DEPARTMENT OF HEALTH & HUMAN SERVICES



ANDA 090894

Food and Drug Administration Silver Spring, MD 20993

ANDA APPROVAL

RECEIVED - REGULATORY AFFAIRS

By John Moran at 7:25 am, Jun 09, 2017

Teva Pharmaceuticals USA, Inc.
425 Privet Road
Horsham, PA 19044
Attention: Rich Leone
Senior Director, Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 26, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg.

Reference is also made to the tentative approval letter issued by this office on August 16, 2011, the complete response letter issued by this office on March 3, 2016, and to your amendments received on April 8, May 5, July 29, August 5, August 30 and September 13, 2016; and March 2, May 1, May 12, May 18, May 22, May 31 and June 2, 2017.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Truvada Tablets, 200 mg/300 mg, of Gilead Sciences, Inc. (Gilead). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The RLD upon which you have based your ANDA, Gilead's Truvada Tablets, 200 mg/300 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

Evniration Date

U.S. Patent Number	Expiration Date
5,914,331 (the '331 patent)	January 2, 2018*
5,922,695 (the '695 patent)	January 25, 2018*
5,935,946 (the '946 patent)	January 25, 2018*
5,977,089 (the '089 patent)	January 25, 2018*
6,043,230 (the '230 patent)	January 25, 2018*
6,642,245 (the '245 patent)	May 4, 2021*
6,703,396 (the '396 patent)	September 9, 2021*

IIS Patent Number

8,592,397 (the '397 patent)	January 13, 2024
8,716,264 (the '264 patent)	January 13, 2024
9,457,036 (the '036 patent)	January 13, 2024

^{*} with pediatric exclusivity added

Your ANDA contains paragraph IV certifications to each of the patents¹ under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg, under this ANDA. You have notified the Agency that Teva Pharmaceuticals USA, Inc. (TEVA) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated within the statutory 45-day period against TEVA for infringement of the '245, '396, '695, '946, '089, '230, and '331 patents in the United States District Court for the Southern District of New York [Gilead Sciences, Inc. and Emory University, v. TEVA Pharmaceuticals USA, Inc. and TEVA Pharmaceutical Industries, Ltd., Civil Action Nos. 08-cv-10838 ('245 and '396 patents), 10-cv-1796 ('695, '946, '089, and '230 patents), and 10-cv-1798 ('331 patent)]. You have also notified the Agency that the cases have been dismissed.

With respect to 180-day generic drug exclusivity, we note that TEVA was the first ANDA applicant for Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, TEVA may be eligible for 180 days of generic drug exclusivity for Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that TEVA failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of TEVA's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after TEVA begins commercial marketing of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets, 200 mg/300 mg, or (b) at any time prior to the expiration of the '245 and '396 patents if TEVA has not begun commercial marketing. Please submit correspondence to this ANDA informing the Agency of the date commercial marketing begins.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

¹ The Agency notes that the '397, '264, and '036 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated August 31, 2012. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Emtricitabine/Tenofovir Disoproxil Fumarate REMS Program, submitted on May 22, 2017, and appended to this letter, is approved. The Emtricitabine/Tenofovir Disoproxil Fumarate REMS is a single, shared system that consists of ETASU.

Your REMS must be fully operational before you introduce Emtricitabine and Tenofovir Disoproxil Fumarate into interstate commerce.

The Emtricitabine/Tenofovir Disoproxil Fumarate REMS uses a single, shared system for the ETASU and the REMS assessments. This single shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 090894 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 090894/S-000 CHANGES BEING EFFECTED IN 30 DAYS PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 090894/S-000 PRIOR APPROVAL SUPPLEMENT PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 090894/S-000 PRIOR APPROVAL SUPPLEMENT PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 090894

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager Food and Drug Administration Center for Drug Evaluation and Research Office of Prescription Drug Promotion 5901-B Ammendale Road Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.
Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL

files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

Heidi Lee, PharmD Acting Deputy Director Office of Regulatory Operations Office of Generic Drugs Center for Drug Evaluation and Research

ENCLOSURE: REMS

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

SINGLE SHARED SYSTEM FOR EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE

I. GOALS

The goals of the REMS for the emtricitabine/tenofovir disoproxil fumarate for a Pre-exposure Prophylaxis (PrEP) Indication are:

To inform and educate prescribers and uninfected individuals at high risk for acquiring HIV-1 infection about:

- The importance of strict adherence to the recommended dosing regimen
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
- The fact that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

II. REMS ELEMENTS

A. ELEMENTS TO ASSURE SAFE USE

- 1. Training must be provided to healthcare providers who prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.
 - a. Training must be provided to healthcare providers that includes information on reducing the risk of development of resistant HIV-1 variants using the following materials:
 - i. Dear Health Care Provider Letter
 - ii. Training Guide for Healthcare Providers
 - iii. Healthcare Provider Education Slide Deck
 - iv. Important Safety Information about emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication for Healthcare Providers
 - v. Important Safety Information about emtricitabine/tenofovir disoproxil fumarate to Reduce the Risk of Getting Human Immunodeficiency Virus-1 (HIV-1) Infection
 - vi. Agreement Form for Initiating emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP)
- vii. Checklist for Prescribers: Initiation of emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP) to manage an uninfected individual considering or taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- viii. Safety Information Fact Sheet for Prescribers about emtricitabine/tenofovir disoproxil fumarate for a Pre-exposure Prophylaxis (PrEP) Indication
 - b. In order to facilitate training, the Emtricitabine/tenofovir disoproxil fumarate Sponsors must:
 - i. Ensure that training is made available to healthcare providers who prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication by the following mechanisms: online by accessing the emtricitabine/tenofovir disoproxil fumarate REMS Program Website (www.ftc-tdf-preprems.com) or by paper copy by calling the emtricitabine/tenofovir disoproxil fumarate REMS Program at (1-800-625-7471).
 - ii. Send an Emtricitabine/tenofovir disoproxil fumarate REMS Dear Health Care Provider Letter within 60 calendar days after the approval of the Emtricitabine/Tenofovir disoproxil fumarate REMS Program that includes a link to the website (www.ftc-tdf-preprems.com) and the phone number (1-800-625-7471) to request a paper copy of the training materials.

