



The ongoing HIV epidemic in American youth: challenges and opportunities

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Abstract: The incidence of human immunodeficiency virus (HIV) infection has been decreasing in the United States overall, except among youth, and in particular among Black and Latinx young men who have sex with men (MSM). In this review we summarize key drivers of the HIV epidemic among youth, as well as novel interventions geared specifically towards combating the epidemic among high-risk populations. Many factors driving the HIV epidemic among youth are related to systemic inequities, including lack of access to healthcare, inadequate education, and internalized and experience homophobia and racism. Developmentally, youth may feel that they are invulnerable and be willing to engage in risks. Moreover, HIV is often invisible for youth given advances in treatment and community stigma, limiting open discussion of risk and new preventive modalities. Outcomes from the HIV treatment cascade suggest that youth are less likely to be aware of their HIV infection status, less likely to link to and be engaged in care, and less likely to be virologically suppressed than older MSM and other populations of people living with HIV. Importantly, pre-exposure prophylaxis (PrEP) has been shown to be an effective tool for prevention of HIV infection that also appears to have disproportionately poor uptake among youth. Barriers to PrEP utilization appear to be quite heterogeneous, and include patient-, provider-, and structural-level barriers. Interventions important in improving HIV prevention will thus have to be multipronged and developed for culturally diverse populations. Cognitive behavioral therapy-based interventions are promising strategies as they are able to address a diverse array of barriers. New formulations of PrEP will also likely be instrumental in improving adherence. Since youth spend considerable amounts of time accessing digital media, the deployment of apps and other mobile phone-based interfaces offer unique opportunities to increase education and to facilitate HIV prevention for at risk youth. Multiple studies are underway to better inform the optimal delivery of treatment and prevention services for this complex and diverse population, and include novel sociobiological interventions and new modes of medication delivery that may lend themselves to overcoming obstacles specific to youth.

Keywords: Human immunodeficiency virus (HIV); youth; United States; MSM; pre-exposure prophylaxis (PrEP)

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Introduction

Modern antiretroviral treatment is highly effective in controlling human immunodeficiency virus (HIV) infection, preventing morbidity and mortality, and rendering virally suppressed persons non-transmittable, and pre-exposure prophylaxis (PrEP) is effective in protecting people not infected with HIV when used as directed. However, there remains significant transmission of HIV infection in the United States, particularly among youth.

Factors driving that disproportionate spread of HIV infection include structural issues such as poverty, racism, homophobia, and youth-specific cultural issues, such as their perceptions of invulnerability and lack of familiarity with HIV. Biological issues, as well, range from the efficiency of anal intercourse for HIV transmission to challenges in impulse control and planful thinking in the immature brain. In this narrative review we describe the epidemiology of HIV infection, PrEP use, and risk behavior among youth in the United States, and discuss the rationale for new and innovative targeted biobehavioral interventions that may facilitate enhanced uptake of preventive strategies and improved HIV medication adherence among at risk youth, who will continue to bear an increasing burden of HIV infection, unless new and effective approaches are brought to scale.

Epidemiology of human immunodeficiency virus (HIV) infection

In recent years, there have been nearly 40,000 new diagnoses of HIV infection in the United States (1), and 1.7 million new cases worldwide (2). Among many factors likely driving continued transmission in the United States, more than 13% of the 1.2 million people living with HIV are unaware of their infection (3). Furthermore, only 50% of those known to be infected are receiving effective treatment (3), thus there remains a large population of individuals who are infectious and capable of transmitting the virus to uninfected partners.

