

# HIV Preexposure Prophylaxis Among Adolescents in the US

## A Review

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**IMPORTANCE** Many adolescents and young adults in the US are disproportionately affected by HIV. Several others who are uninfected are at risk and in need of effective preventive strategies. The uptake rate of preexposure prophylaxis (PrEP) for HIV prevention has remained low among US adolescents. This review assesses the current status of PrEP uptake among at-risk adolescents aged 13 to 19 years and recommendations for improving PrEP access, uptake, and future needed directions, including specific recommendations for health care professionals.

**OBSERVATIONS** Of the 37 377 new HIV diagnoses made in 2018, 7734 diagnoses (21%) occurred in adolescents and young adults aged 12 to 24 years; of these, 1707 diagnoses (22%) occurred in adolescents aged 13 to 19 years. The greatest burden of HIV is found among young African American men who have sex with men, accounting for two-thirds of all HIV infections in adolescents and young adults. Preexposure prophylaxis awareness and engagement are lowest in adolescents with the greatest risk for HIV. Adolescent primary care clinicians and specialists do not routinely offer HIV testing as recommended by the Centers for Disease Control and Prevention or routinely assess sexual risk exposures of patients through sexual history taking. Clinicians' decision to prescribe PrEP for adolescents is often guided by their perceptions of the patient's HIV risk and their knowledge and acceptance of PrEP guidelines. State laws on consent, confidentiality, and the rights of the adolescent to independently access PrEP outside of parental influence differ across jurisdictions, often limiting access and uptake.

**CONCLUSIONS AND RELEVANCE** Use of PrEP in adolescents at risk for HIV is an important component of HIV prevention. Optimizing uptake includes improving clinicians' knowledge about HIV risk and prevention strategies, enhancing sexual history taking and risk assessment through training and retraining, and improving PrEP knowledge and acceptance of prescribing among clinicians. Leveraging the ubiquity of social media, encouraging family support, and performing research aimed at finding lifestyle-congruent formulations can help mitigate HIV transmission in adolescents at greatest risk for HIV.

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In 2018, the US Food and Drug Administration approved a fixed-dose combination of tenofovir disoproxil fumarate with emtricitabine as oral preexposure prophylaxis for HIV prevention in adolescents weighing 35 kg or more.<sup>1</sup> A second combination drug, tenofovir alafenamide with emtricitabine, was approved 1 year later.<sup>2</sup> The decision, 7 years following the initial approval for adults,<sup>3</sup> was a response to the rising need to prevent HIV transmission in adolescents and young adults and the availability of data specific to adolescents.<sup>4</sup> The incidence rate of HIV in adolescents and young adults is the second highest in the US, surpassed only by the incidence of HIV in individuals aged 25 to 34 years. Of the 37 377 new HIV diagnoses made in 2018, 7734 diagnoses (21%) occurred in adolescents and young adults aged 12 to 24 years; of these, 1707 diagnoses (22%) occurred in adolescents aged 13 to 19 years.<sup>5</sup> While overall HIV transmission rates may have declined by 19% in the past decade,<sup>6</sup> adolescents and

young adults remain a high-priority population in need of HIV preventive approaches. Racial/ethnic disparities characteristic of other age groups also extend to adolescents and young adults; black and Latinx youths represent only 28% of the 13- to 24-year age group but account for 77% to 82% of new infections in this population.<sup>7,8</sup> In addition to disparate racial/ethnic burdens, members of identified key populations, ie, sexual and gender minority groups, particularly gay, bisexual, and other men who have sex with men (GBMSM), transgender females, youths who engage in transactional sex, youths who inject drugs, heterosexual girls in serodiscordant partnerships, and other individuals at the intersection of these categories, are also at increased risk for HIV acquisition.<sup>5,9</sup> HIV transmission is high among young GBMSM individuals (a priority group) compared with other risk groups, composing 93% of all youth HIV diagnoses in 2018.<sup>8</sup> These varied and overlapping risk groups reinforce the need for

effective, innovative, and scalable multipronged approaches to HIV prevention in adolescents.