The following organizations must be sent the letter:

- 1) HIV Medicine Association/Infectious Diseases Society of America
- 2) American Academy of HIV Medicine
- 3) Association of Nurses in AIDS Care
- 4) National Medical Association
- 5) American Academy of Family Physicians
- 6) American Society of Addiction Medicine
- 7) American College of Obstetricians and Gynecologists
- 8) National Association of Community Health Centers
- 9) National Association of City and County Health Officials
- 10) American College of Preventive Medicine
- 11) National Association of Public Hospitals
- 12) American Pharmacists Association
- iii. Provide all the following mechanisms for healthcare providers to report that they have completed training: online and mail by postage paid business reply card.
- iv. Maintain the emtricitabine/tenofovir disoproxil fumarate REMS Program Website (www.ftc-tdf-preprems.com). The emtricitabine/tenofovir disoproxil fumarate REMS Program Website must include the capability to complete the healthcare provider training online and the option to print the prescribing information, Medication Guide, and emtricitabine/tenofovir disoproxil fumarate REMS Materials. The emtricitabine/tenofovir disoproxil fumarate product websites must include a prominent REMS specific link to the emtricitabine/tenofovir disoproxil fumarate REMS Program Website.
- v. Ensure that within 60 calendar days of REMS approval the REMS materials listed below are available on the emtricitabine/tenofovir disoproxil fumarate REMS Program Website and are available as paper copies by request.
- vi. Maintain a validated, secure database of healthcare providers who report completing the training.
- 2. The following materials are part of the REMS and are appended
 - Dear Health Care Provider Letter
 - Training Guide for Healthcare Providers

- Healthcare Provider Education Slide Deck
- Important Safety Information about emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication for Healthcare Providers
- Important Safety Information about emtricitabine/tenofovir disoproxil fumarate to Reduce the Risk of Getting Human Immunodeficiency Virus-1 (HIV-1) Infection
- Agreement Form for Initiating emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP)
- Checklist for Prescribers: Initiation of emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP) to manage an uninfected individual considering or taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- Safety Information Fact Sheet for Prescribers about emtricitabine/tenofovir disoproxil fumarate for a Pre-exposure Prophylaxis (PrEP) Indication

B. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

The Emtricitabine/tenofovir disoproxil fumarate NDA Sponsor(s) must submit REMS Assessments to the FDA every 18 months from the date of initial approval of the REMS ([mm/dd/yyyy]). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. The Emtricitabine/tenofovir disoproxil fumarate NDA Sponsor(s) must submit each assessment so that it will be received by the FDA on or before the due date.

Safety Information Fact Sheet for Prescribers About Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for a Pre-exposure Prophylaxis (PrEP) Indication

Emtricitabine/tenofovir disoproxil fumarate is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

BOXED WARNING SPECIFIC FOR USING EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE FOR A PrEP INDICATION:

Emtricitabine/tenofovir disoproxil fumarate used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-1 negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication following undetected acute HIV-1 infection. Do not initiate emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.

Key Safety Information to Communicate Regarding the Use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication:

- 1. Risk of Development of Drug-Resistant HIV-1 Variants in Undiagnosed HIV-1-Infected Individuals
 - HIV-1 variants with resistance have emerged in individuals taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication with undetected acute HIV-1 infection
 - You must confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting emtricitabine/tenofovir disoproxil fumarate for a PrEP indication for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
 - Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
 - Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is contraindicated in individuals with unknown or HIV-1-positive status

- Do not prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed
 - HIV-1—infected patients must take emtricitabine/ tenofovir disoproxil fumarate in combination with other antiretroviral agents to fully suppress virus replication and avoid the development of resistance
- 2. Only Use Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication as Part of a Comprehensive Prevention Strategy
 - Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication does not replace other HIV-1 infection prevention measures, including safer sex practices and correct and consistent condom use
 - Clinical trials included comprehensive prevention counseling, screening for and treatment of other sexually transmitted infections, and strong emphasis regarding consistent use of condoms and other safer sex practices
- 3. The Importance of Strict Adherence to the Recommended Dosing Regimen
 - The effectiveness of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels
 - All uninfected individuals at high risk taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be counseled to strictly adhere to the recommended daily dosing schedule to reduce the risk of acquiring HIV-1 infection

For more information about emtricitabine/tenofovir disoproxil fumarate and its indication for PrEP, please see the Prescribing Information, including the BOXED WARNING, and the Medication Guide. For more information about the REMS program for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, please log on to www.ftc-tdf-preprems.com. You may also obtain additional information and educational materials about the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication at 1-800-625-7471.

IMPORTANT DRUG WARNING

Subject: FDA-Required Risk Evaluation Mitigation Strategy (REMS) for emtricitabine/tenofovir disoproxil fumarate 200mg/300mg for a pre-exposure prophylaxis (PrEP) indication

A negative HIV-1 test must be confirmed immediately before starting emtricitabine/tenofovir disoproxil fumarate for a PrEP indication and reconfirmed during treatment. Drug-resistant HIV-1 variants have been identified with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication following undetected HIV-1 infection.

Dear Healthcare Provider:

A REMS (Risk Evaluation and Mitigation Strategy) has been mandated by the FDA for emtricitabine/tenofovir disoproxil fumarate (a fixed-dose combination of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) for a PrEP indication in combination with safer sex practices to reduce the risk of sexually acquired HIV-1infection in adults at high risk. Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

The FDA has determined that a REMS is necessary to ensure that the benefits of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication outweigh its risks.

The goals of the REMS for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication are:

- 1. to inform and educate prescribers and uninfected individuals at high risk for acquiring HIV-1 infection about:
 - The importance of strict adherence to the recommended dosing regimen
 - The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
 - The fact that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be considered as only a part of a comprehensive prevention strategy in order to reduce the risk of HIV-1 infection, and that other preventive measures should also be used.

Before initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication

You MUST confirm a negative HIV-1 status immediately before prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication in an uninfected individual. Drug-resistant HIV-1 variants have been identified with use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication following undetected HIV-1 infection.

Do NOT prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication to patients with HIV-1 infection or to individuals with signs or symptoms consistent with acute HIV-1 infection, such as fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).

Prescriber Action

You should review and discuss the content of the **Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP)** with an HIV-negative person considering or taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication and refer to the **Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP)** regarding the management of an uninfected individual taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. (*Access Agreement Form and Checklist via www.ftc-tdf-preprems.com* or call 1-800-625-7471.)

The most important information you should know about prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication to reduce the risk of acquiring HIV-1 infection is:

- Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should only be used as part
 of a comprehensive prevention strategy including consistent and correct use of condoms and
 risk reduction counseling
- All uninfected individuals at high risk for acquiring HIV-1 infection should only take emtricitabine/tenofovir disoproxil fumarate for a PrEP indication after HIV-1 negative status is confirmed, to reduce the risk of development of resistant HIV-1 variants
- All uninfected individuals at high risk must strictly adhere to the recommended emtricitabine/tenofovir disoproxil fumarate for a PrEP indication daily oral regimen

Management of Uninfected Individuals

Uninfected individuals at high risk should:

- Be counseled about safer sex practices, including consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission.
- Be tested to confirm that they are HIV-1 negative immediately before starting emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.
- Be tested for acute HIV-1 infection and checked for any signs or symptoms consistent with acute HIV-1 infection, such as fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- Be screened at least every 3 months for HIV-1 status as determined by their prescriber to reconfirm that they are HIV-1 negative while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication to reduce the risk of acquiring HIV-1 infection.

