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HIV Pre-Exposure Prophylaxis for Adolescents and Young Adults

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STRUCTURED ABSTRACT

Purpose of review—This review describes the evidence for HIV pre-exposure prophylaxis (PrEP) with daily combined tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in adolescents and young adults. Current recommendations are described, as are the unique medical, socioeconomic, and legal considerations regarding the use of PrEP for youth.

Recent findings—PrEP with daily oral TDF-FTC has been shown to help prevent new HIV infection among adults at substantial risk. Evidence suggests a protective benefit of PrEP for youth at risk for HIV, although low adherence is emerging as a barrier to effective use.

Summary—Effective use of antiretrovirals for PrEP represents a seminal development in HIV prevention efforts. Improving access and adherence to PrEP for youth has the potential to substantially reduce the incidence of HIV in this population.

Keywords

HIV; pre-exposure prophylaxis; adolescent; youth

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Conflicts of Interest

None.

INTRODUCTION

Adolescents and young adults account for a disproportionate number of new HIV infections globally, and the incidence of new infections is projected to increase [1]. Efforts to prevent new infections among youth are critical to curbing the HIV epidemic.

HIV prevention strategies are evolving, with an emerging role for antiretroviral drugs as a part of combination prevention efforts [2]. Long used for *post*-exposure prophylaxis and prevention of mother-to-child transmission, antiretroviral medications have now been shown to be effective for *pre*-exposure prophylaxis (PrEP) for HIV-uninfected individuals who are at risk of acquiring HIV.

Tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are nucleoside reverse transcriptase inhibitors that have been used in combination (TDF-FTC) for the treatment of HIV in persons ages 13 years and up since 2004. TDF-FTC was first approved for use as PrEP for adults by the United States (U.S.) Food and Drug Association in 2012. In 2014, the U.S. Centers for Disease Control and Prevention recommended that PrEP should be offered to adults at substantial risk of HIV infection [3], and the World Health Organization released similar guidelines—without reference to age—in 2016 [4]. Although youth are a key target for HIV prevention efforts, data regarding efficacy, safety, and implementation of PrEP in this population remains limited. Youth require special consideration when it comes to safe and effective use of PrEP given their unique stage of development marked by significant physical growth as well as dramatic psychological and social changes.

This review describes current evidence and considerations regarding the use of PrEP for HIV prevention among youth, which we define as persons 15–24 years old. We use the term “adolescents” to refer to youth under age 18 years and “young adults” as youth ages 18–24 years.

EVIDENCE FOR PREP IN ADOLESCENTS AND YOUNG ADULTS

Multiple randomized placebo-controlled trials have demonstrated the safety and efficacy of daily oral TDF-FTC—a fixed-dose combination tablet containing TDF and FTC—as PrEP in adult populations at risk of acquiring HIV, including men and women in an endemic setting [5], men and women with HIV-infected partners [6], people with injection drug use (TDF only) [7], and men who have sex with men (MSM) and transgender women who have sex with men (TGW) [8] (Table 1). One trial showed that intermittent dosing of PrEP around episodes of sexual activity (“on demand”) was also effective in reducing HIV transmission among MSM [9]. A 90–92% relative risk reduction was observed among those taking TDF-FTC who had detectable drug levels [6, 8, 9].

None of these studies, however, included adolescents under 18 years old, and only a minority of participants were young adults under 25 years old. The FEM-PrEP trial focused on young adults; participants were African women with a median age of 23 years (range 18 to 35 years). In this group, less than one-third of participants had evidence of taking PrEP based on objective measures (i.e. plasma levels of TDF). Adherence levels were too low to adequately assess efficacy, and the trial was stopped early [10].

Three randomized control trials provide data stratified by age for young adult participants. Age-specific sub-analyses in these 3 individual studies showed no significant differences in efficacy between participants ages 18–24 years and those 25 years and older [6, 8, 10]. Although a meta-regression found that age did not moderate the relationship between PrEP and HIV, in stratified analysis PrEP was not statistically effective for young adults (risk ratio=0.71, 95%CI 0.47–1.06, $p=0.07$), most likely due to the low adherence in this age group [11].

ADOLESCENT AND YOUNG ADULT ADHERENCE TO PREP

PrEP can prevent HIV acquisition, but adherence is essential [11]. Available evidence suggests that a minimum of 4 or more doses per week of PrEP yields protection against HIV acquisition by anal sex [12, 13], though less than daily dosing may not be effective in preventing transmission via vaginal mucosa or intravenous exposure. Daily dosing of TDF-FTC is recommended as PrEP in populations at risk [3, 4*].