In the United States, continued HIV transmission seems to be of particular concern among minority youth. While the overall incidence of HIV infection has been stable or decreasing in most populations, the number of new HIV infections has increased among youth (*Figures 1,2*), particularly among Black and Latinx MSM, who bear the greatest burden of new infections (*Figure 3*) (4,5). In 2017, 21% of new HIV infection diagnoses were among

individuals between the ages of 13 to 24 years old, and were primarily (87%) among men (6). Among males, 93% reported male-to-male sexual contact as their mode of HIV infection, whereas 86% of females reported heterosexual contact (6). The prevalence of HIV infection increased with age, with 21% of cases in youth being diagnosed in those between 15 to 19 years, while the rest were between 20 to 24 years old (6). Furthermore, youth were less likely to be aware of their HIV infection status, with roughly 40% of those infected with HIV aware of the infection compared to the national estimate of over 85% of older individuals (7). Of new HIV infection diagnoses in 2017, 51% were among Black youth, and 25% were among Latinx individuals (6). The number of new HIV infection diagnoses reported in the United States was highest in the South. The increasing concentration of HIV in the South may reflect social and structural issues, such as decreased social mobility associated with poverty, limited access to health care because of a lack of health insurance, and lower average levels of education and health literacy (8). Among youth living with HIV in the South, 13% were economically dependent on a sex partner (8), which has been associated with increased sexual risk taking behaviors.

Behaviors associated with HIV acquisition among youth in the United States are similar to older populations, with the highest burden of HIV infection being among MSM and transgender women who engage in anal intercourse, and, to a lesser extent, people who share needles, and sex workers (7). It has been hard to elucidate specific HIV risk factors for young cisgender women, other than them having condomless sex with a male partner living with HIV. Because of the low rates of serostatus awareness and disclosure by some partners, it has been challenging to identify specific preventive guidance beyond knowing the HIV status of partners, and if infected, whether they are virologically suppressed. Of note, pregnancy and the post-partum period appear to increase the risk for HIV infection (8).

Youth in general are at particularly increased risk for HIV because of biologic and physical factors that occur uniquely during adolescence. The young brain is not fully mature until the mid-20's, which may partially explain impulsiveness and lack of planning (6). Many youth yearn for increasing autonomy from parents and caregivers, while placing increased importance on peer relationships resulting in enhanced vulnerability to peer influence. Those developmental issues may lead to increased risk-taking behavior as a part of experimentation, identity formation, and often in response to peer pressure, with

