

Preexposure Prophylaxis to Prevent Acquisition of HIV

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE An estimated 1.2 million persons in the US currently have HIV, and more than 760 000 persons have died of complications related to HIV since the first cases were reported in 1981. Although treatable, HIV is not curable and has significant health consequences. Therefore, effective strategies to prevent HIV are an important public health and clinical priority.

OBJECTIVE The US Preventive Services Task Force (USPSTF) commissioned a systematic review to evaluate the benefits and harms of preexposure prophylaxis with antiretroviral therapy for the prevention of HIV acquisition, and the diagnostic accuracy of risk assessment tools to identify persons at increased risk of HIV acquisition.

POPULATION Adolescents and adults who do not have HIV and are at increased risk of HIV.

EVIDENCE ASSESSMENT The USPSTF concludes with high certainty that there is a substantial net benefit from the use of effective antiretroviral therapy to reduce the risk of acquisition of HIV in persons at increased risk of acquiring HIV.

RECOMMENDATION The USPSTF recommends that clinicians prescribe preexposure prophylaxis using effective antiretroviral therapy to persons at increased risk of HIV acquisition to decrease the risk of acquiring HIV. (A recommendation)

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Summary of Recommendation

| Population | Recommendation | Grade |
|---|---|-------|
| Adolescents and adults at increased risk of HIV | The USPSTF recommends that clinicians prescribe preexposure prophylaxis using effective antiretroviral therapy to persons at increased risk of HIV acquisition to decrease the risk of acquiring HIV. See the Practice Considerations section for more information about identification of persons at increased risk and about effective antiretroviral therapy. | A |

USPSTF indicates US Preventive Services Task Force.

See the Summary of Recommendation figure.

Pathway to Benefit

To achieve the benefit of HIV preexposure prophylaxis, it is important that persons receive counseling about antiretroviral medication adherence and safer sex, including condom use, regular testing for HIV, and other necessary testing.

See the Practice Considerations section for more information about initial and follow-up assessment, testing, and monitoring.

Table. Summary of USPSTF Rationale

| Rationale | Assessment |
|-------------------------------|--|
| Identification of risk status | <ul style="list-style-type: none"> • Inadequate evidence on risk assessment tools and accuracy of identifying persons at increased risk of HIV acquisition³ • Adequate epidemiologic data on risk factors and behaviors that can be used to identify persons at increased risk of acquiring HIV |
| Benefits of PrEP | <ul style="list-style-type: none"> • Convincing evidence that PrEP is of substantial benefit in decreasing the risk of HIV in persons at increased risk of HIV acquisition • Convincing evidence that adherence to PrEP is highly correlated with its efficacy in preventing the acquisition of HIV |
| Harms of PrEP | Adequate evidence that PrEP is associated with a small magnitude of harms, which include kidney and gastrointestinal adverse effects, weight gain, and injection site reactions, depending on the specific PrEP formulation used. |
| USPSTF assessment | The USPSTF concludes with high certainty that there is a substantial net benefit from the use of effective antiretroviral therapy to reduce the risk of acquisition of HIV in persons at increased risk of acquiring HIV. |

Abbreviations: PrEP, preexposure prophylaxis; USPSTF, US Preventive Services Task Force.

³ See the Practice Considerations section for more information about identification of persons at increased risk of HIV acquisition.

Preamble

The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms to improve the health of people nationwide.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision-making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

The USPSTF is committed to mitigating the health inequities that prevent many people from fully benefiting from preventive services. Systemic or structural racism results in policies and practices, including health care delivery, that can lead to inequities in health. The USPSTF recognizes that race, ethnicity, and gender are all social rather than biological constructs. However, they are also often important predictors of health risk. The USPSTF is committed to helping reverse the negative impacts of systemic and structural racism, gender-based discrimination, bias, and other sources of health inequities, and their effects on health, throughout its work.

Importance

An estimated 1.2 million persons in the US currently have HIV,¹ and more than 760 000 persons have died of complications related to HIV since the first cases were reported in 1981.² In 2020, there were an estimated 30 635 new diagnoses of HIV in the US (although this may be an underestimate due to the COVID-19 pandemic), with 80% (24 488) of new diagnoses occurring among adolescent and adult men and 18% (5450) among adolescent and adult women.³ Men who have sex with men are most affected by HIV, accounting for 68% of new HIV diagnoses in 2020.³

There are also racial and ethnic disparities in the incidence of HIV, with 42% of new diagnoses occurring among Black persons, 27% among Hispanic/Latino persons, and 26% among White persons in 2020.³ Although treatable, HIV is not curable and has sig-

nificant health consequences. Therefore, effective strategies to prevent HIV are an important public health and clinical priority.

USPSTF Assessment of Magnitude of Net Benefit

The USPSTF concludes with high certainty that there is a **substantial net benefit** from the use of effective antiretroviral therapy to reduce the risk of acquisition of HIV in persons at increased risk of acquiring HIV.

