US Public Health Service

# PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE

**What's New in the Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2021 Update – A Clinical Practice Guideline**

The Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update – A Clinical Practice Guideline includes revisions to several sections. These revisions are intended to update existing guidance using the current evidence base, to incorporate recent FDA PrEP medication approvals, and to clarify specific aspects of clinical care. Other revisions were made to improve usability and increase implementation of the guideline based on comments received from clinicians providing PrEP care. Minor revisions were also made to correct typographical errors, add or update references, and update content from cited guidelines and source materials.

**What's new…**

In anticipation of likely FDA approval of a PrEP indication for cabotegravir (CAB) in late 2021, we added a new section about prescribing PrEP with intramuscular injections of CAB every 2 months for sexually active men, women, and transgender persons with indications for PrEP use.

**Summary (of graded recommendations)**

- We added a recommendation to inform all sexually active adults and adolescents about PrEP **(IIIB).**

- We added a recommendation: PrEP with intramuscular cabotegravir (CAB) injections (conditional on FDA approval) is recommended for HIV prevention in adults reporting sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition **(IA).**

**Table Summarizing Clinical Guidance**

- We added a table specific for CAB (as CAB has a different dosing and recommended follow-up schedule than oral PrEP, and no renal or lipid monitoring is required) (Table 1b).

**Identifying Indications for PrEP**
- We simplified the determination of indications for PrEP use for sexually-active persons. We replaced boxes with flow charts for assessing indications for sexually active persons and persons who inject drugs.

**Laboratory Tests and other Diagnostic Procedures**
- We revised the HIV testing algorithm to provide two algorithms; one for assessing HIV status in persons with no history of recent antiretroviral exposure starting (or restarting) PrEP and, the other for assessing HIV status at follow-up visits while persons are taking, or have recently taken, PrEP.

**Providing PrEP**
- We added F/TAF as an FDA-approved choice for sexually active men and transgender women at risk of HIV acquisition; the FDA approval for F/TAF excluded persons at risk through receptive vaginal sex including cisgender women (persons assigned female sex at birth whose gender identity is female).
- We revised and reordered the sections on initiation and follow-up care to first describe guidelines applicable to all PrEP patients and then describe guidelines applicable only to selected patients.
- We revised frequency of assessing eCrCl to every 12 months for persons <50 years of age or with eCrCL ≥90 ml/min at PrEP initiation and every 6 months for all other patients.
- We added medications to Table 4 of drug interactions for TAF.
- We outlined options for PrEP initiation and follow-up care by telehealth ("Tele-PrEP").
- We outlined procedures for providing or prescribing PrEP medication to select patients on the same day as initial evaluation for its use ("same-day PrEP").
- We outlined procedures for the off-label prescription of TDF/FTC to men who have sex with men on a non-daily regimen ("2-1-1") and their follow-up care.
- We added a brief section on primary care considerations for PrEP patients (Table 6).
- We added a section on providing CAB for PrEP.

**Evidence Review**
- We updated the evidence review and moved it to Appendix 2.
- We added evidence reviews for CAB trials.
- We separated clinical trial results for transgender women and MSM into separate rows in evidence tables.

**Revisions post FDA approval of cabotegravir injections for PrEP**

It is anticipated that FDA will review and may approve cabotegravir injections for PrEP within 2-3 months after the publication of this guideline. We will then post a revised version of this guideline that replaces references to pending FDA approval with statements indicating that approval has been given.

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**Potential Conflicts of Interest:**

CDC and individual employees involved in the guideline development process are named in US government patents and patent applications related to methods for HIV prophylaxis.

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- Go to the CDC HIV website for clinician resources at https://www.cdc.gov/hiv/clinicians/index.html.

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## Abbreviations (In Guideline and Clinical Providers' Supplement)

| | |
|---|---|
| ACTG | AIDS Clinical Trials Group |
| AHRQ | Agency for Healthcare Research and Quality |
| AIDS | acquired immunodeficiency syndrome |
| BMD | bone mineral density |
| CAB | cabotegravir |
| CDC | Centers for Disease Control and Prevention |
| CPT | common procedural terminology |
| DEXA | dual-emission X-ray absorptiometry |
| DHAP | Division of HIV/AIDS Prevention, CDC |
| DHHS | Department of Health and Human Services |
| DP | diphosphate |
| eCrCl | estimated creatinine clearance rate (ml/min) |
| EIA | enzyme-linked immunoassay |
| EPT | expedited partner therapy |
| FDA | Food and Drug Administration |
| FHI | Family Health International |
| F | emtricitabine (trade name Emtriva®), also called FTC |
| F/TAF | emtricitabine coformulated with tenofovir alafenamide (trade name Descovy®) |
| F/TDF | emtricitabine coformulated with tenofovir disoproxil fumarate (trade name Truvada®) |
| GEM | Guidelines Elements Model |
| GLIA | GuideLine Implementability Appraisal |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HRSA | Health Resources and Services Administration |
| ICD | International Classification of Diseases |
| IDU | injection drug users (also referred to as PWID) |
| IFA | indirect immunofluorescence assay |
| IHS | Indian Health Service |
| INSTI | integrase strand transfer inhibitor |
| IQR | interquartile range |
| MSM | men who have sex with men |
| MTN | Microbicide Trials Network |
| NASTAD | National Association of State and Territorial AIDS Directors |
| NCHHSTP | National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention |
| NGC | National Guidelines Clearinghouse |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| nPEP | nonoccupational postexposure prophylaxis |
| NSAID | non-steroidal anti-inflammatory drug |
| NQMC | National Quality Measures Clearinghouse |

OHAP        Office of HIV/AIDS Policy, DHHS
ONAP        Office of National AIDS Policy
ONDCP       Office of National Drug Control Policy
OPA         Office of Population Affairs, DHHS
PCR         polymerase chain reaction
PEP         postexposure prophylaxis
PHS         (U.S.) Public Health Service
PWID        persons who inject drugs
PrEP        preexposure prophylaxis
SAMHSA      Substance Abuse and Mental Health Services Administration
STD         sexually transmitted disease
STI         sexually transmitted infection
TB          tuberculosis
TDF         tenofovir disoproxil fumarate (trade name Viread®)
TAF         tenofovir alafenamide
TGW         transgender women
UNAIDS      Joint United National Programme on HIV/AIDS
USPSTF      United States Preventive Services Task Force
VA          Veterans Administration
WHO         World Health Organization

## Summary

*Preexposure Prophylaxis for HIV Prevention in the United States – 2021 Update: A Clinical Practice Guideline* provides comprehensive information for the use of antiretroviral preexposure prophylaxis (PrEP) to reduce the risk of acquiring HIV infection. The key messages of the guideline are as follows:

- Daily oral PrEP with emtricitabine (F) 200 mg in combination with 1) tenofovir disoproxil fumarate (TDF) 300 mg for men and women or 2) tenofovir alafenamide (TAF) 25 mg, for men and transgender women, has been shown to be safe and effective in reducing the risk of sexual HIV acquisition therefore,
    - All sexually active adult and adolescent patients should receive information about PrEP. **(IIIB)**
    - For both men and women, PrEP with daily F/TDF is recommended 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. **(IA)**[1]
    - For both men and women, PrEP with daily F/TDF is recommended for HIV prevention for adult and adolescents weighing at least 35 kg (77 lb) who inject drugs (PWID) (also referred to as injection drug users [IDU]) and report injection practices that place them at substantial ongoing risk of HIV exposure and acquisition. **(IA)**
    - For men only, daily oral PrEP with F/TAF is a recommended option 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. PrEP with F/TAF has not yet been studied in women (persons assigned female sex at birth whose gender identify is female) and so F/TAF is not recommended for HIV prevention for women or other persons at risk through receptive vaginal sex. **(IA)**
    - For transgender women (persons assigned male sex at birth whose gender identity is female) who have sex with men, and who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition, daily oral PrEP with F/TAF is a recommended option for HIV prevention **(IIB)**
    - The efficacy and safety of other daily oral antiretroviral medications for PrEP, either in place of, or in addition to, F/TDF or F/TAF, have not been studied extensively and are not recommended. **(IIIA)**
- Renal function should be assessed by estimated creatinine clearance (eCrCl) at baseline for PrEP patients taking daily oral F/TDF or F/TAF, and monitored periodically so that persons in whom clinically significant renal dysfunction is developing do not continue to take it.
    - Estimated creatinine clearance (eCrCl) should be assessed every 6 months for patients over age 50 or those who have an eCrCl <90 ml/min at initiation. **(IIA)**
    - For all other daily oral PrEP patients, eCrCl should be assessed at least every 12 months. **(IIA)**
- Conditioned on a PrEP indication approved by FDA, PrEP with intramuscular cabotegravir (CAB) injections is recommended for HIV prevention in adults and adolescents who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. **(IA)**
- Acute and chronic HIV infection must be excluded by symptom history and HIV testing immediately before any PrEP regimen is prescribed. **(IA)**
- HIV infection should be assessed at least every 3 months for patients taking daily oral PrEP, and every 2 months for patients receiving CAB injections for PrEP so that persons with incident infection do not continue taking it. The 2-drug regimens of F/TDF or F/TAF and the single drug CAB are inadequate therapy

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[1] See Appendix 1, Grading of Strength of Recommendations and Quality of Evidence (Tables 12-13)

for established HIV infection, and their use in persons with early HIV infection may engender resistance to one or more of the PrEP medications. **(IA)**

- When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to:
    o Support for medication adherence and continuation in follow-up PrEP care, because high medication adherence and persistent use are critical to PrEP effectiveness for prevention of HIV acquisition. **(IIA)**
    o Additional proven effective risk-reduction services, as indicated by reported HIV exposure-prone behaviors, to enable the use of PrEP in combination with other effective prevention methods to reduce risk for sexual acquisition of STIs or acquisition of bloodborne bacterial and viral infections through injection drug use. (**IIIA**)

## Table 1a: Summary of Clinician Guidance for Daily Oral PrEP Use

| | Sexually-Active Adults and Adolescents[1] | Persons Who Inject Drug[2] |
|---|---|---|
| Identifying substantial risk of acquiring HIV infection | Anal or vaginal sex in past 6 months AND any of the following:<br>• HIV-positive sexual partner (especially if partner has an unknown or detectable viral load)<br>• Bacterial STI in past 6 months[3]<br>• History of inconsistent or no condom use with sexual partner(s) | HIV-positive injecting partner<br>OR<br>Sharing injection equipment |
| Clinically eligible | **ALL OF THE FOLLOWING CONDITIONS ARE MET:**<br>• Documented negative HIV Ag/Ab test result within 1 week before initially prescribing PrEP<br>• No signs/symptoms of acute HIV infection<br>• Estimated creatinine clearance ≥30 ml/min[4]<br>• No contraindicated medications ||
| Dosage | • Daily, continuing, oral doses of F/TDF (Truvada®), ≤90-day supply<br>    OR<br>• For men and transgender women at risk for sexual acquisition of HIV; daily, continuing, oral doses of F/TAF (Descovy®), ≤90-day supply ||
| Follow-up care | **Follow-up visits at least every 3 months to provide the following:**<br>• HIV Ag/Ab test and HIV-1 RNA assay, medication adherence and behavioral risk reduction support<br>• Bacterial STI screening for MSM and transgender women who have sex with men[3] – oral, rectal, urine, blood<br>• Access to clean needles/syringes and drug treatment services for PWID<br>**Follow-up visits every 6 months to provide the following:**<br>• Assess renal function for patients aged ≥50 years or who have an eCrCl <90 ml/min at PrEP initiation<br>• Bacterial STI screening for all sexually-active patients[3] – [vaginal, oral, rectal, urine- as indicated], blood<br>**Follow-up visits every 12 months to provide the following:**<br>• Assess renal function for all patients<br>• Chlamydia screening for heterosexually active women and men – vaginal, urine<br>• For patients on F/TAF, assess weight, triglyceride and cholesterol levels ||

[1] adolescents weighing at least 35 kg (77 lb)

[2] Because most PWID are also sexually active, they should be assessed for sexual risk and provided the option of CAB for PrEP when indicated

[3] Sexually transmitted infection (STI):  Gonorrhea, chlamydia, and syphilis for MSM and transgender women who have sex with men including those who inject drugs; Gonorrhea and syphilis for heterosexual women and men including persons who inject drugs

[4] estimated creatine clearance (eCrCl) by Cockcroft Gault formula ≥60 ml/min for F/TDF use, ≥30 ml/min for F/TAF use

## Table 1b: Summary of Clinician Guidance for Cabotegravir Injection PrEP Use

| | Sexually-Active Adults | Persons Who Inject Drugs[1] |
|---|---|---|
| Identifying substantial risk of acquiring HIV infection | Anal or vaginal sex in past 6 months AND any of the following:<br>• HIV-positive sexual partner (especially if partner has an unknown or detectable viral load)<br>• Bacterial STI in past 6 months[2]<br>• History of inconsistent or no condom use with sexual partner(s) | HIV-positive injecting partner<br>OR<br>Sharing injection equipment |
| Clinically eligible | <div align="center">**ALL OF THE FOLLOWING CONDITIONS ARE MET:**</div><br>• Documented negative HIV Ag/Ab test result within 1 week before initial cabotegravir injection<br>• No signs/symptoms of acute HIV infection<br>• No contraindicated medications or conditions | |
| Dosage | • 600 mg cabotegravir administered as one 3 ml intramuscular injection in the gluteal muscle<br>   o Initial dose<br>   o Second dose 4 weeks after first dose (month 1 follow-up visit)<br>   o Every 8 weeks thereafter (month 3,5,7, follow-up visits etc) | |
| Follow-up care | **At follow-up visit 1 month after first injection**<br>• HIV Ag/Ab test and HIV-1 RNA assay<br>**At follow-up visits every 2 months (beginning with the third injection – month 3) provide the following:**<br>• HIV Ag/Ab test and HIV-1 RNA assay<br>• Access to clean needles/syringes and drug treatment services for PWID<br>**At follow-up visits every 4 months (beginning with the third injection- month 3) provide the following:**<br>• Bacterial STI screening[2] for MSM and transgender women who have sex with men[2] – oral, rectal, urine, blood<br>**At follow-up visits every 6 months (beginning with the fifth injection – month 7) provide the following:**<br>• Bacterial STI screening[1] for all heterosexually-active women and men – [vaginal, rectal, urine - as indicated], blood<br>**At follow-up visits at least every 12 months (after the first injection) provide the following:**<br>• Assess desire to continue injections for PrEP<br>• Chlamydia screening for heterosexually active women and men – vaginal, urine<br>**At follow-up visits when discontinuing cabotegravir injections provide the following:** | |

[1] Because most PWID are also sexually active, they should be assessed for sexual risk and provided the option of CAB for PrEP when indicated
[2] Sexually transmitted infection (STI): Gonorrhea, chlamydia, and syphilis for MSM and transgender women who have sex with men including those who inject drugs; Gonorrhea and syphilis for heterosexual women and men including persons who inject drugs

|  | <ul><li>Re-educate patients about the "tail" and the risks during declining CAB levels</li><li>Assess ongoing HIV risk and prevention plans</li><li>If PrEP is indicated, prescribe daily oral F/TDF or F/TAF beginning within 8 weeks after last injection</li><li>Continue follow-up visits with HIV testing quarterly for 12 months</li></ul> |
|---|---|

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## Introduction

Daily oral antiretroviral preexposure prophylaxis (PrEP) with a fixed-dose combination of either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) with emtricitabine (F). has been found to be safe[1] and effective in substantially reducing HIV acquisition in gay, bisexual, and other men who have sex with men (MSM)[2-4], men and women in heterosexual HIV-discordant couples[5], and heterosexual men and women recruited as individuals.[6] In addition, one clinical trial among persons who inject drugs (PWID) (also referred to as injection drug users [IDU])[7] and one among men and women in heterosexual HIV-discordant couples[5] have demonstrated substantial efficacy and safety of daily oral PrEP with TDF alone. The demonstrated efficacy of daily oral PrEP was in addition to the effects of repeated condom provision, sexual risk-reduction counseling, and the diagnosis and treatment of sexually transmitted infections (STI), all of which were provided to trial participants, including persons in the drug treatment group and persons in the placebo group. In July 2012, after reviewing the available trial results, the U.S. Food and Drug Administration (FDA) approved an indication for the use of Truvada (F/TDF) "in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk"[8]. In May 2018, the approval for F/TDF was extended to adolescents weighing at least 35 kg (77 lb) based on safety trials in adolescents[9] and young adults.[10] In June 2019, the US Preventive Services Task Force recommended PrEP for adults and adolescents at risk of HIV acquisition with an "A" rating (high certainty that the net benefit of the use of PrEP to reduce the risk of acquisition of HIV infection in persons at high risk of HIV infection is substantial).[11] In 2021, based on this recommendation, DHHS determined that most commercial insurers and some Medicaid programs are required to provide oral PrEP medication, necessary laboratory tests, and clinic visits with no out-of-pocket cost to patients., And in October 2019, based on a clinical trial conducted with 5,387 MSM and 74 transgender women, the FDA approved a PrEP indication for daily Descovy (F/TAF) for sexually active men and transgender women at risk of HIV acquisition.[3, 4] Women (persons assigned female sex at birth) and other persons at risk through receptive vaginal sex were specifically excluded from the F/TAF approval, because no women or transgender men were included in the efficacy and safety PrEP trial. In 2020, results from a clinical trial conducted with MSM and transgender women, and another conducted with women, reported high efficacy and safety for injections of cabotegravir (CAB) every 2 months for PrEP.[12, 13] Submission of data for review by the FDA for approval of a PrEP indication is planned in 2021.

On the basis of these trial results and the FDA approvals, the U.S. Public Health Service guidelines recommend that clinicians inform all sexually-active patients about PrEP and its role in preventing HIV acquisition. Clinicians should evaluate all adult and adolescent patients who are sexually active or who are injecting illicit drugs and offer to prescribe PrEP to persons whose sexual or injection behaviors and epidemiologic context place them at substantial risk of acquiring HIV infection.

An estimated 1.2 million persons have indications for PrEP use.[14]  Both the soon to be updated HIV National Strategic Plan: A Roadmap to End the Epidemic for the United States - 2021–2025. (https://files.hiv.gov/s3fs-public/HIV-National-Strategic-Plan-2021-2025.pdf) and the federal initiative "Ending the HIV Epidemic in the United States" (https://www.cdc.gov/endhiv/index.html) have called for rapid and large scale up of PrEP provision by clinicians providing health care to HIV-uninfected persons at risk for HIV acquisition.  Since FDA approval, the minimum estimate of the number of persons receiving PrEP prescriptions for F/TDF has risen from 8,800 in 2012 to nearly 220,000 in 2018.[15, 16] However, the geographic, sex, and racial/ethnic distribution of persons prescribed PrEP is not equitable when compared to the distribution of new HIV diagnoses that could be prevented. African Americans, Hispanics, women, and residents of southern states have disproportionately low numbers of PrEP users.[17]

The evidence base for this 2021 update of CDC's PrEP guidelines was derived from a systematic search and review of published literature. To identify all oral PrEP safety and efficacy trials and observational studies pertaining to the prevention of sexual and injection acquisition of HIV, a search was performed of the clinical trials registry (http://www.clinicaltrials.gov) by using combinations of search terms (preexposure prophylaxis, pre-exposure prophylaxis, PrEP, HIV, Truvada, Descovy, tenofovir, and antiretroviral). These search terms were used to search PubMed, Web of Science, MEDLINE, Embase, CINAHL, and Cochrane Library databases for January 2006-December 2020. Finally, a review of references from published PrEP trial data confirmed that no additional trial results were available. For additional information about the systematic review process, see the Clinical Providers' Supplement, Section 12 at https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2021.pdf.

This publication provides a comprehensive clinical practice guideline for the use of PrEP for the prevention of HIV infection in the United States. Currently, prescribing daily oral PrEP with F/TDF is recommended for MSM, heterosexual men, heterosexual women, and PWID at substantial risk of HIV acquisition; F/TAF is a recommended option for sexually active persons except women and other persons at risk through receptive vaginal sex. FDA review of injections of CAB every 2 months as PrEP is pending. As the results of additional PrEP clinical trials and studies in these and other populations at risk of HIV acquisition become known, this guideline will be updated.

Many of the studies that informed these guidelines included small numbers of transgender women and none included transgender men, as a result, data specifically relevant for transgender and non-binary people are often limited or not available. Most sections of these guidelines, therefore, use the terminology, 'women' and 'men' unless specifically referring to transgender women or men. Based on current data showing potentially high levels for protection with PrEP for people exposed to HIV during rectal, vaginal, and /or oral sex we recommend gender-inclusive models of PrEP care to ensure that services encompass and address the needs of all

persons who would benefit from its use including cisgender and transgender adults and adolescents as well as PWID.

The intended users of this guideline include:
- primary care clinicians who provide care to persons at risk of acquiring HIV infection;
- clinicians who provide substance abuse treatment or reproductive health care;
- infectious disease, HIV treatment, and STD treatment specialists who may provide PrEP or serve as consultants to primary care clinicians about the use of antiretroviral medications; and
- health program policymakers
- counselors and other adherence support providers

## Evidence of Need for Additional HIV Prevention Methods

Approximately 36,400 people in the United States acquired HIV in 2018. From 2014 through 2018, overall estimated annual HIV incidence remained stable. No decline or increase was observed in the estimated number of annual HIV infections among persons of both sexes, black/African American, Hispanic/Latino, or white persons, any transmission risk group, or any region of the US. Estimated HIV incidence decreased from 2014 through 2018 among persons of multiple races and among persons aged 13–24, and remained stable among all other age groups.[18]

In 2018, 67% of the 38,739 newly diagnosed HIV infections were attributed to male-male sexual activity without injection drug use, 3% to male-male sexual activity with injection drug use, 24% to male-female sexual contact without injection drug use, and 6% to injection drug use.[17] Among all adults and adolescents, diagnoses of HIV infection among transgender persons accounted for approximately 2% of diagnoses of HIV infections in the United States and 6 dependent areas; of whom 92% of diagnoses of HIV infections were for transgender women. Among the 24% of persons with newly diagnosed HIV infection attributed to heterosexual activity, 62% were African-American women and men.[14] These data indicate a need for additional methods of HIV prevention to further reduce new HIV infections, especially (but not exclusively) among young adult and adolescent MSM of all races and Hispanic/Latino ethnicity and for African American heterosexuals (populations with higher HIV prevalence and at higher risk of HIV infection among persons without HIV infection).

Since 2012, when the FDA first approved a F/TDF indication for PrEP and clinical trial data showed the efficacy and safety of daily, oral F/TDF for HIV prevention, the number of persons prescribed PrEP has gradually increased each year[14]. In 2018, of the estimated 1.2 million adults and adolescents with indication for PrEP use[12], an estimated 220,000 persons received an oral PrEP prescription, or about 18% of persons who would benefit from its use.[13] Equitable provision of PrEP to populations at highest risk of HIV acquisition is not occurring. Black persons constituted 42% of new HIV diagnoses in 2018 but only 6% of Black persons with indications for its use were estimated to have received an oral PrEP prescription. Hispanic/Latino persons constituted 27% of new HIV diagnoses but only 10% of Hispanic/Latino persons with indications for its use had received an oral PrEP prescription. While women are 19% of persons with new HIV diagnoses, they comprise only 7% of those prescribed oral PrEP.[17, 19]

These guidelines are intended to inform clinicians and other partners to respond to both the soon to be updated HIV National Strategic Plan: A Roadmap to End the Epidemic for the United States - 2021–2025 (https://files.hiv.gov/s3fs-public/HIV-National-Strategic-Plan-2021-2025.pdf) and the federal initiative Ending the HIV Epidemic in the United States (https://www.cdc.gov/endhiv/index.html) through rapid expansion of PrEP delivery to all persons who could benefit from its use as highly effective HIV prevention.