The United Nations defines an adolescent as any person between age 10 and 19 years.<sup>10</sup> Adolescence is a developmental period between childhood and adulthood characterized by physical, sociopsychological, and emotional changes.<sup>11</sup> The spectrum of changes characteristic of adolescent individuals encompasses abstract thinking, self-concept, social learning, and conduct.<sup>11</sup> Adolescents transitioning to adulthood are inclined to seek new experiences, which is an adaptation necessary for the development of independence, identity, and self-sufficiency.<sup>12</sup> This transition often entails sexual exploration that predisposes individuals to the acquisition of HIV and other sexually transmitted infections (STIs). According to the 2017 Youth Risk Behavior Survey, a national survey of high school students in grades 9 through 12, nearly one-third of high school students are sexually active and more than 40% engaged in unprotected sexual intercourse during their last sexual encounter. Yet, only 9.3% of these students have had an HIV test, not counting tests preceding blood donations.<sup>13</sup>

Statistical data on HIV are typically reported together for pubertal (10-17 years), immediate postpubertal (17-19 years), and young adulthood (20-24 years) ages. Cognitive differences (differing capacities for abstract, intellectual, and moral reasoning), a lower vs heightened sense of self-identity and worth, and a declining propensity for risk with increasing age differentiates the adolescent from the young adult.<sup>11</sup> These differences dictate that the uptake of PrEP among adolescents aged 13 to 19 years be discussed as a distinct group. The study of PrEP uptake in adolescents is warranted given the unique idiosyncrasies and distinguishing features that set adolescents apart from young adults.

## Data Sources

We searched PubMed (MEDLINE) and Embase for English-language articles published between January 1, 2009, through October 20, 2019, focusing on PrEP uptake among adolescents and young adults in the US. Search strategies were based on a combination of controlled vocabulary, related key words, and the Medical Subject Headings. We searched for the key words *preexposure prophylaxis uptake*, *HIV*, *PrEP*, *adolescents*, *youth*, and *United States* or *US*. We focused on articles published in the last 10 years but included older publications that are highly relevant or commonly referenced. Additional references from seminal articles were reviewed to ensure that important contributions were not excluded. Fifty-eight articles were selected for inclusion based on their relevance to PrEP uptake among US adolescents or youths. Statistical data are presented for adolescents (aged 13-19 years) alone as available and for both adolescents and young adults (aged 13-24 years) when no adolescent-specific information appeared to be available.

## Adolescent PrEP Studies in the US

The first adolescent clinical trial on PrEP (ATN 113) was conducted by the Adolescent Medicine Trials Network for HIV/AIDS in 78 adolescent GBMSM aged 15 to 17 years.<sup>4</sup> The goal was to elucidate the association between PrEP and HIV prevention and evaluate its safety and adherence profile in this age group. In the study, adherence, defined as consistent intake of 4 or more doses of oral tenofovir diso-

proxil fumarate with emtricitabine per week (confirmed by blood levels) progressively waned from 54% at 4 weeks to 22% at 48 weeks. A precipitous decrease in adherence was also observed when follow-up visits were spaced from monthly to quarterly—an indication that frequent follow-up visits may be required to achieve and sustain adherence in adolescents. Poor medication adherence was associated with an HIV incidence rate of 6.4%,<sup>4</sup> which was the highest ever recorded in a PrEP trial of GBMSM compared with other trials.<sup>14</sup>

## PrEP Uptake and Awareness

At present, public awareness about the existence, availability, and indications for PrEP remain limited among adolescents in the US.<sup>15,16</sup> In a New York study of adolescents' PrEP awareness, two-thirds of adolescents were unaware of the existence of PrEP and 86% of those eligible for PrEP reported never being informed about PrEP by their health care professionals.<sup>15</sup> Modest uptake of PrEP among persons with the greatest risk for HIV is a common denominator across studies,<sup>17,18</sup> and adolescent GBMSM and transgender women, both target groups for HIV prevention, paradoxically know the least about PrEP.<sup>19,20</sup> Paucity of knowledge on PrEP has been associated with sexual risk behaviors,<sup>21</sup> and awareness is a well-recognized step toward PrEP uptake. A significant difference in PrEP uptake exists between adolescents and adults; although up to 10% of adults at risk for HIV have been prescribed PrEP (Scott McCallister, MD, Gilead Sciences Inc, written communication, August 13, 2019),<sup>22</sup> only 1.5% of adolescents younger than 18 years in the same category are receiving PrEP.<sup>23</sup> Of these adolescents, 83.5% are heterosexual girls with a relatively lower risk for HIV.<sup>23</sup> Data on PrEP initiation from the manufacturer (Gilead Sciences Inc) indicate that less than 5% of individuals receiving new PrEP in 2012 were adolescents. Although the total number of adolescent PrEP prescriptions has since increased, the proportion of total prescriptions provided to adolescents progressively declined to less than 0.6% in 2018 (Figure) (Scott McCallister, MD, Gilead Sciences Inc, written communication, August 13, 2019).