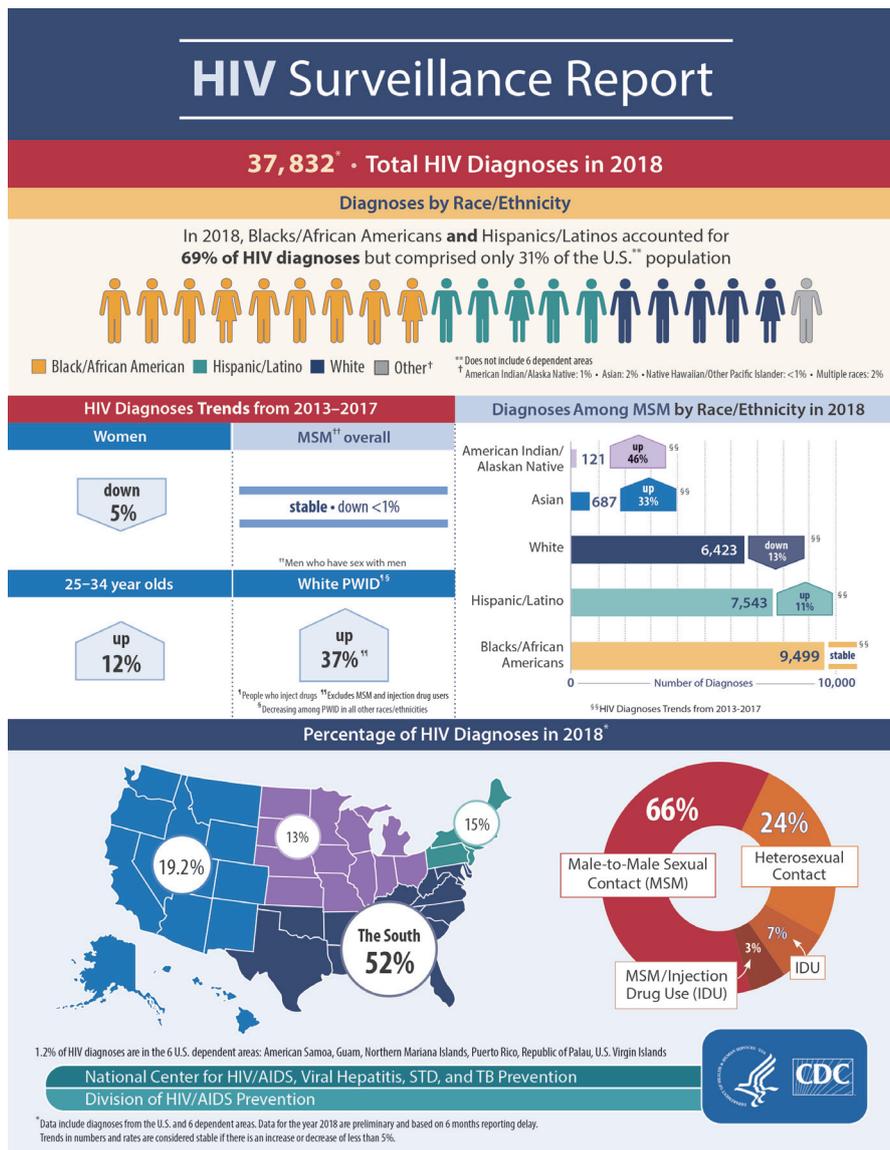


Figure 1 Center for Disease Control and Prevention 2018 HIV Surveillance Report indicating trends in HIV infection among different populations in the United States. HIV, human immunodeficiency virus.

minimal support structures (9). Stigma surrounding HIV infection, in particular, seems to be highly prevalent among youth in the United States, most notably in Southern states compared to Northeastern states (10), where community education and stigma reduction programs may be less prevalent, potentially limiting healthcare seeking behavior even further.

Black and Latinx young MSM appear to be at a disproportionate risk for HIV infection (6). The engagement of racial and ethnic minority youth with the healthcare

system is complex. Although young Black MSM in Chicago reported less high-risk sexual behavior and more HIV testing than young White MSM, they were less likely to achieve viral suppression after diagnoses, reflecting alienation from healthcare services perceived to be culturally insensitive (11). Network analyses, however, identified more homogeneity and higher rates of concurrent sex partners among young Black MSM, which suggests that the social network, rather than individual factors, may be a primary driver of the racial disparities in HIV infection among youth

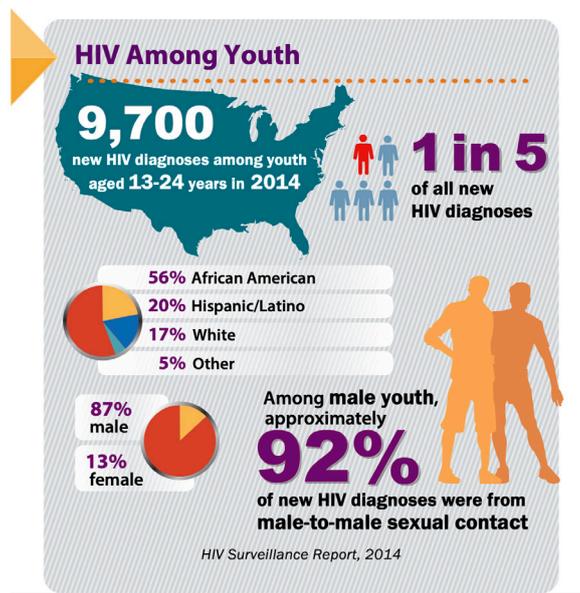


Figure 2 Data from the Center for Disease Control and Prevention 2014 HIV Surveillance Report demonstrating characteristics of youth in the United States who are living with HIV infection. HIV, human immunodeficiency virus.

