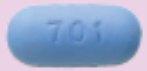
FDA Pregnancy Category D

Combivir (AZT plus 3TC)

Epzicom (ABC plus 3TC)

Trizivir (AZT plus 3TC plus abacavir)

Truvada (TDF plus FTC)



Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Intelence (etravirine, ETV)

Rescriptor (delavirdine, DLV)

Sustiva* (efavirenz, EFV)

FDA Pregnancy Category D

Viramune* (nevirapine, NVP)

Entry Inhibitors

Fuzeon (enfuvirtide, T-20)
Fusion Inhibitor

Selzentry (maraviroc, MVC)
CCR5 Antagonist

Integrase Inhibitors

Isentress (raltegravir, RAL)

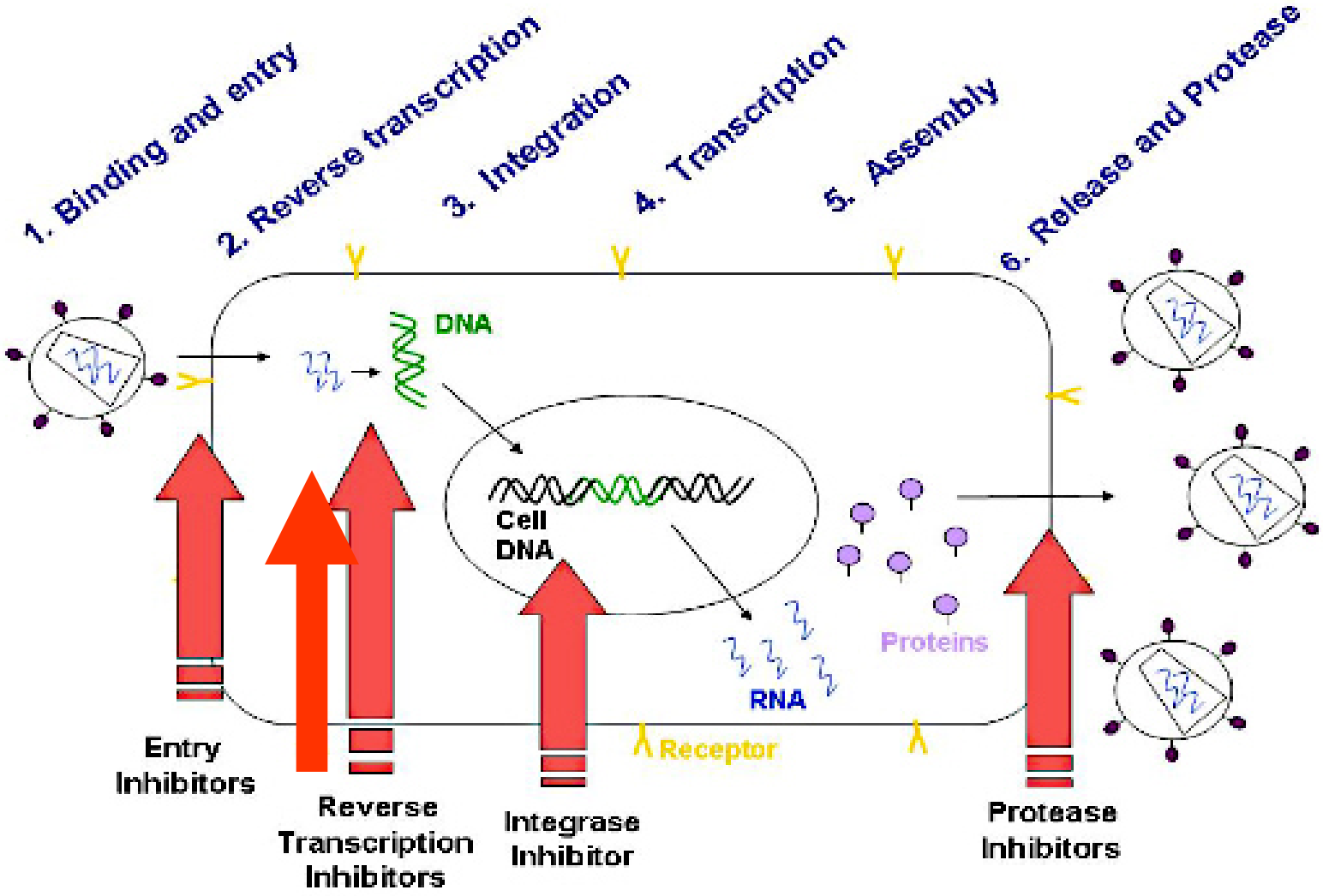
All pills shown in actual size.

Medication brand names appear in bold. Generic names and commonly used abbreviations appear in parentheses.

*Also available in liquid form.

3/08

New classes, new hope



http://www.bcm.edu/molvir/eidbt/eidbt-mvm-hivaids.htm

What to start:
WHO recommendations for adults

- Two NRTI
  1) AZT or TDF
  2) 3TC or FTC

- One NNRTI
  3) NVP or EFV
- For children <3yr

  Maybe boosted PI better then NNRTI

How to monitor on treatment

- When Viral load testing available
  - Use it to determine failure
  - Test strategically or routinely (q 6 months)
  - Persistent VL >5000 = failure
- When not available
  - Use immunologic and clinical criteria

Table 12. ART switching criteria

Failure	Definition	Comments
Clinical failure	New or recurrent WHO stage 4 condition	Condition must be differentiated from immune reconstitution inflammatory syndrome (IRIS) Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections), may be an indication of treatment failure

