STUDENT ARTICLE

Pre-Exposure Prophylaxis (PrEP) for HIV Use in the Adolescent

Joseph Thomas Whelihan, BS[1]; Maureen Anne Novak, MD[2]
[1]4th Year Medical Student, University of Florida College of Medicine
[2]Professor of Pediatrics, University of Florida College of Medicine

INTRODUCTION

In 2018, 36.2% of new HIV infections in the United States were among persons aged 13-24 years, and 8.3% of infections were among individuals aged ≤19-years-old.[1] Data from the Centers for Disease Control and Prevention show relative stability of infection rates over the last decade in this age group.[1] The large proportion of affected young people highlights the pediatrician's role in preventing HIV infection in the United States.

Pediatricians have always played a large role in the prevention, screening, diagnosis, and treatment of sexually transmitted infections (STIs) in children and adolescents. Ideally, well child visits address "safer sex" practices and screening for intimate partner violence, STI risk, LGBTQ+ status, pregnancy risk, and other sexual health concerns. Given the high incidence of HIV infection in the adolescent and immediate post-adolescent period, it is crucial that pediatricians understand all of the tools in their repertoire to combat this epidemic.

In 2018, the U.S. Food and Drug Administration (FDA), expanded its approval of pre-exposure prophylaxis (PrEP) for HIV to the adolescent age group. The approval of PrEP in the adolescent age group gives pediatricians an additional tool to aid in the prevention of HIV infection. Despite approval, there are several barriers to the uptake of PrEP. There are only 100,000 individuals currently on PrEP of the 1.2 million individuals that have a strong indication to be on the medication in the United States.[2,3]

In Florida, the lifetime risk of an individual contracting HIV is 1 in 54 – making it one of the highest risk states in the country.[4] In 2018, there were over 110,000 people living with HIV in Florida with the highest burden of HIV among Black and Latinx populations.[5] Additionally in 2018, there were 4,573 Floridians with new HIV diagnoses – 79.5% of which were male and 17.3% of which were aged 13-24 years old.[5]

PrEP has been identified as a crucial part of the National HIV/AIDS strategy. It has been endorsed by the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the Society for Adolescent Health and Medicine,

and other groups.[6,] In 2018, there were 14,440 PrEP users in Florida – 95.3% identified as male and 11% were aged 13-24 years old.[5] While PrEP is only a piece of the solution, it is an important one.

This review will cover the uses and indications for PrEP, medication initiation and follow-up needed for PrEP, the side effects associated with different formulations of the medication, and barriers to access and uptake.

PRE-EXPOSURE PROPHYLAXIS – MEDICATION OVERVIEW

FDA-Approved Medications

There are currently two FDA-approved medications for pre-exposure prophylaxis against HIV for individuals that weigh ≥35kg – tenofovir disoproxil fumerate/emtricitabine (TDF-FTC), or Truvada® and tenofovir alafenamide/emtricitabine (TAF-FTC), known by trade name Descovy®. TDF/FTC, when taken daily, reduces the risk of contracting HIV from sexual contact by over 95%.[9] TAF/FTC has similar efficacy with less reported side effects. However, TDF/FTC is the only one of the two medications approved for use in individuals having receptive vaginal sex.[10,11]

Indications

PrEP is indicated for individuals who are at high-risk for HIV transmission.[12] According to the United States Preventative Services Task Force (USPSTF), these HIV negative individuals are in four different groups summarized in Table 1.

GROUP A	GROUP B	GROUP C	GROUP D
Sexually active men who have sex with men (MSM) who have ≥1 of the following:	Sexually active heterosexual individuals who have ≥1 of the following:	Persons who inject drugs who have ≥1 of the following:	Any individuals who fall into the below categories:
• A serodiscordant sex partner (i.e. a sex partner who is living with HIV) • Inconsistent condom use • An STI diagnosis of syphilis, gonorrhea, or chlamydia in the last 6 months • Men who have sex with men and women (MSMW)	• A serodiscordant sex partner • Inconsistent condom use with partners whose HIV status is unknown or is at high-risk for HIV transmission • An STI diagnosis of syphilis or gonorrhea in the last 6 months • Sexually active in an area with a high prevalence of HIV	• Any of the characteristics of Groups A, B, or D • Share drug paraphernalia	• Persons who engage in transactional sex • Persons who have been trafficked for sex work • Sexually active transgender men and women

Table 1: Indications for initiation of pre-exposure prophylaxis[7, 12]

Contraindications

Both current PrEP combinations are contraindicated in patients who:

- Are HIV positive
- Have severe renal impairment as defined by creatinine clearance < 30 ml/min[10,11]

Safety Profile and Side Effects

Generally, both medications are well-tolerated with few side effects and safety concerns. Reported side effects are noted in Table 2.