# All Patients Being Assessed for PrEP Provision

## IDENTIFYING INDICATIONS FOR PrEP

All sexually active adults and adolescents should be informed about PrEP for prevention of HIV acquisition. This information will enable patients to both respond openly to risk assessment questions and to discuss PrEP with persons in their social networks and family members who might benefit from its use. Studies have shown that patients often do not disclose stigmatized sexual or substance use behaviors to their health care providers (especially when not asked about specific behaviors).[20-25]

Taking a brief, targeted sexual history is recommended for all adult and adolescent patients as part of ongoing primary care,[26] but the sexual history is often deferred because of urgent care issues, provider discomfort, or anticipated patient discomfort. This deferral is common among providers of primary care,[27] STI care,[28] and HIV care.[29-31]

Routinely taking a sexual history is a necessary first step to identify which patients in a clinical practice are having sex with same-sex partners, which are having sex with partners, and what specific sexual behaviors may place them at risk for, or protect them from, HIV acquisition. To identify the sexual health needs of all their patients, clinicians should not limit sexual history assessments to only selected patients (e.g., young, unmarried persons, or women seeking contraception), because new HIV infections and STIs are occurring in all adult and adolescent age groups, both sexes, all genders, and both married and unmarried persons. The clinician can introduce this topic by stating that taking a brief sexual history is routine practice for all patients, go on to explain that the information is necessary to the provision of individually appropriate sexual health care, and close by reaffirming the confidentiality of patient information.

Transgender persons are those whose sex at birth differs from their current self-identified gender. Although the effectiveness of oral PrEP for transgender women has been more definitively proven in some trials than in others[32], cabotegravir injections for PrEP have been shown to reduce the risk for HIV acquisition among transgender women and MSM during anal sex[13] and women during vaginal sex[12]. Trials have not been conducted among transgender men. Nonetheless, its use should be considered in all persons at risk of acquiring HIV sexually.

Patients may request PrEP because of concern about acquiring HIV  but not feel comfortable reporting sexual or injection behaviors to avoid anticipated stigmatizing responses in health care settings.[33-36] For this reason, after attempts to assess patient sexual and injection behaviors, patients who request PrEP should be offered it, even when no specific risk behaviors are elicited.

## Figure 1      Populations and HIV Acquisition Risk
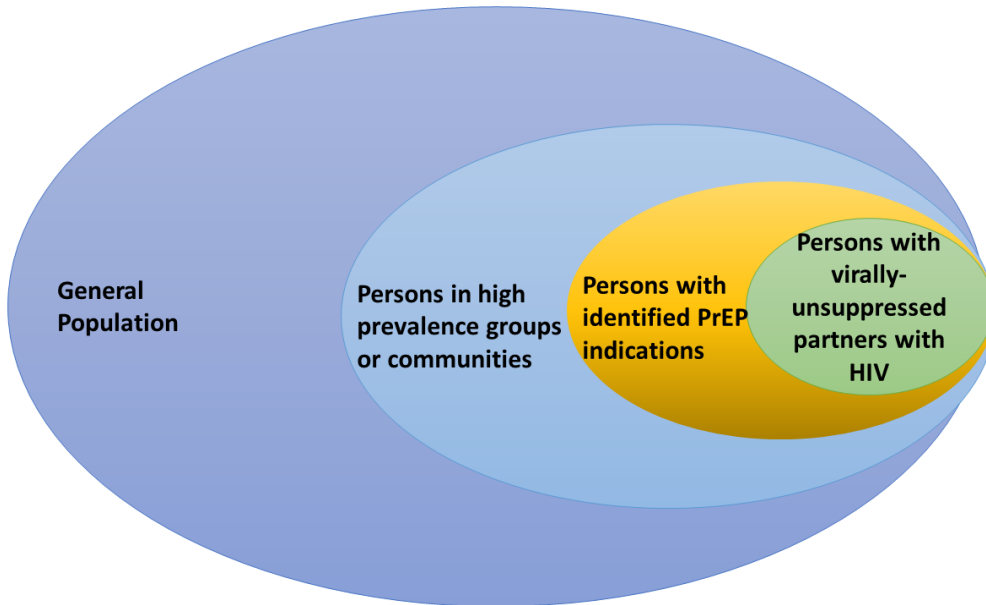


## ASSESSING RISK OF SEXUAL HIV ACQUISITION

PrEP should be offered to sexually active adults and adolescents at substantial risk of HIV acquisition. Figure 2 outlines a set of brief questions designed to assess a key set of sexual practices that are associated with the risk of HIV acquisition.

## Figure 2  Assessing Indications for PrEP in Sexually Active Persons
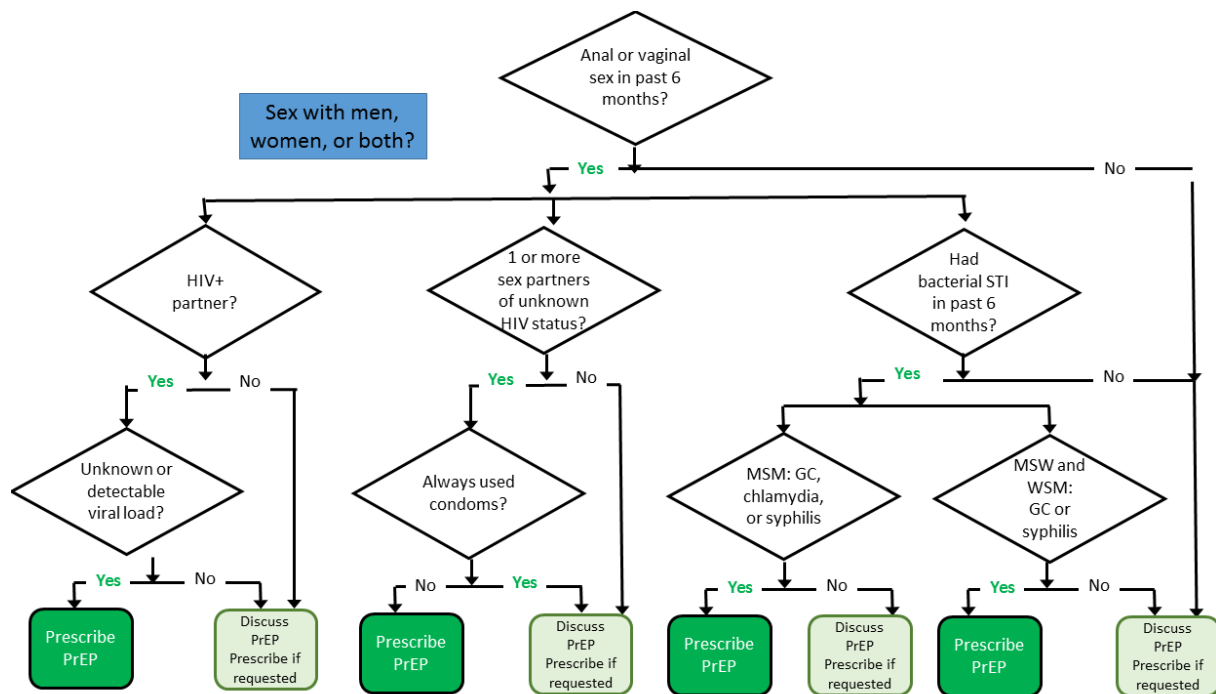
A patient who reports that one or more regular sex partners is of unknown HIV status should be offered HIV testing for those partners, either in the clinician's practice or at a confidential testing site (see zip code lookup at https://www. gettested.cdc.gov/).

When a patient reports that one or more regular sex partners is known to have HIV, the clinician should determine whether the patient being considered for PrEP use knows if the HIV-positive partner is receiving antiretroviral therapy and has had an undetectable viral load (<200 copies/ml) for at least the prior 6 months.[37] Persons with HIV who have an undetectable viral load pose effectively no risk for HIV transmission to sexual partners (see section below on considerations for HIV discordant couples). PrEP for an HIV-uninfected patient may be indicated if a sexual partner with HIV has been inconsistently virally suppressed or his/her viral load status is unknown. In addition, PrEP may be indicated if the partner without HIV seeking PrEP either has other sexual partners or wants the additional reassurance of protection that PrEP can provide.

Clinicians should ask all sexually-active patients about any diagnoses of bacterial STIs (chlamydia, syphilis, gonorrhea) during the past 6 months, because they provide evidence of sexual activity that could result in HIV exposure. For heterosexual women and men, risk of HIV exposure during condomless sex may also be indicated by recent pregnancy of a female patient or a female sexual partner of a male patient considering PrEP. A scored risk index predictive of incident HIV infection among MSM[38, 39] (see Clinical Providers' Supplement, Section 5) is also available.

Only a few questions are needed to establish whether indications for PrEP are present, However, clinicians may want to ask additional questions to obtain a more complete sexual history that includes information about a patient's gender identity, partners, sexual practices, HIV/STI protective practices, past history of STDs, and pregnancy intentions/preventive methods (https://www.cdc.gov/std/treatment/sexualhistory.pdf). Clinicians should become familiar with the evolving terminology referring to sex, gender identity, and sexual orientation.

**Sex** The assignment of a person as male or female usually based on the appearance of their external anatomy at birth. This is what is written on the birth certificate.

**Gender Identity** A person's internal, deeply held sense of their gender. Most people have a gender identity of man or woman (or boy or girl). Gender identity is not visible to others.

**Sexual Orientation** A person's enduring physical, romantic, and/or emotional attraction to another person. Gender identity and sexual orientation are not the same. Persons of varied gender identities may be straight, lesbian, gay, bisexual, or queer

**Transgender (adj.)**
People whose gender identity differs from the sex they were assigned at birth. Many transgender people are prescribed hormones by their doctors and some undergo surgery to bring their bodies into alignment with their gender identity. A transgender identity is not dependent upon physical appearance or medical procedures. Trans can be used as shorthand for transgender

**Cisgender (adj.)** People whose gender identity is the same as the sex they were assigned at birth **Cis** can be used as shorthand for cisgender.

**Gender Expression** External manifestations of gender, expressed through a person's name, pronouns, clothing, haircut, behavior, voice, and/or body characteristics.

**Gender Non-Conforming** People whose gender expression is different from conventional expectations of masculinity and femininity. Many people have gender expressions that are not entirely conventional – that fact alone does not make them transgender. The term is not a synonym for transgender or transsexual and should only be used if someone self-identifies as gender non-conforming.

**Non-binary and/or genderqueer** Terms used by some people who experience their gender identity and/or gender expression as falling outside or somewhere in between the categories of man and woman. The term should only be used if someone self-identifies as non-binary and/or genderqueer.

Adapted from GLAAD Media Reference Guide at
https://www.glaad.org/reference/transgender

Clinicians should also briefly screen all patients for alcohol use disorder[40] (especially before sexual activity), and the use of illicit non-injection drugs (e.g., amyl nitrite, stimulants).[41, 42] The use of these substances may affect sexual risk behavior,[43] hepatic or renal health, or medication adherence, any of which may affect decisions about the appropriateness of prescribing PrEP medication. In addition, if a substance use disorder is identified, the clinician should provide referral for appropriate treatment or harm-reduction services acceptable to the patient.

Lastly, clinicians should consider the epidemiologic context of the sexual practices reported by the patient. The risk of HIV acquisition is determined by both the frequency of specific sexual practices (e.g., condomless anal intercourse) and the likelihood that a sex partner has HIV. The same behaviors when reported as occurring in communities and demographic populations with high HIV prevalence or occurring with partners known to have HIV, are more likely to result in exposure to HIV and so will indicate greater need for intensive risk-reduction methods (e.g., PrEP, multisession behavioral counseling) than when they occur in a community or population with low HIV prevalence (for local prevalence estimates see http://www.AIDSvu.org or http://www.cdc.gov/nchhstp/atlas/).

Reported consistent ("always") condom use is associated with an 80% reduction in HIV acquisition among heterosexual couples[44] and 70% among MSM.[45] Inconsistent condom use is considerably less effective,[46, 47] and studies have reported low rates of recent consistent condom use among MSM[48, 49] and other sexually active adults.[48] Especially low rates have been reported when condom use was measured over several months rather than during most recent sex or the past 30 days.[50] Therefore, unless the patient reports confidence that consistent condom use can be achieved, PrEP should be prescribed while continuing to support condom use for prevention of STIs and unplanned pregnancy (See Supplement Section 5).

## ASSESSING RISK OF HIV ACQUISITION THROUGH INJECTION PRACTICES

Although the annual number of new HIV infections among PWID in the United States has declined, a sizable number occur each year. In 2018, PWID (including MSM/PWID) accounted for 7% of estimated incident HIV infections.[19] According to the National HIV Behavioral Surveillance System (NHBS)[51] data collected in 2018, substantial proportions of HIV-negative PWID report receptive sharing of syringes (33%) and receptive sharing of injection equipment (55%), both of which may lead to HIV exposure. Few (1%) reported using PrEP in the previous 12 months. Data from NHBS also demonstrate that most PWID report sexual behaviors that confer risk of HIV acquisition. Among HIV-negative PWID males, 69% reported having had condomless vaginal sex in the prior 12 months, and 4% reported having had condomless anal sex with a male partner. Among HIV-negative PWID females, 79% reported having had condomless vaginal sex, and 27% reported having had condomless anal sex. 33% of HIV negative PWID reported their most recent sex was condomless sex with a partner known to have HIV. Because most PWID are sexually active, and many acquire HIV from sexual exposures,[52, 53] they should be assessed for both sexual and injection behaviors that indicate HIV risk. The only randomized clinical PrEP trial conducted with PWID found that TDF was effective in preventing HIV acquisition but somewhat less effective than F/TDF in person with only sexual risk of HIV acquisition.[7] In addition, antiretrovirals are effective as post-exposure prophylaxis against needlestick exposures[54] and as treatment for HIV infection in PWID. Therefore, PWID are likely to benefit from PrEP with any FDA-approved medication with or without an identified sexual behavior risk of HIV acquisition.

Lastly, non-sterile injection with shared syringes or other injection equipment sometimes occurs among transgender persons while administering non-prescribed gender-affirming hormones or among persons altering body shape with silicone or other "fillers."[55-57] Providing PrEP to persons who report non-sterile injection behaviors that can place them at substantial risk of acquiring HIV will contribute to HIV prevention efforts.

Current evidence is sufficient to recommend that all adult patients be screened for injection practices or other illicit drug use. The USPSTF[22] recommends that clinicians be alert to the signs and symptoms of illicit drug use in patients. Clinicians should determine whether patients who are currently using illicit drugs are in (or want to receive) medication-assisted therapy, in-patient drug treatment, or behavioral therapy for substance use disorder. For persons with a history of injecting illicit drugs but who are currently not injecting, clinicians should assess the risk of relapse along with the patients' use of relapse prevention services (e.g., a drug-related behavioral support program, use of mental health services, medication-assisted therapy,12-step program).

Figure 3 outlines a set of brief questions designed to assess a key set of injection practices that are associated with the risk of HIV acquisition.  For a scored risk index predictive of incident HIV infection among PWID,[58] see the Clinical Providers' Supplement, Section 7.

**Figure 3       Assessing Indications for PrEP in Persons Who Inject Drugs**
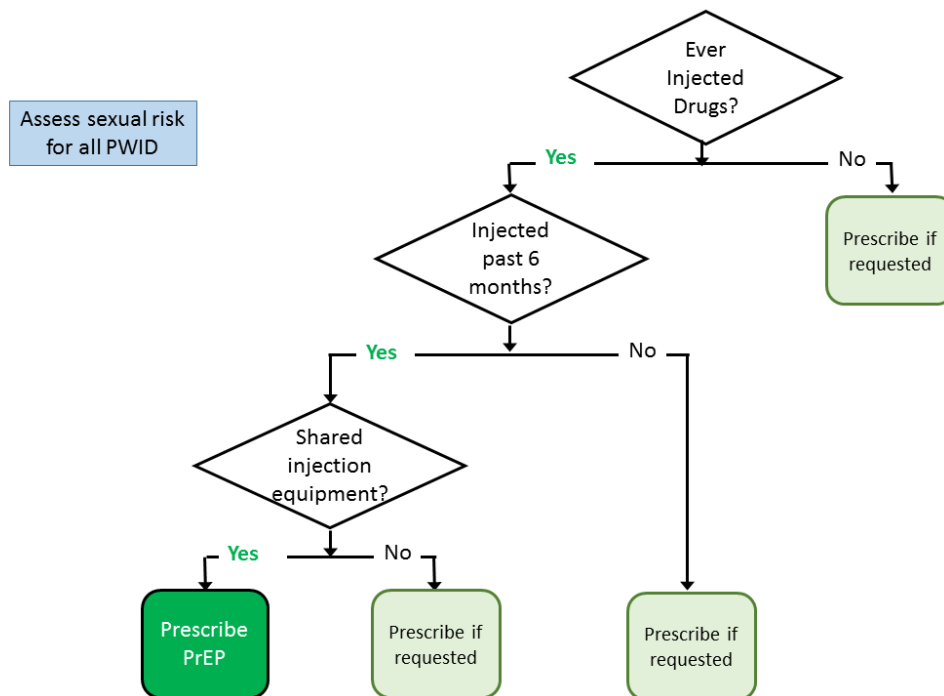
PrEP and other HIV prevention should be provided and integrated with prevention and clinical care services for the other non-HIV health threats PWID may face (e.g., hepatitis B and C infection, abscesses, septicemia, endocarditis, overdose).[59] In addition, referrals for treatment of substance use disorder, mental health services, harm reduction programs, syringe service programs (SSPs) where available or access to sterile injection equipment, and social services may be indicated.

## LABORATORY TESTS AND OTHER DIAGNOSTIC PROCEDURES

All patients whose sexual or drug injection history indicates consideration of PrEP and who are interested in taking PrEP, as well as patients without indications who request PrEP, must undergo laboratory testing to identify persons for whom this intervention could be harmful or for whom it could present specific health risks that would require close monitoring.

### HIV TESTING

HIV testing with confirmed results is required to document that patients do not have HIV when they start taking PrEP medications (Figure 4a). For patient safety, HIV testing should be repeated at least every 3 months after oral PrEP initiation (i.e., before prescriptions are refilled or reissued) or every 2 months when CAB injections are being given. This requirement should be explained to patients during the discussion about whether PrEP is appropriate for them.

The CDC and USPSTF recommend that MSM, PWID, patients with a sex partner who has HIV, and others at substantial risk of HIV acquisition undergo an HIV test at least annually or for those with additional risk factors, every 3-6 months.[60, 61] However, outside the context of PrEP delivery, testing is often not done as frequently as recommended.[62-64]

Clinicians should document a negative HIV test result within the week before initiating (or reinitiating) PrEP medications, ideally with an antigen/antibody test conducted by a laboratory. The required HIV testing before initiation can be accomplished by (1) drawing blood (serum) and sending the specimen to a laboratory for an antigen/antibody test or (2) performing a rapid, point-of-care, FDA-approved, fingerstick antigen/antibody blood test (see figure 4a). In the context of PrEP, rapid tests that use oral fluid should not be used to screen for HIV infection because they are less sensitive for the detection of acute or recent infection than blood tests.[65] Clinicians should not accept patient-reported test results or documented anonymous test results. PrEP should not be prescribed in the event of a preliminary positive HIV antibody-only test unless negative HIV status is confirmed according to the local laboratory standard practice.[66] If a diagnosis of HIV infection is confirmed, HIV viral load, resistance testing, and CD4 lymphocyte tests should be ordered to assist in future treatment decisions.

See http://www.cdc.gov/hiv/testing/laboratorytests.html for FDA-approved HIV tests, specimen requirements, and time to detection of HIV infection.

## ACUTE HIV INFECTION

In clinical trials of oral tenofovir-based PrEP, drug-resistant virus has developed in a small number of trial participants with unrecognized acute HIV infection and for whom PrEP had been dispensed, including most often the M184V/I mutation associated with emtricitabine resistance and less frequently the K65R mutation associated with tenofovir resistance.[67] In these trials, no resistance mutations emerged among persons who acquired antiretroviral-sensitive HIV while taking PrEP as prescribed. Therefore, identifying people with possible acute infection is critical to ensure persons with HIV are not exposed to drug pressure from PrEP that might induce antiretroviral resistance and limit future treatment options.[68] Among persons receiving CAB injections for PrEP, integrase strand transfer inhibitor (INSTI) resistance mutations were found in 4 of 9 patients with incident HIV infections and was not seen in patients who have stopped injections (i.e., during the "tail" period when drug levels are slowly declining).[13]

Clinicians should suspect acute HIV infection in persons who report having engaged in exposure-prone behaviors in the 4 weeks prior to evaluation for PrEP (e.g., a condom broke during sex with an HIV-infected partner, relapse to injection drug use with shared injection equipment). For all PrEP candidates with a negative or an indeterminate result on an HIV antigen/antibody, and those reporting a recent possible HIV exposure event, clinicians should next solicit a history of nonspecific signs or symptoms of viral infection during the preceding month or on the day of evaluation[69, 70] (Table 2).

**Table 2:**     **Clinical Signs and Symptoms of Acute (Primary) HIV Infection[71]**

| | | Sex | | Route of transmission | |
|---|---|---|---|---|---|
| **Features** | **Overall (n = 375) %** | **Male (n = 355) %** | **Female (n = 23) %** | **Sexual (n = 324) %** | **Injection Drug Use (n = 34) %** |
| Fever | 75 | 74 | 83 | 77 | 50 |
| Fatigue | 68 | 67 | 78 | 71 | 50 |
| Myalgia | 49 | 50 | 26 | 52 | 29 |
| Skin rash | 48 | 48 | 48 | 51 | 21 |
| Headache | 45 | 45 | 44 | 47 | 30 |
| Pharyngitis | 40 | 40 | 48 | 43 | 18 |
| Cervical adenopathy | 39 | 39 | 39 | 41 | 27 |
| Arthralgia | 30 | 30 | 26 | 28 | 26 |
| Night sweats | 28 | 28 | 22 | 30 | 27 |
| Diarrhea | 27 | 27 | 21 | 28 | 23 |

Figure 4a below illustrates the recommended clinical testing algorithm to establish HIV status before the initiation of PrEP in persons without recent antiretroviral prophylaxis use. Laboratory

antigen/antibody tests are preferred over rapid antigen/antibody tests (less preferred) because they have the highest sensitivity for detecting acute HIV infection, which is associated with high viral loads. While HIV-1 RNA testing is sensitive (a preferred option), healthcare providers should be aware that available assays might yield false-positive low viral load results (e.g., <200 copies/ml) among persons without HIV.[72, 73] Without confirmatory tests, such false-positive results can lead to misdiagnosis of HIV infection.[37, 74, 75] When clinicians prescribe PrEP based solely on the results of point of care rapid tests, a laboratory antigen/antibody test should always be ordered at the time baseline labs are drawn. This will increase the likelihood of detecting unrecognized acute infection so that the patient can be transitioned from PrEP to antiretroviral treatment in a timely manner.