Failure	Definition	Comments
Immunological failure	Fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR Persistent CD4 levels below 100 cells/mm^3	Without concomitant infection to cause transient CD4 cell decrease
Virological failure	Plasma viral load above 5000 copies/ml	The optimal viral load threshold for defining virological failure has not been determined. Values of >5 000 copies/ml are associated with clinical progression and a decline in the CD4 cell count

How to monitor on treatment: Side effects

• AZT	• Anemia, neutropenia
• TDF	• Renal, bone
• 3TC	• Few
• FTC	• Few
• NVP	• Rash, hepatitis
• EFV	• CNS, rash

Principles of treatment

- Restore CD4 count
- Durable, complete viral suppression
- Life long treatment
  - High tolerability
  - High safety
- Avoid HIV resistance

The challenge of resistance

- Approximately 10 trillion new virions made per day
- High mutation rate
- Estimated one mutation a each nucleotide each day

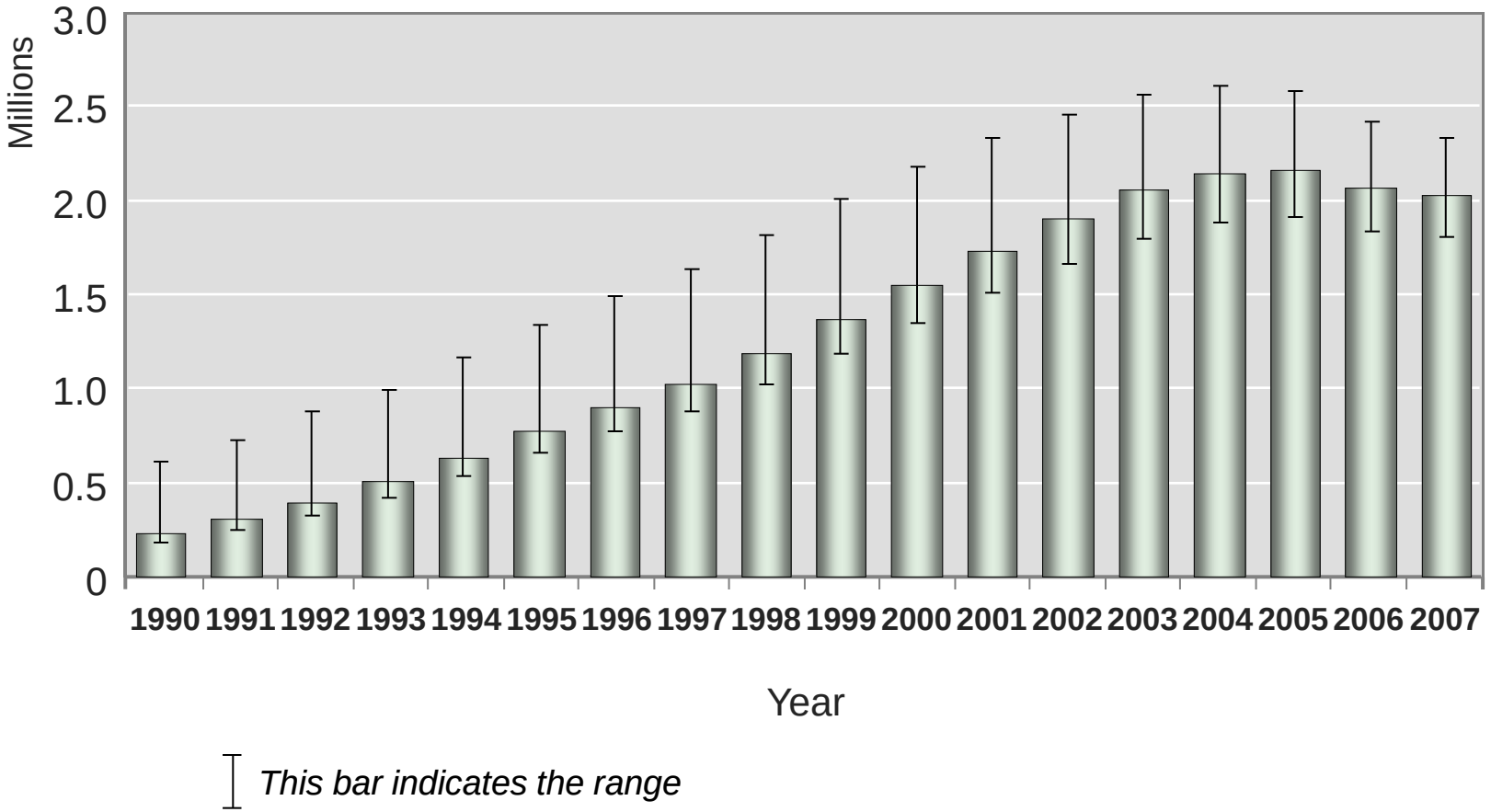
Preventing resistance

- Need to stop all replication
  - No opportunity for mutations
- Need combination treatment w/at least 2 active drugs
  - Statistically unlikely that a particular virus will have mutations for two or three drugs
- Prefer drugs with high barrier to resistance
  - NVP, EVF, 3TC, FTC: one mutation, high level resistance; also cross drug resistance
- Avoid prolonged treatment with detectable virus
  - accumulation of mutations

Concerns with current approach to ARV monitoring in LMIC

- May start with resistant virus
- Adherence/drug supply/logistics
  - Needs to be better than 90% of doses
- 1st line regimens have low barrier to resistance
  - Less likely with PI's but other disadvantages
- Lack of viral load monitoring may result in delay to switch of failing regimen
  - Accumulation of TAMS (thymidine analogue mutations) which may result in broad cross resistance
  - Less likely with TDF

Estimated number of adult and child deaths due to AIDS globally, 1990–2007

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