Preventing HIV Among Young People: Research Priorities for the Future

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Objective: To review the current state of knowledge on the prevention of sexual transmission of HIV in adolescents and to highlight the existing gaps and priority areas for future research.

Background: A disproportionate burden of HIV infections falls on adolescents, a developmental stage marked by unique neural, biological, and social transition. Successful interventions are critical to prevent the spread of HIV in this vulnerable population.

Methods: We summarized the current state of research on HIV prevention in adolescents by providing examples of successful interventions and best practices, and highlighting current research gaps.

Results: Adolescent interventions fall into 3 main categories: biomedical, behavioral, and structural. The majority of current research has focused on individual behavior change, whereas promising biomedical and structural interventions have been largely understudied in adolescents. Combination prevention interventions may be particularly valuable to this group.

Conclusions: Adolescents have unique needs with respect to HIV prevention, and, thus, interventions should be designed to most effectively reach out to this population with information and services that will be relevant to them.

Key Words: adolescence, HIV, prevention

International

INTRODUCTION

Young people are disproportionately affected by HIV globally; 25% of infected persons are aged between 10 and 24 years.1 Those aged 15–24 years have 35% of new infections, resulting in 900,000 new infections occurring annually.2 The greatest burden of HIV among young people is in sub-Saharan Africa. Here, young women have almost 8 times the HIV prevalence as do same-age men,3 and their annual HIV incidence is an estimated 8%.3,4 By contrast, in the United States and in Europe, young men who have sex with men are at the greatest risk of developing infection, particularly young men who have sex with men of color.5 However, in much of Eastern Europe and Central Asia, young injection drug users and their sexual partners have the highest risk.6 Clearly, adolescents make up a heterogeneous population; risk factors for HIV depend both on individual characteristics and social/environmental contexts. This diversity must be addressed in interventions.

In this article, we highlight the unique needs of adolescents with respect to biomedical, behavioral, and structural interventions that present the greatest promise in preventing sexual transmission of HIV. We also highlight the existing gaps and priority areas for future research. We use the terms “adolescent,” “youth,” and “young people” synonymously, defining adolescence as the developmental stage between the ages of 13 and 24 years.

WHY ARE ADOLESCENTS A UNIQUE POPULATION?

Adolescence has been described as “a period of momentous social, psychological, economic, and biological transitions.”5 It is a time when substantial brain development
occurs, including the capacity for complex conceptual thinking. The combination of a heightened responsiveness to rewards coupled with immaturity in the behavioral control areas of the brain may lead to the risky decisions and emotional reactivity that characterize adolescence. The exploration and formation of identity are considered by many to be the primary developmental goal of adolescence. Socially, adolescents are searching for a sense of belonging from peers, who influence their behavior. Adolescence is also marked by social transitions such as finishing school, finding employment, independent living, first sexual relationships, pregnancies, and marriage. These milestones occur during a period of decreased adult supervision when young people still have limited knowledge, self-confidence, and life skills, which can lead to engagement in behaviors that heighten HIV risk.

HIV PREVENTION AMONG ADOLESCENTS

Numerous risk and protective factors operate at multiple levels, including the individual, dyad (peer/partner/parent), community (eg, school environment), and societal levels. Identifying the determinants of risk and protective behaviors is necessary to ensure that interventions are appropriate to the population and context where they are delivered. The need for combination HIV prevention strategies, incorporating interventions that address biological, behavioral, and structural factors has been emphasized as being central to impacting the epidemic. Research is needed on selecting and optimizing these combinations for greatest effect, particularly among adolescents. Significant gaps in HIV prevention knowledge for adolescents remain (Table 1).

Biomedical Interventions

Recent successes in HIV prevention have been predominately biomedical and include antiretroviral therapy (ART) for prevention, voluntary medical male circumcision (VMMC), and vaginal microbicides. Both treatment as prevention (ART taken by HIV-infected individuals to reduce HIV transmission) and preexposure prophylaxis (PrEP; ART taken by HIV negative individuals to prevent HIV acquisition) demonstrate effectiveness in preventing HIV acquisition or transmission. Although PrEP has been found to be effective in 1 randomized controlled trial (RCT) among men who have sex with men, results from 4 trials among heterosexual individuals have been mixed with 2 trials showing that PrEP was effective and 2 trials finding no effect.

There are numerous reasons why the results of trials among heterosexual individuals may be conflicting, although adherence is likely one of the most important drivers of efficacy. In fact, in the VOICE trial, adherence, as measured by drug levels in blood, was particularly low (29%) despite the fact that self-reported adherence and pill count suggested good adherence (90%). Being over the age of 25 years was a significant predictor of drug detection in the blood. In contrast, data from the Partners PrEP trial found that daily oral tenofovir (TDF) and emtricitabine/TDF (FTC/TDF) were as efficacious in young women under the age of 30 years as among all women. Specifically, the efficacy of TDF among women

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<th>TABLE 1. HIV Prevention Research Gaps for Adolescents</th>
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TABLE 1. (Continued) HIV Prevention Research Gaps for Adolescents