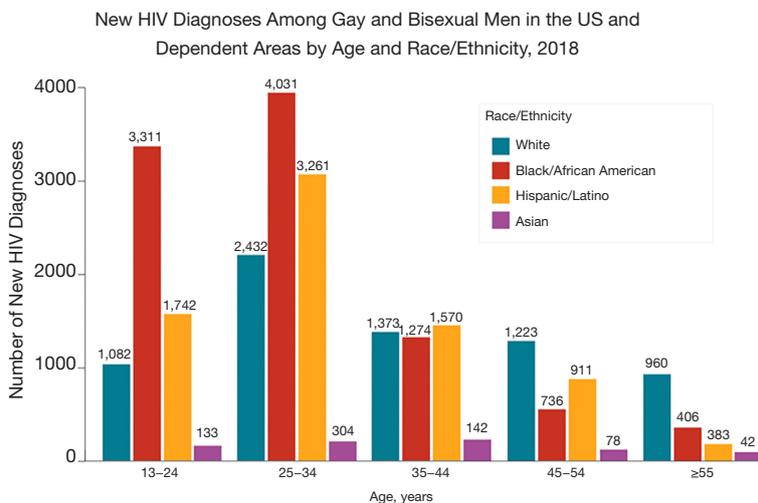


Figure 3 Prevalence of new diagnoses of HIV infection among men who have sex with men in the United States. HIV, human immunodeficiency virus.

(11,12). That pattern of behavior is known as assortative mixing, in which individuals are more likely to choose sex partners from within their own racial or ethnic group. That tends to concentrate HIV infection within subgroups, since HIV prevalence in the limited partner pool tends to be higher than among the larger population of non-minority MSM. Similar logic holds for network factors driving increasing rates of HIV infection among youth overall, as

such youth-focused networks may be more homogenous than their adult counterparts with HIV uninfected youth being more likely to encounter young partners who are not virally suppressed, compared to older individuals with HIV.

The HIV care continuum in youth

The HIV prevention and care continua are the cascades of

Table 1 Factors associated with reduced antiretroviral therapy uptake among youth linked to HIV care in the United States

Patient-level barriers	
Advanced disease	
Asymptomatic infection	
Substance use	
Frustration/dissatisfaction with the health system	
Fear or stigma	
Concomitant psychiatric disorders	
Socioeconomic barriers	
Limited health insurance	
Insufficient youth-friendly services	
Structured racism	
Lack of social support	
Housing insecurity	
Transportation challenges	
Medication related barriers	
Complex therapy regimen	
Anticipated or experienced side effects	
<hr/>	
HIV, human immunodeficiency virus.	

care that include bio-behavioral prevention strategies such as screening, risk-behavior counselling, and PrEP uptake, as well as linkage to antiretroviral therapy and follow-up care for HIV infection (13,14). Youth face challenges at every step of the HIV care continuum. Awareness of HIV infection status is significantly less among youth compared to adults (15). Using HIV testing as a surrogate for awareness of HIV infection, the Centers for Disease Control and Prevention found that HIV testing increased among youth with each increasing educational grade, among those who reported being educated about HIV and AIDS, and those reporting younger age at first sexual encounter (16). HIV testing may be more prevalent among young women compared to young men, and among young Black and Latinx populations (16,17). Other factors associated with increased HIV testing include a history of having a sexually transmitted infection, having three or more sexual partners in the preceding three months, inconsistent condom use, identifying as an MSM or female who has had sex with an MSM, substance use, or reporting sex with a partner known to be living with HIV infection

or of unknown infection status (18,19). Furthermore, youth using Medicaid, those with a primary care physician, and/or those who had received healthcare in the past year were more likely to have been tested for HIV (20).