**Figure 4a      Clinician Determination of HIV Status for PrEP Provision to Persons without Recent Antiretroviral Prophylaxis Use**
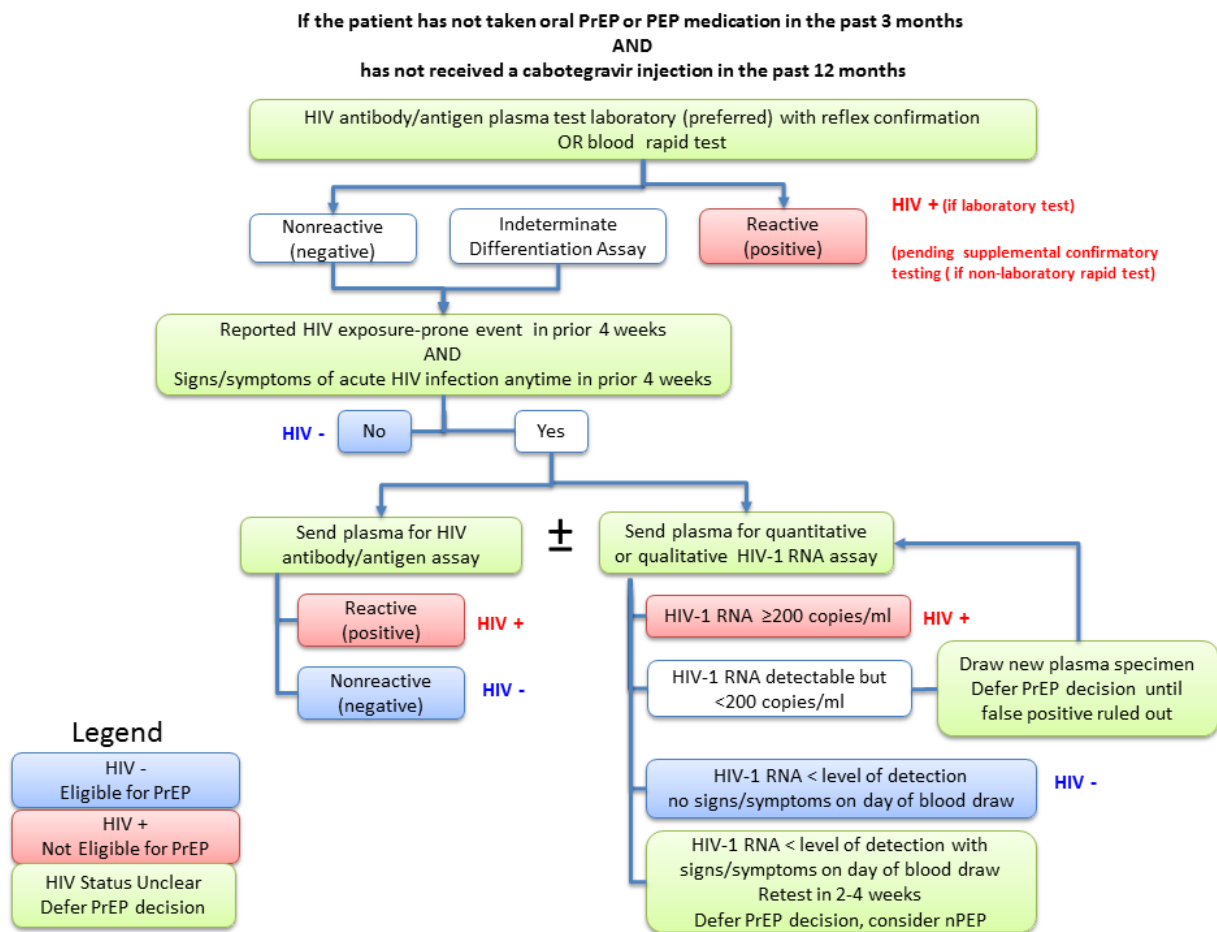


Recent data have shown that the performance of HIV tests in persons who acquire HIV infection while taking antiretroviral medications for PrEP differs from test performance in persons not exposed to antiretrovirals at or after the time of HIV acquisition[76, 77]. The antiretrovirals used for PrEP can suppress early viral replication which can affect the timing of antibody development.

In HPTN 083, detection among participants in the cabotegravir group with antigen/antibody testing was delayed by a mean of 62 days compared to detection by qualitative HIV-1 RNA assay for infections determined to have been present at baseline; the delay was 98 days for incident infections. Among participants in the F/TDF group, detection by antigen/antibody testing was delayed by a mean of 34 days from qualitative HIV-1 RNA detection for baseline infections and 31 days for incident infections[78]. In retrospective testing of stored specimens, reversion of Ag/Ab tests was seen for some specimens from persons who received cabotegravir injections near the time of infection. For that reason, a different HIV testing algorithm is recommended at follow-up visits for persons taking PrEP medication (Figure 4b).

**Figure 4b**      **Clinician Determination of HIV Status for PrEP Provision to Persons with Recent or Ongoing Antiretroviral Prophylaxis Use**
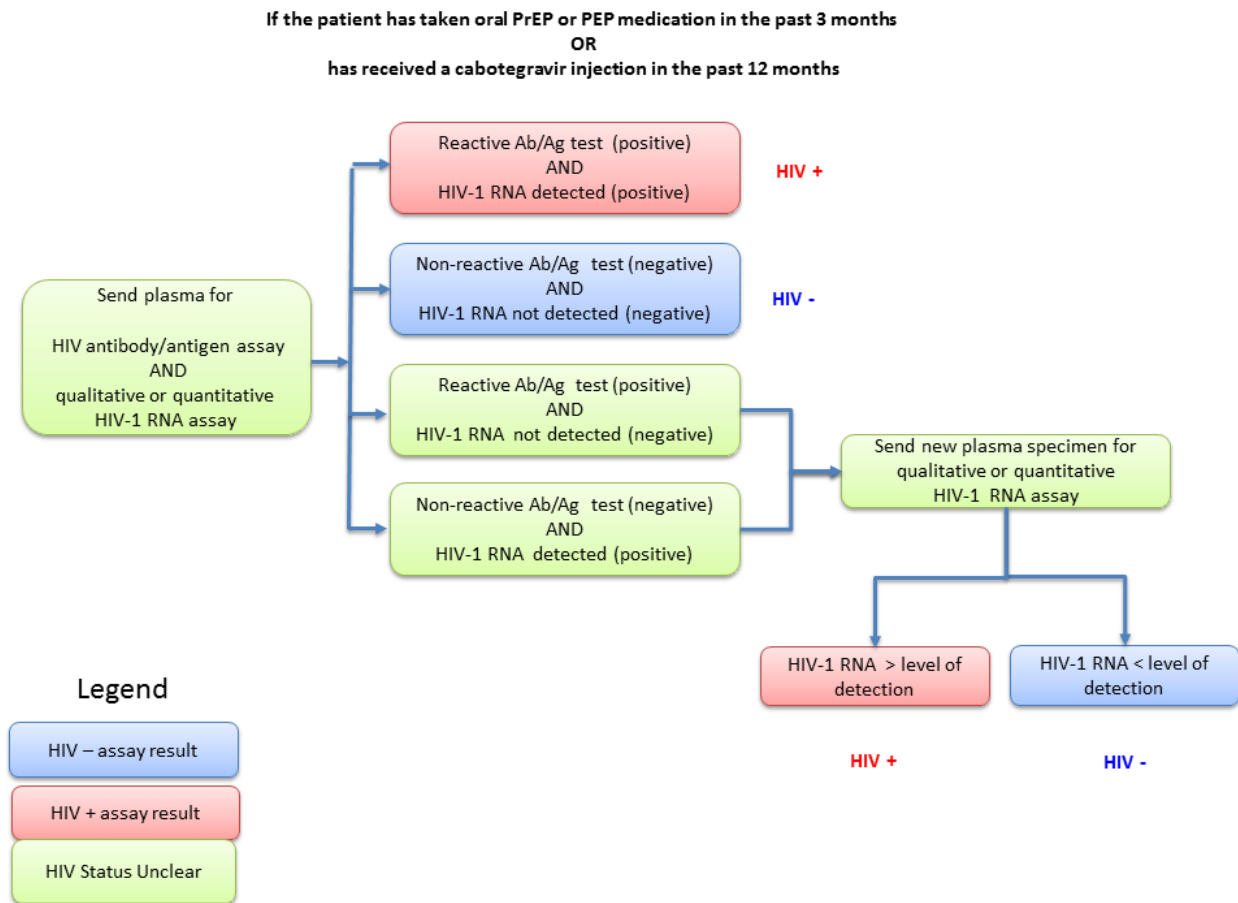


## TESTING FOR SEXUALLY TRANSMITTED INFECTIONS

Tests to screen for syphilis are recommended for all adults prescribed PrEP, both at screening and at semi-annual visits. See the 2021 STD guidelines for recommended assays.[79]

Tests to screen for gonorrhea are recommended for all sexually active adults prescribed PrEP, both at screening, for MSM at quarterly visits, and for women at semi-annual visits. Tests to screen for chlamydia are recommended for all sexually active MSM prescribed PrEP, both at screening prior to initiation and at quarterly visits.

Chlamydia is very common, especially in young women[80] and does not correlate strongly with risk of HIV acquisition[81, 82] so does not serve as an indication for initiating PrEP. However, because it is a frequent infection among sexually active women at high risk, screening for chlamydia is recommended at initiation and every 12 months for all sexually active women as a component of PrEP care.[83]

For MSM, gonorrhea and chlamydia screening using NAAT tests are preferred because of their sensitivity. Pharyngeal, rectal, and urine specimens should be collected ("3-site testing") to maximize the identification of infection, which may occur at any of these sites of exposure during sex. Patient self-collected samples have equivalent performance as clinician-obtained samples[84-86] and can help streamline patient visit flow.

For women, both syphilis and gonorrhea correlate with risk of HIV acquisition.[81, 82, 87] Gonorrhea screening of vaginal specimens by NAAT tests are preferred and may also be self-collected. Although not indicated for all women who report anal sex, women being prescribed PrEP who report engaging in anal sex are at higher risk[88] and so rectal specimens for gonorrhea and chlamydia testing should be collected in addition to vaginal specimens.[88-91] Studies have estimated that 29% of HIV infections in women are linked to sex with MSM (i.e., bisexual men),[92, 93] a population with significantly higher prevalence of gonorrhea than men who have sex only with women. More than one-third of women report having ever had anal sex,[94, 95] and 38% of women at high risk of HIV acquisition in the HPTN 064 trial reported condomless anal sex in the 6 months prior to enrollment.[96] Identifying asymptomatic rectal gonorrhea in women at substantial risk for HIV acquisition and providing treatment can benefit the woman's health and help reduce the burden of infection in her sexual networks as well.[97, 98]

Heterosexually-active adults and adolescents being evaluated for, or being prescribed PrEP, in whom gonorrhea or chlamydia infection is detected, should be offered expedited partner therapy (EPT),[99-101] especially for those patients whose partners are unlikely to access timely evaluation and treatment. EPT is legal in most states but varies by chlamydia or gonorrhea infection. Providers should visit http://www.cdc.gov/std/ept to obtain updated information for their state. In light of limited data on the use of EPT for gonorrhea or chlamydial infection among MSM and the potential for other bacterial STIs in MSM partners, shared clinical decision-making regarding EPT is recommended. Patients with syphilis or HIV diagnosed should be referred for partner services.[102, 103]

## LABORATORY TESTS FOR PATIENTS BEING CONSIDERED FOR ORAL PrEP

## RENAL FUNCTION

In addition to confirming that any patient starting PrEP medication is not infected with HIV, a clinician must assess renal function because decreased renal function is a potential safety issue for the use of F/TDF or F/TAF as PrEP.

Both F/TDF and F/TAF are widely used in combination antiretroviral regimens for HIV treatment.[37] Among persons with HIV prescribed TDF-containing regimens, mild decreases in renal function (as measured by estimated creatinine clearance (eCrCl) have been documented, and occasional cases of acute renal failure, including Fanconi's syndrome, have occurred.

In observational studies and clinical trials of F/TDF PrEP use, small decreases in renal function were likewise observed; these mostly reversed when PrEP was discontinued.[104, 105] In one observational study with F/TDF, the development of decreased renal function was more likely in patients >50 years of age or who had an eCrCl <90 ml/min when initiating PrEP with F/TDF.[106, 107] In the single clinical trial of F/TAF for PrEP among MSM (and a small number of TGW), no decrease in renal function was observed.[4, 108] There was no difference in clinically important renal health measures (e.g., grade 3 or 4 serious adverse renal events) between men taking F/TDF or F/TAF in the DISCOVER trial. However, changes were seen in some biochemical markers of proximal tubular function (e.g., $\beta$2-microlobulin:creatinine ratio, retinol binding protein:creatinine ratio) that favored F/TAF.[4] This may indicate a longer-term safety benefit of prescribing F/TAF for men with pre-existing risk factors for renal dysfunction (e.g., hypertension, diabetes).

Clinical trials and observational studies of F/TDF for PrEP have demonstrated safety when prescribed to healthy, HIV-uninfected adults with an eCrCl≥60 ml/min. Safety data for F/TDF prescribed for PrEP to patients with renal function <60 ml/min are not available. F/TAF is approved for PrEP use in patients with an eCrCl ≥30 ml/min.[4] Therefore, for all persons considered for PrEP with either F/TDF or F/TAF, a serum creatinine test should be done, and an eCrCL should be calculated by using the Cockcroft-Gault formula (see Box A). Any person with an eCrCl of ≥60 ml/min can safely be prescribed PrEP with F/TDF. PrEP with F/TAF can be safely prescribed for persons with eCrCl of <60 ml/min but ≥30 ml/min.

## Box A: Cockcroft-Gault Formula

**Basic Formula[109]**

$eCrCl_{CG}$ = [[(140 - age) × IBW × 0.85 for females] ÷ (serum creatinine × 72)]

IBW = ideal body weight      Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet
                                                Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

Age in years, weight in kg, and serum creatinine in mg/100mL

### TESTING FOR INFECTION WITH HEPATITIS B VIRUS (HBV)

Tenofovir and emtricitabine are also used to treat chronic HBV infection. When these drugs are discontinued, patients with HBV infection may experience clinically significant hepatitis flares. Ideally, prior to prescribing PrEP, patients should be screened for HBV (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf) so that in the event they have HBV infection, they can be informed of the danger of stopping PrEP medication without appropriate monitoring for potential hepatitis flares. However, PrEP initiation should not be withheld while waiting for HBV test results. Patients who are not immune and do not have HBV infection should be vaccinated. Providers prescribing F/TDF or F/TAF as PrEP for patients who have HBV infection (either known or first diagnosed as part of a PrEP evaluation) should do so in consultation with a provider expert in HBV treatment.

### LIPID PROFILE (F/TAF)

In the DISCOVER clinical trial comparing F/TDF and F/TAF for PrEP in MSM and transgender women, higher rates of triglyceride elevation and of weight gain were seen among men taking F/TAF than among men taking F/TDF. F/TDF has been associated with reductions in HDL and LDL cholesterol that are not seen with F/TAF in the DISCOVER Trial.[4] This may indicate a longer-term safety risk when prescribing F/TAF PrEP for men with pre-existing cardiovascular health risk factors (e.g., obesity, age, lipid profiles). All persons prescribed F/TAF for PrEP should have monitoring of triglyceride and cholesterol levels every 12 months. Lipid-lowering medications should be prescribed when indicated.

### TESTING NOT INDICATED ROUTINELY FOR ORAL PrEP PATIENTS

In clinical trials for PrEP with F/TDF or F/TAF, additional testing was done to evaluate safety. Findings in those trials indicated that DEXA scans to monitor bone mineral density (see section on optional tests below), liver function tests, hematologic assays, and urinalysis are not indicated for the routine care of all persons prescribed daily oral PrEP.

# Initial PrEP Prescription Visit for All Patients

## GOALS OF PrEP THERAPY

The ultimate goal of PrEP is to prevent the acquisition of HIV infection with its resulting morbidity, mortality, and cost to individuals and society. Therefore, clinicians initiating the provision of PrEP should:

- Prescribe medication regimens that are proven safe and effective for uninfected patients who meet recommended criteria for PrEP initiation to reduce their risk of HIV acquisition;
- Educate patients about the medications and the regimen to maximize their safe use;
- Provide support for medication-adherence to help patients achieve and maintain protective levels of medication in their bodies;
- Provide HIV risk-reduction support and prevention services or service referrals to help patients minimize their exposure to HIV and other STIs;
- Provide (or refer for) effective contraception to persons with childbearing potential who are taking PrEP and who do not wish to become pregnant; and
Monitor patients to detect HIV infection, medication toxicities, and levels of risk behavior in order to make indicated changes in strategies to support patients' long-term health.

## SAME DAY PrEP PRESCRIBING

For all patients, safely initiating PrEP requires determination of HIV status and assessment of renal function. Safely shortening the time to initiation of PrEP may be useful for some patients. For example, some patients may have time or work constraints that impose a significant burden to return to the clinic a week or two after evaluation for a prescription visit. Other patients report risk behaviors that put them at substantial risk of acquiring HIV infection in the time between visits for evaluation and PrEP prescription. However, for all patients, safely initiating PrEP requires determination of HIV status and assessment of renal function. Some sites have developed protocols that allow them to safely initiate PrEP on the same day as the initial evaluation for many patients.[110-112]

To use a same-day PrEP initiation protocol, the clinic must be able to:

- Conduct point-of-care HIV testing, ideally with an antigen/antibody fingerstick or other blood test
  - Where same-day results can be obtained, laboratory-based antigen/antibody test or an HIV-1 RNA test can be used (and is preferred)
  - Oral fluid HIV testing should not be used in the context of PrEP initiation
- Draw blood for laboratory creatinine and HIV testing when same day HIV and creatinine test results are not available

- o   Where available, a point of care blood creatinine test may be used
- Provide assistance for eligible patients to enroll in health insurance, medication co-payment assistance, or medication assistance programs for those who are uninsured or underinsured
- Provide rapid follow-up contact for patients whose laboratory test results indicate HIV infection or renal dysfunction
- Provide scheduled follow-up care appointments
- Have clinicians available to dispense or prescribe oral PrEP medication, to administer a gluteal intramuscular injection of CAB, or optionally prescribe a daily oral CAB lead-in for 4 weeks.

Optionally, clinics would be able to provide (on the first day):
- STI specimen collection for laboratory testing

Same-day PrEP initiation **is not appropriate** for:
- Patients who express ambivalence about starting PrEP (e.g., need more time to think)
- Patients for whom blood cannot be drawn for laboratory testing
- Patients with signs/symptoms and sexual history indicating possible acute HIV infection
- Patients with history of renal disease or associated conditions (e.g., hypertension, diabetes)
- Patients without insurance or a means to pay when picking up the prescribed medication that day
- Patients who do not have a **confirmed** means of contact should laboratory test indicate a need to discontinue PrEP (e.g., HIV infection, unanticipated renal dysfunction)

Same-day PrEP initiation **may not be appropriate** for:
- Patients with a very recent possible HIV exposure but no signs and symptoms of acute infection (should be evaluated for nPEP before PrEP)
- Patients who may not be easily contacted for return appointments
- Patients with mental health conditions that are severe enough to interfere with understanding of PrEP requirements (adherence, follow-up visits)

## NONOCCUPATIONAL POSTEXPOSURE PROPHYLAXIS

Patients not receiving PrEP who seek care within 72 hours after an isolated sexual or injection-related HIV exposure should be evaluated for the potential need for nPEP.[113] If the exposure is isolated (e.g., sexual assault, infrequent condom failure), nPEP should be prescribed, but PrEP or other continued antiretroviral medication is not indicated after completion of the 28-day PEP course.

Patients who seek one or more courses of nPEP and who are at risk for ongoing HIV exposures should be evaluated for possible PrEP use after confirming they have not acquired HIV[142]. Because HIV infection has been reported in association with exposures soon after completing an nPEP course,[114, 115] daily PrEP may be more protective than repeated intermittent episodes of nPEP. Patients who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of nPEP should be offered PrEP at the conclusion of their 28-day nPEP medication course. Because nPEP is highly effective when taken as prescribed, a gap is unnecessary between ending nPEP and beginning PrEP. Upon documenting HIV-negative status, preferably by using a laboratory-based Ag/Ab test or plasma HIV-1 RNA test (see figure 4), daily use of F/TDF OR F/TAF or CAB injections every 2 months can begin immediately for patients for whom PrEP is indicated. See Clinical Providers' Supplement Section 8 for a recommended transition management strategy.

In contrast, patients fully adhering to a daily PrEP regimen or who have received CAB injections on schedule do not need nPEP if they experience a potential HIV exposure while on PrEP. PrEP is highly effective when taken daily or near daily. For patients who report taking their PrEP medication sporadically, and those who did not take it within the week before the recent exposure, initiating a 28-day course of nPEP might be indicated. In that instance, all nPEP baseline and follow-up laboratory evaluations should be conducted (https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf). If, after the 28-day nPEP regimen is completed, the patient is confirmed to be HIV uninfected, any previously experienced barriers to PrEP adherence should be evaluated and if addressed, a PrEP regimen can be reinitiated.

## PRESCRIBING ORAL PrEP

### RECOMMENDED ORAL MEDICATION

The fixed-dose combination of F/TDF in a single daily dose (see Table 3), is approved by FDA for PrEP in healthy adults and adolescents at risk of acquiring HIV. F/TDF continues to be most commonly prescribed for PrEP (including PWID) who meet criteria for PrEP use.  F/TDF is available as a generic medication that is equivalent to the brand name medication (Truvada).

F/TAF has recently been approved for daily PrEP use by men and transgender women at sexual risk. F/TAF is not approved for PrEP use by women at risk through receptive vaginal sex for whom F/TDF should be prescribed instead. F/TAF and F/TDF have equivalent high efficacy and safety as PrEP for men at sexual risk.[3, 116]  Generic F/TAF is not available.

For most patients, there is no need to switch from F/TDF to F/TAF. While incremental differences in laboratory markers of bone metabolism and renal function have been seen in some studies, no differences in clinically meaningful adverse events have been seen[4]. However, F/TAF is indicated for patients with eCrCl <60 ml/min but ≥30 ml/min. Either F/TDF or F/TAF can be

used when eCrCl ≥60 ml/min.[117] Clinicians may prefer F/TAF for persons with previously documented osteoporosis or related bone disease but routine screening for bone density is not recommended for PrEP patients.

**Table 3: Recommended Oral PrEP Medications**

| Generic Name | Trade Name | Dose | Frequency | Most Common Side Effects[109,110] |
|---|---|---|---|---|
| F/TDF | Truvada | 200 mg/300 mg | Once a day | Headache, abdominal pain, weight loss |
| F/TAF | Descovy | 200 mg/25 mg | Once a day | Diarrhea |

## WHAT NOT TO USE FOR ORAL PrEP

No antiretroviral regimens should be used for PrEP other than a daily oral dose of F/TDF or F/TAF or injections of CAB every 2 months
No other medications or other dosing schedules are approved by FDA for PrEP to prevent HIV acquisition among otherwise healthy adults and adolescents.

- Do not prescribe other antiretroviral medications either in place of, or in addition to F/TDF or F/TAF.
- Do not prescribe other than continuous daily dosing of oral PrEP with the possible exception of MSM (see section on clinical considerations for MSM).
- Do not provide oral PrEP as expedited partner therapy (i.e., do not prescribe for a person not in your care).

Data on drug interactions and longer-term toxicities of TDF and TAF have been obtained mostly from studies of their use in treatment of HIV-infected persons. Small studies have also been done in HIV-uninfected, healthy adults (see Table 4).