## The Role of Health Care Professionals

Despite recommendations for routine HIV testing of persons aged 13 to 64 years by the Centers for Disease Control and Prevention<sup>24</sup> and the US Preventive Services Task Force,<sup>25</sup> most adolescent specialist and generalist care clinicians do not routinely offer HIV testing.<sup>26</sup> Many primary care clinicians are either unaware of the recommendation to routinely test adolescents or do not see the need.<sup>27</sup> Other clinicians have expressed concerns about patients' discomfort with discussing HIV risks, preferring to test only at patients' request.<sup>26</sup> Notwithstanding, HIV testing remains an essential component of HIV prevention and the initial step toward PrEP initiation.<sup>25</sup> The prescribing of PrEP by clinicians is associated with their personal convictions<sup>28</sup> and confidence in their understanding of the PrEP guidelines.<sup>29,30</sup> Many primary care clinicians consider PrEP to be beyond their purview.<sup>26</sup> A study on adolescent HIV care professionals' attitudes toward the Centers for Disease Control and Prevention's 2015 PrEP guidelines showed substantial variability in the professionals' understanding of high-risk groups, with many expressing uncertainties about the indications for PrEP in adolescents.<sup>31</sup> The purview paradox, in which adolescent HIV care specialists cannot prescribe PrEP because their patients are already HIV positive,

and PrEP-eligible clients are managed by generalists less versed in HIV risk assessment and PrEP prescription, also contributes to limited uptake.<sup>32,33</sup> Additional barriers to PrEP prescription include the clinician's perceptions of adolescents' capacity for adherence to use of daily medications and legal concerns about confidentiality and consent in unaccompanied adolescents.<sup>16,29</sup>

### Consent, Confidentiality, and the Rights of a Minor

States and jurisdictions across the US have enacted laws that allow adolescents to consent to services independently of their parents or guardians.<sup>34</sup> Specific statutes and provisions to these laws vary by jurisdiction, and provision of PrEP and other HIV prevention services to adolescents is often muddled by the ambiguity of confidentiality and consent laws.<sup>35</sup> Variations in medicolegal protections of adolescents' right to confidential health care access present a barrier to PrEP initiation for many adolescents who wish to keep their sexual identities a secret from their parents or guardians.<sup>35,36</sup> While it is unclear in many jurisdictions whether adolescents' legal ability to consent to other sexual and reproductive health services extends to PrEP, legal statutes do not prohibit the prescription of PrEP for adolescents without parental consent. Furthermore, several jurisdictions have considered or passed statutes allowing adolescents to consent to PrEP medications and other HIV prevention services.<sup>37</sup> The Health Insurance Portability and Accountability Act of 1996, which establishes the confidentiality of health information, also applies to adolescents for health services for which they can legally consent independently of a parent or guardian.<sup>38</sup> These statutory protections are reassuring in theory. However, in practice there are several gaps that continue to create barriers to PrEP for adolescents even within jurisdictions that specifically permit minors to consent. Many of these gaps are related to disclosures to parents through explanation of benefits from third party payers.<sup>39</sup> Adolescents who rely on their parents' health insurance plans have lower odds of accepting PrEP<sup>34</sup> and situations that require confiding in parents/guardians about adverse effects, the disclosure of sexual identity, or sexual risk exposures discourage its acceptance.<sup>40</sup>