However, once linked to care, initiation of antiretroviral therapy may be limited by several factors including unstable housing or substance abuse (21). Even after initiation, adherence to therapy can be a significant challenge for youth for a myriad of reasons (22-28). See *Table 1* for a summary of factors associated with reduced antiretroviral therapy use among youth connected to HIV care in the United States.

Retention in HIV care is also a challenge for youth beyond adherence to antiretroviral medications. Youth are less likely to be retained in care compared to adults (29,30). Lack of services for medical gender affirmation and experienced stigma in HIV care were independently associated with increased odds of missing an HIV care appointment in a study among young transgender women in the United States (31).

Further complicating the matter, viral resistance—either transmitted or developed as a consequence of poor adherence, drug interactions, malabsorption, or other causes—may result in poor viral suppression. The prevalence of transmitted HIV infection with resistance to first-line therapy among youth range from 9% to 18% in recent studies (32,33).

Thus, for diverse reasons youth are less likely to know their HIV infection status, be linked to or retained in care, adhere to antiretroviral therapy regimens, and to achieve and maintain viral suppression. Overall, estimates suggest that between 29% to 73% of youth aware of being infected with HIV engage in medical care within 12 months of diagnosis (15). Furthermore, only 54% of youth initiated on antiretroviral therapy achieve viral suppression, while more than half are not retained in care (15). In total, less than 10% of youth living with HIV in the United States achieve and maintain viral suppression (15).

Pre-exposure prophylaxis use and high-risk youth

PrEP using a combination once daily pill of tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) and emtricitabine (FTC) is an effective tool for the prevention of HIV infection, and when taken consistently, prevents more than 95% of infections (34,35). The effectiveness of PrEP, however, is highly dependent on medication adherence. Drug levels consistent with participants taking four doses of TDF/FTC per week

Table 2 Factors associated with reduced PrEP uptake among youth in the United States

Patient-level barriers
Lack of awareness
Lack of access to healthcare
Stigma
Poverty
Concerns about side effects or drug-drug interactions
Concerns about proper storage of medication
Lack of social support
Low perceived risk of HIV infection
Burden of daily-dosing
Burden of frequent clinic visits and lab testing
Structural barriers
Limited health insurance
Insufficient youth-friendly services
Stigma
Structural racism
Provider-level barriers
Lack of comfort prescribing to minors
The purview paradox
PrEP, pre-exposure prophylaxis.

have been associated with a 96% reduction in risk for HIV infection for cisgender men and transgender women who have sex with men, while levels consistent with daily use were associated with greater than 99% risk reduction for all populations; conversely, taking fewer than four doses per week may not provide adequate protection (34). Medication adherence is a particular challenge among young MSM (36). Furthermore, young MSM are more likely to engage in high-risk sexual behavior than older MSM (37), and are therefore at higher risk for HIV infection (38), suggesting their need for PrEP is greater than older MSM.

While PrEP uptake in the United States has increased in recent years, the uptake has been slowest among those younger than 24 years old (39). PrEP use in the United States among youth is lowest in the South and highest in the Northeast (39), a discrepancy which is likely driven by related disparities of healthcare financing, health literacy, stigma—all similar drivers of HIV infection among the same population. Youth are more likely to report a low

perceived risk for HIV infection (40), and thus may be less inclined to take PrEP, and, once started, younger men are more likely to discontinue PrEP (41). There are numerous barriers that drive such low PrEP uptake among youth (Table 2), which must be overcome in order to combat the HIV epidemic.