Adherence is a potential barrier to effective use of PrEP in adolescent and young adult populations. Some studies have shown that older age is associated with greater adherence as measured by drug levels [8, 10]. Adolescent Trials Network (ATN) 113 and ATN 110—U.S.-based studies that tested the acceptability, safety, and adherence to PrEP among 78 MSM ages 15–17 years and 200 MSM 18–24 years, respectively—show lower adherence among these groups than what has been described in adult studies [14**,15]. In ATN 110, over 90% of participants had some detectable drug level through the first 12 weeks of the study, and over 50% had levels consistent with at least 4 pills per week. Adherence declined at week 24, however, when visit frequency declined from monthly to every 3 months. By week 48, protective levels of drug were detected in only 34% of participants. Racial disparities in adherence were described; median drug levels for black participants were below the protective threshold at all time points [14**]. In ATN 113, the majority of participants reached protective drug levels through 12 weeks, with similar drop off at 24 weeks, when visits became less frequent [15]. Early data from PlusPills, an open-label study exploring the acceptability, safety, and use of oral PrEP for HIV-negative youth 15–19 years old in Soweto and Cape Town, South Africa, similarly showed 76% of participants with levels of TDF considered adequate for prevention at 12 weeks [16].

Lower adherence to PrEP among youth compared to adults is likely due to multiple factors, including developmental, psychosocial, socio-economic, and structural variables. Multiple studies have described lower adherence to antiretroviral treatment among HIV-infected youth compared to HIV-infected adults, and may provide insight into barriers to adherence to PrEP for youth. Previously described considerations include declining caregiver support and increasing autonomy, as well as the importance of peer approval in the presence of stigma. Factors such as unstable or transient housing, food insecurity, access to providers, implicit biases, and poverty may disproportionately impact youth who may have less knowledge, experience, and social capital to navigate around these barriers [17].

TOLERABILITY AND SAFETY OF PREP

Trials to date have demonstrated overall safety and tolerability of TDF-FTC used for PrEP, though few studies have examined the safety and tolerability of PrEP in youth specifically. Because adolescence and young adulthood are times of marked physical and psychological development, there are potential adverse effects of PrEP that warrant additional consideration for youth.

Approximately 10% of people may experience mild to moderate nausea, abdominal pain, or headache within the first 4 weeks of starting PrEP. These symptoms are typically mild and self-limited, and often do not require that PrEP be discontinued, but there are reports of missing doses and discontinuing medication due to these side effects [5, 6, 7, 8, 14**]. The WHO recommends providing anticipatory guidance regarding this “start-up syndrome” to improve adherence [4*].

Several studies have described a small decrease in bone mineral density (BMD) of uncertain clinical significance among adult trial participants assigned to use TDF-based PrEP as compared to participants assigned to placebo [18, 19]. ATN 110 found similar modest decreases in BMD in young adults at risk of new HIV infection [14**]. Given that adolescence and young adulthood is a critical time for bone development, there is a concern that small decreases in BMD during this time may carry a more significant long-term risk of fracture. Youth who acquire HIV, on the other hand, face the BMD effects of HIV itself and lifelong treatment with medications that may also decrease their BMD. Fortunately, there is also evidence that the effect of TDF on BMD in PrEP users is reversible, with the greatest recovery among young participants under 25 years old [20]. The CDC and WHO do not currently recommend DXA scans for otherwise healthy individuals on PrEP [3, 4*].

Although TDF-FTC has been associated with nephrotoxicity in a minority of adult patients when used as PrEP [9, 21], the potential for renal harm in youth is likely low. In ATN 110 one participant out of 200 experienced a minor elevation of serum creatinine that self-resolved at follow up [14**]. In the iPrEx Open Label Extension study, clinically-significant decreases in renal function were rare among participants under 40 years old [22]. In PrEP trials, participants had to have a creatinine clearance of at least 60 ml/min to be eligible for trial participation. WHO guidelines recommend that clinicians monitor for changes in renal function by obtaining a serum creatinine prior to starting PrEP, quarterly during the first year, and annually thereafter [4*].

Adolescents may also face unique social risks when taking PrEP. In ATN 110, the parent of one participant threatened to evict him from his home if he did not stop taking PrEP [14**]. Providers should consider the social environment for individuals who use PrEP. Comprehensive behavioral health care and social supports for youth may be needed to optimize their PrEP-related outcomes and overall well-being.