- Have their creatinine clearance (CrCl) estimated prior to initiating and as clinically appropriate during therapy with emtricitabine/tenofovir disoproxil fumarate. Do NOT use emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if the estimated CrCl is <60 mL/min. In patients at risk for renal dysfunction, assess estimated CrCl, serum phosphorus, urine glucose and urine protein prior to initiation of emtricitabine/tenofovir disoproxil fumarate, and periodically during emtricitabine/tenofovir disoproxil fumarate therapy. If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, the prescriber should evaluate potential causes and re-assess potential risks and benefits of continued use.</p>
- Be tested for the presence of hepatitis B virus (HBV) before starting on emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. Severe acute exacerbations of hepatitis B have been reported in individuals who are co-infected with HBV and HIV-1 and have discontinued emtricitabine/tenofovir disoproxil fumarate. Uninfected individuals taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication who are infected with HBV need close medical follow-up for several months to monitor for exacerbations of hepatitis B in the event emtricitabine/tenofovir disoproxil fumarate is discontinued. HBV-uninfected individuals should be offered vaccination as appropriate.
- Be informed that emtricitabine/tenofovir disoproxil fumarate has only been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that emtricitabine/tenofovir disoproxil fumarate does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, emtricitabine/tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, careful consideration should be given to whether use of emtricitabine/tenofovir disoproxil fumarate should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

REMS Website (www.ftc-tdf-preprems.com)

The REMS website provides access to the following:

- Specific information regarding the risks of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- Training and educational materials for prescribers and uninfected individuals considering or taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, including the Agreement Form for Initiating emtricitabine/tenofovir disoproxil fumarate for Pre-Exposure Prophylaxis (PrEP) and the Checklist for Prescribers: Initiation of emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP).
- A mechanism to report completion of review of the REMS training material

• A link to participate in the knowledge, attitude and behavior (KAB) survey regarding important safety information associated with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication

Reporting Adverse Events

To report any adverse events, suspected to be associated with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, contact:

• The manufacturer of the product taken or FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not intended as a comprehensive description of the risks associated with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. Please read the enclosed Prescribing Information and Medication Guide, including the BOXED WARNING for more information.

Sincerely,

Emtricitabine/Tenofovir Disoproxil Fumarate REMS Team REMS-SSS-0011 XX/1X

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Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for a Pre-exposure Prophylaxis (PrEP) Indication

Training Guide for Healthcare Providers

About emtricitabine/tenofovir disoproxil fumarate for a PrEP indication to reduce the risk of sexually acquired HIV-1 infection in high-risk adults

INDICATION

Emtricitabine/tenofovir disoproxil fumarate is indicated 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.* This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

PRESCRIBING CONSIDERATIONS: When prescribing emtricitabine/ tenofovir disoproxil fumarate for pre-exposure prophylaxis:

- Only prescribe emtricitabine/tenofovir disoproxil fumarate as part of a comprehensive prevention strategy because emtricitabine/ tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to their emtricitabine/tenofovir disoproxil fumarate daily dosing schedule because the effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and measurable drug levels
- Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection

 Do not prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed

BOXED WARNING:

- Emtricitabine/tenofovir disoproxil fumarate used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-1 negative immediately prior to initial use and periodically (at least every 3 months) during use. Drugresistant HIV-1 variants have been identified with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication following undetected acute HIV-1 infection. Do not initiate emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed
- Emtricitabine/tenofovir disoproxil fumarate is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients infected with HBV who have discontinued emtricitabine/tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue emtricitabine/tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted

Screen uninfected individuals for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for PrEP

^{*}Factors that may help to identify individuals at high risk include individuals having partner(s) known to be HIV-1 infected or engaging in sexual activity within a high prevalence area or social network and one or more of the following: inconsistent or no condom use, diagnosis of sexually transmitted infections, exchange of sex for commodities (such as money, food, shelter, or drugs), use of illicit drugs or alcohol dependence, incarceration, or partner(s) of unknown HIV-1 status with any of the factors listed above.

Why Use Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication?

By inhibiting HIV-1 from replicating as it enters the body, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication works to prevent the virus from establishing permanent infection. However, emtricitabine/tenofovir disoproxil fumarate should not be seen as the first line of defense against HIV-1 infection. Because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be used in combination with a comprehensive prevention strategy that includes safer sex practices, such as regular and correct condom use, regular HIV-1 testing for themselves (and their sexual partners), and other proven HIV-1 prevention methods to safely and effectively reduce the risk of acquiring HIV-1 infection.

- Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must only be prescribed to uninfected individuals at high risk who are confirmed to be HIV-1 negative
- Uninfected individuals who are prescribed emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should not miss any doses. Missing doses raises the risk of acquiring HIV-1 infection

Emtricitabine/tenofovir disoproxil fumarate is also indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Emtricitabine/tenofovir disoproxil fumarate should never be used alone in an individual infected with HIV-1 because of the increased risk of resistance. Therefore, it is critical to confirm negative HIV-1 status immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection. Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for PrEP.

Key Findings of the Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication Trials

The iPrEx Trial

- In one clinical trial of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, emtricitabine/tenofovir disoproxil fumarate was shown to reduce the risk of HIV-1 infection acquisition by 42% for high risk men who have sex with men who also received comprehensive prevention services, including monthly HIV-1 testing, condom provision, risk-reduction counseling, and management of other sexually transmitted infections
- In a post hoc case control study of plasma and intracellular drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence
- Because of the intensive risk reduction counseling provided as part of the trial, self-reported risk behavior among the subjects in this clinical trial declined overall during the trial, both in terms of decreases in the number of sexual partners and increases in condom use

The Partners PrEP Trial

- In another clinical trial of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication in serodiscordant couples, emtricitabine/ tenofovir disoproxil fumarate was shown to reduce HIV-1 infection acquisition by 75% for the uninfected individuals exposed to the virus through heterosexual sex
- In a post hoc case control study of plasma drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence

Emtricitabine/Tenofovir Disoproxil Fumarate Safety Profile

IMPORTANT SAFETY INFORMATION

Contraindications:

 Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is contraindicated in individuals with positive or unknown HIV-1 status

Warnings and Precautions Relating to the Use of Emtricitabine/ Tenofovir Disoproxil Fumarate for a PrEP Indication

- Comprehensive management to reduce the risk of acquiring HIV-1: Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should only be used as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1
 - Counsel uninfected individuals at high risk about safer sex practices, including:
 - Using condoms consistently and correctly
 - Knowing their HIV-1 status and that of their partner(s)
 - Being regularly tested for other sexually transmitted infections that can facilitate HIV-1 transmission (eg, syphilis and gonorrhea)
 - Informing individuals about the importance of reducing sexually risky behaviors and supporting their efforts to do so
 - Use emtricitabine/tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative. HIV resistance substitutions may emerge with individuals with undetected HIV-1 infection who are taking only emtricitabine/tenofovir disoproxil fumarate because emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete treatment regimen for HIV-1 infection. Therefore:
 - Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. Many HIV-1 tests, such as rapid tests, detect anti-

HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections and ask about potential exposure events that may have occurred within the last month. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection

- Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for PrEP
- Evaluate for signs or symptoms of acute HIV-1 infection prior to prescribing and during treatment with emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to their emtricitabine/tenofovir disoproxil fumarate daily dosing schedule. The effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and measurable drug levels
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance (CrCl) before prescribing and periodically during treatment with emtricitabine/tenofovir disoproxil fumarate. In patients at risk of renal dysfunction, monitor estimated CrCl, serum phosphorus, urine glucose, and urine protein before prescribing emtricitabine/tenofovir disoproxil fumarate and periodically while emtricitabine/tenofovir disoproxil fumarate is being used. Avoid administering emtricitabine/tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients

- Do not prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication for uninfected individuals with an estimated CrCl below 60 mL/min. If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/ tenofovir disoproxil fumarate for PrEP, evaluate potential causes and reassess potential risks and benefits of continued use
- **HBV infection:** It is recommended that all individuals be tested for the presence of chronic HBV before initiating emtricitabine/tenofovir disoproxil fumarate
 - HBV-uninfected individuals should be offered vaccination
- Lactic acidosis/severe hepatomegaly with steatosis: Lactic
 acidosis and severe hepatomegaly with steatosis, including fatal
 cases, have been reported. Discontinue treatment in patients who
 develop symptoms or laboratory findings suggestive of lactic
 acidosis or pronounced hepatotoxicity
- Bone effects: Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir disoproxil fumarate. Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
 Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients
- Coadministration with other products: Do not use emtricitabine/ tenofovir disoproxil fumarate with drugs containing emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide, with drugs containing lamivudine, or with adefovir dipivoxil

Important Safety Information

Common Adverse Events

 In HIV-1—uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of emtricitabine/tenofovir disoproxil fumarate subjects and more frequently than by placebo subjects were headache, abdominal pain, and decreased weight

Important Safety Information About the Use of Emtricitabine/ Tenofovir Disoproxil Fumarate for a PrEP Indication in Specific Populations

- Pregnancy: There are no adequate and well-controlled trials in pregnant women. Emtricitabine/tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, careful consideration should be given to whether use of emtricitabine/tenofovir disoproxil fumarate should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy
 - A pregnancy registry is available. Enroll women taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication by calling 1-800-258-4263
- Nursing mothers: The components of emtricitabine/tenofovir disoproxil fumarate are excreted in breast milk. Because the risks to the infant are not known, mothers taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should be instructed not to breastfeed. If an uninfected individual acquires HIV-1 infection, it is recommended that she not breastfeed to avoid risking postnatal transmission of HIV-1
- Pediatrics: The emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is based on trials in adults

Reminder about the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication: It is important to confirm and regularly reconfirm negative HIV-1 status before and while the individual is taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.

- Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for PrEP

- It is important to be alert to the signs of potential acute HIV-1 infection when prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. These include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and cervical and inguinal adenopathy
- If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection
- HIV-1 resistance mutations may emerge in individuals with undetected HIV-1 infection who are taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication

Drug Interactions

 Coadministration of emtricitabine/tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir

For further details about emtricitabine/tenofovir disoproxil fumarate drug interactions, please see Prescribing Information for emtricitabine/tenofovir disoproxil fumarate in back pocket.

Use the Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP) and the Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP) to help manage and counsel individuals about the correct and safe use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.

For more information about emtricitabine/tenofovir disoproxil fumarate and its indication for PrEP, please see the Prescribing Information, including the BOXED WARNING, and the Medication Guide. For more information about the REMS program for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, please log on to www.ftc-tdf-preprems.com. You may also obtain additional information and educational materials about the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication at 1-800-625-7471.

Post-Training Review Questions

- 1. Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should be used only:
 - a. As part of a comprehensive HIV-1 prevention strategy that includes other preventive measures since emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection
 - b. In individuals who have been counseled to strictly adhere to their emtricitabine/tenofovir disoproxil fumarate daily dosing schedule since the effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels
 - **c.** In individuals who have a confirmed negative HIV-1 test prior to initiating and routinely while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - d. All of the above

2. Which of the following statements is false?

- **a.** Emtricitabine/tenofovir disoproxil fumarate should be used for a PrEP indication only in individuals confirmed to be HIV-1 negative
- **b.** Emtricitabine/tenofovir disoproxil fumarate has been found to be safe and effective for pre-exposure prophylaxis to reduce the risk of acquiring HIV-1 infection through injection drug use
- **c.** Women taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should not breastfeed their babies
- **d.** Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is not always effective in preventing HIV-1 infection
- 3. Which of the following items are not included on the Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP)?
 - a. Perform HBV screening test
 - **b.** Perform testing for TB
 - c. Confirm negative HIV-1 status of the individual
 - **d.**Confirm creatinine clearance is ≥60 mL/min

4. Hepatic function should be monitored closely in:

- a. HBV-infected individuals who discontinue emtricitabine/tenofovir disoproxil fumarate
- **b.** All people taking emtricitabine/tenofovir disoproxil fumarate
- **c.** All people who discontinue emtricitabine/tenofovir disoproxil fumarate
- d. None of the above
- 5. In clinical trials evaluating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, which of the following adverse reactions was not common?
 - a. Abdominal pain
 - b. Headache
 - c. Dizziness
 - d. Decreased weight
- 6. Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is indicated only for:
 - a. Men who are at high risk for sexually acquired HIV-1 infection
 - b. Adults who are at high risk of acquiring HIV-1 infection by any means
 - **c.** Adults who are at high risk of acquiring HIV-1 infection through injection drug use
 - d. Adults who are at high risk for sexually acquired HIV-1 infection
- 7. The Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP) provides which of the following information:
 - **a.** A list of activities that put individuals at risk for sexually acquired HIV-1 infection
 - **b.** A confirmation that the prescriber has discussed the risks and benefits of using emtricitabine/tenofovir disoproxil fumarate for a PrEP indication with the uninfected individual
 - c. A signature from the individual asserting that the prescriber has explained the risks and benefits of taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, including the need for adherence and a comprehensive prevention strategy, which includes safer sex practices
 - d. All of the above

yuswer key: 1-d; 2-b; 3-b; 4-a; 5-c; 6-d; 7-d

Help uninfected individuals learn more about emtricitabine/tenofovir disoproxil fumarate for a pre-exposure prophylaxis (PrEP) indication

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Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300mg for a Preexposure Prophylaxis (PrEP) Indication

Healthcare Provider Training

Pre-exposure Prophylaxis (PrEP) Indication

 Emtricitabine/tenofovir disoproxil fumarate is indicated 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. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

Factors to Help Identify Individuals at High Risk

- Has a partner known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
 - Inconsistent or no condom use
 - Diagnosis of sexually transmitted infections
 - Exchange of sex for commodities (such as money, food, shelter, or drugs)
 - Use of illicit drugs or alcohol dependence
 - Incarceration
 - Partner(s) of unknown HIV-1 status with any of the factors listed above

When Prescribing Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication, Healthcare Providers MUST:

- Prescribe Emtricitabine/Tenofovir Disoproxil Fumarate as part of a comprehensive prevention strategy because Emtricitabine/Tenofovir Disoproxil Fumarate is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to the recommended daily Emtricitabine/Tenofovir Disoproxil Fumarate dosing schedule because the effectiveness of Emtricitabine/Tenofovir Disoproxil Fumarate in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and detectable blood levels
- Confirm a negative HIV-1 test immediately prior to initiating Emtricitabine/Tenofovir
 Disoproxil Fumarate for a PrEP indication. If clinical signs or symptoms consistent with
 acute viral infection are present or recent (<1 month) exposures are suspected,
 - delay starting PrEP for at least one month and reconfirm HIV-1 status or
 - use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- While using Emtricitabine/Tenofovir Disoproxil Fumarate for PrEP HIV-1 screening tests should be repeated at least every 3 months.
 - If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection

BOXED WARNING

 Emtricitabine/Tenofovir Disoproxil Fumarate used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with the use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP indication following undetected acute HIV-1 infection. Do not initiate Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed

BOXED WARNING, cont.