Patient-level barriers among youth include limited familiarity with antiretroviral medications, concerns about product storage, and lack of social support (38). Stigma is of particular concern as there may be individual as well as structural factors driving such perceptions. And beyond experienced stigma, anticipatory stigma may deter healthcare seeking in the first place. Other structural barriers include: limited health insurance and insufficient access to youth-friendly services (38). And finally, there are provider-level barriers. Although US-based clinicians specializing in Adolescent Medicine generally reported that prescribing PrEP in accordance with the 2012 Centers for Disease Control and Prevention guidelines was compatible with their practice (42), several prescribers preferred to prescribe to those 18 years of age or older because of their perceptions of ethical and legal issues when prescribing to a minor (42). The laws regarding the ability of adolescents to consent for treatment and prevention of HIV infection differ by state (43), thus further complicating prescribers ability to offer PrEP.

Specific populations with the lowest PrEP uptake include young Black and Latinx MSM, women (cis- and transgender), and people who inject drugs (8,44). Drivers of such disparities are multifactorial and often overlap. Lack of awareness about PrEP, particularly among Black MSM, was shown to be related to lack of access to healthcare. In general, young Black MSM with some access to healthcare (e.g., prior testing for sexually transmitted infections or with a documented primary care provider) were more likely to be aware of PrEP than those who had not been tested or who had not seen a primary care provider (45). Black MSM are also more likely than other races to report PrEP related stigma (46). Perceived racism and medical mistrust also contribute suboptimal PrEP uptake, particularly among racial and ethnic minority MSM (47). Among young Latinx MSM, a qualitative study noted specific barriers to PrEP including perceived burden of daily dosing, concern regarding risks associated with PrEP use as well as side effects (specifically renal injury and decreased bone density), stigma in their social environment, and finally provider influences discouraging PrEP use (48).

Another barrier to understanding PrEP uptake in young

MSM has been the limited number of research studies specifically focused on youth (49). There have been two PrEP safety and acceptability trials among youth in the United States (44,50). The Adolescent Trials Network (ATN) study 110 enrolled youth 18 to 24 and ATN 113 enrolled youth 15-17, but were essentially the same protocol, which evaluated PrEP adherence among youth randomized to an individualized versus a group behavioral intervention. Although both studies demonstrated safety and overall PrEP acceptability, over the course of 6 months, the majority of youth did not maintain protective PrEP levels and HIV incidence remained high. Interestingly, a large number of the youth had drug levels consistent with taking 2 to 4 pills a week. Such infrequency of dosing does not meet standards for sufficient HIV prevention, but seems to reflect an attempt to comply with the dosing regimen. Notably, both studies also documented a decline in adherence after three months, once the follow-up visits went from monthly to quarterly visits. That finding suggests that more frequent visit schedules for youth may be a strategy for improving adherence, which deserves further study. Similar findings have been reported in preliminary data from other ongoing international studies (51). A recent study confirmed the capacity of young Black MSM to self-consent to research, thus supporting youth autonomy, since requiring parental consent may inhibit youth's willingness to access PrEP and/or participate in prevention studies (52).

Young transgender populations constitute another sub-population at high risk for HIV infection who may benefit from, but who have notably poor uptake of PrEP (53). Again, a paucity of data limits our understanding of the perceptions about PrEP use and barriers to PrEP uptake among that population. Part of the reason for such limited data is the lack of participation from transgender youth in PrEP and HIV prevention trials, which may be related to a reluctance to discuss gender identity with study staff, the need for guardian consent, concerns over medication side effects, perceived burden of care (e.g., daily medication dosing and quarterly meetings), and lack of concern about HIV infection (54). Primary barriers to PrEP use among transgender and nonbinary youth in the United States include medication cost and concerns about drug interaction with hormone therapy (55), as well as fear of stigma (56). In one study, young male and transgender female sex workers in Puerto Rico expressed an interest in oral PrEP, but reported concerns about side effects as a primary barrier to use (57). Low awareness of PrEP was another barrier in a multi-center study of young transgender women in the

United States, which found that only 5% of PrEP-eligible individuals reported ever taking PrEP (58). Similar barriers have been reported among transgender adults from other countries (59,60).