Increases in risk behaviors among those on PrEP—known as “risk compensation”—have been described in few studies in adults. In a San Francisco-based study, 41% of 188 surveyed PrEP users reported decreased condom use since starting on PrEP. Rectal STI rates remained high during PrEP treatment, though there were no new HIV infections over a 12-

month study period when a high incidence (8.9 per 100-person-years) would have been expected in the absence of PrEP [23]. Other studies, including ATN 110, have found no evidence of risk compensation for those on PrEP, but did find high rates of STIs at baseline that were maintained throughout the study period, underscoring the importance of counseling, screening, and treatment of STIs, as well as PrEP adherence counseling, for youth on PrEP [9, 14**, 24].

Since the use of antiretrovirals for PrEP was introduced, there has been a theoretical concern about increasing drug resistance. In efficacy studies of PrEP, resistance mutations to TDF and FTC were more commonly detected only among those who acquired HIV just prior to starting PrEP (and were missed as acute HIV infections); resistance mutations were infrequently observed among participants who acquired HIV during the rest of the study period [5, 6, 7, 8, 11]. Thus, clinicians will need to take steps to exclude the possibility of acute HIV prior to prescribing oral PrEP, including assessing for recent signs or symptoms that could be consistent with acute HIV (e.g. flu-like symptoms, rash) and using more sensitive assays than routine antibody-based screening tests, such as HIV RNA assays, to rule out acute HIV when these symptoms are present [3]. Modeling studies suggest that levels of drug resistance associated with use of PrEP are likely lower than if PrEP is not used to prevent HIV [25].

OTHER CONSIDERATIONS REGARDING PREP FOR YOUTH

Youth Perspectives on PrEP

While adolescent and young adult perspectives on using PrEP are diverse—as expected given variations in values, knowledge, cultural norms, and concerns about stigma—youth are generally open to and interested in PrEP. A systematic review described strong interest and support for PrEP use among many younger populations at risk of HIV infection including adolescent girls and young women, youth who identify as transgender, and, to a lesser extent, youth who inject drugs [26]. Two recent mixed-method studies of MSM, one in Kenya and one in the UK, found that younger men were more willing than older MSM to take daily oral PrEP [27, 28]. A mixed-methods study in South Africa, found that 90% of 16–17 year olds reported that they would want to use PrEP if they had a partner who was HIV-infected or whose HIV status was unknown, or would support PrEP use for their partners [29]. One qualitative study that focused on young Black MSM ages 20–24 years in California identified stigma related to having multiple partners as a possible barrier to using PrEP in this group [30].

Healthcare Provider Perspectives on PrEP for Youth

Understanding adolescent healthcare provider knowledge, attitudes, and willingness to prescribe PrEP will be critical in the successful implementation of PrEP for youth. Few studies have examined providers' perspectives on PrEP specifically for adolescent and young adult patients. In some studies, clinicians have expressed concerns about potential challenges with adherence, adverse effects, high costs, and risk compensation for both adults and adolescents [31].

A “purview paradox” has been described in the U.S. among primary care providers and HIV-care providers such that HIV-care providers may have few opportunities to prescribe PrEP because they often see few HIV-uninfected patients. Yet primary care doctors—who may have more opportunity to provide PrEP to patients who are HIV-uninfected but at risk—describe concerns about feasibility given their limited experience with antiretroviral medications [32].

A recent U.S. survey study of family planning providers, who may be expected to provide care to youth, found they had limited knowledge of PrEP; although three quarters of respondents thought HIV education was an essential part of a family planning visit, only a quarter thought PrEP education was essential as a part of HIV prevention counseling [33]. When asked to consider PrEP specifically for adolescent minors, U.S. providers described additional concerns including lack of clarity about confidentiality laws and ability to consent patients without parental involvement [31]. In a mixed-methods study in South Africa, 100% of clinicians in an HIV-treatment clinic said they would prescribe PrEP to adolescents who were sexually active [29].

Providers well-positioned to offer PrEP to youth may be interested in doing so, but more education and information about PrEP is needed if it is to be an option in providers’ HIV prevention toolkit.