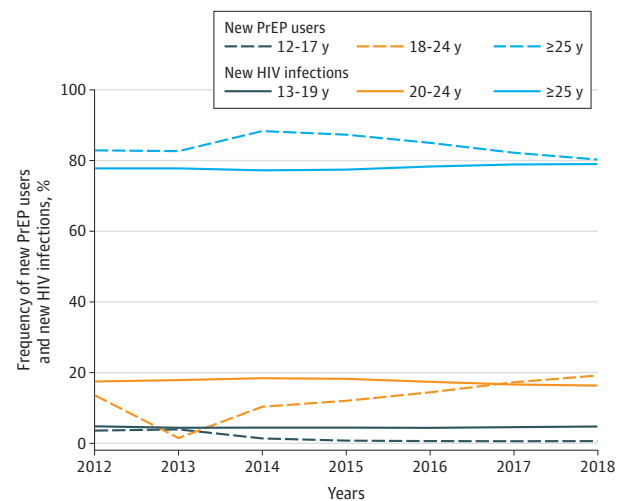
### Cost and Availability

The cost and uptake of PrEP are closely associated, especially for adolescents.<sup>40</sup> The prohibitive cost of PrEP is covered by many insurance plans and assistance programs for partially insured and some uninsured adults.<sup>41,42</sup> In contrast, PrEP for adolescents is a relatively new concept and modalities for payment assistance are limited. Medication assistance and insurance copay programs offered by Gilead Sciences are currently unavailable to adolescents<sup>43</sup> and, while this is expected to change with time, it is presently a drawback. The sum total cost of PrEP extends beyond the scope of prescription costs to laboratory and health care professional fees and mandatory follow-up visits.<sup>44</sup> Thus, adolescents are vulnerable to financial barriers that limit access to PrEP services.<sup>33</sup>

### Optimizing PrEP Uptake

Given the aforementioned high STI rates and increased risk of HIV acquisition for some adolescents, the limitations and challenges of current PrEP mitigation and practice, it is critically important to discuss ways to mitigate these challenges and optimize prevention for adolescents.

**Figure. Comparison of New HIV Infections and New Preexposure Prophylaxis (PrEP) Users in the US by Age Group, 2012-2018**



Data from Gilead Sciences (Scott McCallister, MD, Gilead Sciences Inc, written communication, August 13, 2019) and Centers for Disease Control and Prevention.<sup>5</sup>

Technological interventions are becoming increasingly popular, serving as delivery tools for sexual health information and for promoting HIV testing and medication adherence.<sup>45,46</sup> Widespread media and internet coverage led to a 50% increase in PrEP awareness over a 3-year period.<sup>47</sup> The success of social media, gaming apps, and ubiquitous internet access have since been used in PrEP campaigns and have proven beneficial. For example, in an online to offline intervention that recruited GBMSM and transgender women online (approximately 5% < 18 years), 53% of participants who agreed to a clinic visit began PrEP.<sup>48</sup> Participants in the study were more likely to seek sexual partners and health information online compared with non-GBMSM, which is an increasingly common practice with GBMSM and transgender women<sup>49</sup> that creates a ready pool of youths for recruitment into internet-based studies, outreaches, and HIV interventions. The outcomes of social media messaging are potentially far reaching.<sup>50</sup>

In addition, adolescents tend to be receptive to information presented by social influencers or persons perceived as popular or cool, as demonstrated by a study that incorporated health educational content into entertainment pieces of popular celebrity icons.<sup>51</sup> The Centers for Disease Control and Prevention's Act Against AIDS campaign uses this opportunity to engage internet influencers and on-site ambassadors in its HIV prevention messaging targeted toward identified key populations.<sup>52</sup> This and other strategic means of promoting PrEP uptake are outlined in the Box.

Access to youth-friendly health services in schools and at the community level may influence the health of adolescents.<sup>53</sup> Linkage of comparable services to PrEP can facilitate communal participation and promote a sense of ownership as seen with certain community-focused interventions.<sup>54</sup> By the same token, parents and guardians have key roles in the sexual health choices of adolescents.<sup>16</sup> Parental reactions to disclosure of sexual identities by GBMSM can range from ready acceptance to outright rejection, withdrawal of family support, verbal abuse, and violence.<sup>55</sup> Supportive parents