Data from the United States are limited among youth who inject drugs. One study from Canada reported that younger age was associated with an increased willingness to use PrEP among people who inject drugs (61). Overall, however, willingness to use PrEP among people who use drugs may not be as high as in other high-risk groups, and is reportedly contingent upon demonstrable efficacy in preventing HIV infection (62). Notably, there have been trials demonstrating the benefits for PrEP use among people who inject drugs, though not specifically among youth who inject drugs in the United States (63). Primary barriers to PrEP use among people who inject drugs are similar to other high-risk groups, and include concerns about cost, frequency of dosing, condom use, and regular blood draws, clinic visits, and HIV testing (62). Integrating PrEP into substance abuse treatment settings, such as methadone clinics, is another promising strategy to overcome access barriers among individuals either currently on or seeking treatment for drug abuse (64), though acceptability specifically among youth remains to be studied.

Another important population for whom PrEP is underutilized is at risk young women. Challenges have included the identification of the young women who could benefit most from PrEP, given the challenges in ascertaining partners' risks. Additionally, the bar for adherence appears to be higher for women, requiring stricter adherence to daily pill use. Data generated from studies that enrolled women 18 years of age and older have suggested that higher adherence is necessary to establish effective drug levels of tenofovir and its active intracellular metabolite in cervical tissues compared to rectal tissues (65,66). Similarly, the time it takes to achieve protective levels in cervical and vaginal tissue may be significantly longer than in rectal mucosa. Thus, adherence is particularly important in young women, especially considering the potential for disinhibited sexual risk behavior among those taking PrEP (67). In addition, gender-related dynamics may complicate HIV prevention for young women. For example, one study noted that women who report an inability or reluctance to negotiate condom use may be more likely to experience partner violence (68). Thus, among young women, while PrEP may be intended as a tool for HIV prevention, issues like the potential for disinhibited sexual risk behavior, the heightened dependence on adherence, and how partners

react, could paradoxically increase the risks for HIV acquisition.

Novel strategies to improve HIV prevention among youth

There are limited data from trials evaluating interventions to improve PrEP adherence among youth. More frequent visits, as mentioned above, may be one approach unique to adolescents. Other interventions which may specifically improve PrEP use among youth include mobile and web-based applications, gamification, social interventions including relationship skill building and cognitive behavioral therapy-based interventions, as well as home PrEP delivery systems (69,70), all of which are under study in the University of North Carolina and Emory Center for Innovative Technology (iTECH) consortium. The iTECH consortium specifically aims to reduce the burden of HIV infection via the development and implementation of novel treatment and prevention strategies utilizing technology-based interventions among youth (71). One such intervention utilized a computer simulation model to evaluate the effectiveness of ongoing and forthcoming ATN interventions (72). The use of online and social media platforms as a medium for HIV and PrEP related interventions is also a vital component of novel strategies particularly among youth; such interventions facilitate content tailored to individual needs on a scale otherwise not feasible for in-person visits (73).

Given the unique, heterogeneous, and culturally complex framework limiting the HIV prevention continuum among youth in the United States, a holistic approach is warranted. A study among racially diverse minority (predominantly Black and Latinx) young MSM, demonstrated feasibility and acceptability of enrollment and retention in a PrEP study when the intervention was combined with a group-based behavioral intervention that was culturally-tailored to address HIV risk and the social stigmas experienced by being someone who is both a racial and sexual minority person (74). A separate cognitive behavioral therapy-based intervention originally developed for antiretroviral medication adherence was shown to be beneficial in improving PrEP adherence among adolescents in a pilot study (75), and is now the focus of an ongoing study using those same methods coupled with SMS reminders (76).

SMS-based interventions themselves may be an important intervention in isolation or coupled with other interventions among youth, given the recurrent findings of waning

adherence with less frequent clinic visits. Such reminders have been shown to augment short term behavior (77), and antiretroviral medication adherence (78,79).