 Emtricitabine/tenofovir disoproxil fumarate is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued emtricitabine/tenofovir disoproxil fumarate. Therefore, hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue emtricitabine/tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted

Why Use Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication?

- By inhibiting HIV-1 from replicating as it enters the body, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication works to prevent the virus from establishing permanent infection. However, emtricitabine/tenofovir disoproxil fumarate should not be seen as the first line of defense against HIV-1
- Because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be used in combination with a comprehensive prevention strategy that includes safer sex practices, such as regular and correct condom use, regular HIV testing for themselves (and their sexual partners), and other proven HIV prevention methods to safely and effectively reduce the risk of acquiring HIV-1
 - Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must only be prescribed to uninfected individuals at high risk who are confirmed to be HIV-1 negative
 - Uninfected individuals who are prescribed emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should not miss any doses. Missing doses may increase the risk of acquiring HIV

Key Findings of the Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication Studies: The iPrEx Trial

- In one clinical trial of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, emtricitabine/tenofovir disoproxil fumarate was shown to reduce the risk of HIV-1 acquisition by 42% for high risk men who have sex with men who also received comprehensive prevention services, including monthly HIV-1 testing, condom provision, counseling, and management of other sexually transmitted infections
- In a post hoc case control study of plasma and intracellular drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence
- Because of the intensive risk reduction counseling provided as part of the study, self-reported risk behavior among the subjects in this clinical study declined overall during the study, both in terms of decreases in the number of self-reported sexual partners and increases in condom use

Key Findings of the Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication Studies: The Partners PrEP Trial

- In another clinical trial of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, emtricitabine/tenofovir disoproxil fumarate was shown to reduce HIV-1 acquisition by 75% in uninfected individuals in stable heterosexual serodiscordant relationships who also received comprehensive prevention services, including monthly HIV testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations
- In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence. Risk reduction increased further in subjects with detectable plasma tenofovir

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1

- Prescribe emtricitabine/tenofovir disoproxil fumarate for PrEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1
 - Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea)
 - Inform uninfected individuals about and support their efforts in reducing sexual risk behavior

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1

- Prescribe emtricitabine/tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative
 - HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine/tenofovir disoproxil fumarate, because emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete regimen for HIV-1 treatment; therefore, care should be taken to minimize drug exposure in HIVinfected individuals
 - Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, evaluate seronegative individuals for current or recent signs and symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1

- Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical signs or symptoms consistent with acute viral infection are present or recent (<1 month) exposures are suspected,
 - delay starting PrEP for at least one month and reconfirm HIV-1 status or
 - use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- While using emtricitabine/tenofovir disoproxil fumarate for PrEP, HIV-1 screening tests should be repeated at least every 3 months.
 - If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1

 Counsel uninfected individuals to strictly adhere to the recommended daily emtricitabine/tenofovir disoproxil fumarate dosing schedule. The effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in a subgroup of clinical trials subjects

New Onset or Worsening Renal Impairment

- Can include acute renal failure and Fanconi syndrome
- Assess estimated creatinine clearance (CrCl) before prescribing emtricitabine/tenofovir disoproxil fumarate and periodically during therapy
- In individuals at risk of renal impairment, assess estimated CrCl, serum phosphorus, urine glucose and urine protein before prescribing emtricitabine/tenofovir disoproxil fumarate and periodically while emtricitabine/tenofovir disoproxil fumarate is being used

New Onset or Worsening Renal Impairment

- Avoid administering emtricitabine/tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy have been reported after initiation of high dose or multiple NSAIDs in patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients.
- Do not use emtricitabine/tenofovir disoproxil fumarate for a PrEP indication in HIV-1 uninfected individuals with an estimated CrCl below 60 mL/min
 - If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/tenofovir disoproxil fumarate for PrEP, evaluate potential causes and reassess potential risks and benefits of continued use

Lactic acidosis/severe hepatomegaly with steatosis

 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

Bone effects

- Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir DF. Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
- Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

HBV Infection

- It is recommended that all individuals be tested for the presence of chronic hepatitis B virus (HBV) before initiating emtricitabine/tenofovir disoproxil fumarate
- HBV-uninfected individuals should be offered vaccination

Coadministration with other products

 Do not use emtricitabine/tenofovir disoproxil fumarate with drugs containing emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide, with drugs containing lamivudine, or with adefovir dipivoxil

Important Safety Information: Use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication in Specific Populations

Pregnancy

- There are no adequate and well controlled trials in pregnant women
- emtricitabine/tenofovir disoproxil fumarate should be used in pregnancy only if clearly needed.
- If an uninfected individual becomes pregnant while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, careful consideration should be given to whether the use of emtricitabine/tenofovir disoproxil fumarate should be continued, taking into account the potential increased risk of HIV infection during pregnancy*
- A pregnancy registry is available. Enroll pregnant women taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication by calling 1-800-258-4263

Important Safety Information: Use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication in Specific Populations

Nursing Mothers

 The components of emtricitabine/tenofovir disoproxil fumarate are excreted in breast milk. Because the risks to the infant are not known, mothers taking emtricitabine/tenofovir disoproxil fumarate for PrEP should be instructed not to breastfeed. If an uninfected individual acquires HIV-1 infection, it is recommended that she not breastfeed to avoid risking postnatal transmission of HIV-1

Pediatrics

 Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is based on trials in adults

Important Safety Information: Confirming and Regularly Reconfirming Negative HIV Status

- Emtricitabine/tenofovir disoproxil fumarate should be used to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative
 - A negative HIV-1 status should be confirmed before prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Individuals should be regularly tested (at least every 3 months)
 while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP
 indication to reconfirm that they are HIV-1 negative
 - If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection

Important Safety Information: Confirming and Regularly Reconfirming Negative HIV Status

- Potential for Resistance in Undetected Acute HIV-1 Infection
 - It is important to be alert to the signs of potential acute HIV-1 infection when prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. These include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and cervical and inguinal adenopathy
 - HIV-1 resistance mutations may emerge in individuals with undetected HIV-1 infection who are taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Although emtricitabine/tenofovir disoproxil fumarate is active against HIV-1, emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete treatment regimen for HIV-1 infection
 - HIV-1—infected patients taking emtricitabine/tenofovir disoproxil fumarate must take it with other antiretroviral agents to fully suppress virus replication and avoid the development of resistance

Important Safety Information: Drug Interactions and Common Adverse Events

Drug Interactions

- Coadministration of emtricitabine/tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir.
- For further details about emtricitabine/tenofovir disoproxil fumarate drug interactions, please see full Prescribing Information for emtricitabine/tenofovir disoproxil fumarate

Common Adverse Events

 In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of emtricitabine/tenofovir disoproxil fumarate subjects and more frequently than by placebo subjects were headache, abdominal pain and weight decreased.