SIDE EFFECT	TAF-FTC (Descovy®)	TDF-FTC (Truvada®)
Diarrhea	5%	6%
Nausea	4%	5%
Headache	2%	2%
Fatigue	2%	3%
Abdominal Pain	2%	3%

Table 2: Side effect profiles reported as percentage of patients who experience these symptoms within 96 weeks[10]

TDF-FTC, the older of the two medications, has been associated with cases of mild worsening renal function, mild bone demineralization, and extremely rare cases of lactic acidosis and hepatic steatosis. The listed side effects, with the exception of fulminant hepatic steatosis, the rarest of the complications, resolve with discontinuation of TDF-FTC.[11]

MEDICATION INITIATION AND FOLLOW-UP

Step 1: Identifying Candidates for PrEP

The identification of adolescents who would benefit from PrEP should occur at routine well-child visits. However, acute care visits for sexual or mental health concerns also provide an opportune moment to discuss PrEP initiation. One critical component of well-child visits is a comprehensive and inclusive sexual history. A 2014 study found that only 3.3% of sexual histories taken by pediatricians were "inclusive," using language that avoids use of specific gender, sex, or sexual orientation.[13] Taking a comprehensive and inclusive sexual history can be accomplished by following the CDC's guide of the "5 P's" (Table 3). The goal of the sexual history is to understand the patient's STI risk based on their reported behaviors and anticipated future behaviors. For transgender or gender non-binary patients, it may be useful to have a candid conversation to understand sex behaviors. For example, it is important to clarify which anatomical parts are being used in order to properly stratify risk. This can take place during a routine HEADDSS assessment. As always, it is important to ask these questions in a developmentally-appropriate and private manner.

TAKING A COMPREHENSIVE AND INCLUSIVE SEXUAL HISTORY		
Partners	Identification of number and type of sexual contacts	• Are you currently sexually active? • Do you have sex with men, women, both or neither? • How many sexual partners have you had over the last 12 months? • Are you and your partner(s) monogamous? • Do you feel safe in your relationship(s)? • Have you ever experienced abuse or violence from your partner(s)?
Practices	Identification of sexual behaviors	• What type of sex do you have – oral, anal, vaginal, or other? • Have you or any of your partners ever engaged in transactional sex? • Have you or any of your partners ever used intravenous drugs? • Have you ever engaged in sexual behavior while under the influence of a drug or substance?
Protection	Identification of patient's knowledge and use of protection against STIs	• What do you do to protect against sexually transmitted infections? • How frequently do you use this protection – never, sometimes, always? • When do you use this protection – with oral, anal, and/or vaginal sex? • Do you know the STI status of your sexual partner(s)?
Past History	Identification of history of STIs	• Have you ever had a sexually transmitted disease – namely gonorrhea, chlamydia, syphilis, or HIV? • If yes, how did you get treated?
Pregnancy	For patients with a uterus and ovaries – identification of obstetric history, use of contraception	• Have you ever been pregnant? • If yes, how many times, and what were the outcomes of those pregnancies? • Are you currently trying to become pregnant? • If no, what are you using for contraception – are you never, sometimes, or always using this? • Are you currently satisfied with the contraception that you are using?

Table 3: The 5 P's of a comprehensive and inclusive sexual history[14]

It is important to ensure confidentiality and establish trust with the patient when taking a sexual history. Conversations about sexual behaviors may be especially difficult in patients who have recently had their sexual debut. However, having an understanding of the patient's behaviors and the partner(s)' behaviors is important to risk stratification concerning HIV transmission. Additionally, one must obtain a comprehensive and inclusive sexual history at every visit, since patients may not disclose all behaviors initially or their behaviors may change over time.

As a general guideline, the following five groups of individuals are considered to be at high risk for HIV and therefore should be counseled about HIV risk mitigation and PrEP.