Finally, reducing the burden of care that is associated with PrEP may target specific barriers identified among young high-risk populations. One ongoing study is evaluating the utility of a home-care system for PrEP which will obviate the need to travel to a clinician's office or laboratory for testing by incorporating at-home specimen collection and behavioral surveillance (80). Similarly, new formulations of PrEP which require a less rigid dosing regimen will likely improve adherence.

Future formulations of PrEP in the Pipeline

Important to any discussion of new formulations of PrEP is the preface that demonstrating similar effectiveness will be a challenge for clinical trials in the era of effective control and prevention strategies. That being said, there are several new formulations in the pipeline. However, any new formulation of PrEP alone will not be successful unless underlying youth-specific social, structural and behavioral issues are not fully addressed.

The United States Food and Drug Administration recently approved the use of Tenofovir alafenamide (TAF)/FTC combination pill (81). TAF is similar to TDF and has been shown to have less of an impact on renal and bone function, and can be administered at a lower dose (i.e., a smaller pill). A recent study comparing the preventative efficacy of TAF/FTC and TDF/FTC among MSM and transgender women demonstrated non-inferiority of TAF/FTC (82). TAF/FTC may directly address youth's concerns over side effects, however will likely still require daily dosing, until studies of alternative dosing regimens are completed.

There are efficacy trials underway for injectable, long-acting cabotegravir (an integrase strand transfer inhibitor) which can be dosed every eight weeks, and has previously been shown to be safe and well tolerated (83). Those ongoing studies include joint protocols sponsored by the ATN and the HIV Prevention Trials Network.

Similarly, there are ongoing trials evaluating implanted or transdermal antiretroviral medications that can be dosed every few months (84,85). Such formulations of PrEP may show much higher rates of adherence, particularly among youth, however, other logistic challenges will need to be addressed, such as ensuring that youth remember when they need to come to clinic for infrequent dose administration.

Other creative modes of delivery, including home visits, may be warranted, but will have to address concerns about stigma if they are to be successful. Furthermore, the risk of induced drug-resistant HIV infection is worth noting for any long-acting form of PrEP; as circulating drug levels fall below the threshold for protection upon discontinuation, a new exposure at that time may result in a resistant strain of the virus. Such a phenomenon is akin to what was noted in the PrEP efficacy trials among cases of PrEP initiation during acute HIV infection (86).

An intravaginal ring with dapivirine (a non-nucleoside reverse-transcriptase inhibitor) decreased the incidence of HIV infection in African women compared to placebo (87), and may specifically address the concerns over achieving optimally effective drug levels in cervical and vaginal mucosa with oral daily tenofovir-based regimens. Importantly, however, while studies have demonstrated a significant reduction in the incidence of HIV infection with consistent use of the dapivirine intravaginal ring, the level of protection was notably less than with oral PrEP (88).

Another preventive approach is immunoprophylaxis utilizing broadly neutralizing monoclonal antibodies (bnAb). Animal studies have been promising, and now efficacy trials are underway in humans evaluating one such antibody, VRCO1, which has been shown to be safe and well tolerated (89), while other bnAb with broader ranges of neutralizing activity are in development (90). Future studies will be necessary to evaluate optimal dosing regimens and while considering the challenges of maintaining adherence among youth. In future studies evaluating bnAbs or any other iteration of PrEP, explicit data among youth will be important for practical implementation to achieve meaningful preventive effectiveness.

Conclusions

Although effective treatment and prevention strategies for HIV infection have been developed, youth in the United States are still burdened with disproportionately high prevalence and incidence of infection. The uptake of prevention strategies, most notably PrEP, is also poorest among youth. Such disparities predominantly impact racial, ethnic, sexual and gender minority groups, and are driven by a heterogeneous and culturally complex set of factors, comparable to the diversity of youth populations in the United States. While new formulations of PrEP are in the pipeline and may address some youth-specific obstacles, much more work is needed to address the structural factors

that contribute to the perpetuation of HIV among those populations.

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