## Table 4: Oral PrEP Medication Drug Interactions[37, 118, 119]

| | TDF | TAF |
|---|---|---|
| Buprenorphine | No significant effect<br>No dosage adjustment necessary | |
| Methadone | No significant effect<br>No dosage adjustment necessary | |
| Oral contraceptives | No significant effect<br>No dosage adjustment necessary | |
| Feminizing hormones (Spironolactone, estrogens) | Lower tenofovir-diphosphate rectal tissue levels (unknown if it affects PrEP effectiveness). TDF does not affect hormone levels | *No data available* |
| Acyclovir, valacyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides, high-dose or multiple NSAIDS or other drugs that reduce renal function or compete for active renal tubular secretion | Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related renal toxicities | *No data available* |
| Adefovir | **Do not co-administer with TDF**<br>Serum concentration of TDF may be increased, monitor for toxicities | *No data available* |
| Ledipasvir, sofosbuvir, velpatasvir, voxilaprevir | Serum concentrations of TDF may be increased. Monitor for toxicities | No significant effect |
| St John's Wort | No significant effect | **Do not co-administer with TAF**<br>Decrease in TAF concentration possible |
| Rifampin | No significant effect | **Do not co-administer with TAF unless benefits outweigh risks** |
| Rifabutin, Rifapentine | No significant effect | **Do not co-administer with TAF** |

## PROVIDING PrEP BY TELEHEALTH

Recent expansion of telehealth visits to replace some or all in-clinic visits have led to adaptations for provision of PrEP.[120, 121] These adaptations can include the following procedures:

- Conduct PrEP screening, initiation, or follow-up visits by phone or web-based consult with clinicians
- Obtain specimens for HIV, STI, or other PrEP-related laboratory tests by:
  - Laboratory visits for specimen collection only
  - Order home specimen collection kits for specified tests.
    - Specimen kits are mailed to the patient's home and contain supplies to collect blood from a fingerstick or other appropriate method (e.g. self-collected swabs and urine).
    - The kit is then mailed back to the lab with test results returned to the clinician who acts on results accordingly.
  - For HIV testing, only if a patient has no possible access to a lab (in-person or by mail), clinicians can provide an oral swab-based self-test that the patient can conduct and report the result to the clinician (e.g., photo of the test result). Because of the low sensitivity of oral Ab tests in detection of acute HIV infection, this should only be used for PrEP patients as a last resort.
- When HIV-negative status is confirmed, provide a prescription for a 90-day supply of PrEP medication (rather than a 30-day supply with two refills) to minimize trips to the pharmacy and to facilitate PrEP adherence.

## COUNSELING TO SUPPORT ORAL MEDICATION ADHERENCE AND PERSISTENCE IN CARE

Data from the published clinical trials and observational studies of daily oral PrEP indicate that medication adherence is critical to achieving the maximum prevention benefit (see Figure 5) and reduce the risk of selecting for a drug-resistant virus if HIV infection occurs.[122-124]

Data from a pharmacokinetics study with MSM given directly observed TDF dosing were applied in a statistical model to assess the relationship of dosing frequency to protective efficacy. Based on the intracellular concentrations of the active form of TDF (tenofovir diphosphate), HIV risk reduction efficacy was estimated to be of 99% for 7 doses per week, 96% for 4 doses per

**Figure 5: Adherence and F/TDF PrEP Efficacy in MSM**

| Weekly Medication Adherence Estimated by Drug Concentration | HIV Incidence per 100 person/years |
|---|---|
| None | 4.2 |
| ≤2 pills/week | 2.3 |
| 2-3 pills/week | 0.6 |
| ≥4 pills/week | 0.0 |

week, and 76% for 2 doses per week.[125, 126] This finding suggests that although there is some "forgiveness" for occasional missed doses of F/TDF PrEP for MSM, a high level of prevention efficacy requires a high level of adherence to daily medication.

However, a laboratory study comparing vaginal and colorectal tissue levels of active metabolites of TDF and FTC found that drug levels associated with significant protection against HIV

infection required 6-7 doses per week (>85% adherence) for lower vaginal tract tissues but only 2 doses per week (28% adherence) for colorectal tissues.[127] This strongly suggests that there is less "forgiveness" for missed doses among women than among MSM.

Approaches that can effectively support medication adherence include educating patients about their medications; helping them anticipate and manage side effects; asking about adherence successes and issues at follow-up visits (Box B),[128] helping them establish dosing routines that mesh with their work and social schedules; providing reminder systems and tools; addressing financial, substance use disorder, or mental health needs that may impede adherence; and facilitating social support. Data from PrEP trials and observational studies have observed lower adherence among younger MSM when seen quarterly but higher adherence when visits were monthly.[9, 10]

| **A brief medication adherence question** |
|---|
| "Many people find it difficult to take a medicine every day. |
| Thinking about the last week; on how many days have you **not** taken your medicine?" |

In terms of patient education, clinicians must ensure that patients understand clearly how to take their medications (i.e., when to take them, how many pills to take at each dose) and what to do if they experience problems (e.g., what constitutes a missed dose [number of hours after the failure to take a scheduled dose], what to do if they miss a dose). Patients should be told to take a single missed dose as soon as they remember it, unless it is almost time for the next dose. If it is almost time for the next dose, patients should skip the missed dose and continue with the regular dosing schedule.

Side effects can lead to non-adherence, so clinicians need a plan for addressing them. Clinicians should tell patients about the most common side effects and should work with patients to develop a specific plan for handling them, including the use of specific over-the-counter medications that can mitigate symptoms. The importance of using condoms during sex for STI prevention, and for HIV prevention in patients who decide to stop taking their PrEP medications, should be reinforced.

Clinicians should reinforce patient understanding that the benefits of PrEP medication use outweigh its reported risks and that the schedule of follow-up monitoring visits is designed to address any potential medication-related harm in a timely manner. Clinician should review signs and symptoms of active HIV infection and the need for rapid evaluation and HIV testing and should review how to safely discontinue or restart PrEP use (e.g., get an HIV test).

## Box B: Key Components of Oral Medication Adherence Counseling

> **Establish trust and bidirectional communication**
> **Provide simple explanations and education**
> - Medication dosage and schedule
> - Management of common side effects
> - Relationship of adherence to the efficacy of PrEP
> - Signs and symptoms of acute HIV infection and recommended actions
>
> **Support adherence**
> - Tailor daily dose to patient's daily routine
> - Identify reminders and devices to minimize forgetting doses
> - Identify and address barriers to adherence
> - Reinforce benefit relative to uncommon harms
>
> **Monitor medication adherence in a non-judgmental manner**
> - Normalize occasional missed doses, while ensuring patient understands importance of daily dosing for optimal protection
> - Reinforce success
> - Identify factors interfering with adherence and plan with patient to address them
> - Assess side effects and plan how to manage them

Using a broad array of health care professionals (e.g., physicians, nurses, case-managers, physician assistants, clinic-based and community pharmacists) that work together on a health care team to influence and reinforce adherence instructions[129] significantly improves medication adherence and may alleviate the time constraints of individual providers.[130, 131] This team-based approach may also provide a larger number of providers to counsel patients about self-management of behavioral risks.

### MANAGING SIDE EFFECTS OF ORAL PrEP

Patients taking PrEP should be informed of potential side effects. Some (<10%) of patients prescribed F/TDF or F/TAF experience a "start-up syndrome" that usually resolves within the first month of taking PrEP medication. This may include headache, nausea, or abdominal discomfort. Clinicians should discuss the use of over-the-counter medications should these temporary side effects occur. Patients should also be counseled about signs or symptoms that indicate a need for urgent evaluation when they occur between scheduled follow-up visits (e.g., those suggesting possible acute renal injury or acute HIV infection).  Weight gain is a reported side effect of F/TAF for PrEP.[4, 119]

### TIME TO ACHIEVING PROTECTION WITH DAILY ORAL PrEP

The time from initiation of daily PrEP use to maximal protection against HIV infection is unknown.  It has been shown that the pharmacokinetics of TDF and FTC vary by tissue,[127, 132]

but there is not scientific consensus on what tissue-specific intracellular concentrations are protective (see review of available data here: https://www.youtube.com/watch?v=5WfNqJPIIH8).

Data from exploratory F/TDF pharmacokinetic studies suggest that maximum intracellular concentrations of TFV-DP, the active form of tenofovir, are reached in blood PMBCs after approximately 7 days of daily oral dosing, in rectal tissue at approximately 7 days, and in cervicovaginal tissues at approximately 20 days.

F/TAF pharmacokinetic study data related to potential time to tissue-specific maximum concentrations are not yet available, so the time from initiation of daily F/TAF for PrEP to maximal tissue protection from HIV infection is not known.

Data is not available for either F/TDF or F/TAF PrEP in penile tissues susceptible to HIV infection to inform considerations of time to protection for male insertive sex partners.

## FOLLOW-UP PrEP CARE VISITS FOR ORAL PrEP PATIENTS

### CLINICAL FOLLOW-UP AND MONITORING FOR ORAL PrEP

Once daily oral PrEP is initiated, patients should return for follow-up approximately every 3 months by in-person, virtual, or phone visits. Clinicians may wish to schedule contact with patients more frequently at the beginning of PrEP either by phone or clinic visit (e.g., 1 month after initiation, to assess and confirm HIV-negative test status, assess for early side effects, discuss any difficulties with medication adherence, and answer questions.

All patients receiving oral PrEP should be seen in follow-up:

- **At least every 3 months to:**
  o Repeat HIV testing and assess for signs or symptoms of acute infection to document that patients are still HIV negative (see Figure 4);
  o Provide a prescription or refill authorization of daily PrEP medication for no more than 90 days (until the next HIV test);
  o Assess and provide support for medication adherence and risk-reduction behaviors;
  o Conduct STI testing for sexually active persons with signs or symptoms of infection and screening for asymptomatic MSM at high risk for recurrent bacterial STIs (e.g., those with syphilis, gonorrhea, or chlamydia at prior visits or multiple sex partners); and
  o Respond to new questions and provide any new information about PrEP use.
- **At least every 6 months to:**
  o Monitor eCrCl for persons age ≥50 years or who have an eCrCl <90 ml/min at PrEP initiation.

- If other threats to renal safety are present (e.g., hypertension, diabetes), renal function may require more frequent monitoring or may need to include additional tests (e.g., urinalysis for proteinuria).
- A rise in serum creatinine is not a reason to withhold treatment if eCrCl remains ≥60 ml/min for F/TDF or ≥30 for F/TAF.
- If eCrCl is declining steadily (but still ≥60 ml/min for F/TDF or ≥30 ml/min for F/TAF), ask if the patient is taking high doses of NSAID or using protein powders; consultation with a nephrologist or other evaluation of possible threats to renal health may be indicated.
  - o Conduct STI screening for sexually active persons (i.e., syphilis, gonorrhea, for all PrEP patients and chlamydia for MSM and TGW even if asymptomatic.
  - o Assess interest in continuing or discontinuing PrEP.
- **At least every 12 months to:**
  - o Monitor eCrCl for all patients continuing on PrEP medication.
  - o Monitor triglyceride, cholesterol levels, and weight for patients prescribed F/TAF for PrEP.
  - o Conduct chlamydia screening for heterosexual women and men even if asymptomatic

## LABORATORY TESTING SCHEDULE FOR ORAL PrEP PATIENTS

**Table 5  Timing of Oral PrEP-associated Laboratory Tests**

| Test | Screening/Baseline Visit | Q 3 months | Q 6 months | Q 12 months | When stopping PrEP |
|---|---|---|---|---|---|
| **HIV Test** | X* | X | | | X* |
| **eCrCl** | X | | If age ≥50 or eCrCL <90 ml/min at PrEP initiation | If age <50 and eCrCl ≥90 ml/min at PrEP initiation | X |
| **Syphilis** | X | MSM /TGW | X | | MSM/TGW |
| **Gonorrhea** | X | MSM /TGW | X | | MSM /TGW |
| **Chlamydia** | X | MSM /TGW | X | | MSM /TGW |
| **Lipid panel (F/TAF)** | X | | | X | |
| **Hep B serology** | X | | | | |
| **Hep C serology** | MSM, TGW, and PWID only | | | MSM,TGW, and PWID only | |

* Assess for acute HIV infection (see Figure 4)

## Optional Assessments for Patients Prescribed Oral PrEP

### Bone Health

Decreases in bone mineral density (BMD) have been observed in HIV-infected persons treated with combination antiretroviral therapy (including TDF-containing regimes).[114,115] However, it is unclear whether this 3%-4% decline would be seen in HIV-uninfected persons taking fewer antiretroviral medications for PrEP. The iPrEx trial evaluating F/TDF and the CDC PrEP safety trial in MSM evaluating TDF conducted serial dual-emission x-ray absorptiometry (DEXA) scans on a subset of MSM in the trials and determined that a small (~1%) decline in BMD that occurred during the first few months of PrEP either stabilized or returned to normal.[23,116] There was no increase in fragility (atraumatic) fractures over the 1-2 years of observation in these studies comparing those persons randomized to receive PrEP medication and those randomized to receive placebo.[117] In the DEXA substudy of the DISCOVER trial, men randomized to F/TAF showed slight mean percentage increases in BMD at the hip and spine through 96 weeks of observation, while men randomized to F/TDF showed mild decreases at both anatomic sites. However, there was no difference in the frequency of fractures between the treatment groups with 91% of fractures related to trauma.[3,76]

Therefore, DEXA scans or other assessments of bone health are not recommended before the initiation of PrEP or for the monitoring of persons while taking PrEP. However, any person being considered for PrEP who has a history of pathologic or fragility bone fractures or who has significant risk factors for osteoporosis should be referred for appropriate consultation and management.

### Medication adherence drug monitoring

Several factors limit the utility of routine use of laboratory measures of medication adherence during PrEP. These factors include: (1) a lack of established concentrations in blood associated with robust efficacy of tenofovir (either TDF or TAF),  or emtricitabine for the prevention of HIV acquisition in adults after exposure during penile-rectal or penile-vaginal intercourse[133] and (2) the limited but growing availability of clinical laboratories that can perform quantitation of antiretroviral medicine concentrations under rigorous quality assurance and quality control standards.

Several point-of-care tests are being used in research to assess adherence to daily oral PrEP. None are yet FDA approved and CLIA waived for point-of-care use. These tests include: a urine test that can assess adherence over the past few days,[134, 135] and a dried blood spot test that measures red blood cell concentrations of tenofovir (from either TDF or TAF) and emtricitabine active metabolites and can measure both short term (past few days) and longer term (past 6 weeks) adherence. [126, 136] A hair analysis test is being used in research to measure longer term adherence (from past 1-6 months, depending on the length of hair available).[137] For any of these measures, undetectable or low PrEP drug levels indicate the need to reinforce medication adherence. Conversely, documented high drug levels may positively reinforce patients'

adherence efforts. A home specimen-collection kit for a validated, CLIA-waived urine (very recent adherence) or dried blood spot (longer term adherence) tenofovir assay is now available from some laboratories.[121]

## DISCONTINUING AND RESTARTING DAILY ORAL PrEP

PrEP medication may be discontinued for several reasons, including patient choice, changed life situations resulting in lowered risk of HIV acquisition, intolerable toxicities, chronic nonadherence to the prescribed dosing regimen or scheduled follow-up care visits, or acquisition of HIV. How to safely discontinue and restart daily PrEP use should be discussed with patients both when starting PrEP and when discontinuing PrEP. Protection from HIV infection will wane over 7-10 days after ceasing daily PrEP use.[138, 139] Because some patients have acquired HIV soon after stopping PrEP use,[140] alternative methods to reduce risk for HIV acquisition should be discussed, including indications for nPEP and how to access it quickly if needed.

**Figure 6  HIV Incidence in MSM Before, While Taking, and After Discontinuing F/TDF PrEP Use[140, 141]**



Source: Hojilla et al, JAMA Network Open, 2021
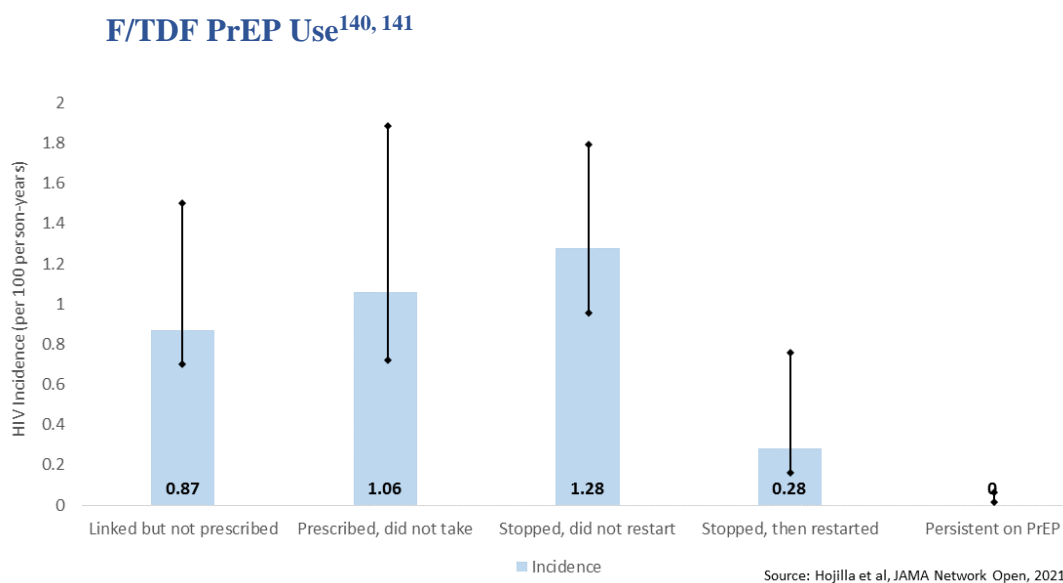
Upon discontinuation of PrEP for any reason, the following should be documented in the health record:
- HIV status at the time of discontinuation;
- Reason for discontinuation; and
- Recent medication adherence and reported sexual risk behavior.

For persons with incident HIV infection, see Persons with Documented HIV Infection. See also Clinical Providers' Supplement Section 8 for a suggested management protocol.

Patients with HBV infection who discontinue taking PrEP medication should be monitored closely for hepatitis flares. Although documented to occur in some patients discontinuing tenofovir-containing medication as part of their treatment regimens, such flares have not yet been seen in HIV-uninfected patients with chronic active HBV infection who have stopped taking TDF-containing PrEP regimens. Nonetheless, when such patients discontinue PrEP, they should continue to receive care from a clinician experienced in the management of HBV infection so that if flares occur, they can be detected promptly and treated appropriately.

Any person who wishes to resume taking PrEP medications after having stopped requires the same pre-prescription evaluation as a person being newly prescribed PrEP, including an HIV test to establish that they have not acquired HIV. In addition, discuss and document the changed circumstances since discontinuing PrEP that indicate the need to restart medication and confirm the commitment to take it as prescribed.

## PRESCRIBING CABOTEGRAVIR PrEP INJECTIONS

Patients considering PrEP should be informed of all FDA approved options. Cabotegravir injections may be especially appropriate for patients with significant renal disease, those who have had difficulty with adherent use of oral PrEP and those who prefer injections every 2 months to an oral PrEP dosing schedule. Cabotegravir should not be administered to persons with a history of hypersensitivity reaction to cabotegravir.

### RECOMMENDED MEDICATION
- 600 mg of cabotegravir injected into gluteal muscle every 2 months is recommended (conditional on FDA approval) for PrEP in adults at risk of acquiring HIV.
- 30 mg daily oral cabotegravir is optional for a 4-week lead-in prior to injections.

### WHAT NOT TO USE
Other than those recommended in this guideline, no other injectable antiretrovirals, injection sites, or dosing schedules should be used as their efficacy is unknown.

- Do not administer or prescribe other antiretroviral medications in combination with CAB for PrEP.
- Do not administer CAB injections at any site other than gluteal muscle because the pharmacokinetics of drug absorption with injection at other sites is unknown
- Do not dispense CAB injections for use by patients for home administration (unless and until self-administration is FDA approved).
- Do not prescribe ongoing daily oral CAB (other than for lead-in prior to initiating or restarting injections).

**Table 6   Cabotegravir PrEP Drug Interactions (https://www.hiv-druginteractions.org/)**

| Rifampicin, rifapentin | **Do not co-administer with CAB**<br><br>Rifampicin and rifapentine increase metabolism of CAB and may result in significantly reduced exposure to protective levels of CAB [142, 143] |
|---|---|
| Rifabutin | **Co-administer with caution**<br><br>Rifabutin moderately increases metabolism of CAB and may result in somewhat reduced exposure to protective levels of CAB[144] |
| Hormonal contraceptives | No significant effect[145] |
| Feminizing hormones (Spironolactone, estrogens) | No data yet available[146] |
| Carbamazepine, oxcarbazepine, phenytoin, phenobarbital | **Do not co-administer with CAB**<br><br>Concern that these anticonvulsants may result in significantly reduced exposure to protective levels of CAB but strength of evidence is weak |

## CAB PrEP Initiation Visit

In the clinical trials of CAB injections for PrEP, patients were provided oral CAB 30 mg tablets daily for 5 weeks prior to receiving the first injection.[147] Because there were no safety concerns identified during this lead-in period or during the injection phase of the studies, an oral lead-in is not required when initiating CAB PrEP. It may be optionally used for patients who are especially worried about side effects to relieve anxiety about using the long-acting CAB injection. However, continued daily oral CAB is not recommended or FDA-approved for PrEP.

Patients who have been taking daily oral PrEP, can initiate CAB injections as soon as HIV-1 RNA test results confirm that they remain HIV negative.

## Laboratory Testing For CAB PrEP Patients

Patients whose HIV test results indicate that they do not have acute or chronic HIV infection can be considered for initiation of cabotegravir injections (see Figure 4b). Because of the long duration of drug exposure following injection, exclusion of acute HIV infection is necessary with the most sensitive test available, an HIV-1 RNA assay. Ideally, this testing will be done within 1

week prior to the initiation visit. If clinicians wish to provide the first injection at the first PrEP evaluation visit based on the result of a rapid combined antigen/antibody assay, blood should always be drawn for laboratory confirmatory testing that includes an HIV RNA assay.

All PrEP patients should have baseline STI tests (see Table 1b).

**Table 7        Timing of CAB PrEP-associated Laboratory Tests**

| Test | Initiation Visit | 1 month visit | Q2 months | Q4 months | Q6 months | Q12 months | When Stopping CAB |
|---|---|---|---|---|---|---|---|
| **HIV*** | X | X | X | X | X | X | X |
| **Syphilis** | X | | | MSM^/TGW˜ only | Heterosexually active women and men only | X | MSM/TGW only |
| **Gonorrhea** | X | | | MSM/TGW only | Heterosexually active women and men only | X | MSM/TGW only |
| **Chlamydia** | X | | | MSM/TGW only | MSM/TGW only | Heterosexually active women and men only | MSM/TGW only |

\* HIV-1 RNA assay

X   all PrEP patients

^ men who have sex with men

˜ persons assigned male sex at birth whose gender identification is female

## TESTING NOT INDICATED ROUTINELY FOR CAB PrEP PATIENTS

Based on the results of the CAB clinical trials,[12, 147, 148] the following laboratory tests are NOT indicated before starting CAB injection or for monitoring patients during its use: creatinine, eCrCl, hepatitis B serology, lipid panels, liver function tests.

Screening tests associated with routine primary care and not specific to the provision of CAB for PrEP are discussed in the primary care section (see Table 8)

## RECOMMENDED CAB INJECTION

- o 3 ml suspension of CAB 600 mg IM in gluteal muscle (gluteus medius or gluteus maximus)
- o The use of a 2-inch needle is recommended for intramuscular injection for participants with a body-mass index (BMI) of 30 or greater, and a 1.5-inch needle for participants with a BMI of less than 30

## MANAGING INJECTION SITE REACTIONS

In the clinical trials, injection site reactions (pain, tenderness, induration) were frequent following CAB injections. These reactions were generally mild or moderate, lasted only a few days, and occurred most frequently after the first 2-3 injections. Patients should be informed that these reactions are common and transient. In addition, they should be provided with proactive management advice

- for the first 2-3 injections
    - o take an over-the-counter pain medication within a couple of hours before or soon after the injection and continue as needed for one to two days
    - o apply a warm compress or heating pad to the injection site for 15-20 minutes after the injection (e.g., after arriving back at home)
- thereafter, as needed for subsequent injections

## PATIENT EDUCATION/COUNSELING

Patients should be provided an appointment for the next injection 1 month after the initial one. Patients should be educated about:
- o the long "tail" of gradually declining drug levels when discontinuing CAB injections and the risk of developing a drug-resistant strain if HIV infection is acquired during that time
- o the importance of keeping their follow-up appointments if they have decided not to continue with CAB injections for PrEP

## CLINICAL FOLLOW-UP AND MONITORING FOR CAB INJECTIONS

Once CAB injections are initiated, patients should return for follow-up visits 1 month after the initial injection and then every 2 months.