1. History of past or current STIs
2. Sexual activity in a location or in a network with a high prevalence of HIV. Given the prevalence of HIV in Florida, PrEP should be considered in all high-risk youth and young adults.
3. Any sex without the use of condoms
4. Self-identified as high-risk
5. Sexual partners with unknown HIV status[10]

The CDC has a tool for estimating HIV risk and risk-reduction using various methods. https://hivrisk.cdc.gov/#[7]

Step 2: Initiation of PrEP

After identifying the appropriate patient, the next step in initiating PrEP is obtaining baseline laboratories including a renal function panel, serologies for HIV, hepatitis B, hepatitis C, STIs at baseline, and a pregnancy test. Each of these is explained in more detail below:

- **HIV Testing – 4th Generation**. Since the medications which compose both TDF-FTC and TAF-FTC are used in the treatment of HIV, their solo use in a patient who is infected with HIV leads to viral resistance. Patients must abstain from sexual contact or consistently use condoms between HIV testing and therapeutic effect of PrEP. This is primarily to ensure that HIV is not contracted in the window period between HIV testing and PrEP therapeutic effect.
- **Kidney Function.** Both TDF-FTC and TAF-FTC have a relative contraindication for patients with CrCl < 60 ml/min or < 30 ml/min, respectively.
- **Hepatitis B Status.** Hepatitis B serologies should be drawn as part of the baseline assessment for initiation of PrEP. Individuals without immunity should be offered immunization. While hepatitis B infection is not a contraindication to PrEP initiation, in some patients with active or chronic hepatitis B infection, discontinuation of PrEP has led to severe acute exacerbations of viral hepatitis.
- **Hepatitis C Status**. TDF-FTC and TAF-FTC can interact with the newer antiviral medications that are used to treat hepatitis C such as sufosbovir.
- **Pregnancy Test**. Limited data indicate that TDF-FTC and TAF-FTC are safe during pregnancy and breastfeeding.
- **STI Testing**. Screen for syphilis, gonorrhea, and chlamydia in the blood, urine, pharynx, and rectum as indicated.[7, 10, 11]

Along with the laboratory testing shown in Table 4, there is also important counseling to be done for the patients at the initial visit. The cornerstones of counseling are:

Medication Adherence. It is extremely important to take PrEP as prescribed: daily. The medication is >95% effective when taken daily, and the effectiveness decreases with decreasing adherence. There are currently no reported cases of compliant individuals on PrEP who have contracted HIV. Studies have suggested that ways to improve medication adherence include patient education about the medication dosing and side effects, providing reminder systems and tools, and addressing social and financial needs that may impact adherence.[15]

STI Prevention. Since these patients are already identified as being high-risk for STIs, it is important to discuss that PrEP is only a part of a comprehensive STI-prevention plan. This includes encouragement of conversations with partners and use of condoms and other barrier protection.[7] Importantly, a recent systematic review concluded that it is unclear if PrEP use is associated with increased rates of other STIs.[16]

Step 3: Routine Monitoring and Follow-Up

Routine follow-up is key in ensuring adherence to PrEP, especially in the adolescent population. Current practice guidelines suggest follow-up appointments every three months; however, with the adolescent population there is indication that more frequent follow-up may be beneficial in improving adherence, especially at medication initiation.[10,11] The purpose of the follow

EVERY THREE MONTHS	EVERY SIX MONTHS
Reassess STI and HIV risk Counsel about adherence Perform HIV testing Indicated STI screening based on risk Repeat pregnancy testing and contraception counseling	Assess renal function

Table 4: Routine Follow-up visits [7, 10, 11]

up visits is to counsel about adherence and proper medication use, reassess HIV and STI risk, and do routine lab monitoring, as needed. Table 4 summarizes current best practice for follow-up.

With the recent increased adoption of telehealth visits, this modality may lend itself well for patients who may have barriers to care access. At follow-up visits, there should always be a discussion of continuing need for PrEP as sex behaviors may change over time.

The CDC has more comprehensive information about PrEP, including comprehensive clinical guidelines, resources for patient access, testing flowcharts and more at: https://www.cdc.gov/hiv/clinicians/prevention/prep.html

BARRIERS AND SOLUTIONS

While PrEP has proven benefit in reducing HIV infection rates among its users, there are identified barriers which have led to decreased use, uptake, and lack of adherence. Unfortunately, these barriers are amplified among the adolescent population, and adolescents have their own set of barriers which prevent uptake and adherence.

Confidentiality and Consent

A 2010 study found that only 20% of pediatricians had asked their patients about sexual orientation.[17] The 2018 Human Rights Campaign LGBTQ+ Youth Survey of >10,000 youth across the country found that 5% of youth had disclosed their sexual orientation to all of their healthcare providers, and 20% had disclosed to some of their healthcare providers.[18] These data highlight the importance of establishing a strong therapeutic relationship with patients, provider comfort in discussing sexual health, the normalization of sexual health conversations at well-child visits.