Additional Educational Materials

- Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate for PrEP of Sexually Acquired HIV-1 Infection
 - Designed for prescribers to use with uninfected individuals to facilitate discussion
 of appropriate use of emtricitabine/tenofovir disoproxil fumarate for a PrEP
 indication
 - Form covers safety risks associated with use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, the importance of adherence to the recommended daily dosing regimen, regular assessment of HIV-1 test results, and screening for sexually transmitted infections
- Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for PrEP
 - Checklist of key components for prescribers to consider before starting an uninfected individual on emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Checklist items include confirming a negative HIV-1 test result, screening for signs or symptoms of acute HIV infection, counseling on safety risks and importance of adherence, and other components to ensure a comprehensive prevention strategy
- Copies available from <u>www.ftc-tdf-preprems.com</u> or by filling out business reply card at the back of the Training Guide for Healthcare Providers booklet

Additional Educational Materials

- Additional educational materials can be reviewed and downloaded at <u>www.ftc-tdf-preprems.com</u> or by hard copy by 1-800-625-7471.
- Please confirm completion of training by going to <u>www.ftc-tdf-</u> <u>preprems.com</u> or by filling out business reply card at back of the Training Guide for Healthcare Providers booklet.
- A survey is being conducted to fulfill an FDA Risk Evaluation and Mitigation Strategy (REMS) requirement to assess prescribers' knowledge regarding important safety information associated with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. To participate, please go to www.ftc-tdf-preprems.com.

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Important Safety Information About Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for a Pre-exposure Prophylaxis (PrEP) Indication

For Healthcare Providers

About Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication

INDICATION AND PRESCRIBING CONSIDERATIONS

The combination of emtricitabine and tenofovir disoproxil fumarate is indicated 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. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

The following factors may help to identify individuals at high risk:

- · Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
 - Inconsistent or no condom use
 - Diagnosis of a sexually transmitted infection (STI)
 - Exchange of sex for commodities (such as money, food, shelter, or drugs)
 - Use of illicit drugs, alcohol dependence
 - Incarceration
 - Partner(s) of unknown HIV-1 status with any of the factors listed above

When prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication:

- Only prescribe emtricitabine/tenofovir disoproxil fumarate as part of a comprehensive prevention strategy because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to their emtricitabine/tenofovir disoproxil fumarate daily dosing schedule because the effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels

- Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- Screen uninfected individuals for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- Do not prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed

Potential for Resistance in Undetected Acute HIV-1 Infection

It is important to be alert to the signs or symptoms of potential acute HIV-1 infection when prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, including:

 Fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal)

It is recommended that negative HIV-1 status be reconfirmed on a regular basis (at least every 3 months) using HIV-1 screening tests while uninfected individuals are taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.

Emtricitabine/Tenofovir Disoproxil Fumarate Safety Profile

BOXED WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE FOR A PREP INDICATION IN UNDIAGNOSED EARLY HIV-1 INFECTION

- Emtricitabine/tenofovir disoproxil fumarate used for a PrEP indication must only be prescribed to individuals confirmed to be HIV negative immediately prior to initial use and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication following undetected acute HIV-1 infection. Do not initiate emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed
- Emtricitabine/tenofovir disoproxil fumarate is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued emtricitabine/tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue emtricitabine/tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted

Important Safety Information About Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication

Contraindications:

• Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is contraindicated in individuals with positive or unknown HIV-1 status.

Warnings and Precautions

 Comprehensive management to reduce the risk of acquiring HIV-1 infection

Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should be used only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection.

- Counsel uninfected individuals at high risk about safer sex practices, including:
 - Using condoms consistently and correctly
 - Knowing their HIV-1 status and that of their partner(s)
 - Being regularly tested for other sexually transmitted infections that can facilitate HIV-1 transmission (eg, syphilis and gonorrhea)
- Inform uninfected individuals at high risk about and support their efforts to reduce sexual risk behavior
- Use emtricitabine/tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine/tenofovir disoproxil fumarate because emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete treatment regimen for HIV-1 infection

- Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections and ask about potential exposure events that may have occurred within the last month. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting emtricitabine/tenofovir disoproxil fumarate for a PrEP indication for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection</p>
- Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection
- Evaluate for signs or symptoms of acute HIV-1 infection prior to prescribing and during treatment with emtricitabine/ tenofovir disoproxil fumarate for a PrEP indication
- Counsel all uninfected individuals to strictly adhere to a daily dosing schedule for emtricitabine/tenofovir disoproxil fumarate. The effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and measurable drug levels

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance (CrCl) before prescribing and during treatment with emtricitabine/tenofovir disoproxil fumarate. In patients at risk of renal dysfunction, monitor estimated CrCl, serum phosphorus, urine glucose, and urine protein before prescribing emtricitabine/tenofovir disoproxil fumarate and periodically while emtricitabine/tenofovir disoproxil fumarate is being used. Avoid administering emtricitabine/tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients
 - For pre-exposure prophylaxis: Do not prescribe emtricitabine/tenofovir disoproxil fumarate for uninfected individuals with an estimated CrCl below 60 mL/min. If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, evaluate potential causes and reassess potential risks and benefits of continued use
- HBV infection: It is recommended that all individuals be tested for the presence of chronic HBV before initiating emtricitabine/ tenofovir disoproxil fumarate
 - HBV-uninfected individuals should be offered vaccination
- Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity
- Bone effects: Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir disoproxil fumarate. Consider assessment of BMD in individuals with a history of pathologic

- fracture or other risk factors for osteoporosis or bone loss. Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients
- Coadministration with other products: Do not use emtricitabine/tenofovir disoproxil fumarate with drugs containing emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide, with drugs containing lamivudine, or with adefovir dipivoxil

Important Safety Information

Common Adverse Reactions With Emtricitabine/Tenofovir Disoproxil Fumarate

 In HIV-1—uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of emtricitabine/tenofovir disoproxil fumarate subjects and more frequently than by placebo subjects were headache, abdominal pain, and decreased weight

Use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication in Specific Populations

- Pregnancy: There are no adequate and well-controlled trials in pregnant women. Emtricitabine/tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, careful consideration should be given to whether use of emtricitabine/tenofovir disoproxil fumarate should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy
 - A pregnancy registry is available. Enroll women taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication by calling 1-800-258-4263

- Nursing mothers: The components of emtricitabine/tenofovir disoproxil fumarate are excreted in breast milk. Because the risks to the infant are not known, mothers taking emtricitabine/ tenofovir disoproxil fumarate for a PrEP indication should be instructed not to breastfeed. If an uninfected individual acquires HIV-1 infection, it is recommended that she not breastfeed to avoid risking postnatal transmission of HIV-1 infection
- Pediatrics: The emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is based on trials in adults

Emtricitabine/Tenofovir Disoproxil Fumarate Drug Interactions

 Coadministration of emtricitabine/tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir

For further details about emtricitabine/tenofovir disoproxil fumarate drug interactions, please see the full Prescribing Information for emtricitabine/tenofovir disoproxil fumarate in back pocket.