Legal And Financial Issues Affecting Access to PrEP for Adolescents

For adolescent minors below the age of legal adulthood, the lack of clarity regarding parental consent requirements and inconsistencies in other legal frameworks relevant to sexual and reproductive health may complicate efforts to provide PrEP to youth. A legal analysis of minor consent laws in the U.S. as they relate to PrEP found no laws that expressly prohibited minor access to PrEP or other HIV prevention methods. PrEP may be permitted by implication for adolescents in the eight jurisdictions (California, Iowa, Kansas, Montana, Nebraska, North Carolina, South Dakota, and the District of Columbia) that allow minors to consent to STI preventive care, since HIV can be considered an STI. In the remaining 43 jurisdictions, minors’ access to PrEP may rest on whether “treatment” is defined broadly (inclusive of prevention), or narrowly (only for diagnosed STIs). Of note, Title X-funded clinics must maintain confidentiality and cannot require parental consent, so therefore may represent privileged settings where minors could access PrEP confidentially [34].

Inconsistencies in legal frameworks related to adolescent HIV and sexual and reproductive health services have been described within and across Southern African countries, as well. For example, the age of consent for HIV counseling and treatment may be lower than the age of consent to sex and for other sexual and reproductive health services, and policies prioritizing focus on MSM exist in countries where same-sex sexual activity is criminalized [35].

Another issue specific to adolescent minors is the expense of treatment. One year of TDF-FTC costs more than \$10,000, and while pharmaceutical company cost-support programs are available to adults, adolescents do not currently have access because use of PrEP for

adolescents is considered off-label. At the same time, cost effectiveness of PrEP has been shown to depend on in which age groups PrEP is promoted; the cost of preventing each HIV infection is lower when PrEP is provided to adolescents [36].

CURRENT RECOMMENDATIONS REGARDING PREP FOR YOUTH

The WHO recommends offering daily oral PrEP to all populations at “substantial risk”—defined as those with an incidence of HIV above 3 per 100 person-years—without specification regarding age [4*]. The U.S. Food and Drug Administration labeling information for TDF-FTC includes an indication for use as HIV treatment in adolescents ages 12 years and older, though for use as PrEP, the indication for TDF-FTC is limited to “adults,” without specifying the age of adulthood [37]. The U.S. CDC leaves room for prescribing oral PrEP for adolescents. They cite the relative lack of data for youth and recommend careful consideration of the potential risks and benefits of providing PrEP for adolescents under the age of 18 years [3].

In light of the high and increasing rates of new HIV infections among adolescents in the U.S., and a preponderance of data suggesting that PrEP is highly protective in diverse populations when used with adequate adherence, there is clear need to move forward with efforts to implement PrEP among youth. Table 2 provides a summary of general clinical recommendations for PrEP in youth. We recommend case-by-case consideration of PrEP use by those under 18 years old. For adolescents, we encourage discussion about involving a parent/guardian, and advise parent/guardian involvement when it is safe to do so. We also recommend awareness of local consent, confidentiality, reporting, and parental disclosure laws [38**].

FUTURE DIRECTIONS

Strategies to improve youth adherence to oral daily PrEP are currently being investigated [39, 40]. The use of phone text reminders, peer support, and phone apps each may have potential to increase adherence, and thereby effectiveness, of daily oral PrEP.

Fixed-dose combined tenofovir *alafenamide* and emtricitabine (as opposed to tenofovir *disoproxil fumarate* and emtricitabine) has recently been approved for HIV treatment and is now in trials to assess safety and efficacy for use as daily oral pre-exposure prophylaxis [41]. Evidence thus far suggests a more favorable adverse effect profile including less impact on bone density [42].

There are also clinical trials underway investigating the safety and efficacy of different mechanisms of delivery of various antiretrovirals and other biomedical modalities for the purpose of PrEP. For example, other forms of PrEP currently being studied include long-acting injectables with cabotegravir, an HIV integrase inhibitor, intravaginal rings with dapivirine, a non-nucleoside reverse transcriptase inhibitor, a monoclonal antibody infusions against HIV, and novel HIV vaccine strategies [43*]. Choice of method and availability of longer-acting PrEP may improve adherence and effectiveness for adolescents and young adults. The landscape of HIV biomedical prevention interventions is likely to evolve, as did

the landscape of pregnancy prevention options following the introduction of oral contraceptives.

CONCLUSION

When considering the unfavorable trajectory of the HIV epidemic in adolescents and young adults, as well as the evidence to suggest a protective benefit of PrEP in this population, it is clear that improving access and adherence to daily oral PrEP for youth are current public health priorities. Many youth likely to benefit from PrEP appear interested in accessing this intervention. It is up to providers, public health authorities, and advocacy organizations to advance PrEP implementation for this population. The availability of effective daily oral PrEP represents a landmark in HIV prevention innovation and the future holds promise for PrEP to have a substantial impact not only on the HIV incidence among youth but also on the HIV epidemic globally.