See the **Table** for more information on the USPSTF recommendation rationale and assessment and the eFigure in the Supplement for information on the recommendation grade. See the **Figure** for a summary of the recommendation for clinicians. For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.⁴

Practice Considerations

Patient Population Under Consideration

This recommendation applies to adolescents and adults who do not have HIV and are at increased risk of HIV.

Assessment of Risk for HIV Acquisition

HIV is primarily acquired via sexual activity or injection drug use. It is important that clinicians routinely take a sexual and injection drug use history for all their patients in an open and nonjudgmental manner. All adolescents and adults who are sexually active or who inject drugs should be informed that acquisition of HIV can be prevented, to facilitate subsequent risk assessment and discussions about preexposure prophylaxis (PrEP) and other ways to prevent acquisition of HIV. Importantly, risk of HIV acquisition exists on a continuum, and currently available risk assessment tools all have limitations. However, certain risk factors or behaviors are known to place persons at increased risk of HIV.

Risk of HIV acquisition depends on the likelihood that a specific act or activity will transmit HIV and the likelihood that a sex partner or drug injection partner has HIV. Likelihood of HIV transmission is highest with needle-sharing injection drug use and condomless receptive anal intercourse. Condomless receptive anal intercourse has an approximately 10- to 15-fold higher risk of transmission than condomless insertive anal sex and condomless receptive and insertive penile-vaginal sex.⁵ A 2018 study estimated the prevalence

Figure. Clinician Summary: Preexposure Prophylaxis to Prevent Acquisition of HIV

| | |
|---|---|
| What does the USPSTF recommend? | <p>Adults and adolescents weighing at least 35 kg (77 lb) at increased risk* of HIV acquisition: Prescribe preexposure prophylaxis (PrEP) with effective antiretroviral therapy* to decrease the risk of acquiring HIV.</p> <p>Grade: A</p> <p>*See the “How to implement this recommendation” section for more information on identifying persons at increased risk and for information on effective antiretroviral therapy for PrEP.</p> |
| To whom does this recommendation apply? | This recommendation applies to adolescents and adults who do not have HIV and are at increased risk of HIV. |
| What’s new? | <ul style="list-style-type: none"> This recommendation is consistent with the 2019 USPSTF recommendation on PrEP for the prevention of HIV. For the current recommendation, the USPSTF reviewed additional evidence on new formulations of PrEP (tenofovir alafenamide/emtricitabine [TAF/FTC] and cabotegravir). |
| How to implement this recommendation? | <ul style="list-style-type: none"> Routinely take a sexual and injection drug use history for all patients. Inform all adolescents and adults who are sexually active or who inject drugs that there are ways to help prevent acquisition of HIV. <p>The USPSTF recommends that the following persons be considered for HIV PrEP:</p> <ol style="list-style-type: none"> Sexually active adults and adolescents weighing at least 35 kg (77 lb) who have engaged in anal or vaginal sex in the past 6 months and have any of the following: <ul style="list-style-type: none"> A sexual partner who has HIV (especially if the partner has an unknown or detectable viral load). A bacterial sexually transmitted infection (syphilis, gonorrhea, or chlamydia for men who have sex with men and transgender women; gonorrhea and syphilis for heterosexual women and men) in the past 6 months. A history of inconsistent or no condom use with sex partner(s) whose HIV status is not known; assessing risk in conversation with the patient and considering factors such as number of partners, the specific sexual activities a person engages in, and whether their sex partner or partners are in a group with a higher prevalence of HIV (eg, men who have sex with men or with men and women, transgender women, persons who inject drugs, and persons who engage in transactional sex). Persons who inject drugs and have a drug-injecting partner who has HIV or who shares injection equipment. Transgender women are at especially high risk of HIV acquisition and should be considered for PrEP based on the criteria outlined above. <p>Persons who engage in transactional sex, such as sex for money, drugs, or housing, including commercial sex workers or persons trafficked for sex work, constitute a group at increased risk of HIV acquisition and should be considered for PrEP based on the criteria outlined above.</p> <p>Persons who request PrEP may have undisclosed behaviors that put them at risk.</p> <p>Effective formulations of PrEP with current US Food and Drug Administration approval include:</p> <ul style="list-style-type: none"> Oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and injectable cabotegravir are approved for use in at-risk adults and adolescents weighing at least 35 kg (77 lb) to reduce the risk of sexually acquired HIV. Oral TAF/FTC is approved for use in at-risk adults and adolescents weighing at least 35 kg (77 lb) to reduce the risk of sexually acquired HIV, excluding individuals at risk from receptive vaginal sex. No PrEP medications have FDA approval for the indication of reducing the risk of acquiring HIV via injection drug use, but Centers for Disease Control and Prevention (CDC) guidelines note that persons who inject drugs are likely to benefit from PrEP with any FDA-approved PrEP medication. It is important that persons taking PrEP receive counseling about medication adherence and safer sex including condom use, regular testing for HIV, and other necessary testing. |
| What additional information should clinicians know about this recommendation? | PrEP is underutilized, particularly for Black and Hispanic/Latino persons with indications for PrEP. |
| Why is this recommendation and topic important? | An estimated 1.2 million persons in the US currently have HIV and more than 760 000 persons have died of complications related to HIV since 1981. |
| What are other relevant USPSTF recommendations? | The USPSTF has issued recommendations on behavioral counseling to reduce risk of sexually transmitted infections and on screening for HIV infection (https://uspreventiveservicestaskforce.org/uspstf/). |
| What are additional tools and resources? | <ul style="list-style-type: none"> The CDC provides guidelines on PrEP for the prevention of HIV infection (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf and https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2021.pdf). The CDC provides additional resources on PrEP for both clinicians and consumers (https://www.cdc.gov/hiv/risk/prep/index.html). The CDC has compiled a list of PrEP interventions and best practices (https://www.cdc.gov/hiv/research/interventionresearch/compendium/prep/complete-list.html). County- and state-level HIV prevalence data for the US are available (https://www.cdc.gov/nchhstp/atlas). The USPSTF has developed a “Let’s Talk About It” guide for clinicians and patients about the use of HIV PrEP (https://uspreventiveservicestaskforce.org/uspstf/recommendation-topics/lets-talk-about-it-discussion-guides). |
| Where to read the full recommendation statement? | Visit the USPSTF website (https://www.uspreventiveservicestaskforce.org/uspstf/) or the JAMA website (https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force) to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others. |