**Box. Strategies to Improve PrEP Uptake in Adolescents****Knowledge/awareness**

Adolescent-directed support groups  
 Integration of PrEP into school health programs  
 Social media campaigns  
 Key population targeted messaging  
 Physician- or other professional-initiated patient education  
 Comprehensive sex education and HIV/STI prevention programs

**Acceptability**

Adolescent-congruent, technology-centered messaging  
 Availability of on-demand formulations (using medications only at times of exposure)  
 Stigma reduction through continued community education and awareness  
 Provision of youth-friendly PrEP care centers  
 Integration of PrEP services into primary or general adolescent health care  
 Culturally appropriate messaging  
 Messaging by celebrities or other influencers  
 Strengthening of relationships between parents/guardians and adolescents  
 Ensuring confidentiality of adolescent's communication with physicians and other professionals  
 Community engagement  
 Availability of implants and other long-acting alternatives to oral PrEP

**Confidentiality/consent laws**

Harmonization of consent laws across states  
 Guarantee of confidentiality to minors when desired

**Health care professionals**

Training and retraining of generalist health care professionals on adolescent PrEP guidelines  
 Routine HIV risk history taking in all adolescents at primary care visits  
 Simplified and unified PrEP guidelines for physicians and other health care professionals  
 Engagement of community navigators in PrEP enrollment and follow-up  
 Use of HIV risk prediction tools for identifying adolescents at risk for HIV

**Financial limitations**

Expansion of medication assistance programs  
 Incorporation of comprehensive PrEP services into Title X programs  
 Subsidization of transportation and other related costs (eg, laboratory and health care professionals visits)

Abbreviations: PrEP, preexposure prophylaxis; STI, sexually transmitted infection.

risk.<sup>57,58</sup> When done correctly, uninhibited communication about sexuality between parents/guardians and adolescents raises adolescents' awareness and willingness to enroll for PrEP.<sup>16</sup> Open conversations are particularly pertinent in GBMSM and transgender women of color, who despite their greater need for support, face rejection and violence as a result of their sexual identity.<sup>59</sup>

Clinicians who encounter adolescents in a variety of settings need to be aware of PrEP and its potential value for HIV prevention in adolescents. They should, in a youth-friendly, confidential, and empowering way, ask about sexual interest, identity, and activity; test for STIs and HIV; offer prevention packages including risk reduction education and barrier methods; and, when indicated, prescribe PrEP. These steps should be repeated with each encounter as long as HIV risk is determined to persist. Clinicians should be familiar with treatment guidelines and become comfortable with sexual history taking before prescribing PrEP because comprehensive and nonjudgmental sexual history taking is a means of relaying relevant sex education and recommending PrEP to patients.<sup>59,60</sup> Taking a comprehensive, inclusive, nonjudgmental social and sexual history builds rapport, establishes trust, and informs education, counseling, risk stratifications, and risk reduction strategies, including PrEP.<sup>61</sup> The fear of invading a patient's sexual privacy, which prevents most clinicians from obtaining sexual history, must be overcome as part of efforts toward sensitizing adolescents to adopt PrEP as a component of multiple HIV prevention strategies.

Current PrEP guidelines stipulate that eligible clients must be screened for HIV before PrEP initiation, meet 1 or more indications for PrEP (eg, HIV-positive partner or multiple sexual partners and recent STI), attend quarterly follow-up visits, and undergo adherence counseling. Clinicians are expected to be abreast of adolescent-centered PrEP guidelines, laws, and the nuances between adolescents and adults— factors that significantly improve clinicians' confidence and willingness to encourage PrEP use by patients.<sup>28,31</sup> Maintaining up-to-date knowledge is particularly important to clinicians practicing in areas with high HIV incidence and prevalence, such as the 48 counties in the Ending the HIV Epidemic: A Plan for America campaign.<sup>62</sup> Generalists and family physicians can garner the skills to identify adolescents in need of PrEP through practical training.<sup>63</sup> Newer screening and HIV risk prediction tools have been tested and may aid generalists in identifying at-risk adolescents for active screening and subsequent PrEP initiation.<sup>64</sup>