Use the Checklist for Prescribers: Initiation of Emtricitabine/
Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis
(PrEP) and the Agreement Form for Initiating Emtricitabine/
Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP)
to help manage and counsel individuals about the safe use of
emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.

For more information about emtricitabine/tenofovir disoproxil fumarate and its indication for PrEP, please see the Prescribing Information, including the BOXED WARNING, and the Medication Guide. For more information about the REMS program for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, please log on to www.ftc-tdf-preprems.com. You may also obtain additional information and educational materials about the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication at 1-800-625-7471.

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Reference: Emtricitabine/tenofovir disoproxil fumarate Prescribing Information; XXXX.

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Important Safety Information
About Emtricitabine/Tenofovir
Disoproxil Fumarate 200 mg/300 mg
to Reduce the Risk of Getting
Human Immunodeficiency Virus-1
(HIV-1) Infection

This booklet is for adults taking emtricitabine/ tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection.

If you are taking emtricitabine/tenofovir disoproxil fumarate to treat HIV-1, please see the Medication Guide for other important information.

Emtricitabine/Tenofovir Disoproxil Fumarate to Reduce the Risk of Getting HIV-1 Infection

Emtricitabine/tenofovir disoproxil fumarate is a prescription medicine to reduce the chance of getting HIV-1 infection in adults when used with safer sex practices. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Emtricitabine/tenofovir disoproxil fumarate, to reduce the risk of getting HIV-1 infection, is meant for adults who are:

- HIV negative, and
- At high risk for getting HIV-1 infection through sex

Emtricitabine/tenofovir disoproxil fumarate only works to reduce the risk of getting HIV-1 infection as part of a complete prevention strategy that includes safer sex practices and regular testing for HIV-1.

- Emtricitabine/tenofovir disoproxil fumarate works better to reduce the risk of getting HIV-1 infection when the medicines are in your bloodstream before you are exposed to HIV-1
- You need to take emtricitabine/tenofovir disoproxil fumarate every day, not just when you think you have been exposed
- Just taking emtricitabine/tenofovir disoproxil fumarate alone may not keep you from getting HIV-1 infection

You must be HIV negative to start emtricitabine/tenofovir disoproxil fumarate. You must get tested to make sure that you do not already have HIV-1 infection. Do not take emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection unless you are confirmed to be HIV negative.

The most important information you should know about emtricitabine/tenofovir disoproxil fumarate

If you also have hepatitis B virus (HBV) infection and take emtricitabine/tenofovir disoproxil fumarate, your hepatitis B may become worse if you stop taking emtricitabine/tenofovir disoproxil fumarate.

- Do not stop taking emtricitabine/tenofovir disoproxil fumarate without first talking with your healthcare provider
- If your healthcare provider stops emtricitabine/tenofovir disoproxil fumarate, your healthcare provider will need to watch you closely for several months to check your hepatitis B infection, or give you a medication to treat hepatitis B

Tell your healthcare provider about any new or unusual symptoms you have after you stop taking emtricitabine/tenofovir disoproxil fumarate.

Before taking emtricitabine/tenofovir disoproxil fumarate to reduce your risk of getting HIV-1 infection

- You must be HIV negative to start emtricitabine/tenofovir disoproxil fumarate. You must get tested to make sure that you do not already have HIV-1 infection
- Many HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting emtricitabine/ tenofovir disoproxil fumarate or at any time while taking emtricitabine/tenofovir disoproxil fumarate. Symptoms of new HIV-1 infection include:
 - Tiredness
 - Fever
 - Joint or muscle aches
 - Headache
 - Sore throat
 - Vomiting or diarrhea
 - Rash
 - Night sweats
 - Enlarged lymph nodes in the neck or groin

While you are taking emtricitabine/tenofovir disoproxil fumarate to reduce your risk of getting HIV-1 infection:

- Just taking emtricitabine/tenofovir disoproxil fumarate alone may not keep you from getting HIV-1 infection
- You must continue using safer sex practices while you are taking emtricitabine/tenofovir disoproxil fumarate to reduce your risk of getting HIV-1 infection
- You must stay HIV-1 negative to keep taking emtricitabine/ tenofovir disoproxil fumarate to reduce your risk of infection
 - Know your HIV-1 status and the HIV-1 status of your partners
 - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you
 - Get tested for other sexually transmitted infections, such as syphilis and gonorrhea. These infections make it easier for HIV-1 to infect you
 - If you think you were exposed to HIV-1, tell your healthcare provider right away. Your healthcare provider may want to do more tests to be sure you are still HIV negative
 - Get information and support to help reduce risky sexual behavior
 - Have fewer sex partners
 - Do not miss any doses of emtricitabine/tenofovir disoproxil fumarate. Missing doses may increase your risk of getting HIV infection

- If you do become HIV positive, you need more medicine than emtricitabine/tenofovir disoproxil fumarate alone to treat HIV-1 infection. Emtricitabine/tenofovir disoproxil fumarate by itself is not a complete treatment for HIV-1 infection
 - If you have HIV-1 and take only emtricitabine/tenofovir disoproxil fumarate, over time your HIV-1 infection may become harder to treat

See the section "Things you should avoid while taking emtricitabine/tenofovir disoproxil fumarate" and talk with your healthcare provider for more information about how to prevent HIV-1 infection.

Things you should avoid while taking emtricitabine/tenofovir disoproxil fumarate

There are things you should avoid while taking emtricitabine/ tenofovir disoproxil fumarate that can increase your risk of getting infected with HIV-1. While taking emtricitabine/ tenofovir disoproxil fumarate:

- Do NOT have any kind of sex without protection. Always practice safer sex. Use latex or non-latex condoms, except lambskin, to reduce contact with semen, vaginal fluids, or blood
- Do NOT share personal items that can have blood or body fluids on them, such as toothbrushes and razor blades
- Do NOT share or reuse needles or other injection equipment

Ask your healthcare provider if you have any questions about how to prevent getting infected with HIV-1.

Do not take emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection if...

Emtricitabine/tenofovir disoproxil fumarate can only help reduce your risk of getting HIV-1 **before** you are infected. **Do not take emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection if:**

- You already have HIV-1 infection. If you are HIV positive, you need to take other medicines with emtricitabine/ tenofovir disoproxil fumarate to treat HIV-1. Emtricitabine/ tenofovir disoproxil fumarate by itself is not a complete treatment for HIV-1 infection
- You do not know your HIV-1 infection status. You may already be HIV positive. You need to take over HIV-1 medicines with emtricitabine/tenofovir disoproxil fumarate to treat HIV-1 infection

Things to tell your healthcare provider before taking emtricitabine/tenofovir disoproxil fumarate

Tell your healthcare provider if you:

- Have liver problems, including hepatitis B virus infection
- Have kidney problems or receive kidney dialysis treatment
- Have bone problems
- Have any other medical conditions

 Are pregnant or plan to become pregnant. It is not known if emtricitabine/tenofovir disoproxil fumarate can harm your unborn child

If you are a female who is taking emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection and you become pregnant while taking emtricitabine/tenofovir disoproxil fumarate, talk with your healthcare provider to decide if you should keep taking emtricitabine/tenofovir disoproxil fumarate.