- **At visit 1 month after initial injection (month 1, second injection)**
    - Repeat HIV-1 RNA test and assess for signs or symptoms of acute infection
    - Administer CAB injection
    - Respond to new questions

- **At each bimonthly visit (beginning with the third injection – month 3)**
    - Repeat HIV-1 RNA test and assess for signs or symptoms of acute infection
    - Administer CAB injection
    - Provide access to clean needles/syringes and drug treatment services for PWID
    - Respond to new questions and provide any new information about CAB PrEP
    - Discuss the benefits of persistent CAB PrEP use and adherence to scheduled injection visits

- **At least every 4 months (every other injection visit, beginning with the third injection-month 3)**
    - Conduct bacterial STI screening for MSM and transgender women who have sex with men – oral, rectal, urethral, blood (see Table 1b)

- **At least every 6 months (beginning with the fifth injection – month 7)**
    - Conduct bacterial STI screening for all heterosexually active women and men– [vaginal, rectal, urine - as indicated], blood (see Table 1b)

- **At least every 12 months (after the first injection)**
    - Assess desire to continue injections for PrEP
    - Conduct chlamydia screening for heterosexually active women and men even if asymptomatic

### DISCONTINUING OR RESTARTING CAB PrEP

Patients without HIV on follow-up visit who wish to discontinue CAB injections for PrEP or those who are a month or more late for an injection should be counseled about:
- How to safely discontinue or restart CAB injections for PrEP
- The risk of developing drug resistant HIV during the period of waning drug levels (the "tail period")
- Need for daily oral PrEP or other effective HIV prevention methods if ongoing risk of HIV exposure is anticipated

CAB levels slowly wane over many months after injections are discontinued. In the HPTN 077 trial, the median time to undetectable CAB plasma levels was 44 weeks for men and 67 weeks for women with a wide range for both sexes [149]. At some point during this "tail" phase, CAB levels will fall below a protective threshold and persist for some time at nonprotective levels exposing the patient to the risk of HIV acquisition. These lower levels of CAB may however be sufficient to apply selective pressure that selects for existing or de-novo viral strains with mutations that confer resistance to CAB or other INSTI medications. Infection with INSTI-resistant virus may complicate HIV treatment[150, 151].

**Figure 7      The trade-off of PrEP drug levels and risk of HIV infection with resistant virus**
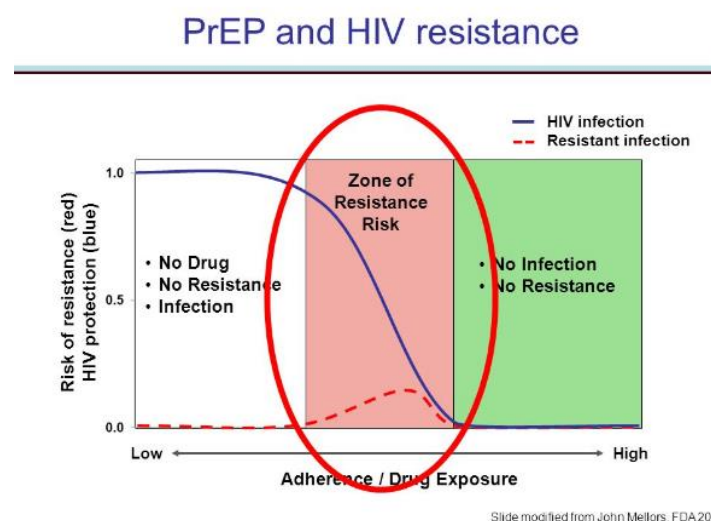


For these reasons, patients discontinuing CAB injections who may be at ongoing risk of sexual and injection HIV exposure should be provided with another highly effective HIV prevention method during the months following their last injection. As with daily oral PrEP, CAB PrEP has been associated with delayed seroconversion and detection of HIV acquisition. CAB injections can be restarted at any point after determining HIV status with HIV-1 RNA testing.

When helping patients discontinue CAB PrEP safely, clinicians should:

- Re-educate patients about the "tail" and the risks during declining CAB levels
- Assess ongoing risk/indications
- If PrEP is indicated, prescribe daily oral F/TDF or F/TAF beginning within 8 weeks after last injection
- Educate about nPEP
- Continue follow-up visits quarterly for 12 months
- Conduct HIV-1 RNA tests at each quarterly follow-up visit after discontinuing CAB injections

### TIME TO PROTECTION WITH CAB PrEP

No data are yet available from clinical trials in men or women to estimate the time from initiation of CAB injections to maximal protection against HIV acquisition.

## Managing PrEP Patients with Ambiguous HIV test Results

Acquiring HIV while taking daily PrEP as prescribed is very uncommon. While PrEP use has steadily increased since 2012, with more than 220,000 persons prescribed PrEP in 2018,[152] only a handful of incident HIV infections in PrEP-adherent patients have been documented in the US. However, with quarterly HIV testing of persons prescribed PrEP, there is a small but increasing number of PrEP patients with test results that are indeterminate (ambiguous) or that may be false positive.[153, 154] Use of antiretroviral PrEP medications at the time of infection can alter the dynamics of viremia and the patient's immune response and lead to ambiguous test results using standard HIV testing algorithms. For example, such patients may have positive point-of-care antibody results but negative antigen results or may have a reactive qualitative NAT test result but no virus detected by quantitative NAT testing.

> CLINICIANS CAN CALL THE NATIONAL CLINICIANS CONSULTATION CENTER PREPLINE AT 855-448-7737 FOR ADVICE ABOUT INTERPRETATION OF HIV TEST RESULTS AND MANAGEMENT OF PATIENTS WHO ACQUIRE HIV INFECTION WHILE TAKING PrEP MEDICATION.

Clinicians who encounter ambiguous test results for a PrEP patient at a follow-up visit have several options to confirm true HIV status:

- Carefully assess with the patient their medication adherence since the last negative HIV test visit;
- Draw a new blood specimen after a few days for repeat laboratory HIV testing including Ag/Ab and quantitative NAT testing; and
- If results are still ambiguous, contact the PrEPline (855-448-7737) for further testing advice and identification of a laboratory that can do specialized testing.

While HIV status is being confirmed, clinicians have 3 antiretroviral management options for the patient.

- Continue PrEP medication
  - Because of the high effectiveness of PrEP, the pretest probability that adherent patients are uninfected is high. If infected with HIV, continuing PrEP offers some level of viral suppression but may select for drug resistance (particularly M184v). However, if resistance occurs, well-tolerated and high effective treatment regimens are available to the patient.
- Add a third drug to provide PEP for 28 days
  - Adding a third drug to the PrEP regimen while HIV status is being confirmed provides a fully suppressive treatment regimen while avoiding the need for an

HIV diagnosis that may be difficult to undo if the patient is truly uninfected. If the patient is confirmed to have acquired HIV, the three-drug regimen constitutes early ART initiation and can be continued. This option is especially applicable when a patient reports nonadherence to daily PrEP.

- Discontinue PrEP for 1-2 weeks
    - o Drawing blood for retesting after a patient has discontinued PrEP may facilitate diagnosis by allowing viral replication resulting in a detectable viral load in a patient who has acquired HIV. However, in persons who have not acquired HIV, this leaves them without the protection of PrEP for a period of time.
- For patients receiving CAB injections for PrEP
    - o While HIV status is being confirmed, clinicians should not administer a new CAB injection. During the 1-2 weeks needed for additional HIV testing to determine HIV status, CAB is likely to remain at protective levels.
    - o If the final determination is that the patient has acquired HIV, treatment should be immediately started. Follow guidance in section on "Persons with Documented HIV Infection"
    - o If determined not to have acquired HIV, CAB injections every 2 months should resume.

## Considerations and Options for Selected Patients

The patient with certain clinical conditions may have indications for specific PrEP regimens or may require special attention and follow-up by the clinician.

### NONDAILY ORAL PREP REGIMENS FOR MSM

The "2-1-1" regimen (also called event-driven, intermittent, or "on-demand") is a nondaily PrEP regimen that times oral F/TDF doses in relation to sexual intercourse events. While not an FDA-approved regimen, two clinical trials, IPERGAY[155] and the subsequent Prévenir open label study in Paris,[156] have demonstrated the HIV prevention efficacy of 2-1-1 dosing only with F/TDF and only for MSM. These trials were conducted with European and Canadian adult MSM.

Based on trial experience, MSM prescribed the 2-1-1 regimen should be instructed to take F/TDF as follows:
- 2 pills in the 2-24 hours before sex (closer to 24 hours preferred)
- 1 pill 24 hours after the initial two-pill dose
- 1 pill 48 hours after the initial two-pill dose

**Figure 8     Schedule for "2-1-1" Dosing**



| | | | |
|---|---|---|---|
| 2 to 24 hours before sex | | 24 hours after first 2 pills | 48 hours after first 2 pills |
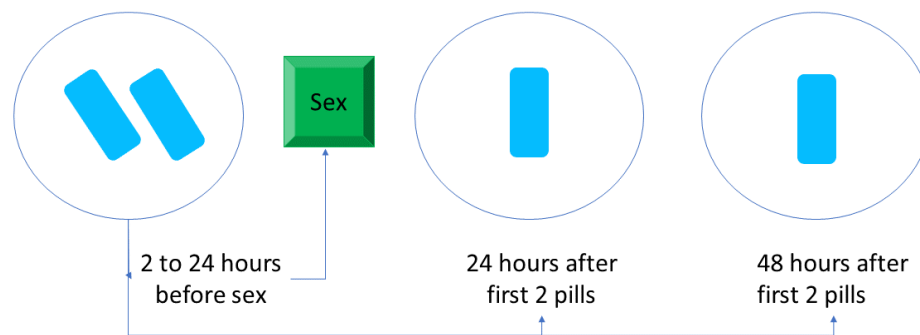
Based on the timing of subsequent sexual events, MSM should be instructed to take additional doses as follows:

- If sex occurs on the consecutive day after completing the 2-1-1 doses, take 1 pill per day until 48 hours after the last sexual event.
- If a gap of <7 days occurs between the last pill and the next sexual event, resume 1 pill daily.
- If a gap of ≥7 days occurs between the last pill and next sexual event, start again with 2 pills.

The dosing was designed and tested primarily to meet the needs of men who had infrequent sex and thus for whom daily dosing might not be necessary. Yet in these trials, men took an average 3-4 doses per week which has been associated with high levels of protection in men prescribed daily F/TDF. The IPERGAY and Prévenir trials showed high preventive efficacy of 86% or more (see evidence review in Appendix 2). There are fewer data on the efficacy of "2-1-1" dosing in MSM having less frequent sex.[157]

The only U.S. data concerning nondaily dosing among MSM came from the ADAPT HPTN 067 study participants in Harlem, New York. Investigators estimated PrEP effectiveness among those MSM prescribed a time-driven regimen (two doses per week 3-4 days apart) or an event-driven regimen (one pill taken before and another after sex) compared to MSM who were prescribed daily dosing. When assessing PrEP coverage of reported sex acts, predicted effectiveness was significantly lower for the two nondaily dosing patterns (62% and 68%, respectively) compared to daily dosing (80%).[158]

No clinical trial or observational cohort data are yet available that assess the efficacy of the 2-1-1 regimen in US MSM and no submission of data has been made for FDA review and approval of this dosing schedule. However, given the efficacy demonstrated in the IPERGAY and Prévenir trials, the International AIDS Society-USA has recommended "2-1-1" dosing as an optional, off-label, alternative to daily dosing for MSM,[159] and some local guidelines have also recommended it for selected MSM.

Some clinicians may choose to prescribe F/TDF off-label using "2-1-1" dosing for adult MSM who request non-daily dosing and who:

- have sex infrequently (e.g., less often than once a week) and
- can anticipate sex (or delay sex) to permit the doses at least 2 hours prior to sex.

Clinicians who elect to provide the 2-1-1 regimen off-label should prescribe no more than 30 pills without follow-up and documentation of another negative HIV test. Patients having sex less than once weekly will have sufficient medication to cover up to 7 intermittent sexual events.

Clinicians who elect to provide the 2-1-1 regimen should also discuss with patients:

- the importance of taking both pre-sex and post-sex doses of F/TDF to achieve good protection;
- the importance of using PrEP for all sexual encounters, not for only some partners or events;
- the possibility of recurrent "start-up" symptoms with infrequent PrEP dosing;
- the possibility of inadvertent disclosure of same-sex behavior to peers or family members since 2-1-1 dosing is only used by MSM;
- how to change between daily and 2-1-1 dosing;
- the continued need for follow-up visits for HIV and STI testing; and
- the possibility that this off-label use will not be covered by insurance.

2-1-1 dosing should not be prescribed:

- for populations other than adult MSM because it has been studied only in adult MSM;
- for MSM who it is anticipated will have difficulty adhering to a complex dosing regimen (e.g., adolescents, patient with an active substance use disorder);
- with F/TAF because its use for pericoital dosing has not been studied; or
- for MSM with active hepatitis B infection because of the danger of hepatic flares with episodic F/TDF exposure.

## TRANSGENDER PERSONS

Transgender persons are those whose gender identity or expression differs from their sex at birth. Among all adults and adolescents, diagnoses of HIV infection among transgender persons accounted for approximately 2% of diagnoses of HIV infections in the United States and 6 dependent areas; of whom 92% of diagnoses of HIV infections were for transgender women.[19] The effectiveness of PrEP with either F/TDF or F/TAF for transgender women has not yet been definitively proven in trials that were underpowered because of the small number of transgender women included.[3, 4, 32] All studies conducted to date have shown no effect of F/TDF on hormone levels. Some studies have shown that the high-doses of feminizing hormones prescribed to

transgender women result in lowering of activated tenofovir diphosphate levels in rectal tissue.[160, 161] However, other studies do not show significantly lower levels of tenofovir diphosphate among TGW taking PrEP with a feminizing hormone regimen.[162] It is unclear whether the extent of any possible reduction at the site of exposure affects PrEP effectiveness but the observed decrease in some studies suggests that daily adherence is especially important for transgender women taking feminizing hormones. Other studies have shown that medication adherence and persistence is low in some cohorts of transgender women.[163, 164] Transgender women were not specifically included in the FDA approval for F/TDF for PrEP. However, FDA approved F/TAF for PrEP was based on an analysis that combined 5,387 MSM (2,694 given F/TAF) and 74 transgender women (45 given F/TAF). Only 24 transgender women remained in the study and on PrEP through the period of analysis. There were too few transgender women remaining in the study for a separate analysis, leaving unresolved questions about the level of proof of effectiveness for them.[3] No data are available about the prevention effectiveness of either F/TDF or F/TAF for PrEP in transgender men.

In HPTN 083, there were a sufficient number of transgender women analyzed separately from MSM. Transgender women in the F/TDF group had similar HIV incidence (1.8 per 100 py) as MSM (1.14 per 100 py) and similar hazard ratios compared to the cabotegravir MSM groups (0.34 for TGW, 0.35 for MSM). F/TDF PrEP has been shown to reduce the risk for HIV acquisition during both anal sex and penile-vaginal sex. F/TAF has been proven effective in persons exposed to HIV through non-vaginal sex, and efficacy has been shown for cabotegravir injection, therefore PrEP is recommended for transgender women at risk for HIV acquisition[165]. When prescribed, clinicians should discuss the need for high medication adherence and reassure patients that PrEP medications do not impact the effects of feminizing hormones.

## PERSONS WHO INJECT DRUGS

Persons who inject drugs not prescribed to them should be offered PrEP. In addition, reducing or eliminating injection risk practices can be achieved by providing access to drug treatment and relapse prevention services[59]. Persons who inject opioids can be offered medication-assisted treatment, either within the PrEP clinical setting (e.g., provision of daily oral buprenorphine or naltrexone) or by referral to a drug treatment clinic (e.g., methadone program). Local substance use disorder treatment resources can be found at https://findtreatment.samhsa.gov/locator.

For persons not able (e.g., on a waiting list or lacking insurance) or not motivated to engage in drug treatment, providing access to sterile injection equipment through syringe service programs (where legal and available), and through prescriptions of syringes or purchase of syringes from pharmacies without a prescription (where legal), can reduce exposure to HIV and other infectious agents (e.g., HCV). In addition, providing or referring PWID for cognitive or behavioral counseling and any indicated mental health or social services may help reduce risky injection practices.

## PATIENTS WITH RENAL DISEASE

Patients with eCrCl ≥ 60 ml/min may be prescribed daily F/TDF for PrEP; those with an eCrCl between 30 and 60 ml/min may be prescribed daily F/TAF (but not F/TDF) for PrEP.[119] Persons with an eCrCl of <30 ml/min, should not be prescribed F/TDF or F/TAF for PrEP, because the safety of tenofovir-containing regimens for such persons was not evaluated in the clinical trials.

Dose reduction of either F/TDF or F/TAF is not recommended for PrEP prescribed to patients with significant renal disease.

CAB for PrEP can be especially considered for patients with significant renal disease (e.g., eCrCl <30 ml/min) in whom tenofovir-containing regimens are not recommended.

## HIV DISCORDANT PARTNERSHIPS

When assessing indications for PrEP use in an HIV discordant couple, clinicians should ask about the treatment and viral load status of the partner with HIV (if the negative partner knows it). Persons with HIV who achieve and maintain a plasma HIV RNA viral load <200 copies/ml with antiretroviral therapy have effectively no risk of sexually transmitting HIV.[166] This is sometimes referred to as "undetectable equals untransmittable" ("U=U") or "treatment as prevention" (TASP).[167]

However, some partners who know they have HIV  may not be in care, may not be receiving antiretroviral therapy, may not be receiving highly effective regimens, may not be adherent to their medications, or for other reasons may not consistently have viral loads that are associated with the least risk of transmission to an uninfected sex partner. In addition, studies have shown that patient-reported viral load status may not be accurate, [168, 169] but clinicians providing care to the HIV-negative patient may not have access to the medical records of the HIV-positive partner to document their recent viral load status and the consistency of their viral suppression over time. In the HIV discordant couples studies, reported sex with outside partners was not uncommon and HIV infections occurred that were genetically unlinked to the partner in the couple with HIV.[170-172]

PrEP may be indicated if the partner with HIV has been inconsistently virally suppressed or their viral load status is unknown, if the partner without HIV has other sexual partners (especially if of unknown HIV status), or if the partner without HIV wants the additional reassurance of protection that PrEP can provide. PrEP should not be withheld from HIV-uninfected patients who request it even if their sexual partner with HIV is reported to have achieved and maintained a suppressed viral load. Several studies, using viral genotyping, have documented HIV infection in a previously uninfected patient that was acquired from a partner outside the relationship with the partner known to have HIV[173].

For patients in an HIV discordant partnership for whom PrEP is being considered, especially where the partner with HIV is not virally suppressed, either CAB injections or daily oral PrEP are recommended options.

## PERSONS WITH DOCUMENTED HIV INFECTION

All persons with an HIV-positive test result whether at screening or while taking F/TDF or F/TAF or receiving CAB injections as PrEP should be provided the following services:[37]

- Laboratory confirmation of HIV status (see Figure 4).
- Determination of CD4 lymphocyte count and plasma HIV RNA viral load to guide therapeutic decisions.
- Documentation of results of genotypic HIV viral resistance testing to guide future treatment decisions.
- If on PrEP, conversion of the PrEP regimen to an HIV treatment regimen recommended by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents [37] without waiting for additional laboratory test results. See Clinical Providers' Supplement Section 8.
- Provision of, or referral to, an experienced provider for the ongoing medical management of HIV infection.
- Counseling about their HIV status and steps they should take to prevent HIV transmission to others and to improve their own health.
- Assistance with, or referral to, the local health department for the identification of sex partners who may have been recently exposed to HIV so that they can be tested for HIV infection, considered for nonoccupational postexposure prophylaxis (nPEP),[113] and counseled about their risk-reduction practices.

> **CLINICIANS CAN CALL THE NATIONAL CLINICIANS CONSULTATION CENTER PREPLINE AT 855-448-7737 FOR ADVICE ABOUT INTERPRETATION OF HIV TEST RESULTS AND MANAGEMENT OF PATIENTS WHO ACQUIRE HIV INFECTION WHILE TAKING PREP MEDICATION.**

In addition, a confidential report of new HIV infection should be provided to the local health department.

## WOMEN WHO BECOME PREGNANT OR BREASTFEED WHILE TAKING PREP

The guidance in this section focuses on the use of PrEP during periconception, pregnancy, and breastfeeding. All research on PrEP cited here was conducted with cisgender women. There are no data yet about transgender men, genderqueer, or non-binary individuals who have become pregnant and given birth while taking PrEP medication. Therefore, this section uses the terminology, 'women'.

An increased risk of HIV acquisition has been documented for women during periods of conception, pregnancy, and breastfeeding.[174, 175] Providers should offer PrEP with F/TDF to

women seeking to conceive (i.e., sex without a condom) and pregnant or breastfeeding women whose sexual partner has HIV, especially when their current partner's viral load is unknown, is detectable, or cannot be documented as undetectable.[176] Women whose sexual partner with HIV achieves and maintains an HIV-1 viral load <200 copies/ml are at effectively no risk of sexual acquisition of HIV.[177] The extent to which PrEP use further decreases risk of HIV acquisition when the male partner has a documented recent undetectable viral load is unknown but there may be benefit when viral suppression is not durable or the woman has other partners. F/TAF is not approved for PrEP for women.

Clinicians providing pre-conception and pregnancy care to women often do not provide care to their male partners. When partner's HIV status is unknown or not recently assessed, clinicians should offer HIV testing for the partner. When a woman's sexual partner is reported to be HIV-positive, but his recent viral load status is not known, documentation of the recent viral load status can be requested.

The FDA labeling information[6] is permissive of use of F/TDF for PrEP in pregnant and breastfeeding women. The perinatal antiretroviral treatment guidelines[178] recommend PrEP with F/TDF. Data directly related to the safety of PrEP use for a developing fetus were initially limited.[179] In the F/TDF PrEP trials with heterosexual women, medication was promptly discontinued for women who became pregnant, so the safety for exposed fetuses could not be adequately assessed. However a recent analysis of 206 Kenyan women with prenatal PrEP use and 1,324 without found no difference in pregnancy outcomes (preterm birth of low birthweight) and similar infant growth at 6 weeks postpartum.[180] In the parent Kenyan study, of 193 pregnant or postpartum women with partners living with HIV, 153 initiated PrEP and none acquired HIV.[181]

Additionally, TDF and FTC (also TAF) are widely used for the treatment of HIV infection and are continued during pregnancies that occur.[182-184] Data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications when used for either HIV treatment or prevention of HIV acquisition during pregnancy.[185]

Providers should discuss the potential risks and benefits of all available alternatives for safer conception[186] and if indicated make referrals for assisted reproduction therapies. Providers should include discussion of the potential risks and benefits of beginning or continuing PrEP during pregnancy and breastfeeding so that an informed decision can be made. Whether or not PrEP is elected, the partner with HIV should be taking maximally effective antiretroviral therapy before conception attempts.[5]

Health care providers are strongly encouraged to prospectively and anonymously submit information about any pregnancies in which PrEP is used to the Antiretroviral Pregnancy Registry at: http://www.apregistry.com/.