**Research Needs for Adolescents**

As ongoing clinical trials seek to expand the HIV prevention toolbox, it is increasingly important to recognize the relevance of research to the prevention of HIV transmission in adolescents.<sup>65</sup> At present, adolescents are poorly represented in sexual and reproductive health research, including HIV. In a 2017 study conducted to examine the extent to which adolescents are included in clinical trials, barely 9% of studies on STIs, HIV, PrEP, or related fields recruited adolescents. Of these, only 1 of the 10 studies with adolescents was limited to adolescent participants.<sup>66</sup>

The challenges of enrolling adolescents in biomedical research relate to ethical concerns, particularly the acceptability and uncertainty associated with administering novel and unproven treatments to a physiologically maturing and vulnerable group. Parents

aware of their children's homosexuality often express concerns about their well-being and sexual risks.<sup>56</sup> Such support facilitates communication about sex with adolescents, which in turn encourages routine HIV testing, healthy sexual choices, and a reduction in HIV



and guardians are wary of the potential risks of engaging in such trials (ie, drug toxic effects and adverse reactions, and development of drug resistance owing to nonadherence),<sup>67</sup> and vulnerable adolescents are less likely to participate in trials in which parental consent is required. However, exclusion of adolescents from clinical trials also presents an ethical dilemma. When adolescents are systematically excluded from research on conditions that directly affect their health and well-being, Belmont Report's 3 basic ethical principles—respect for persons, beneficence, and justice—are violated.<sup>68</sup> Adolescent-tailored research trials are indispensable to determining the efficacy, feasibility, acceptability, and pharmacokinetics of biomedical interventions and are, therefore, a necessity.<sup>4</sup> Extrapolation of findings from adults to adolescents is a less challenging task than conducting research on adolescents but is often insufficient.

## Addressing Drug Toxic Effects and Adverse Reactions

Adolescents' responses to medications may differ markedly from adults,<sup>69</sup> although constitutional symptoms, such as nausea, diarrhea, mild weight loss, and anorexia associated with tenofovir disoproxil fumarate with emtricitabine are common and independent of age.<sup>70,71</sup> Prolonged use of tenofovir disoproxil fumarate, an integral component of PrEP in adults, may result in renal and bone toxic effects that are reversible when treatment is stopped. The long-term sequelae of tenofovir disoproxil fumarate use on adolescent bone maturity is still being studied but results from the first clinical trial showed a higher rate of bone resorption after a 48-week period.<sup>71</sup> Further studies may be needed to understand the extent of bone resorption with prolonged use of PrEP as well as any clinically significant consequences. While it is not devoid of the constitutional symptoms seen with tenofovir disoproxil fumarate with emtricitabine,<sup>72</sup> renal and bone toxic effects are lower in the more recently approved PrEP agent, tenofovir alafenamide with emtricitabine, and may improve tolerability in adolescents.

Even with the adverse effects and risk of toxic effects that accompany tenofovir disoproxil fumarate with emtricitabine-based PrEP in adolescents, this combination drug remained the singular biomedical intervention for preventing HIV transmission until recently.<sup>1</sup> It remains to be seen how the approval of tenofovir alafenamide with emtricitabine will influence the PrEP landscape for adolescents. The low uptake of PrEP witnessed so far calls for more acceptable, and lifestyle-congruent PrEP formulations and strategies (eg, on-demand strategies, and long-acting oral, injectable, and implantable modalities) in the future.<sup>73</sup> In the meantime, the continued use of tenofovir disoproxil fumarate with emtricitabine must be carefully considered and the benefits of HIV prevention weighed against the risk of toxic effects when prescribing for adolescents until such a time when safer alternatives become routinely available.<sup>74</sup> Lessons learned from current PrEP availability and uptake will likely be relevant to any of the newer modalities.

## Conclusions

There is a rising risk of HIV transmission among adolescents in the US. Although effective, PrEP remains unpopular, especially among at-risk adolescents, owing to limited awareness, social and structural limitations to access, equivocal consent laws, clinician-associated factors, and financial inaccessibility. As the HIV biomedical prevention armamentarium expands with the introduction of newer drugs, identification and transformation of individual, community, systemic, and organizational barriers remain necessary to increase the use of PrEP in this unique group.

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**Drafting of the manuscript:** Yusuf, Agwu.

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**Administrative, technical, or material support:** Yusuf, Fields, Griffith.

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