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of HIV (ie, an estimate of the likelihood that a partner whose HIV status is unknown has HIV at a population level) as 12.4% among men who have sex with men and 1.9% among persons who inject drugs.⁶ The overall prevalence of HIV in the US is estimated at 0.3%.³ Of note, both the frequency of specific sexual activities and a person's number of sexual partners will also affect their risk of HIV.

The USPSTF recommends that the following persons be considered for PrEP:

1. Sexually active adults and adolescents weighing at least 35 kg (77 lb) who have engaged in anal or vaginal sex in the past 6 months and have any of the following:
 - A sexual partner who has HIV (especially if the partner has an unknown or detectable viral load).
 - A bacterial sexually transmitted infection (STI) (syphilis, gonorrhea, or chlamydia for men who have sex with men and transgender women; gonorrhea and syphilis for heterosexual women and men) in the past 6 months.
 - A history of inconsistent or no condom use with sex partner(s) whose HIV status is not known; assessing risk in conversation with the patient and considering factors such as number of partners, the specific sexual activities a person engages in, and whether their sex partner or partners are in a group with a higher prevalence of HIV (eg, men who have sex with men or with men and women, transgender women, persons who inject drugs, and persons who engage in transactional sex).
2. Persons who inject drugs and have a drug-injecting partner who has HIV or who shares injection equipment.

Persons who engage in transactional sex, such as sex for money, drugs, or housing, including commercial sex workers or persons trafficked for sex work, constitute a group at increased risk of HIV acquisition and should be considered for PrEP based on the criteria outlined above. Persons who request PrEP may have undisclosed behaviors that put them at risk. Transgender women and men who are sexually active should be considered for PrEP based on the criteria outlined above. Transgender women are at especially high risk of HIV acquisition. A Centers for Disease Control and Prevention (CDC) survey in 7 cities found an HIV prevalence of 42% among transgender women. Prevalence was highest among Black transgender women (62%) and Native American/Alaska Native transgender women (65%).⁷

In addition, studies have found that transmission of HIV to a seronegative partner from a partner with HIV has not been observed when the partner with HIV was being treated with antiretroviral therapy and had a suppressed viral load.⁸⁻¹⁰ It is not known whether PrEP use further decreases the risk of HIV transmission when a partner with HIV has a documented undetectable viral load. Factors such as the consistency or inconsistency of a partner's viral load being suppressed, a partner's adherence to antiretroviral therapy, and the degree of certainty that a partner's viral load is suppressed (eg, self-report vs availability of laboratory test results) may help inform decisions about the use of PrEP in this situation.

All persons being considered for PrEP must have a recently documented negative HIV antigen-antibody test result, and if they have taken oral PrEP or postexposure prophylaxis in the past 3 months, or injectable cabotegravir in the past 12 months, the CDC recommends testing with both an HIV antigen-antibody assay and an HIV-1 RNA assay.¹¹

Medication for Prevention of HIV Acquisition

Currently, several medications are approved by the US Food and Drug Administration (FDA) for use as PrEP. Oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and injectable cabotegravir are approved by the FDA for use in at-risk adults and adolescents weighing at least 35 kg (77 lb) to reduce the risk of sexually acquired HIV.^{12,13} Oral tenofovir alafenamide/emtricitabine (TAF/FTC) is approved by the FDA for use in at-risk adults and adolescents weighing at least 35 kg (77 lb) to reduce the risk of sexually acquired HIV, excluding individuals at risk from receptive vaginal sex.¹⁴ No PrEP medications have FDA approval for the indication of reducing the risk of acquiring HIV via injection drug use, but CDC guidelines note that persons who inject drugs are likely to benefit from PrEP with any FDA-approved PrEP medication.¹¹ No trials of PrEP enrolled persons who were pregnant. FDA labeling permits the use of TDF/FTC in pregnant persons. It also permits the use of TDF/FTC in persons who are breastfeeding and recommends that the potential benefits should be considered along with any potential adverse effects on the breastfed child.