The safety of PrEP with F/TDF or F/TAF for infants exposed during lactation has not been adequately studied. However, data from studies of infants born to HIV-infected mothers and exposed to TDF or FTC through breast milk suggest limited drug exposure.[187-189] The World Health Organization recommends the use of F/TDF (or 3TC/efavirenz) for all pregnant and breastfeeding women with HIV to prevent perinatal and postpartum mother-to-child HIV transmission.[190] Therefore, providers should discuss current evidence about the potential risks and benefits of beginning or continuing PrEP during breastfeeding so that an informed decision can be made.[§]

Conditioned on FDA approval, CAB for PrEP may be initiated or continued in women who may become pregnant while receiving injections when it is determined that the anticipated benefits outweigh the risks.

Health care providers should prospectively and anonymously submit information about any pregnancies in which F/TDF or cabotegravir for PrEP is used to the Antiretroviral Pregnancy Registry at: http://www.apregistry.com/.

The published data on cabotegravir-exposed pregnancies among women without HIV are sparse, with only 4 pregnancies documented in HPTN 077[148]. Data from additional pregnancies that occurred among participants in HPTN 084 will be available in the near term.

The known increased risk of HIV acquisition during pregnancy and subsequent risk of HIV transmission to the infant during pregnancy and breastfeeding exceed any theoretical risk to maternal or infant health yet identified or observed in cabotegravir PrEP trials or in pregnancies occurring during treatment trials with cabotegravir-containing regimens.

## ADOLESCENT MINORS

PrEP is recommended for adolescents (weighing at least 35 kg or 77 lb) who report sexual or injection behaviors that indicate a risk of HIV acquisition. As a part of primary health care, HIV screening should be discussed with all adolescents who are sexually active or have a history of injection drug use. USPSTF recommends (grade "A") that all adolescents (age ≥15 years) be screened for HIV.[61] Parental/guardian involvement in an adolescent's health care is often desirable but is sometimes contraindicated for the safety of the adolescent. Laws and regulations that may be relevant for PrEP-related services provided to adolescent minors (including HIV

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[§]The DHHS Perinatal HIV Guidelines state that "Health care providers should offer and promote oral combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) pre-exposure prophylaxis (PrEP) to individuals who are at risk for HIV and are trying to conceive or arepregnant, postpartum, or breastfeeding:"[9] The FDA-approved package insert for F/TDF[6] says "In HIV-uninfected women, the developmental and health benefits of breastfeeding and the mother's clinical need for TRUVADA for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from TRUVADA and the risk of HIV-1 acquisition due to nonadherence and subsequent mother to child transmission."

testing), such as those concerning consent, confidentiality,[191] parental disclosure, and circumstances requiring reporting to local agencies, differ by jurisdiction. Clinicians considering providing PrEP to a person under the age of legal adulthood (a minor) should be aware of local laws, regulations, and policies that may apply[192] (see (https://www.cdc.gov/hiv/policies/law/states/minors.html). Clinicians should explicitly discuss any limits of confidentiality based on these local laws, regulations and policies and what methods will be used to assure confidentiality is maintained to the extent permitted.

Nearly all trials and observational studies have shown lower adherence and persistence rates in adolescents and young adults prescribed daily F/TDF for PrEP, particularly African American young MSM.[193] This is not unexpected as adolescents have low adherence to many medications they are prescribed.[194, 195] Therefore, to help adolescents achieve adequate protection from acquiring HIV, it will be critical to provide supportive counseling and interventions (e.g., phone apps) when they have been proven effective.

In the ATN 110 (ages 18-22 years) and 113 studies (ages 15-17 years), bone density changes in young MSM were measured during PrEP use and after completing the PrEP trial period (48 weeks). They reported decreased bone mineral density during the period of F/TDF PrEP use with larger declines in those ages 15-19 years than in those ages 20-22 years. While men ages 18-22 years had full improvement during the 48 weeks after PrEP use stopped, declines were persistent in younger men.[196] The bone changes were more frequently seen in young men with greatest adherence (i.e., higher drug exposure).[197]

Likelihood of adherence problems and effects on long-term bone health should be weighed against the potential benefit of providing PrEP for an individual adolescent at substantial risk of HIV acquisition. Because differences in pharmacodynamics suggest less bone effect with F/TAF than with F/TDF, clinicians may want to preferentially prescribe F/TAF to adolescent males initiating PrEP.

CAB for PrEP has not been studied in men or women < 18 years of age. These studies are underway but until safety is determined for this population, and reviewed by FDA, CAB is not recommended for adolescents <18 years old.

## Primary Care Considerations

Provision of PrEP affords the opportunity to manage other preventive health measures during both initial and follow-up visits, especially for persons who may not otherwise be engaged in primary care. These health measures include: vaccinations, screening for sex-specific conditions, and screening for mental health, tobacco/nicotine use, and alcohol use disorder. When providing sex-specific health care for transgender persons, the principle of "screen what you have" should be applied. For example, all persons with a cervix should be screened for cervical cancer and all persons with a prostate should be considered for prostate cancer screening, regardless of gender identification.

**Table 8        Primary Care Health Measures**

| | | MSM | MSW* | Women* | PWID |
|---|---|---|---|---|---|
| **Vaccines#** (if not previously vaccinated) | Hepatitis A vaccine | Yes | Yes | Yes | Yes |
| | Hepatitis B vaccine | Yes | Yes | Yes | Yes |
| | HPV vaccine | Through age 26 | Through age 26 | Through age 26 | Through age 26 |
| | Meningococcal B vaccine | Ages 16-18 | Ages 16-18 | Ages 16-18 | Ages 16-18 |
| | Influenza vaccine | Yes | Yes | Yes | Yes |
| **General Health** | Hepatitis C infection^ | Ages 18-79 | Ages 18-79 | Ages 18-79 | Ages 18-79 |
| | Screen for depression^ | Yes | Yes | Yes | Yes |
| | Screen for unhealthy alcohol use^ | Ages 18 and older | Ages 18 and older | Ages 18 and older | Ages 18 and older |
| | Screen for smoking^ | Yes | Yes | Yes | Yes |
| | Screen for Intimate Partner Violence^ | Yes | | Yes | If female, Yes |
| **Women's Health** | Mammography^ | | | Ages 50-74 every two years | If female, Ages 50-74 every two years |
| | Screen for cervical cancer^~ | | | Ages 21-65 every three years | If female, Ages 21-65 every three years |
| **Men's Health** | Screen for prostate cancer^ | Ages 55-69 | Ages 55-69 | | If male, Ages 55-69 |

*"screen what you have" principle for transgender persons
# per ACIP recommendations
^per USPSTF recommendations
~per ASCCP (American Society of Colposcopy and Cervical Pathology} guidelines[198]

## Financial Case-Management Issues for PrEP

A means to pay for PrEP medications and recommended clinical and counseling services is required for successful PrEP use. Nearly all public and private insurers cover PrEP, but co-pay, co-insurance, and prior authorization policies differ.

Clinicians should provide benefits counseling to assist eligible patients to obtain insurance (e.g., Medicaid, Medicare, ACA plans) either by in-clinic benefits counseling or by referral to community resources.

The USPSTF recommends that PrEP be provided to "persons who are at high risk of HIV acquisition" with an A grade indicating that there is high certainty that the net benefit is substantial.[11] This rating requires most commercial insurers and some Medicaid programs to provide oral PrEP with no out-of-pocket cost to patients. In addition to PrEP medication, DHHS has determined that laboratory tests necessary for PrEP are included in this provision as well as clinic visits when the primary purpose of the office visit is the delivery of PrEP care[199].

> A guide to billing codes for PrEP coverage is available at https://www.nastad.org/resource/billing-coding-guide-hiv-prevention (see Clinical Providers' Supplement Section 10)

For patients residing in the US without health insurance or whose insurance does not cover PrEP medication, there are two programs that can provide free F/TDF or F/TAF for PrEP.

For patients who lack outpatient prescription drug coverage, the HHS "Ready, Set, PrEP" program makes prescribed PrEP medication (either F/TDF or F/TAF) available at no cost. With a clinician's prescription, patients can enroll on the website at https://www.getyourprep.com/ or by calling toll-free 855-447-8410.

For patients without health insurance or whose insurance does not cover PrEP medication, and whose household income is <500% of the federal poverty level, Gilead Sciences has established a PrEP medication assistance program (includes both F/TDF and F/TAF). In addition to providing medication at no cost for eligible patients, this program also provides access to free HIV testing. For commercially insured patients whose personal resources are insufficient to pay out-of-pocket costs for medication co-pay or co-insurance, the Gilead co-pay assistance program provides assistance and other co-pay programs are also available.[165] Providers may obtain, complete, and sign applications for their patients to receive free PrEP medication or co-pay assistance at www.gileadadvancingaccess.com or by calling toll-free 855-330-5479.

In addition, some states have PrEP-specific financial assistance programs that cover medication, clinical care, or both. (see Table 9). These change over time and a current list can be found at https://www.nastad.org/prepcost-resources/prep-assistance-programs.

**Table 9    NASTAD Table of State PrEP Financial Assistance Programs** (as of August 2022)

| STATE | DRUG ASSISTANCE | | CLINICAL VISITS AND LAB TEST ASSISTANCE | PATIENT INCOME LIMIT |
|---|---|---|---|---|
| | COPAY ASSISTANCE | MEDICATION ASSISTANCE | | |
| California | Yes | Yes | Any participating provider | Up to 500% |
| Colorado | Yes | Yes | Any participating provider | Below 500% |
| District of Columbia | Yes | No | Local health department clinicst | Up to 500% |
| Florida | No | Yes* | Local health department clinics | No threshold |
| Illinois | Yes | No | Select grantees | No threshold |
| Indiana | Yes | No | Contracted Providers | 400% |
| Iowa | Yes | No | Sub-recipients | No threshold |
| Massachusetts | Yes | No | Select Grantees | Up to 500% |
| New Mexico | Yes | Yes | Contracted Providers | No threshold |
| New York State | No | No | Any participating provider | Up to 435% |
| Ohio | Yes | No | Any participating provider | Up to 500% |
| Oklahoma | Yes | Yes | Contracted Providers | No threshold |
| Virginia | No | Yes* | Local health departments and contracted providers | No Threshold |
| Washington State | Yes | Yes | Any participating provider | No Threshold |

** Table provided by NASTAD (source: https://www.nastad.org/prepcost-resources/prep-assistance-programs )

At the time of this guideline update, FDA approval of CAB has not yet occurred. So no medication assistance programs are yet available. It is anticipated that when FDA approves a CAB indication for PrEP, one or more assistance programs will become available for uninsured and underinsured patients with low income. A USPSTF determination about CAB for PrEP has not yet been made.

## Decision Support, Training and Technical Assistance

Decision support systems (electronic and paper), flow sheets, checklists (see Clinical Providers' Supplement, Section 1 for a PrEP provider/patient checklist at https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2021.pdf), feedback reminders, and involvement of nurse clinicians and pharmacists can help manage the many steps indicated for the safe use of PrEP and increase the likelihood that patients will follow them. Often these systems are locally developed but may become available from various sources

including training centers and Websites funded by government agencies, professional associations, or interested private companies. Examples include downloadable applications (widgets) to support the delivery of nPEP or locate nearby sites for confidential HIV tests (http://www.hivtest.org); and confidential commercial services to electronically monitor medication-taking, send text message reminders, or provide telephone assistance to help patients with problems concerning medication adherence.

Training and technical assistance in providing components of PrEP-related services, medications, and counseling are available at the following Web sites:

- PrEPline: National Clinician's Consultation Center (http://nccc.ucsf.edu/clinical-resources/prep-guidelines-and-resources/)
- Integrating HIV Care, Treatment & Prevention Services into Primary Care – A Toolkit for Health Centers (https://bphc.hrsa.gov/media/p4c-toolkit-2018.pdf)
- National PrEP Clinician Locator (https://preplocator.org/)
- Decision-Making Guide for the Provision of PrEP Services in Title X-Funded Family Planning Service Sites (https://opa.hhs.gov/sites/default/files/2020-07/OPA-PrEP-Decision-Guide_0.pdf)
- HIV Nexus Clinician Resources (https://www.cdc.gov/hiv/clinicians/index.html)
- The AIDS Education Training Centers National Resource Center (http://www.aids-ed.org)
- The Addiction Technology Transfer Center Network (http://www.attcnetwork.org)
- AIDS Info (http://www.aidsinfo.nih.gov, http://www.aids.gov)
- The National Network of STD Clinical Prevention Training Centers (http://nnptc.org/)

## Related DHHS Guidelines

This document is consistent with several other guidelines from several organizations related to sexual health, HIV prevention, and the use of antiretroviral medications. Clinicians should refer to these other documents for detailed guidance in their respective areas of care.
- Prevention of Human Immunodeficiency Virus (HIV) Infection: Preexposure Prophylaxis Final Recommendation USPSTF, 2019[11]
- Screening For HIV Infection: Current Recommendations USPSTF, 2019[61]
- Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings[200]
- Recommendations for HIV Screening of Gay, Bisexual, and Other Men Who Have Sex with Men — United States, 2017[60]
- Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[201]
- Recommendations for Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States[158]

- Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Non-occupational Exposure to HIV -United States, 2017[202]
- Sexually Transmitted Diseases Treatment Guidelines, 2021[79]
- Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infection[102]
- Expedited Partner Therapy in the Management of Sexually Transmitted Diseases, 2006[101]
- Guidance on the Use of Expedited Partner Therapy in the Treatment of Gonorrhea, 2016[100]
- Behavioral counseling interventions to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement[203]
- CDC Recommendations for Hepatitis C Screening Among Adults — United States, 2020[204]
- Hepatitis C guidance: AASLD-I DSA recommendations for testing, managing, and treating adults infected with hepatitis C virus[205]
- Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the U.S. Department of Health and Human Services[185]

# Appendices

# APPENDIX 1 GRADING OF STRENGTH OF RECOMMENDATIONS AND QUALITY OF EVIDENCE

Key recommendations in this guideline are based on the review of published scientific evidence and expert opinions. For details on the guidelines development process used, see the Clinical Providers' Supplement, Section 11 at https://www.cdc.gov/hiv/pdf/risk/prep-cdc-hiv-prep-provider-supplement-2021.pdf.

Using the same grading system as the DHHS antiretroviral treatment guidelines,[201] these key recommendations are rated with a letter to indicate the strength of the recommendation and with a numeral to indicate the quality of the combined evidence supporting each recommendation.

**Table 10:     Rating Scheme for Recommendations**

| Strength of Recommendation | Quality of Evidence Supporting a Recommendation | |
|---|---|---|
| A. **Strong recommendation for the statement** | I. | One or more well-executed randomized, controlled trials with clinical outcomes, validated laboratory endpoints, or both |
| B. **Moderate recommendation for the statement** | II. | One or more well-executed, nonrandomized trials or observational cohort studies with clinical outcomes |
| C. **Optional recommendation for the statement** | III. | Expert opinion |

The quality of scientific evidence ratings in Table 11 are based on the GRADE rating system[206].

**Table 11:    Criteria for rating quality of scientific evidence**

| Type of evidence | Randomized trial = high |
|---|---|
| | Observational study = low |
| | Any other evidence = very low |
| Decrease grade if** | ▪ Serious or very serious limitation to study quality |
| | ▪ Important inconsistency |
| | ▪ Some or major uncertainty about directness |
| | ▪ Imprecise or sparse data |
| | ▪ High probability of reporting bias |
| Increase grade if | ▪ Strong evidence of association – significant relative risk >2 based on consistent evidence from 2 or more observational studies, with no plausible confounders (+1) |
| | ▪ Very strong evidence of association – significant relative risk of >5 based on direct evidence with no major threats to validity (+2) |
| | ▪ Evidence of a dose-response gradient (+1) |
| | ▪ All plausible confounders would have reduced the effect (+1) |
| Range | High-quality evidence |
| | Moderate-quality evidence |
| | Low-quality evidence |
| | Very-low quality evidence |

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** Each quality criterion can reduce or increase the quality by 1 or, if very significant, by 2 levels.

Clinical trials were conducted to evaluate the safety and efficacy of oral PrEP in populations at risk of HIV acquisition through several routes of exposure. The results of completed trials and open label or observational studies published as of January 2020 are summarized below. See also Tables 12-17 that follow. The quality of evidence in each study was assessed using GRADE criteria (https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/) and the strength of evidence for all studies relevant to a specific recommendation was assessed by the method used in the DHHS antiretroviral treatment guidelines (See Appendix 1).

## PUBLISHED TRIALS OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG MEN WHO HAVE SEX WITH MEN

### iPrEx (Preexposure Prophylaxis Initiative) Trial

The iPrEx study [2] was a phase 3, randomized, double-blind, placebo-controlled trial conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States among men and male-to-female transgender adults who reported sex with a man during the 6 months preceding enrollment. Participants were randomly assigned to receive a daily oral dose of either the fixed-dose combination of TDF and FTC or a placebo. All participants (drug and placebo groups) were seen every 4 weeks for an interview, HIV testing, counseling about risk- reduction and adherence to PrEP medication doses, verifying returned pill count, and dispensing of pills and condoms.

Analysis of data through May 1, 2010, revealed that after the exclusion of 58 participants (10 later determined to be HIV- infected at enrollment and 48 who did not have an HIV test after enrollment), 36 of 1,224 participants in the F/TDF group and 64 of 1,217 in the placebo group had acquired HIV. Enrollment in the F/TDF group was associated with a 44% reduction in the risk of HIV acquisition (95% CI, 15-63). The reduction was greater in the as-treated analysis: at the visits at which adherence was ≥50% (by self-report and pill count/dispensing), the reduction in HIV acquisition was 50% (95% CI, 18-70). The reduction in the risk of HIV acquisition was 73% at visits at which self-reported adherence was ≥90% (95% CI, 41-88) during the preceding 30 days. Among participants randomly assigned to the F/TDF group, plasma and intracellular drug-level testing was performed for all persons who acquired HIV during the trial and for a matched subset who remained HIV- uninfected: a 92% reduction in the risk of HIV acquisition (95% CI, 40-99) was found in participants with detectable levels of F/TDF versus those with no drug detected.

Generally, F/TDF was well tolerated, although nausea in the first month was more common among participants taking medication than among those taking placebo (9% versus 5%). No differences in severe (grade 3) or life-threatening (grade 4) adverse laboratory events were observed between the active and placebo group, and no drug-resistant virus was found in the 100 participants infected after enrollment. Among 10 participants who were HIV-negative at enrollment but later found to have been infected before enrollment, FTC-resistant virus was detected in 2 of 2 men in the active group and 1 of 8 men in the placebo group. Compared to participant reports at baseline, over the course of the study, participants in both the F/TDF and placebo groups reported fewer total numbers of sex partners with

whom the participants had receptive anal intercourse and higher percentages of partners who used condoms.

In the original iPrEx publication, [2, 125] of 2,499 MSM, 29 identified as female (i.e., transgender women). In a subsequent subgroup analysis,[19] men were categorized as transgender women (n=339) if they were born male and either identified as women (n=29), identified as transgender (n=296), or identified as male and used feminizing hormones (n=14). Using this expanded definition, among transgender women, no efficacy of F/TDF for PrEP was demonstrated.[207] There were 11 infections among the PrEP group and 10 in the placebo group (HR 1.1, 95% CI: 0.5-2.7). By drug level testing (*always* versus *less than always*), compared with MSM, transgender women had less consistent PrEP use OR 0.39 (95% CI: 0.16-0.96). In the subsequent open-label extension study (see below), one transgender woman seroconverted while receiving PrEP and one seroconversion occurred in a woman who elected not to use PrEP.

### US MSM Safety Trial

The US MSM Safety Trial[1] was a phase 2 randomized, double-blind, placebo-controlled study of the clinical safety and behavioral effects of TDF for HIV prevention among 400 MSM in San Francisco, Boston, and Atlanta. Participants were randomly assigned 1:1:1:1 to receive daily oral TDF or placebo immediately or after a 9- month delay. Participants were seen for follow-up visits 1 month after enrollment and quarterly thereafter. Among MSM without directed drug interruptions, medication adherence was high: 92% by pill count and 77% by pill bottle openings recorded by Medication Event Monitoring System (MEMS) caps. Temporary drug interruptions and the overall frequency of adverse events did not differ significantly between TDF and placebo groups. In multivariable analyses, back pain was the only adverse event associated with receipt of TDF. In a subset of men at the San Francisco site (n=184) for whom bone mineral density (BMD) was assessed, receipt of TDF was associated with small decrease in BMD (1% decrease at the femoral neck, 0.8% decrease for total hip). TDF was not associated with reported bone fractures at any anatomical site. Among 7 seroconversions, no HIV with mutations associated with TDF resistance was detected. No HIV infections occurred while participants were being given TDF; 3 occurred in men while taking placebo; 3 occurred among men in the delayed TDF group who had not started receiving drug; 1 occurred in a man who had been randomly assigned to receive placebo and who was later determined to have had acute HIV infection at the enrollment visit.

### Adolescent Trials Network (ATN) 082

ATN 082[208] was a randomized, blinded, pilot feasibility study comparing daily PrEP with F/TDF with and without a behavioral intervention (Many Men, Many Voices) to a third group with no pill and no behavioral intervention. Participants had study visits every 4 weeks with audio-computer assisted interviews (ACASI), blood draws, and risk-reduction counseling. The outcomes of interest were acceptability of study procedures, adherence to pill-taking, safety of F/TDF, and levels of sexual risk behaviors among a population of young (ages 18-22 years) MSM in Chicago. One hundred participants

were to be followed for 24 weeks, but enrollment was stopped, and the study was unblinded early when the iPrEx study published its efficacy result. Sixty-eight participants were enrolled. By drug level detection, adherence was modest at week 4 (62%), and declined to 20% by week 24. No HIV seroconversions were observed.

**IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays)**

The results of a randomized, blinded, trial of non-daily dosing of F/TDF or placebo for HIV preexposure prophylaxis has also been published[155] and is included here for completeness, although non-daily dosing is not currently recommended by the FDA or CDC.

Four-hundred MSM in France and Canada were randomized to a complex peri-coital dosing regimen that involved taking: 1) 2 pills (F/TDF or placebo) between 2 and 24 hours before sex, 2) 1 pill 24 hours after the first dose, 3) 1 pill 48 hours after the first dose, 4) continuing daily pills if sexual activity continues until 48 hours after the last sex. If more than a 1week break occurred since the last pill, retreatment initiation was with 2 pills before sex or if less than a 1 week break occurred since the last pill, retreatment initiation was with 1 pill before sex. Each pre-sex dose was then followed by the 2 post-sex doses. Study visits were scheduled at 4 and 8 weeks after enrollment, and then every 8 weeks. At study visits, participants completed a computer-assisted interview, had blood drawn, received adherence and risk reduction counseling, received diagnosis and treatment of STIs as indicated, and had a pill count and a medication refill. Following an interim analysis by the data and safety monitoring board at which efficacy was determined, the placebo group was discontinued and all study participants were offered F/TDF. In the blinded phase of the trial, efficacy was 86% (95% CI: 40-98). By self-report, patients took a median of 15 pills per month. By measured plasma drug levels in a subset of those randomized to F/TDF, 86% had TDF levels consistent with having taken the drug during the previous week.