Guardian permission is frequently cited as a barrier to PrEP uptake among eligible candidates, especially among patients who may not have disclosed their sexual orientation, gender identity, and/or sex behaviors to their parents or peers.[19] These patients may fear rejection or punishment from their parents and therefore are not likely to agree to start PrEP. The legal-medical landscape of PrEP use in minors varies state-to-state. At the time of this writing, in Florida, based on explicit language in statute and/or regulation, clinicians are not able to offer prescription HIV or STI prevention services (including PrEP) to minors without parental consent. However, providers are able to offer HIV testing and treatment to minors without parental consent.[20] Therefore, in Florida, parents should be involved in the discussion of PrEP.

In other states allowing minor consent for PrEP, confidentiality is still a barrier. For patients that are under their guardian(s)' medical insurance, billing information could disclose PrEP visits and use to parents. Taken altogether, clinicians should partner with both the adolescent and the parent in navigating conversations about sexual health and PrEP in a way that is safe and respectful to all parties.

Cost

Cost continues to be a barrier both for patients who have insurance and patients who do not have insurance. TDF-FTC and TAF-FTC are increasingly covered by most major insurers, but some patients with insurance may still have difficulty with access and payment. At the time of this writing, Florida Medicaid covers the cost of both TDF-FTC and TAF-FTC.

The cost of clinic visits, lab testing, and the medication itself are all separate barriers.

With regard to medication access, there are several programs at the local, state, and federal level for both patients who are insured and uninsured. The Ready, Set, PrEP program sponsored by the United States Department of Health and Human Services was started in early 2020 to provide free PrEP to individuals without prescription drug coverage.[21] For insured and uninsured patients, Gilead, the parent company that produces Truvada® and Descovy®, has several co-pay and payment assistance programs which are available on their website.[22] At the time of this writing, both TDF-FTC and TAF-FTC are still under patent and there are no generic formulations available.

For clinic visits and lab tests, patients can access PrEP services at community health clinics, many of which offer PrEP services on a sliding-scale fee schedule. Additionally, there are fee assistance programs from Gilead and other patient assistance

programs which are available on the CDC's website: https://www.cdc.gov/hiv/risk/prep/index.html[7]

Stigma, Health Disparities, and Medical Mistrust

Historically HIV-prevention strategies have been targeted toward men who have sex with men; however, in 2017, approximately 24% of new HIV infections in the United States were due to heterosexual contact.[1] Moreover, recent evidence has shown the disproportionate rates of HIV transmission among racial and ethnic minorities, namely Black/African-American and Latinx groups. In 2017, the African American population and Hispanic population collectively accounted for 69% of HIV diagnoses, despite comprising only 31% of the U.S. population.[1] Furthermore, 69% of individuals that could benefit from PrEP are Black or Hispanic, yet these individuals comprise only 4% of the individuals that are prescribed it.[3, 23]

Particularly among communities of color and in the southern United States, there is a larger stigma surrounding sexual and gender minorities, HIV, and PrEP.[24] Many MSM or MSMW may identify as "straight" or "heterosexual" as there continues to be a large stigma surrounding these groups in some communities[24].

It is important to build a therapeutic alliance with patients, especially those who may benefit from PrEP use.

Patient Knowledge and Comfort

A 2018 survey found that only 54.8% of adolescents who were assigned the male sex at birth and have sex with men had ever heard of PrEP and 56.1% did not know how they would access PrEP.[25]

CONCLUSION

PrEP is an effective and safe tool to combat the HIV epidemic among our adolescents and young adults in the United States. There is a need for improved HIV prevention strategies in the young adult and adolescent population, as this group accounts for a significant proportion of new HIV diagnoses every year. Pediatricians, as stewards of health in this age group, have an important role to play.

Now more than ever, it is important to know which patients are at high risk for contracting HIV. This starts with sometimes difficult conversations regarding sexual activity and sexual health. There are several opportunities to discuss PrEP with adolescents. Both preventative health visits and acute care visits for sexual health concerns both should serve as an entry to discuss PrEP. As individuals with high risk are identified, it is important to discuss risk mitigation strategies, of which PrEP is one. Due to the complex interaction of confidentiality, cost, and stigma, it may take persistence and creativity to find the proper risk mitigation plan for each individual patient. The current laws in Florida make it even more difficult for providers to have conservations with patients about PrEP. This presents an opportunity for important advocacy to be had at the state level to have allowances for PrEP without parental consent as it is for nine other states.[20]

Per CDC and USPSTF guidelines, PrEP should be a topic in the care of the adolescent. The pediatrician can play a key role to improve the long-term health of this vulnerable population. With these tools, pediatricians can help put a stop to the HIV epidemic.

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