Implementation

The first step in implementing PrEP is identifying persons at increased risk of HIV acquisition who may benefit from PrEP. However, identifying persons at risk of HIV can be challenging because of stigma and discrimination against gay, bisexual, transgender, and nonbinary persons and persons who inject drugs, or the lack of a trusting relationship between the patient and clinician. It is important that clinicians routinely take a sexual and injection drug use history for all their patients in an open and nonjudgmental manner and inform all persons who are sexually active or who inject drugs that acquisition of HIV can be prevented. This can facilitate the subsequent discussion between clinician and patient about factors or behaviors that may make a person an appropriate candidate for PrEP.

As noted, FDA labeling permits the use of TDF/FTC in pregnant persons at risk of acquiring HIV.¹² PrEP with TDF/FTC, TAF/FTC, and cabotegravir are also approved for use in adolescents at risk of acquiring HIV who weigh at least 35 kg (77 lb).¹²⁻¹⁴ Clinicians need to be aware of any local laws and regulations that may apply when providing PrEP to an adolescent minor.

The CDC provides a complete discussion of implementation considerations for PrEP, including baseline and follow-up testing and monitoring and discontinuing PrEP.¹¹ A few particularly important points regarding the provision of PrEP are outlined below.

Before prescribing PrEP, clinicians should exclude persons with acute or chronic HIV through taking a medical history and HIV testing. In persons who have taken oral PrEP or postexposure prophylaxis in the past 3 months, or a cabotegravir injection in the past 12 months, the CDC recommends HIV testing with both an HIV antigen-antibody assay and an HIV-1 RNA assay. If they have not, an HIV antigen-antibody assay is recommended as the initial test.¹¹ The antiretroviral regimens used in PrEP, when used alone, are not effective treatments for HIV, and their use in persons with HIV can lead to the emergence of, or selection for, drug-resistant HIV. It is also recommended that testing for other STIs and pregnancy testing (when appropriate) be conducted prior to initiating PrEP; kidney function testing and serologic testing for hepatitis B virus are recommended prior to initiating PrEP containing tenofovir (TDF/FTC or TAF/FTC), and lipid profile testing is recommended

prior to initiating TAF/FTC. Ongoing follow-up and monitoring, including HIV testing every 2 to 3 months depending on PrEP formulation used, is also recommended. The time from initiation of PrEP to achieving protection against acquisition of HIV is unknown. Pharmacokinetic studies of TDF/FTC suggest that maximum intracellular concentrations of the active form of tenofovir are reached in peripheral blood mononuclear cells and rectal tissue after approximately 7 days of daily oral dosing and in cervicovaginal tissues at approximately 20 days.¹¹

Patients can continue PrEP as long as risk of HIV acquisition continues. Patients may discontinue PrEP for several reasons, including personal preference, decreased risk of HIV acquisition, or adverse medication effects. Patients may reinstate PrEP if they are again at increased risk of HIV acquisition. Persons reinstating PrEP should have the same evaluation and testing prior to resuming PrEP as those newly initiating PrEP, including HIV testing. When cabotegravir injections are discontinued, patients should be informed of the long period of gradually declining drug levels, the risk of developing a drug-resistant strain if HIV is acquired during that time, and that the CDC recommends patients use daily oral PrEP or other effective HIV prevention methods if ongoing risk of HIV exposure is anticipated.¹¹

PrEP does not reduce the risk of other STIs. Consistent use of condoms decreases risk of HIV acquisition by approximately 80%⁵ and reduces the risk of other STIs. Promoting consistent condom use is an important component of successful PrEP implementation. The CDC also recommends regular screening for STIs in persons taking PrEP and STI and HIV testing in anyone with signs or symptoms.¹¹

Clinical trials demonstrate a strong connection between adherence to PrEP and its effectiveness in preventing HIV acquisition.¹⁵ Low adherence is associated with a marked decrease in effectiveness. Therefore, adherence support is a key component of providing PrEP. Components of adherence support include establishing trust and open communication with patients, patient education, reminder systems for taking medication, and attention to medication adverse effects and having a plan to address them. Additional information on adherence support is available in the CDC guidelines.^{11,16} Adherence support is especially important in populations known to have lower adherence to PrEP, such as Black persons and young persons.^{17,18}