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<td>Issues of consent and consent waiver</td>
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<td>Crosscutting</td>
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<td>practice/research</td>
<td>Cost effectiveness</td>
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<td>Modeling of effect sizes and potential impact of various interventions</td>
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<td>Combination prevention interventions</td>
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$<30$ years of age was $77\%$ [95\% confidence interval (CI), 29 to 92] and the efﬁcacy of FTC/TDF was $72\%$ (95\% CI, 25 to 90) compared with all women in whom the efﬁcacy of TDF was $71\%$ (95\% CI, 37 to 87) and FTC/TDF was $66\%$ (95\% CI, 28 to 84). These discrepant ﬁndings in PrEP trials for young women highlight the need for well-designed PrEP pilot studies to better understand discrepancies between self-reported measures of adherence and actual use, best dosing for young women (e.g. daily vs. intermittent), motivations for young women to participate in trials, and appropriate messages and interventions to support adherence and methods that allow participants to accurately report usage and likes and dislikes of products in trial settings. Thus, while promising, questions remain about the scalability and generalizability of ART for prevention in general and in particular to adolescents.

Although adherence to ART is critical for treatment and prevention, taking medication in the long term is challenging. Adolescents with HIV are less likely than are adults to be adherent to ART. A literature review examining medication nonadherence among adolescents suggests that simple solutions remain elusive. For HIV-uninfected youth, low HIV risk perception may result in a lack of interest in or poor adherence to interventions such as PrEP or microbicides. Furthermore, adolescents are often not in long-term relationships; it is unclear how partnership characteristics affect adherence to prevention interventions. More research is needed among adolescents to understand testing, linkage to and retention in care, and understand factors affecting the uptake of biomedical prevention interventions.

Vaginal and rectal microbicides, applied topically before sex, may be appropriate for young women and men who have sex intermittently. Although 1 trial of coitally dependent vaginal TDF was found to show signs of efﬁcacy among women in South Africa, the use of daily topical TDF was found not to be effective in a second trial in Africa. The explanation for differences in the studies has been attributed to women not using the product, again stressing the fact that adherence is critical to the efﬁcacy of these interventions. Two safety and acceptability trials of a TDF gel-based microbicides in adolescent women are planned in the United States (Kapogianis B. National Institute of Health and Microbicides Trial Network plan safety and acceptability trial of tenoﬁvar gel-based microbicide in adolescent women. 2012. Written personal communication) and in South Africa. A phase 2 trial of rectally applied TDF gel among men and transgendered women will begin enrollment soon and would beneﬁt from bridging studies to adolescents following sufﬁcient safety signals. Research evaluating how best to support uptake, delivery, and adherence will be required to facilitate wide-spread implementation.

Given the high levels of unplanned pregnancy and unmet need for contraception among many young women in high-prevalence settings, multipurpose technologies, methods that could prevent HIV, other sexually transmitted infections and pregnancy, are urgently needed. Some products are in development, but their acceptability and safety for adolescent girls are unknown. Interventions integrating the provision and uptake of sexual and reproductive health services with HIV prevention need to be evaluated.

VMMC reduces HIV risk by approximately 65\% and reduces the risk of sexually transmitted infection acquisition and transmission. An additional beneﬁt of encouraging early VMMC is that it is almost invariably preceded by HIV testing and counseling (HTC). Given the low uptake of HTC in young men in some settings, there is a need to better link adolescent VMMC with interventions to encourage healthy behaviors including regular HIV testing.

Special Considerations

Most of the research on biomedical interventions has been conducted in adults, partly due to the ethical complexities of research in minors. Although there is increasing recognition of the importance of engaging children and adolescents in research, there remain ethical, legal, and logistical challenges. Inclusion of minors in clinical research is governed by ethical principles that vary globally but generally consider need, risk, beneﬁt, and consent. Who consents for adolescent involvement is typically governed by the age of the majority by state and/or country with some exceptions. There are also important considerations of the appropriate timing of adolescent involvement in the research of the clinical development of a product or intervention. Excluding adolescents from these studies may delay access to prevention interventions. It is essential that biomedical prevention interventions be implemented with a better understanding of behavioral and contextual factors that impede uptake and adherence. Clearer guidance around safety bridging studies, and when extrapolation to adolescents is acceptable versus when efﬁcacy and/or effectiveness should be demonstrated, is vital for newly developed biomedical interventions.

Behavioral Interventions

Behavioral interventions have been used with the aim of reducing the risk for HIV by delaying sexual debut, promoting condom use, and/or reducing concurrency, partner change, or substance use. Numerous behavioral interventions have been evaluated; however, few have HIV endpoints, and...
those that have, have not shown a reduction in HIV incidence.\textsuperscript{45–47} The US Centers for Disease Control and Prevention has identified interventions with good or best evidence for HIV risk reduction based on their impact on proximate determinants of incidence.\textsuperscript{48} However, there is the need for critical consideration of the role of these interventions in high-prevalence settings. Interventions offered in group settings, such as in schools, may be most feasible in resource-constrained environments.