Because of the high frequency of sex and therefore of pill-taking among MSM in this study, it is not yet known whether the regimen will work if taken only a few hours or days before sex, without any buildup of the drug in rectal tissue from prior use. Studies suggest that it may take days, depending on the site of sexual exposure, for the active drug in PrEP to build up to an optimal level for preventing HIV infection. No data yet exist on how effective this regimen would be for heterosexual persons or those who inject drugs, or on adherence to this relatively complex PrEP regimen outside a trial setting. IPERGAY findings, combined with other recent research, suggest that even with less than perfect daily adherence, PrEP may still offer substantial protection for MSM if taken consistently.

**DISCOVER Trial**

The DISCOVER Trial [3, 4] was a phase 3, randomized, double-blind, active-controlled, non-inferiority trial conducted in 11 European and North American countries among men and male-to-female transgender persons ≥ 18 years of age who reported: 1) two or more condomless anal sex episodes with a man during the 12 weeks preceding enrollment or 2) a diagnosis of syphilis, rectal gonorrhea or rectal chlamydia in the 24 weeks prior to enrollment. Participants were randomly assigned to receive a daily oral dose of either F/TDF or F/TAF. All participants were seen at 4 weeks, 12 weeks, and every 12 weeks thereafter for an interview, HIV testing, focused physical exam, specimen collection for clinical

laboratory tests, counseling about risk- reduction and adherence to PrEP medication doses, pill count, and dispensing of pills and condoms. 200 persons in each study group (F/TDF or F/TAF) were enrolled in a substudy to assess BMD by DEXA scans at the hip and spine.

Analysis of data through 96 weeks of follow-up, revealed that after 8,756 person-years of follow-up, 15 HIV infections occurred in the F/TDF group and 7 infections occurred in the F/TAF group. The incidence rate ratio (0.47, 95% CI=0.19-1.15) was below the upper bound of the value (1.62) needed to demonstrate non-inferiority of F/TAF compared to F/TDF. Five participants (4 in the F/TDF arm and 1 in the F/TAF arm) were suspected to have acquired HIV before baseline; M184V or M184I mutations were found in the 4 participants in the F/TDF arm who may have acquired HIV before initiating PrEP at baseline. No resistance was detected among persons in either arm with incident infections that occurred after baseline.

Generally, F/TDF and F/TAF were equally well tolerated and low rates of side-effects (≤6% of participants) were observed with no difference between treatment groups. No differences were observed between the treatment groups in severe (grade 3) or life-threatening (grade 4) adverse laboratory or clinical events. No clinically significant declines in median eGFR were seen in either treatment group between baseline and 48 weeks: +1.8 ml/min for F/TAF (from baseline median 123 ml/min) and -2.3 ml/min for F/TDF (from baseline median 121 ml/min). Compared to participants randomized to F/TAF, participants randomized to F/TDF had greater decreases from baseline in serum fasting lipid levels. Conversely, participants randomized to F/TAF had increases in fasting triglycerides while participants receiving F/TDF had declines. The number and percentage of subjects who initiated lipid-lowering agents was two-fold higher in the F/TAF group (43 [1.6%]) compared to the F/TDF group (21 [0.8%]; p=0.008). BMD declines of >3% were more common in participants taking F/TDF than participants taking F/TAF with larger differences in younger men.

Daily oral PrEP with F/TDF or F/TAF is recommended for sexually-active MSM at substantial risk of HIV acquisition, because the iPrEx and DISCOVER trials present evidence of safety and efficacy in this population, especially when medication adherence is high. **(IA).**

Daily oral PrEP with F/TDF or F/TAF is recommended for sexually-active TGW at substantial risk of HIV acquisition although the evidence of efficacy in this population is limited **(IIIB).**

## PUBLISHED OBSERVATIONAL AND OPEN-LABEL STUDIES OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG MEN WHO HAVE SEX WITH MEN

### iPrEx Open-Label Extension (OLE) Study

Persons previously enrolled in the iPrEx, ATN 082, and CDC safety PrEP clinical trials were enrolled in a 72-week open-label study and were offered PrEP free of charge.[125] Seventy-six percent of 1,603 persons (1,428 MSM and 175 transgender women) enrolled received PrEP. HIV incidence among participants receiving PrEP was 1.8 per 100 person-years (py) versus 2.6 per 100 py in participants concurrently not choosing PrEP (HR 0.51, 95% CI: 0.26-1.01), adjusted for baseline sexual behaviors. Among participants receiving PrEP, by dried blood spot drug levels, there were no infections in persons

with drug levels associated with having taken 4 or more doses per week ($p<0.0001$) compared with participants taking $<2$ doses per week.

### PROUD Open-Label Extension (OLE) Study

PROUD was an open-label, randomized, wait-list controlled trial designed for MSM attending sexual health clinics in England.[209] A pilot was initiated to enroll 500 MSM, in which 275 men were randomized to receive daily oral F/TDF immediately, and 269 were deferred to start after 1 year. At an interim analysis, the data monitoring committee stopped the trial early for efficacy at an interim analysis and recommended that all deferred participants be offered PrEP. Follow-up was completed for 94% of those in the immediate PrEP arm and 90% of participants in the deferred arm. PrEP efficacy was 86% (90% CI: 64-96).

### Kaiser Permanente Observational Study

An evaluation of a specialized PrEP program provided at the Kaiser Permanente San Francisco Medical Center[210] reported on a cohort of 653 MSM, 3 heterosexual women, and 1 transgender man (with male sexual partners) who initiated F/TDF for PrEP between July 2012 and February 2015. Of these participants, 20 restarted PrEP after discontinuing it during the study period. The mean duration of use was 7.2 months. No HIV diagnoses were made during 388 py of follow-up on PrEP. No medication adherence measures were reported. After 12 months of use, 50% of PrEP users had received a diagnosis of one or more STI (95% CI: 26-35). In a subsequent report on PrEP patients seen at this center, as of February 2017, there were no HIV infections during 5,104 py of PrEP use while they were being prescribed medication.[26]

### Demo Project Open-Label Study

In this demonstration project, conducted at 3 community-based clinics in the United States,[211] MSM (n = 430) and transgender women (n=5) were offered daily oral F/TDF free of charge for 48 weeks. All patients received HIV testing, brief counseling, clinical monitoring, and STI diagnosis and treatment at quarterly follow-up visits. A subset of men underwent drug level monitoring with dried-blood spot testing and protective levels (associated with ≥4 doses per week) were high (80.0%-85.6%) at follow-up visits across the sites. STI incidence remained high but did not increase over time. Two men became infected (HIV incidence 0.43 infections per 100 py, 95% CI: 0.05-1.54), both of whom had drug levels consistent with having taken fewer than 2 doses per week at the visit when seroconversion was detected.

### IPERGAY Open-Label Extension (OLE) Study

Findings have been reported from the open-label phase of the IPERGAY trial that enrolled 361 of the original trial participants.[212] All of the open-label study participants were provided peri-coital PrEP as in the original trial. After a mean follow-up time of 18.4 months (IQR: 17.7-19.1), the HIV incidence observed was 0.19 per 100 py which, compared to the incidence in the placebo group of the original trial (6.60 per 100 py), represented a 97% (95% CI: 81-100) relative reduction in HIV incidence. The one participant who acquired HIV had not taken any PrEP in the 30 days before his reactive HIV test and was in an ongoing relationship with an HIV positive partner. Of 336 participants with plasma drug levels obtained at the 6-month visit, 71% had tenofovir detected. By self-report, PrEP was used at the

prescribed dosing for the most recent sexual intercourse by 50% of participants, with suboptimal dosing by 24%, and not used by 26%. Reported condomless receptive anal sex at most recent sexual intercourse increased from 77% at baseline to 86% at the 18-month follow-up visit ($p$=0.0004). The incidence of a first bacterial STI in the observational study (59.0 per 100 py) was not higher than that seen in the randomized trial (49.1 per 100 py) ($p$=0.11).

The frequency of pill-taking in the open label study population was higher (median 18 pills per month) than that in the original trial (median 15 pills per month). Therefore, it remains unclear whether the regimen will be highly protective if taken only a few hours or days before sex, without any buildup of the drug from prior use.

## PUBLISHED TRIALS OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG HETEROSEXUAL MEN AND WOMEN

### Partners PrEP Trial

The Partners PrEP trial [5] was a phase 3 randomized, double-blind, placebo-controlled study of daily oral F/TDF or TDF for the prevention of acquisition of HIV by the uninfected partner in 4,758 HIV-discordant heterosexual couples in Uganda and Kenya. The trial was stopped after an interim analysis in mid-2011 showed statistically significant efficacy in the medication groups (F/TDF or TDF) compared with the placebo group. In 48% of couples, the infected partner was male. HIV-positive partners had a median CD4 count of 495 cells/μL and were not being prescribed antiretroviral therapy, because they were not eligible by local treatment guidelines. Participants had monthly follow-up visits, and the study drug was discontinued among women who became pregnant during the trial.

Adherence to medication was very high: 98% by pills dispensed, 92% by pill count, and 82% by plasma drug-level testing among randomly selected participants in the TDF and F/TDF study groups. Rates of serious adverse events and serum creatinine or phosphorus abnormalities did not differ by study group. Modest increases in gastrointestinal symptoms and fatigue were reported in the antiretroviral medication groups compared with the placebo group, primarily in the first month of use. Among participants of both sexes combined, efficacy estimates for each of the 2 antiretroviral regimens compared with placebo were 67% (95% CI, 44-81) for TDF and 75% (95% CI, 55-87) for F/TDF. Among women, the estimated efficacy was 71% for TDF and 66% for F/TDF. Among men, the estimated efficacy was 63% for TDF and 84% for F/TDF. Efficacy estimates by drug regimen were not statistically different among men, women, men and women combined, or between men and women. In a Partners PrEP substudy that measured plasma TFV levels among participants randomly assigned to receive F/TDF, detectable drug was associated with a 90% reduction in the risk of HIV acquisition. TDF- or FTC- resistant virus was detected in 3 of 14 persons determined to have been infected when enrolled (2 of 5 in the TDF group; 1 of 3 in the F/TDF group).[213] No TDF or FTC resistant virus was detected among those infected after enrollment. Among women, the pregnancy rate was high (10.3 per 100 py), and rates did not differ significantly between the study groups.

### TDF2 Trial

The Botswana TDF2 Trial[6], a phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of daily oral F/TDF, enrolled 1,219 heterosexual men and women in Botswana, and follow-up has been completed. Participants were seen for monthly follow-up visits, and study drug was discontinued in women who became pregnant during the trial.

Among participants of both sexes combined, the efficacy of F/TDF was 62% (95% CI 22%-83%). Efficacy estimates by sex did not statistically differ from each other or from the overall estimate, although the small number of endpoints in the subsets of men and women limited the statistical power to detect a difference. Compliance with study visits was low: 33.1% of participants did not complete the study per protocol. However, many were re-engaged for an exit visit, and 89.3% of enrolled participants had a final HIV test.

Among 3 participants later found to have been infected at enrollment, F/TDF -resistant virus was detected in 1 participant in the F/TDF group and a low level of F/TDF -resistant virus was transiently detected in 1 participant in the placebo group. No resistant virus was detected in the 33 participants who seroconverted after enrollment.

Medication adherence by pill count was 84% in both groups. Nausea, vomiting, and dizziness occurred more commonly, primarily during the first month of use, among those randomly assigned to F/TDF than among those assigned to placebo. The groups did not differ in rates of serious clinical or laboratory adverse events. Pregnancy rates and rates of fetal loss did not differ by study group.

### FEM-PrEP Trial

The FEM-PrEP trial [214] was a phase 3 randomized, double-blind, placebo-controlled study of the HIV prevention efficacy and clinical safety of daily F/TDF among heterosexual women in South Africa, Kenya, and Tanzania. Participants were seen at monthly follow-up visits, and study drug was discontinued among women who became pregnant during the trial. The trial was stopped in 2011, when an interim analysis determined that the trial would be unlikely to detect a statistically significant difference in efficacy between the two study groups.

Adherence was low in this trial: study drug was detected in plasma samples of <50% of women randomly assigned to F/TDF. Among adverse events, only nausea and vomiting (in the first month) and transient, modest elevations in liver function test values were more common among those assigned to F/TDF than those assigned to placebo. No changes in renal function were seen in either group. Initial analyses of efficacy results showed 4.7 infections per 100/ person-years in the F/TDF group and 5.0 infections per 100 person-years in the placebo group. The hazard ratio 0.94 (95% CI, 0.59-1.52) indicated no reduction in HIV incidence associated with F/TDF use. Of the 68 women who acquired HIV during the trial, TDF or FTC resistant virus was detected in 5 women: 1 in the placebo group and 4 in the F/TDF group. In multivariate analyses, there was no association between pregnancy rate and study group.

### Phase 2 Trial of Preexposure Prophylaxis with Tenofovir Among Women in Ghana, Cameroon, and Nigeria

A randomized, double-blind, placebo-controlled trial of oral tenofovir TDF was conducted among heterosexual women in West Africa - Ghana (n = 200), Cameroon (n = 200), and Nigeria (n = 136).[215] The study was designed to assess the safety of TDF use and the efficacy of daily TDF in reducing the rate of HIV infection. The Cameroon and Nigeria study sites were closed prematurely because operational obstacles developed, so participant follow-up data were insufficient for the planned efficacy analysis. Analysis of trial safety data from Ghana and Cameroon found no statistically significant differences in grade 3 or 4 hepatic or renal events or in reports of clinical adverse events. Eight HIV seroconversions occurred among women in the trial: 2 among women in the TDF group (rate=0.86 per 100 person-years) and 6 among women receiving placebo (rate= 2.48 per 100 person-years), yielding a rate ratio of 0.35 (95% CI, 0.03-1.93; $p$=0.24). Blood specimens were available from 1 of the 2 participants who seroconverted while taking TDF; standard genotypic analysis revealed no evidence of drug-resistance mutations.

## VOICE (Vaginal and Oral Interventions to Control the Epidemic) Trial

VOICE (MTN-003)[216] was a phase 2B randomized, double-blind study comparing oral (TDF or F/TDF) and topical vaginal (tenofovir) antiretroviral regimens against corresponding oral and topical placebos among 5,029 heterosexual women enrolled in eastern and southern Africa. Of these women, 3,019 were randomly assigned to daily oral medication (F/TDF, 1,003; TDF, 1,007; oral placebo, 1,009). In 2011, the trial group receiving oral TDF and the group receiving topical tenofovir were stopped after interim analyses determined futility. The group receiving oral F/TDF continued to the planned trial conclusion.

After the exclusion of 15 women later determined to have had acute HIV infection when enrolled in an oral medication group and 27 with no follow-up visit after baseline, 52 incident HIV infections occurred in the oral TDF group, 61 in the F/TDF group, and 60 in the oral placebo group. Effectiveness was not significant for either oral PrEP medication group; −49%% for TDF (hazard ratio [HR] 1.49; 95% CI, 0.97-2.29) and −4.4% for F/TDF (HR, 1.04; 95% CI, 0.73-1.49) in the modified-intent-to-treat (mITT) analysis.

Face-to-face interview, audio computer-assisted self-interview, and pill-count medication adherence were high in all 3 groups (84%-91%). However, among 315 participants in the random cohort of the case-cohort subset for whom quarterly plasma samples were available, tenofovir was detected, on average, in 30% of samples from women randomly assigned to TDF and in 29% of samples from women randomly assigned to F/TDF. No drug was detected at any quarterly visit during study participation for 58% of women in the TDF group and 50% of women in the F/TDF group. The percentage of samples with detectable drug was less than 40% in all study drug groups and declined throughout the study. In a multivariate analysis that adjusted for baseline confounding variables (including age, marital status), the detection of study drug was not associated with reduced risk of HIV acquisition.

The number of confirmed creatinine elevations (grade not specified) observed was higher in the oral F/TDF group than in the oral placebo group. However, there were no significant differences between active product and placebo groups for other safety outcomes. Of women determined after enrollment to have had acute HIV infection at baseline, two women from the F/TDF group had virus with the M184I/V mutation associated with FTC resistance. One woman in the F/TDF group who acquired HIV

after enrollment had virus with the M184I/V mutation; no participants with HIV had virus with a mutation associated with tenofovir resistance.

In summary, although low adherence and operational issues precluded reliable conclusions regarding efficacy in 3 trials (VOICE, FEM-PrEP and the West African trial),[217] 2 trials (Partners PrEP and TDF2) with high medication adherence have provided substantial evidence of efficacy among heterosexual men and women. All 5 trials have found PrEP to be safe for these populations.

Daily oral PrEP with F/TDF is recommended for heterosexually-active men and women at substantial risk of HIV acquisition, because these trials present evidence of its safety and 2 present evidence of efficacy in these populations, especially when medication adherence is high. Daily oral PrEP with F/TAF is recommended for heterosexually active men based on the results of the DISCOVER trial but is not yet recommended for women (assigned female sex at birth) who may be exposed to HIV through vaginal sex, because no trial data for women are available (IA).

## PUBLISHED TRIAL OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG PERSONS WHO INJECT DRUGS

### Bangkok Tenofovir Study (BTS)

BTS was a phase 3 randomized, double-blind, placebo-controlled study of the safety and efficacy of daily oral TDF for HIV prevention among 2,413 PWID (also called IDU) in Bangkok, Thailand[7]. The study was conducted at drug treatment clinics; 22% of participants were receiving methadone treatment at baseline. At each monthly visit, participants could choose to receive either a 28-day supply of pills or to receive medication daily by directly-observed therapy. Study clinics (n=17) provided condoms, bleach (for cleaning injection equipment), methadone, primary medical care, and social services free of charge. Participants were followed for 4.6 years (mean) and received directly- observed therapy 87% of the time.

In the modified intent- to-treat analysis (excluding 2 participants with evidence of HIV infection at enrollment), efficacy of TDF was 48.9% (95% CI, 9.6-72.2; $P$ = .01). A post-hoc modified intent-to-treat analysis was done, removing 2 additional participants in whom HIV infection was identified within 28 days of enrollment, including only participants on directly observed therapy who met pre-established criteria for high adherence (taking a pill at least 71% of days and missing no more than two consecutive doses), and had detectable levels of tenofovir in their blood. Among this set of participants, the efficacy of TDF in plasma was associated with a 73.5% reduction in the risk for HIV acquisition (95% CI, 16.6-94.0; $P$ = .03). Among participants in an unmatched case-control study that included the 50 persons with incident HIV infection and 282 participants at 4 clinics who remained HIV uninfected, detection of TDF in plasma was associated with a 70.0% reduction in the risk for acquiring HIV (95% CI, 2.3-90.6; $P$ = .04).

Rates of nausea and vomiting were higher among TDF than among placebo recipients in the first 2 months of medication but not thereafter. The rates of adverse events, deaths, or elevated creatinine did not differ significantly between the TDF and the placebo groups. Among the 49 HIV infections for

which viral RNA could be amplified (of 50 incident infections and 2 infections later determined to have been present at enrollment), no viruses with mutations associated with TDF resistance were identified.

Among participants with HIV followed up for a maximum of 24 months, HIV plasma viral load was lower in the TDF than in the placebo group at the visit when HIV infection was detected ($P$ =0.01) but not thereafter ($P$ =0.10).

## PUBLISHED OPEN-LABEL STUDY OF ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS AMONG PERSON WHO INJECT DRUGS

### Bangkok Tenofovir Study (BTS) Open-Label Extension (OLE) Study

All 1,315 participants in the randomized trial (BTS) who were HIV-negative and had no renal contraindication were offered daily oral TDF for 1 year in an open label extension study.[218] Sixty-one percent (n=798) elected to take PrEP. Participants who were older (≥30 years, $p<0.0001$), injected heroin ($p=0.007$) or had been in prison ($p=0.0007$) were more likely to start PrEP than participants without these characteristics. Twenty-eight percent (n=220) did not return for any follow-up visits. Participants who had injected heroin ($p=0.01$) or had been in prison ($p=0.0007$) during the 3 months before the open label study returned for a follow-up visit. Overall, by diary, adherence was lower in the open label study (38.5 % of days) than in the randomized clinical trial (83.8% of days). Participants who injected midazolam ($p=0.02$) or were in prison ($p<0.0001$) during the open label study were more likely to be more than 90% adherent than those without these characteristics. During a median 335 days of follow-up, one HIV infection occurred in a participant who reported not taking any doses during the 60 days before the positive test, yielding an HIV incidence of 2.1 per 1000 py (95% CI: 0.05-11.7). Among the 339 (42%) who completed a 12-month follow-up visit, injection and needle sharing did not increase during the open-label study.

> Daily oral PrEP with F/TDF is recommended for PWID at substantial risk of HIV acquisition, because this trial presents evidence of the safety and efficacy of TDF as PrEP in this population, especially when medication adherence is high. **(IA)**

## TRIALS OF INJECTABLE ANTIRETROVIRAL PREEXPOSURE PROPHYLAXIS

### HPTN 077

HPTN 077[219] was a double-blind, placebo-controlled phase 2a trial conducted in Brazil, Malawi, South Africa, and the US. Healthy men and women (sex at birth) age 18-65 years at low HIV risk were randomized (3:1) to receive cabotegravir or placebo injections. For the initial 4 weeks, trial participants received 1 daily oral tablet containing either CAB or placebo to monitor for short term adverse events. Participants without safety concerns in the oral phase then received injections in one of two cohorts that were enrolled sequentially. Cohort 1 enrolled 110 participants to receive 3 intramuscular (IM) injections of CAB 800 mg or 0.9% saline as placebo every 12 weeks for 3 injection cycles. Cohort 2 enrolled 89 participants to receive IM injections of CAB 600 mg or placebo for 5 injection cycles with the first 2

injections separated by 4 weeks and the remaining 3 injections separated by 8 weeks. Primary analyses assessed safety tolerability, and pharmacokinetics during the injection phase (weeks 5-41) and adverse events during both the oral and injection phases. After the last CAB injection at 41 weeks had been completed for all participants, the study was unblinded. Consenting participants were then seen for quarterly follow-up visits through 52-76 weeks to assess adverse events and pharmacokinetics during the "tail" (post-injection) period. HPTN 077 followed the ÉCLAIR trial that showed safety, acceptability, and tolerability of CAB 800 mg injections in US men without HIV.[220]

In the primary analysis through 41 weeks of observation, the only statistically significant difference in clinical adverse events between those receiving CAB and those receiving placebo was for injection site pain. A grade 2 (moderate) or higher injection site reaction (ISR) occurred in 38% of participants receiving CAB and 2% of participants receiving placebo injections ($p<0.001$). Approximately 90% of participants in both CAB cohorts experienced any ISRs but most were mild or moderate, and led to discontinuation of injections for only 1 participant.

Analysis of the pharmacokinetic data through 41 weeks of follow-up showed that the 600 mg every 8 weeks dose used in cohort 2 consistently met prespecified pharmacokinetic targets (e.g., trough concentrations). All participants met the targets of 80% and 95% of participants with trough concentrations above 4× and 1× PA-IC90 (protein-adjusted 90% maximum inhibitory concentration), respectively. Participants with lower body mass index were found to generally exhibit higher pharmacokinetic peak concentrations after injection, as well as increased AUC (area under the curve) concentrations. However, the 800 mg every 12 weeks dose used in cohort 1 did not consistently achieve target concentrations with some differences between male and female participants.

Among 85 women (46 in cohort 1, 39 in cohort 2), 79 reported using hormonal contraception at baseline and 6 reported that they did not[221]. Reported oral contraception use was associated with lower peak CAB concentration but was not associated with significant differences in other pharmacokinetic parameters (including trough levels, AUC, and time to LLOQ) when compared to reported non-use of hormonal contraception. No other hormonal contraceptive type (injectable, implants, and other) was associated with significant differences in CAB pharmacokinetic parameters.