It is important for clinicians to recognize that barriers to the implementation and uptake of PrEP exist. These barriers can include structural barriers, such as lack of health insurance, and other factors, such as an individual's belief that they are not a candidate for PrEP or lack of willingness to take PrEP. There are also racial and ethnic disparities in the use of PrEP. Although Black persons are estimated to account for approximately 40% of persons in the US with indications for PrEP, CDC data indicate that the number of White persons prescribed PrEP was approximately 5 times higher than the number of Black persons in 2019.¹⁹ The CDC has estimated that the proportion of persons with indications for PrEP who received it was 60.5% among White persons vs 7.9% in Black persons and 13.8% in Hispanic/Latino persons.¹⁹ Another study reported that Black women, who are also disproportionately affected by HIV, were more than 4 times less likely to have initiated PrEP than White women.²⁰ CDC data also showed disparities in PrEP use relative to indications for PrEP (PrEP coverage) by sex (lower in females than in males) and age (lower in persons aged 16

to 24 years than in those 25 years or older).¹⁹ Limited data suggest that PrEP use is lower in transgender women than in men who have sex with men.²¹ These barriers and disparities need to be addressed to achieve the full benefit of PrEP.

Additional Tools and Resources

The CDC provides guidelines on PrEP for the prevention of HIV (<https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf> and <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2021.pdf>). The CDC provides additional resources on PrEP for both clinicians and consumers (<https://www.cdc.gov/hiv/risk/prep/index.html>). The CDC has compiled a list of PrEP interventions and best practices (<https://www.cdc.gov/hiv/research/interventionresearch/compendium/prep/complete-list.html>). County- and state-level HIV prevalence data for the US are available (<https://www.cdc.gov/nchhstp/atlas>).

The USPSTF has developed a "Let's Talk About It" guide for clinicians and patients about the use of HIV PrEP (<https://uspreventiveservicestaskforce.org/uspstf/recommendation-topics/lets-talk-about-it-discussion-guides>).

Other Related USPSTF Recommendations

The USPSTF has issued recommendations on behavioral counseling to reduce risk of STIs,²² screening for HIV,²³ screening for syphilis in pregnant²⁴ and nonpregnant²⁵ persons, screening for genital herpes,²⁶ screening for chlamydia and gonorrhea,²⁷ and screening for hepatitis B^{28,29} and hepatitis C.³⁰

Update of Previous USPSTF Recommendation

This recommendation replaces the 2019 USPSTF recommendation on PrEP for the prevention of HIV. In 2019, the USPSTF recommended that clinicians offer PrEP with effective antiretroviral therapy to persons at high risk of HIV acquisition.³¹ This recommendation is consistent with the 2019 recommendation. For the current recommendation, the USPSTF reviewed additional evidence on new formulations of PrEP and recommends that clinicians prescribe PrEP using effective antiretroviral therapy to persons at increased risk of HIV acquisition, after the clinician and patient have discussed PrEP and the patient agrees.

Supporting Evidence

Scope of Review

To update its 2019 recommendation statement, the USPSTF commissioned a systematic review^{15,32} of the evidence on the benefits and harms of PrEP with TDF/FTC, tenofovir disoproxil fumarate alone, the dapivirine vaginal ring, TAF/FTC, and injectable cabotegravir for the prevention of HIV acquisition, and the diagnostic accuracy of risk assessment tools to identify persons at increased risk of HIV acquisition.

Effectiveness of Risk Assessment

The USPSTF found 12 studies that evaluated risk assessment tools developed in US cohorts for predicting incident HIV. Eight studies were conducted in men who have sex with men,

1 in persons who inject drugs, 1 in cisgender women, and 2 in the general population.^{15,32} Among the studies in men who have sex with men and persons who inject drugs that reported this measure, discrimination of the risk assessment tool was moderate, with an area under the receiver operating characteristic curve of 0.60 to 0.73.^{15,32} The 2 studies conducted in the general population evaluated 2 different risk assessment tools (number of items, 23 and 44) that used automated algorithms on electronic medical record data. These 2 studies reported moderate to high discrimination for incident HIV (area under the receiver operating characteristic curve, 0.77 [95% CI, 0.74-0.79] and 0.84 [95% CI, 0.80-0.89]).^{33,34} One study focused on cisgender women who had a positive HIV test result. It found that a 6-item risk assessment tool, based on electronic medical record data, had sensitivity of 95% for incident HIV (21 cases).³⁵

All these studies had some limitations. Most of the risk assessment tools were developed and validated using previously collected data (ie, not prospectively validated). The study of cisgender women focused only on persons with a new positive HIV test result; thus, only sensitivity but no other measures of test accuracy could be calculated. Additionally, it was based on a small number of incident cases. The feasibility of implementation of risk assessment tools based on automated algorithms of electronic medical record data are unknown. Last, some studies used cohorts from prior to 2001, and several studies did not predefine the cutoff for a positive test result.^{15,32}

Benefits of Preventive Medication

The USPSTF found 17 trials that compared a variety of formulations of PrEP with placebo or PrEP with TDF/FTC. Twelve trials compared TDF/FTC or tenofovir disoproxil fumarate alone with placebo, 2 trials compared the dapivirine vaginal ring with placebo, 1 trial compared TAF/FTC with TDF/FTC, and 2 trials compared injectable cabotegravir with TDF/FTC.^{15,32}