Schools are often used to deliver behavioral interventions because they reach a large number of youth, often before sexual debut. Of the 3 published adolescent HIV prevention RCTs conducted with HIV incidence endpoints, 2 have been school based.\textsuperscript{49–51} None of the studies found an impact on HIV, and results were mixed for sexual behavior. Overall, those with greatest success were curriculum based, adult led, and followed specific guidelines ("Kirby characteristics").\textsuperscript{52,53} Combining modalities to deliver biomedical interventions, such as HCT, in schools may lead to a greater program uptake.

Understanding the larger context of behavioral interventions is critical to their success.\textsuperscript{54} Many school-based interventions were implemented in settings where massive gender and power inequities may undermine programs’ success.\textsuperscript{55} Further, issues related to proper intervention implementation and fidelity likely compromised efficacy.\textsuperscript{56}

There is increasing emphasis on addressing prevention issues with HIV-infected individuals. Positive health dignity and prevention (PHDP) interventions help people living with HIV to lead complete and healthy lives and reduce HIV transmission. PHDP involves the systematic delivery of a range of combination, behavioral, and sociocultural services within local communities.\textsuperscript{56} Although the core components of PHDP have been defined, evidence is required to tailor these for use with adolescents in diverse settings and evaluate cost effectiveness.

**Structural/Contextual Interventions**

At the structural and contextual levels, important drivers of adolescent risk are poverty, discrimination, gender and power inequities, stigma, and environments that are not youth friendly.\textsuperscript{47,57} Few interventions address these structural factors. Given the high prevalence of rape in sub-Saharan Africa,\textsuperscript{58} and that HIV transmission in the context of gender-based violence is common,\textsuperscript{59} we must examine approaches that tackle HIV prevention within the broader context of gender inequity.

Structural barriers to accessing care need to be addressed for adolescents. Youth-friendly reproductive health services can attract and retain youth in care.\textsuperscript{60} Health facilities that are successful in making services more adolescent friendly have consistently included provider training and community activities.\textsuperscript{55} Given the central role of HTC and biomedical interventions in the prevention landscape, we need to identify the successes of reproductive health services and adapt and/or integrate HIV prevention in these services. Models for youth-friendly services offering testing have been developed\textsuperscript{61–63}; however, adolescents’ uptake of HTC is not well understood. Research to explore how to increase HTC uptake, disclosure of serostatus, and linkages to prevention (eg, PrEP) and care (eg, treatment as prevention) is required.

It is critical to address limited education and poverty that increase the risk for HIV infection.\textsuperscript{64–67} A recent trial among young women in Malawi showed that cash transfers lowered HIV and HSV-2 prevalence and demonstrated positive changes in the age of the sex partner and frequency of sex acts.\textsuperscript{68} Providing cash to young women may have allowed them to change partnership characteristics, reducing their risk of contracting HIV infection; however, the mechanism through which such programs work is still unclear. Several large RCTs examining cash transfers with HIV incidence endpoints are currently underway and may help identify the mechanism of action of such interventions.\textsuperscript{59,70} There is a need to explore a range of interventions to reduce poverty and improve the financial independence of young people.

Other structural approaches that change social norms through media campaigns or community mobilization can reach out to a large number of adolescents. Messages that target larger audiences and work to reinforce HIV prevention and care messages play a key role in normalizing HIV testing and in the uptake of newer prevention technologies.\textsuperscript{71} The role of community mobilization to increase the uptake of HTC or VMMC is promising, yet it is understudied. Ultimately, interventions combining multiple strategies with sufficient community coverage are likely to have the greatest impact.

Youth are the greatest users of the Internet and mobile devices globally,\textsuperscript{72,73} with high usage reported even in developing countries.\textsuperscript{74,75} The use of such methods should easily and cost effectively reach a large youth population using this medium and develop tailored programs to make messages relevant to each recipient.\textsuperscript{76} Early computer-based interventions showed potential to improve sexual health outcomes for youth.\textsuperscript{77–79} Current interventions are harnessing the interactive power of social media sites such as Facebook and Twitter with promising results.\textsuperscript{80–82} Mobile phones can also be used as a platform to deliver preventive interventions\textsuperscript{83,84} or to improve adherence to ART.\textsuperscript{85} There is a need for rigorously evaluated interventions that effectively link technology to clinic-based efforts to foster safer sexual health behaviors and treatment adherence.\textsuperscript{76}

**CONCLUSIONS**

Despite the high risk of HIV transmission among young people, few rigorously designed prevention interventions with HIV endpoints have been evaluated. Many interventions focus on changing individual-level behaviors rather than on addressing the larger contextual and structural landscape within which young people live. Further, few studies have explored the use of biomedical interventions among young people. Although biomedical prevention offers considerable promise, further research is needed to determine the applicability, safety, and efficacy of these approaches among the youth. The factors affecting HIV risk are complex and will require a combination approach incorporating a supportive behavioral, structural, and/or biomedical intervention.
Developing a prevention menu where adolescents, depending on their phase of transition and sexual activity, may tailor their individual prevention package would represent a major advance in preventing HIV among youth.

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