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KEY POINTS

- PrEP with daily oral TDF-FTC is safe and effective when used in combination with other prevention strategies for reducing the likelihood of acquiring HIV in diverse populations at risk.
- For adolescents and young adults, low adherence is a barrier to effective use of PrEP.
- Improving youth access and adherence to PrEP is a public health priority.
- Further innovation in PrEP adherence strategies and new delivery mechanisms is expected.

Table 1

Summary of phase III trials examining efficacy of oral PrEP.

Trial Name (Location)	Study Population	Number Enrolled	Intervention	Median age (range)	Young Adults N (%)	Efficacy (%), Modified Intent-To-Treat Population (95% CI, p-value)	Efficacy (%) by Age Group (95%CI)
TDF 2 (Botswana) [5]	Men and women	1219	Daily TDF-FTC	25 (18 – 39)	18–20 years: 25 (2)	62.2 (21.5–83.4, p=0.03)	Unavailable
Partners PrEP (Kenya, Uganda) [6]	Serodiscordant couples	4758	Daily TDF-FTC, Daily TDF	Women: 33 (18 – 65) 34 (18 – 65)	18–24 years: 533 (11)	TDF: 67 (44–81, p<0.001); TDF-FTC: 75 (55–87, p<0.001)	TDF 18–24 years: 72 (–1 – 92)
							TDF 25 years: 66 (39 – 82)
							TDF-FTC 18–24 years: 41 (–61 – 79)
							TDF-FTC 25 years: 83 (63 – 93)
CDC 4370 Bangkok Tenofovir Study (Thailand) [7]	PWID	2413	Daily TDF	31 (20 – 60)	Unavailable	48.9 (9.6–72.2, p=0.01)	20–29 years: 33.6 (–40.1 – 69.8)
							30–39 years: 29.2 (–121.7 – 79.1)
							40 years: 88.9 (41.1 – 99.4)
iPrEx (US, Brazil, Peru, Ecuador, Thailand, South Africa) [8]	MSM, TGW	2499	Daily TDF-FTC	27* (18 – 67)	18–24 years: 1153 (46)	44 (15–63, p=0.005)	18–24 years: 33 (–14 – 60)
							25 years: 59 (13 – 76)
IPERGAY (France, Canada) [9]	MSM	400	"On demand" TDF-FTC	TDF-FTC: 35 (29 – 43**) Placebo: 34 (29–42**)	18–24 years: 58 (14.5)	86 (40–98, p=0.002)	Unavailable
FEM-PrEP (Kenya, South Africa, Tanzania) [10]	Women	2120	Daily TDF-FTC	23 (18 – 35)	18–24 years: 1213 (59)	6 (–52–41, p=0.81) (stopped early)	18–24 years: 3 (–73 – 46)
							25 years: 9 (–106 – 60)

PWID (people with injection drug use); MSM (men who have sex with men); TGW (transgender women)

Interquartile range
**
Mean
*
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Table 2

Summary of clinical recommendations for PrEP [3, 4*, 38**].

Risk assessment	<ul style="list-style-type: none"> Indicated for those at "substantial risk" of HIV infection based on local epidemiology and individual assessment *
Eligibility	<ul style="list-style-type: none"> 18 years old (consider on individual basis for adolescent minors) Normal renal function (creatinine clearance ≥ 60 ml/min) Negative HIV antibody test within prior week Negative HIV viral load (if acute "flu-like" symptoms) Negative HBsAg Negative pregnancy test Able to adhere to daily medication and follow up
Counseling	<ul style="list-style-type: none"> PrEP is effective when taken daily Encourage other HIV prevention methods (e.g. condoms and dental dams, sterile injection materials) Counsel that PrEP should be taken for 7 consecutive days to reach maximum drug levels in anal tissues; at least 20 days daily use are needed to reach maximum drug levels in cervicovaginal tissues or blood Provide individualized adherence support Anticipatory guidance regarding "start up syndrome"
Follow up every 1–3 months	<ul style="list-style-type: none"> Repeat HIV antibody test STI screening Repeat pregnancy test Repeat serum creatinine every 3 months for the first year, annually thereafter Assess side effects, adherence, risk-reduction behaviors Provide non-judgmental support for medication adherence and risk-reduction behaviors
Discontinuation	<ul style="list-style-type: none"> If no longer at substantial risk

* Per WHO, this includes but is not limited to: some groups of MSM, transgender women in many settings, HIV-negative persons with HIV-positive partner