In the 12 trials of TDF/FTC or tenofovir disoproxil fumarate alone, duration of follow-up ranged from 4 months to 4 years. Six trials enrolled men and women at risk of acquiring HIV via heterosexual contact, 4 trials enrolled men who have sex with men or transgender women, 1 trial enrolled at-risk women and men who have sex with men, and 1 trial enrolled persons who inject drugs. No trial enrolled pregnant persons or persons younger than 18 years. Seven trials were conducted in Africa, 1 in Thailand, 2 in Europe or Canada, and 1 in the US; 1 trial was multinational. All trials of persons at risk of HIV acquisition via heterosexual contact were conducted in Africa. All trials included behavioral and adherence counseling, and most provided condoms to all trial participants.^{15,32}

In a pooled analysis, TDF/FTC or tenofovir disoproxil fumarate alone was associated with significantly decreased risk of HIV acquisition vs placebo or no PrEP (11 trials [$n = 18\,172$]; relative risk [RR], 0.46 [95% CI, 0.33-0.66]; absolute risk reduction, -2.0% [95% CI, -2.8% to -1.2%] after 4 months to 4 years).^{15,32}

There was a strong association between degree of adherence (assessed in different studies by methods such as patient self-report, pill counts, adherence monitoring devices, plasma drug levels, and prescription fill data) and the effectiveness of oral PrEP ($P < .001$ for interaction). In 6 trials in which adherence was 70% or greater, the RR of HIV acquisition was 0.27 (95% CI, 0.19-0.39), in 3 trials in which adherence was greater than 40% to less than 70%, the RR was 0.51 (95% CI, 0.38-0.70), and in 2 trials in which adher-

ence was 40% or less, oral PrEP was not associated with a decreased risk of HIV (RR, 0.93 [95% CI, 0.72-1.20]).^{15,32}

Oral PrEP with TDF/FTC or tenofovir disoproxil fumarate alone was consistently associated with decreased risk of HIV acquisition vs placebo when trials were stratified according to HIV risk category (men who have sex with men, men and women at risk via heterosexual contact, or persons who inject drugs) or setting (highly developed or less highly developed countries).^{15,32} The effectiveness of tenofovir disoproxil fumarate alone (RR, 0.49 [95% CI, 0.28-0.84]) and TDF/FTC (RR, 0.44 [95% CI, 0.27-0.72]) were similar.^{15,32} All trials evaluated daily PrEP, except for 1 trial of event-driven PrEP (consisting of 2 tablets of TDF/FTC 2 to 24 hours before intercourse, followed by 1 tablet 24 hours and 48 hours after the first dose) in men who have sex with men. This trial found event-driven PrEP was associated with a significantly decreased risk of HIV acquisition compared with placebo (RR, 0.14 [95% CI, 0.03-0.63]),³⁶ although in that trial, men randomly assigned to PrEP took an average of about 4 doses of PrEP per week, so it is uncertain whether this finding would apply to less-frequent use of event-driven dosing.

In a pooled analysis of 2 trials, the dapivirine vaginal ring was associated with decreased risk of HIV acquisition compared with a placebo ring in African women at risk of HIV ($n = 4564$; RR, 0.71 [95% CI, 0.57-0.89]).^{15,32} The absolute risk reduction was -2.23% (95% CI, -3.75% to -0.74%) at 1.4 to 1.6 years.^{15,32} Notably, the dapivirine vaginal ring is not approved by the FDA and is not available for use in the US.

One trial, DISCOVER ($n = 5335$), compared PrEP with oral TAF/FTC vs TDF/FTC. It was conducted in Europe and North America and enrolled HIV-negative cisgender adult men (98.6%) and transgender women (1.4%) who have sex with men and are at risk of HIV acquisition, based on having condomless anal intercourse with at least 2 partners in the previous 12 weeks or an STI (syphilis, rectal gonorrhea, or rectal chlamydia) in the previous 24 weeks. At 96 weeks, TAF/FTC was associated with a statistically nonsignificant decreased risk of HIV acquisition vs TDF/FTC (0.3% vs 0.6%; RR, 0.47 [95% CI, 0.19-1.14]); results were within the prespecified noninferiority margin (ie, TAF/FTC was noninferior to TDF/FTC).^{37,38}