The tail-phase analyses[149] included 177 participants, including 43 placebo recipients and 134 persons who had at least one CAB injection and had at least three cabotegravir measurements higher than the LLOQ after the final injection at 41 weeks. 117 women and 60 men were followed, 74 participants in CAB cohort 1 and in CAB cohort 2, 25 in placebo cohort 1 and 18 in placebo cohort 2.

The incidence of grade 2 or worse adverse events was significantly lower during the tail phase than the injection phase ($p<0·0001$). The pharmacokinetic analysis found that the median time from the last injection to the time when cabotegravir concentration decreased below the LLOQ was approximately 33% longer for women (67.3 weeks [IQR 29.1–89.6; range 17.7–225.5] ($p=0·0003$)) than for men (43.7 weeks [IQR 31·1–66·6; range 20.4–152.5] (geometric mean by sex at birth found a fold-change 1.33, 95% CI 1·06–1·68; $p=0.014$)). The median time to LLOQ was 31% longer 65.4 weeks (IQR 49.8–95.3; range 19.7–198.2) for participants with a high body-mass index (BMI) than for those with a low BMI

57.7 weeks (IQR 36.2–76.3; range 17.7–225.5) (geometric mean fold-change 1.31, 95% CI 1.06–1.63; $p$=0·015). However, sex at birth and BMI accounted for, less than 10% of the variability observed in the duration of the pharmacologic tail.

In these low-risk cohorts, one female participant in cohort 1 acquired HIV. The seroconversion occurred 48 weeks after the final injection of CAB. Her plasma CAB concentrations were below the level of quantitation at both the visit when HIV infection was first detected and at her visit 12 weeks earlier when she had undetectable HIV RNA. No integrase resistance mutations were detected with next generation sequencing.

Four pregnancies occurred, two among women receiving placebo (one full-term healthy infant, 1one miscarriage likely due to Zika virus infection) and 2 among women receiving CAB. Both CAB pregnancies occurred during the tail phase one 32 weeks after her final CAB injection (early term, healthy infant) cohort 2) and one 108 weeks after her final injection (full-term, healthy infant, cohort 1). No birth defects were identified in newborns.

A post-hoc analysis[222] found no significant changes in weight or fasting glucose or lipid parameters when comparing participants receiving CAB injections to those receiving placebo.

The low number of transgender men (n=6) and transgender women (n=1) in this low-risk cohort did not allow the investigation of the effects of gender affirming hormone therapy.

## HPTN 083

HPTN 083 is a phase 3, randomized, double-blind, active control trial conducted in Argentina, Peru, Brazil, Thailand, Vietnam, South Africa, and the United States among adult men and transgender women who reported sex with a man during the 6 months preceding enrollment. Participants were randomly assigned to receive cabotegravir [13]or oral F/TDF. During a 5-week lead-in phase, 2282 persons in the cabotegravir group received daily oral cabotegravir tablets (30 mg) and 2284 persons in the F/TDF arm received placebo tablets for daily use. Following completion of the lead-in period, those randomized to the cabotegravir group received daily oral placebo tablets and intramuscular injections of 600 mg cabotegravir at weeks 5 and 9 and every 8 weeks thereafter. Those randomized to the F/TDF group received F/TDF tablets for daily use and placebo intramuscular injections at weeks 5 and 9 and every 8 weeks thereafter. All participants (cabotegravir and F/TDF groups) had regularly scheduled interviews, HIV testing, counseling about risk-reduction and adherence to oral pills prescribed.

A scheduled interim analysis review by the Data Safety and Monitoring Board in May 2020 determined that CAB was non-inferior to F/TDF, the study was unblinded, and CAB was offered to all study participants and study follow-up visits were continued. The final prespecified primary analysis determined that the statistical criteria for superiority of CAB compared to F/TDF was met. After the exclusion of participants later determined to have been HIV- infected at enrollment and those who did not have an HIV test after enrollment, 39 of 2247 participants in the F/TDF group and 13 of 2243 in the

CAB group had acquired HIV. HIV incidence was low in both groups; 1.22/100 person-years in the F/TDF group and 0.41/100 person-years in the CAB group. Participation in the CAB group was associated with a 66% reduction in the risk of HIV acquisition (95% CI, 38%-82%) compared to the F/TDF group. Post-hoc centralized testing of stored plasma specimens led to readjudication of the timing identification of the first HIV-positive test from incident to baseline infection for 2 participants in the CAB group and none in the F/TDF group. Based on this post-hoc readjudication, incidence in the CAB group was revised to 0.37/100 person-years with a 68% reduction in the risk of HIV acquisition (95% CI, 35%-81%) compared to the F/TDF group.

In the group randomized to CAB, 1 in 4 baseline infections and 4 of 9 incident infections with a resistance test result had one or more INSTI resistance mutations detected[78]. No resistance mutations were detected among 4 infections that occurred after the last CAB injection (i.e., during the tail phase). Among the 5 participants with INSTI resistance mutations detected, phenotyping results for 3 participants found low replication capacity and susceptibility to dolutegravir. Some showed partial or significant resistance to one or more INSTI medications.

CAB was well tolerated. ISRs (e.g., pain, tenderness, induration at the site) occurred in 81% of participants in the CAB group and 31% of those in the F/TDF group who received normal saline placebo injections. These were most common after the first, second, or third injection. Nearly all were mild or moderate severity and resolved within 1 week of injection. Only 2.4% of CAB participants discontinued receiving injections because of the discomfort of injection site reactions. 33% of participants had grade 3 or higher laboratory adverse events with no statistically significant differences between the CAB and F/TDF groups. In the first 40 weeks of the study, participants in the CAB group had a median weight gain from enrollment of 1.54 kg (95% CI 1.0-2.0). but from week 40-105, median weight gain was only 1.07 kg (95% CI 0.61-1.5).

Additional trials to assess the safety of PrEP with CAB injections for adolescent men and transgender women who have sex with men are planned.

### HPTN 084

HPTN 084[13] is a phase 3, randomized, double-blind, active control trial conducted in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe among adult women who reported sex with a man during the 6 months preceding enrollment. Participants were randomly assigned to receive cabotegravir or oral F/TDF. During a 5-week lead-in phase, 2282 women in the cabotegravir group received daily oral cabotegravir tablets and 2284 women in the F/TDF arm received placebo tablets for daily use. Following completion of the lead-in period, those randomized to the cabotegravir group received daily oral placebo tablets and intramuscular injections of cabotegravir at weeks 5 and 9 and every 8 weeks thereafter. Those randomized to the F/TDF group received F/TDF tablets for daily use and placebo intramuscular injections at weeks 5 and 9 and every 8 weeks thereafter. All participants (cabotegravir and F/TDF groups) had regularly scheduled interviews, HIV testing, counseling about risk-reduction and adherence to oral pills prescribed.

A scheduled interim analysis review by the Data Safety and Monitoring Board in November 2020 determined that CAB was superior to F/TDF, the study was unblinded, CAB was offered to all study participants, and study follow-up visits were continued. After the exclusion of participants later determined to have been HIV-infected at enrollment and those who did not have an HIV test after enrollment, 38 HIV infections occurred during follow-up, with 4 infections in the CAB group (incidence rate 0.21/100 person/years) and 34 infections in the F/TDF group (incidence rate 1.79/100 person/years). The hazard ratio comparing the CAB and F/TDF groups was 0.11 (95% CI 0.04-0.32). HIV incidence was lower than expected in both groups demonstrating that both drugs offered high levels of protection but participation in the CAB group was associated with an 89% reduction in the risk of HIV acquisition compared to the F/TDF group.

CAB was well tolerated with ISRs (e.g., pain, tenderness, induration at the site) the most commonly occurring adverse event. Nearly all were mild or moderate severity.

Additional studies to determine the safety of PrEP with CAB injections for adolescent women and confirm safety for pregnant women and their newborns are planned.

PrEP with cabotegravir intramuscular injections is recommended for adults at substantial risk of HIV acquisition, because clinical trials present evidence of its safety and efficacy in these populations (**IA**).

## TABLE 12: EVIDENCE SUMMARY — OVERALL EVIDENCE QUALITY OF RANDOMIZED PrEP CLINICAL TRIALS (PER GRADE CRITERIA[186])

### Oral Tenofovir-based PrEP Trials

| Study | Design[a] | Participants | | Limitations | Quality of Evidence (See Table 11, Appendix 1) |
|-------|-----------|--------------|--------|-------------|------------------|
| | | **Agent** | **Control** | | |
| Among Men Who have Sex with Men | | | | | |
| iPrEx Trial | Phase 3 | F/TDF (n = 1251) | Placebo (n = 1248) | Adherence | High |
| US MSM Safety Trial | Phase 2 | TDF (n = 201) | Placebo (n = 199) | Minimal | High |
| ATN 082 | Pilot | F/TDF (n=20) | Placebo (n=19) No pill (n=19) | Small size, stopped early, limited follow-up time, low medication adherence | Low |
| DISCOVER | Phase 3 | F/TAF (n=2694) | F/TDF (n=2693) | Minimal | High |
| Among Heterosexual Men and Women | | | | | |
| Partners PrEP | Phase 3 | TDF (n = 1589) F/TDF (n = 1583) | Placebo (n = 1586) | Minimal | High |
| TDF2 | Phase 2 | F/TDF (n = 611) | Placebo (n = 608) | High loss to follow-up; modest sample size | Moderate |
| Among Heterosexual Women | | | | | |
| FEM-PrEP | Phase 3 | F/TDF (n = 1062) | Placebo (n = 1058) | Stopped at interim analysis, limited follow-up time; very low adherence to drug regimen | Low |
| West African Trial | Phase 2 | TDF (n = 469) | Placebo (n = 467) | Stopped early for operational concerns; small sample size; limited follow-up time on assigned drug | Low |
| VOICE | Phase 2B | TDF (n = 1007) F/TDF (n = 1003) | Placebo (n = 1009) | TDF arm stopped at interim analysis (futility); very low adherence to drug regimen in both TDF and F/TDF arms | Low |

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[a] All trials in this table were randomized, double-blind, prospective clinical trials of daily oral PrEP

| | | | | | |
|---|---|---|---|---|---|
| Among Injection Drug Users |
| BTS | Phase 3 | TDF (n = 1204) | Placebo (n = 1207) | Minimal | High |

## Injectable Cabotegravir PrEP Trials

| Study | Design | Participants | | Limitations | Quality of Evidence |
|---|---|---|---|---|---|
| | | Agent | Control | | |
| Among Men and Women |
| HPTN 077 | Phase 2a | Cabotegravir 800 mg injection (n=82) Cabotegravir 600 mg injection(n=69) | Placebo (n=28) Placebo (n=20) | High follow-up discontinuation rates Limited sample size | Moderate |
| Among Men Who have Sex with Men and Transgender Women |
| HPTN 083 | Phase 2b/3 | Cabotegravir 600 mg injection (n=2282) | F/TDF daily oral (n=2284) | Minimal | High |
| Among Transgender Women |
| HPTN 083 | Phase 2b/3 | Cabotegravir 600 mg injection (n=) | F/TDF daily oral (n=) | Minimal | High |
| Among Heterosexual Women |
| HPTN 084 | Phase 3 | Cabotegravir 600 mg injection (n=1613) | F/TDF daily oral (n=1610) | Minimal | High |

Note: GRADE quality ratings:

    high = further research is very unlikely to change our confidence in the estimate of effect;

    moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;

    low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;

    very low = any estimate of effect is very uncertain.

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**TABLE 13: EVIDENCE SUMMARY OF RANDOMIZED CLINICAL TRIALS — HIV INCIDENCE FINDINGS**

| Study | Outcome Analyses— HIV incidence (mITT) | | Effect — HR [Efficacy Estimate] (95% CI) | | |
|---|---|---|---|---|---|
| | Agent | Control | | | |
| iPrEx (MSM and TGW) | 36 infections among 1,224 persons | 64 infections among 1,217 persons | 0.56 [44%] (0.37–0.85) | | |
| iPrEx (TGW)    expanded TGW definition | 11 infections (# on F/TDF not reported) | 10 infections (# on placebo not reported) | 1.1 (0.5-2.7) | | |
| US MSM Safety Trial | 3 infections among 201 persons (all 3 in delayed arm, not on TDF) | 4 infections among 199 persons (1 acute infection at enrollment) | Not Reported | | |
| Partners PrEP (heterosexual men and women) | TDF 17 infections among 1572 persons<br><br>F/TDF 13 infections among 1568 persons | 52 infections among 1568 persons | | TDF | F/TDF |
| | | | All | 0. 33 [67%] (0.19–0.56) | 0.25 [75%] (0.13–0.45) |
| | | | Women | 0.29 [71%] (0.13–0.63) | 0.34 [66%] (0.16–0.72) |
| | | | Men | 0.37 [63%] (0.17–0.80) | 0.16 [84%] (0.06–0.46) |
| TDF2 (heterosexual men and women) | 9 infections among 601 persons 1.2 infections/100 person-years | 24 infections among 599 persons 3.1 infections per 100 person-years | 0.38 [62%] (0.17–0.79) | | |
| FEM-PrEP (heterosexual women) | 33 infections among 1024 persons 4.7 infections per 100 person-years | 35 infections among 1032 persons 5.0 infections per 100 person-years | 0.94 [6%] [a] (0.59–1.52) | | |
| West African Trial (heterosexual women) | 2 infections among 427 persons 0.86 infections per 100 person-years | 6 infections among 432 persons 2.48 infections per 100 person-years | 0.35 [65%][a] (0.03–1.93) | | |

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[a] Not statistically significant.

| | | | | |
|---|---|---|---|---|
| VOICE (heterosexual women) | TDF<br>52 infections among 993 persons<br>6.3 infections per 100 person-years<br>F/TDF<br>61 infections among 985 persons<br>4.7 infections per 100 person-years | 35 infections among 999 persons<br>4.2 infections per 100 person-years | TDF<br><br>1.49 [-50 %][a]<br>(0.97–2.3) | F/TDF<br><br>1.04 [-4%][a]<br>(0.73, 1.5) |
| BTS (persons who inject drugs) | 17 infections among 1204 persons<br>0.35 infections per 100 person-years | 33 infections among 1207 persons<br>0.68 infections per 100 person-years | 0.51 [49%]<br>(9.6, 72.2) | |
| DISCOVER (MSM and TGW) | F/TAF<br>7 infections among 2670 persons<br>0.16 infections per 100 person-years | F/TDF<br>15 infections among 2665 persons<br>0.34 infections per 100 person-years | 0.47 [-53%]<br>(0.19-1.15) | |
| DISCOVER (TGW) | Not reported | Not reported | Not reported<br><br>Included 74 TGW of which 26 prematurely discontinued study drug (F/TAF 16, F/TDF 10) and 24 dropped out of the study by 48 weeks of follow-up | |
| HPTN 077 (men and women) | Cabotegravir 800 mg injection<br>1 infection among 82 persons<br>48 weeks after final injection<br><br>Cabotegravir 600 mg injection<br>0 infections among 69 persons | Placebo injection<br>0 infections among 151 persons | Not reported | |
| HPTN 083 (MSM and TGW) | Cabotegravir 600 mg injection<br>13 infections among 2244 persons<br>5 during continuous, on-time injections<br>3 during oral lead in phase<br>5 after hiatus of injections<br>0.41 infections per 100 person-years | daily oral F/TDF<br>39 infections among 2250 persons<br>7 after hiatus of pill receipt<br>32 during continuous, on-time pill receipt<br>1.22 infections per 100 person-years | 0.34 (0.18-0.62) | |
| HPTN 083 (TGW) | Cabotegravir 600 mg injection<br>2 infections among 266 persons<br>0.54 infections per 100 person-years | daily oral F/TDF<br>7 infections among 304 persons<br>1.80 infections per 100 person-years | 0.34 (.08-1.56) | |

| HPTN 084 (heterosexual women) | Cabotegravir 600 mg injection<br>4 infections among 1613 persons | daily oral F/TDF<br>34 infections among 1613 persons | 0.11 (0.04-0.32) |
|---|---|---|---|

mITT: modified intent to treat analysis; HR: hazard ratio; IRR: incidence rate ratio

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**TABLE 14: MEASURES OF EFFICACY, BY MEDICATION ADHERENCE, PERCENTAGE REDUCTION IN HIV INCIDENCE IN RANDOMIZED CLINICAL TRIALS**

| Study | Modified Intent-to-Treat Efficacy | | | Efficacy by Self-report Adherence Measures | Efficacy by Pill-count Adherence Measures (95% CI) | Efficacy by Blood Detection of Drug Measures [a] (95% CI) |
|---|---|---|---|---|---|---|
| iPrEx (F/TDF) | 44%    (15–63%) | | | >50%   50%<br>>90%   73% | (18–70%)<br>(41–88%) | 92%    (40–99%) |
| Partners PrEP | All<br>TDF: 67%<br>F/TDF: 75% | Men<br>TDF: 63%<br>F/TDF: 84% | Women<br>TDF: 71%<br>F/TDF: 66% | NR | 100%    (87–100%) | TDF: 86%        (67–94%)<br>F/TDF: 90%     (58–98%) |
| TDF2 (F/TDF) | All<br>63% | Men<br>80% | Women<br>49% [b] | NR | NR | TDF detected: 85% [b] |
| FEM-PrEP (F/TDF) | NR | | | NR | NR | NR |
| VOICE (TDF, F/TDF) | NR | | | NR | NR | NR |
| BTS (TDF) | 49% | | | NR | 56% (-19 to 86%) [c] | 74% (17–94%) |

NR, not reported.

[a] Tenofovir detection assays were done in subsets of persons randomly assigned to receive TDF or TDF/FTC

[b] Finding not statistically significant

[c] Among participants on directly observed therapy

## TABLE 15: EVIDENCE SUMMARY OF RANDOMIZED CLINICAL TRIALS — SAFETY AND TOXICITY

| Study | Outcome Analyses | |
|---|---|---|
| | **Agent** | **Control** |
| **Grade 3/4 Adverse Clinical Events[a]** | | |
| iPrEx | 52 events | 59 events |
| ATN 082 | 1 event | 1 event |
| TDF2 | 21 events | 32 events |
| West African Trial | NR | NR |
| **Grade 3/4 Adverse Laboratory Events [a]** | | |
| iPrEx | 59 events | 48 events |
| ATN 082 | 3 events | 0 events |
| TDF2 | 32 events | 32 events |
| West African Trial | 1 event | 5 events |
| **Grade 3/4 Adverse Events (Clinical and Laboratory)[a]** | | |
| Partners PrEP | TDF: 323 events TDF/FTC: 337 events | 307 events |
| FEM-PrEP | NR | NR |
| US MSM Safety Trial | 36 events | 26 events |
| VOICE | NR | NR |
| BTS | 175 events | 173 events |
| DISCOVER | F/TAF: 6% of participants | F/TDF: 5 % of participants |
| HPTN 077 | Not reported | Not reported |
| HPTN 083 | Cabotegravir: 31.8% of participants | F/TDF: 33.6% of participants |
| HPTN 084 | Pending* | Pending* |
| **Injection Site Reactions (≥ Grade 2)** | | |
| HPTN 077 | Cabotegravir: 38.1% | Placebo: 2.3% |
| HPTN 083 | Cabotegravir: 31.8% of participants | Not applicable |
| HPTN 084 | Pending* | Not applicable |

NR, not reported.

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[a] RDBPCT = randomized, double-blind, prospective clinical trial

## TABLE 16: EVIDENCE SUMMARY OF RANDOMIZED CLINICAL TRIALS — HIV RESISTANCE FINDINGS

| Study | Outcome Analyses | |
|---|---|---|
| | **Agent** | **Control** |
| iPrEx | 2 resistant viruses among 2 persons infected at baseline<br>0 resistant viruses among 36 persons infected after baseline | 1 resistant virus among 8 persons infected at baseline<br>0 resistant viruses among 64 persons infected after baseline |
| US MSM Safety Trial | 0 resistant viruses among 3 persons infected after baseline (in delayed arm before starting drug) | 1 resistant virus among 1 person infected at baseline<br>0 resistant viruses among 3 persons infected after baseline |
| Partners PrEP | 2 resistant viruses among 5 persons infected at baseline and randomly assigned to TDF<br>1 resistant virus among 3 persons infected at baseline and randomly assigned to F/TDF<br>0 resistant viruses among 27 persons infected after baseline | 0 resistant viruses among 6 persons infected at baseline<br>0 resistant viruses among 51 persons infected after baseline |
| TDF2 | 1 resistant virus in 1 person infected at baseline<br>0 resistant viruses among 9 persons infected after baseline | 1 resistant virus in 1 person infected at baseline (very low frequency and transient detection)<br>0 resistant viruses among 24 persons infected after baseline |
| FEM-PrEP | 4 resistant viruses among 33 persons infected after baseline | 1 resistant virus in 35 persons infected after baseline |
| West African Trial | 0 resistant viruses among 2 persons infected while on TDF | NR |
| VOICE | NR | — |
| BTS | 0 resistant viruses among 49 persons infected after baseline | |
| DISCOVER | 0 resistant viruses among 1 person infected at baseline and randomly assigned to F/TAF<br>0 resistant viruses among 7 persons infected after baseline | 4 resistant viruses among 4 persons infected at baseline and randomly assigned to F/TDF<br>0 resistant viruses among 11 persons infected after baseline |
| HPTN 083 | 1 resistant virus among 4 persons infected at baseline and randomly assigned to F/TAF<br>4 resistant viruses among 9 persons infected after baseline | 2 resistant viruses among 3 persons infected at baseline and randomly assigned to F/TDF<br>4 resistant viruses among 39 persons infected after baseline |
| HPTN 084 | Not yet reported | Not yet reported |

NR, not reported.

## TABLE 17: EVIDENCE SUMMARY OF OPEN-LABEL STUDIES

| Study | Design | Population | Effect HR [Efficacy Estimate] | Efficacy by Blood Detection of Drug Measure | Resistance |
|---|---|---|---|---|---|
| PROUD | Wait-list Control | MSM | [86%] [90% CI: 64%-96%] comparing immediate vs. deferred group | Not reported | 2 resistant viruses among 3 persons infected at baseline<br>0 resistant viruses among 23 persons infected after baseline |
| iPrEx OLE[a] | RCT Open-Label Extension | MSM | 0.51 [49%] (95% CI: 0.26-1.01) comparing those electing to use PrEP with those who did not, adjusted for baseline sexual risk behavior | Compared with being off PrEP, HRs for seroconversion stratified by weekly dosing inferred from blood drug levels:<br><2 doses/week<br>   0.56 [44%] (0.23-1.31)<br>2-3 doses/week<br>   0.16 [84%] (0.01-0.79)<br>4-6 doses/week<br>   0.0 [100%] (0.0-0.21)<br>7 doses/week<br>   0.0 [100%] (0.0-0.43) | 0 resistant viruses among 2 persons infected at baseline (not started on PrEP)<br>1 resistant virus among 28 persons infected after baseline started on PrEP<br>0 resistant viruses among 13 persons infected after baseline not started on PrEP |
| Demo Project | Clinical Cohort | MSM[b] | HIV incidence 0.43 per 100 py (no comparison group) in a population with an STI incidence of 90 per 100 py observed during follow-up.[b] | Both seroconverters had blood drug levels associated with <2 doses/week | 1 resistant virus among 3 persons infected at enrollment and started on PrEP<br>0 resistant viruses among 2 persons infected after baseline started on PrEP |
| Kaiser Permanente | Clinical Cohort | MSM | 0 HIV diagnoses in 5104 py of follow-up | Not reported | Not applicable |

[a] included men who had participated in the iPrEx, CDC Safety, and Adolescent Trials Network 082 PrEP trials
[b] 653 MSM, 3 heterosexual women, 1 transgender man who has sex with men

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