Two trials (HIV Prevention Trials Network [HPTN] trials O83 and O84) compared long-acting injectable cabotegravir (600 mg intramuscularly every 8 weeks, following a 5-week oral lead-in phase of 30 mg daily) vs daily oral TDF/FTC.^{39,40} In HPTN O83 ($n = 4566$), 87% of participants were men who have sex with men and 12% were transgender women who have sex with men. Among US participants (37% of total participants), 50% were Black. At median follow-up of 1.4 years, injectable cabotegravir was associated with a significantly decreased risk of HIV acquisition vs oral TDF/FTC (0.6% vs 1.7%; RR, 0.33 [95% CI, 0.18-0.62]). In stratified analysis, results were similar in men who have sex with men (hazard ratio, 0.35 [95% CI, 0.18-0.68]) and transgender women (hazard ratio, 0.34 [95% CI, 0.08-1.56]), although the estimate for transgender women was imprecise.³⁹ HPTN O84 ($n = 3178$) was conducted in 7 countries in sub-Saharan Africa. Participants were female (sex assigned at birth), were aged 18 to 45 years (median, 25 years), reported engaging in vaginal intercourse in the prior 30 days, and were assessed as being at risk for HIV acquisition using a risk prediction instrument developed and validated in African women. At median follow-up of 1.2 years, injectable cabotegravir was associated with a significantly

decreased risk of HIV acquisition vs oral TDF/FTC (0.3% vs 2.3%; RR, 0.11 [95% CI, 0.04-0.31]).⁴⁰

Harms of Preventive Medication

The trials that investigated the effectiveness of PrEP also reported on harms. Oral PrEP with TDF/FTC or tenofovir disoproxil fumarate alone was associated with increased risk of kidney adverse events (primarily grade 1 or higher creatinine level elevation) (12 trials [n = 18 170]; RR, 1.43 [95% CI, 1.18-1.75]; absolute risk difference, 0.56% [95% CI, 0.09%-1.04%]). Kidney abnormalities generally resolved following PrEP cessation. Oral PrEP with TDF/FTC or tenofovir disoproxil fumarate alone was associated with increased risk of gastrointestinal adverse events (12 trials [n = 18 300]; RR, 1.63 [95% CI, 1.26-2.11]; absolute risk difference, 1.95% [95% CI, 0.48%-3.43%]), which were generally not serious and diminished over time. TDF/FTC and tenofovir disoproxil fumarate alone were associated with a statistically nonsignificant increased risk of fracture vs placebo (7 trials [n = 15 241]; RR, 1.23 [95% CI, 0.97-1.56]); this outcome was heavily weighted by 1 trial conducted in persons who inject drugs.^{15,32}

One trial (n = 5387) reported no differences between TAF/FTC and TDF/FTC in rates of any kidney adverse events (1% vs 1%) or risk of fracture (2% vs 2%).³⁸ Two trials (n = 7786) reported no differences between long-acting injectable cabotegravir and TDF/FTC in risk of decreased creatinine clearance or elevations in alanine aminotransferase or aspartate aminotransferase levels. Cabotegravir was associated with increased weight gain compared with TDF/FTC (mean differences, 0.86 and 0.4 kg) and increased risk of injection site reactions (most commonly pain) that were usually mild.^{39,40}

One concern about PrEP is that its use may lead to persons at risk of HIV acquisition not using condoms or engaging in other behaviors that could increase their risk of STIs (ie, behavioral risk compensation). In pooled analyses of randomized trials, there were no differences between PrEP with TDF/FTC or tenofovir disoproxil fumarate alone and placebo in risk of syphilis (4 trials [n = 10 775]; RR, 1.08 [95% CI, 0.98-1.18]), gonorrhea (5 trials; RR, 1.07 [95% CI, 0.82-1.39]), chlamydia (5 trials; RR, 0.97 [95% CI, 0.80-1.18]), or combined bacterial STIs (2 trials; RR, 1.14 [95% CI, 0.97-1.34]),^{15,32} although all trials except for 1 were blinded, which could affect risk of STIs if participants who do not know whether they are taking PrEP or placebo behave differently than those who know they are taking PrEP. In the 1 open-label trial, there was also no statistically significant association between PrEP and the risk of STIs, although estimates were imprecise.⁴¹ Two trials of the dapivirine vaginal ring^{42,43} also reported no differences in risk of STIs vs placebo.

An additional concern is the possibility that the use of antiretroviral drugs as PrEP could lead to the development or acquisition of drug-resistant HIV. Among all patients randomized to oral PrEP with TDF/FTC or tenofovir disoproxil fumarate alone, 2 of 3149 patients taking tenofovir disoproxil fumarate alone (0.06%) (4 trials) and 14 of 5085 patients taking TDF/FTC (0.3%) (7 trials) were identified as having incident HIV with a drug resistance variant.^{15,32} Most resistance variants occurred in persons who already had HIV on trial enrollment but were not recognized as such, highlighting the importance of testing for HIV and excluding persons with HIV before initiating PrEP. In 5 observational studies of PrEP with TDF/FTC, 2 of 1936 participants (0.1%) were diagnosed with an antiretroviral drug resistance variant.^{15,32} In the DISCOVER trial (n = 5335), among

19 patients who tested positive for HIV and had resistance testing results, an emtricitabine resistance variant was detected in 4 patients. All cases occurred in patients randomized to TDF/FTC who were suspected of having HIV at baseline.³⁷

In 2 trials of the dapivirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]) vaginal ring, the proportion of patients randomized to dapivirine with an NNRTI resistance variant was 0.8% (22/2620). In both trials, the rate of NNRTI resistance variants among patients with incident HIV was similar in patients randomized to the dapivirine vaginal ring vs those randomized to placebo (11.8% [8/68] vs 10.4% [10/96]; *P* = .80⁴¹ and 18.2% [14/77] vs 16.1% [9/56]; *P* = .75).⁴³

In the HPTN 083 and HPTN 084 trials, which compared cabotegravir (an integrase strand transfer inhibitor [INSTI]) with TDF/FTC, among all patients randomized to cabotegravir, the proportion with an INSTI resistance variant was 0.1% (4/3874), although only 13 of 17 individuals with incident HIV across both trials underwent resistance testing. Among individuals randomized to TDF/FTC across both trials, the proportion found to have antiretroviral resistance variants was also 0.1% (5/3870).^{39,40}

Evidence on the effect of acquiring antiretroviral-resistant HIV on clinical outcomes is very limited. One study reported that among 5 patients previously exposed to PrEP and diagnosed with HIV with an M184V or M184I (emtricitabine) variant, 4 had an undetectable viral load 3 months after starting antiretroviral therapy and 1 patient was lost to follow-up.⁴⁴ Another study included 52 persons diagnosed with HIV who reported recent PrEP exposure. All 39 individuals with a viral load greater than 200 copies/mL at baseline who received antiretroviral therapy achieved an undetectable viral load at 24 weeks. Results were not reported separately for patients with an antiretroviral resistance variant.⁴⁵

No trials of PrEP enrolled persons who were pregnant. However, among persons who became pregnant, a pooled analysis of 3 trials of TDF/FTC or tenofovir disoproxil fumarate alone found that PrEP was not associated with increased risk of spontaneous abortion (3 trials [n = 415]; RR, 1.09 [95% CI, 0.79-1.50]).^{15,32} One trial found no differences between TDF/FTC or tenofovir disoproxil fumarate alone and placebo in pregnancy rate, risk of preterm birth, congenital anomalies, or postpartum infant mortality.⁴⁶ There were no differences between the dapivirine vaginal ring and placebo in incidence of pregnancy.^{42,43} In 1 trial of cabotegravir enrolling female participants, pregnancy incidence was low with both cabotegravir and TDF/FTC, and no congenital abnormalities were observed.⁴⁰

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from December 13, 2022, to January 17, 2023. Most comments were supportive of the USPSTF recommendation. Comments suggested that alternate wording for the term *HIV infection* be used. The USPSTF is committed to the use of nonstigmatizing and inclusive language, and in response removed the word "infection" from its recommendation. The USPSTF agrees with comments that adherence support is an important component of providing PrEP and notes this in the Implementation section. In response to public comment, the USPSTF clarified that persons who request PrEP may have undisclosed behaviors that put them at risk of HIV acquisition. The USPSTF also added detail about considerations when discontinuing cabotegravir to the

Implementation section. Last, the USPSTF clarified that gender-diverse persons are among the included individuals for the research gap on the need for accurate and validated risk assessment tools.

Research Needs and Gaps

Studies are needed that provide the following information.

- Research is needed to develop and validate tools that are accurate for identifying persons at increased risk of HIV acquisition who would benefit from PrEP. When being developed and validated, risk assessment instruments should include those populations most at risk of acquiring HIV, including racial and ethnic groups such as Black and Hispanic/Latino populations and gender-diverse persons.
- Research is needed on different drug regimens and dosing strategies for PrEP.
- Research is needed on factors associated with adherence to and persistence with PrEP and methods to increase uptake, adherence, and persistence, especially in populations with lower use of and adherence to PrEP, such as younger persons and racial and ethnic groups most affected by HIV.
- Studies or demonstration projects of PrEP in US populations of heterosexual persons, persons who inject drugs, and transgender women and men are needed to better quantify effectiveness in those populations.

- Research is needed on the safety and effectiveness of PrEP during pregnancy and breastfeeding.
- Additional research is needed to determine whether the use of PrEP is associated with an increased risk of other STIs.
- Research is needed on the long-term safety and effectiveness of PrEP, including the longer-term effects of PrEP in adolescents, and the effect of antiretroviral resistance variants, particularly INSTI resistance variants, on clinical outcomes.

Recommendations of Others

The US Public Health Service recommends PrEP for HIV prevention for sexually active adults and adolescents weighing at least 35 kg (77 lb) who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition or who inject drugs and report injection practices that place them at substantial ongoing risk of HIV exposure and acquisition.¹¹ The American College of Obstetricians and Gynecologists recommends discussing PrEP with all sexually active adolescents and adults and offering PrEP to those at substantial risk of HIV acquisition.⁴⁷ The International Antiviral Society–USA Panel recommends PrEP for individuals at risk of HIV. It notes that identification of at-risk individuals for whom PrEP is recommended requires individualized approaches that consider past and future anticipated risk.⁴⁸

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