Pregnancy Registry: A pregnancy registry collects information about your health and the health of your baby. There is a pregnancy registry for women who take medicines to treat or prevent HIV-1 during pregnancy. For more information about the registry and how it works, talk with your healthcare provider.

Are breastfeeding or plan to breastfeed

- If you become HIV-1 positive while taking emtricitabine/ tenofovir disoproxil fumarate, do not breastfeed because the virus can pass to your baby through the breast milk
- Do not breastfeed if you take emtricitabine/tenofovir disoproxil fumarate. Emtricitabine/tenofovir disoproxil fumarate can pass to your baby in your breast milk
- Talk with your healthcare provider about the best way to feed your baby

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Do not take emtricitabine/tenofovir disoproxil fumarate if you already take any of the medicines listed below:

- Medicines which also contain emtricitabine or tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, EMTRIVA, DESCOVY®, GENVOYA®, ODEFSEY®, STRIBILD®, VEMLIDY®, or VIREAD). These medicines contain one or more of the same active ingredients as emtricitabine/tenofovir disoproxil fumarate
- Medicines which contain tenofovir alafenamide (GENVOYA or ODEFSEY)
- Medicines which contain lamivudine (Combivir, Dutrebis, Epivir, Epivir-HBV, Epzicom, Triumeg, or Trizivir)
- Adefovir (HEPSERA®)

Emtricitabine/tenofovir disoproxil fumarate may interact with other medicines. Especially tell your healthcare provider if you take:

- Didanosine (Videx EC)
- Atazanavir (Reyataz)
- Darunavir (Prezista)
- Lopinavir with ritonavir (Kaletra)
- Ledipasvir with sofosbuvir (HARVONI®)
- Sofosbuvir with velpatasvir (EPCLUSA®)

Your doctor may need to check you more often or change your dose if you take any of these medicines and emtricitabine/tenofovir disoproxil fumarate.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How to take emtricitabine/tenofovir disoproxil fumarate

- Take emtricitabine/tenofovir disoproxil fumarate exactly as prescribed
- Take emtricitabine/tenofovir disoproxil fumarate by mouth, with or without food
- Emtricitabine/tenofovir disoproxil fumarate is usually taken 1 time each day. Take emtricitabine/tenofovir disoproxil fumarate at the same time each day to keep emtricitabine/ tenofovir disoproxil fumarate blood levels constant
- Do not miss any doses of emtricitabine/tenofovir disoproxil fumarate. Missing a dose lowers the amount of medicine in your blood
- If you miss a dose of emtricitabine/tenofovir disoproxil fumarate, take it as soon as you remember that day. Do not take more than 1 dose of emtricitabine/tenofovir disoproxil fumarate in a day. Do not take 2 doses at the same time to make up for a missed dose. Call your healthcare provider or pharmacist if you are not sure what to do
- Do not change your dose or stop taking emtricitabine/ tenofovir disoproxil fumarate without first talking with your healthcare provider. Stay under a healthcare provider's care when taking emtricitabine/tenofovir disoproxil fumarate
- Refill your emtricitabine/tenofovir disoproxil fumarate prescription before you run out of medicine
- If you take too much emtricitabine/tenofovir disoproxil fumarate, call your healthcare provider or go to the nearest hospital emergency room right away

- If you take emtricitabine/tenofovir disoproxil fumarate to reduce your risk of getting HIV-1 infection:
 - You must also use other methods to reduce your risk of getting infected with HIV-1. See the section "Things you should avoid while taking emtricitabine/tenofovir disoproxil fumarate" in this booklet
 - Take emtricitabine/tenofovir disoproxil fumarate every day, not just when you think you have been exposed to HIV-1

Possible side effects of emtricitabine/ tenofovir disoproxil fumarate

Emtricitabine/tenofovir disoproxil fumarate may cause serious side effects, including:

- See "The most important information you should know about emtricitabine/tenofovir disoproxil fumarate"
- New or worse kidney problems, including kidney failure. If you have had kidney problems in the past or take medicines that can cause kidney problems, your healthcare provider may do blood tests to check your kidneys before you start and while you are taking emtricitabine/tenofovir disoproxil fumarate. Your healthcare provider may tell you to stop taking it if you have kidney problems
- Too much lactic acid in your blood (lactic acidosis). Too
 much lactic acid is a serious but rare medical emergency.
 Tell your healthcare provider right away if you get these
 symptoms: weakness or being more tired than usual,
 unusual muscle pain, being short of breath or fast
 breathing, stomach pain with nausea and vomiting, cold or
 blue hands and feet, feel dizzy or lightheaded, or a fast or
 abnormal heartbeat

- Severe liver problems. In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain
- Bone problems can happen in some people who take emtricitabine/tenofovir disoproxil fumarate. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones

Common side effects of emtricitabine/tenofovir disoproxil fumarate

Common side effects in people who take emtricitabine/ tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection include: stomach-area (abdomen) pain, headache, and decreased weight.

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of emtricitabine/tenofovir disoproxil fumarate. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may also report side effects to FDA at 1-800-FDA-1088.

How to store emtricitabine/tenofovir disoproxil fumarate

- Store emtricitabine/tenofovir disoproxil fumarate at room temperature between 68 °F to 77 °F (20 °C to 25 °C)
- Keep emtricitabine/tenofovir disoproxil fumarate in its original container and keep the container tightly closed
- Do not use emtricitabine/tenofovir disoproxil fumarate if seal over bottle opening is broken or missing

Keep emtricitabine/tenofovir disoproxil fumarate and all other medicines out of reach of children.

Notes	Notes
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You can find this booklet and other important information about emtricitabine/ tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection at www.ftc-tdf-preprems.com or call 1-800-625-7471.

Agreement Form

for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for Pre-exposure Prophylaxis (PrEP)

Individual Label

Instructions:

Review form with an HIV-negative person who is about to start or is taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication at each visit. File form in the person's medical record.

Emtricitabine/tenofovir disoproxil fumarate is indicated 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. The following factors may help to identify individuals at high risk:

- Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
 - Inconsistent or no condom use
 - Diagnosis of sexually transmitted infections
 - Exchange of sex for commodities (such as money, shelter, food, or drugs)
 - Use of illicit drugs, alcohol dependence
 - Incarceration
 - Partner(s) of unknown HIV-1 status with any of the factors listed above

Healthcare Provider Agreement

By signing below, I signify my understanding of the risks and benefits of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication and my obligation as a prescriber to educate the HIV-negative person about these risks, counsel the person on risk reduction, monitor the person appropriately, and report adverse events. Specifically, I attest to having done the following:

- Confirmed the negative HIV-1 status of this person prior to starting emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- Read the Prescribing Information, including the BOXED WARNING
- Discussed with the HIV-negative person the known safety risks with use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- Reviewed the importance of adherence with a comprehensive prevention strategy, including practicing safer sex
- Discussed the importance of regular HIV-1 testing (at least every 3 months) while taking emtricitabine/ tenofovir disoproxil fumarate for a PrEP indication
- Reviewed the Emtricitabine/Tenofovir Disoproxil
 Fumarate Medication Guide with the HIV-negative
 person at high risk prior to prescribing emtricitabine/
 tenofovir disoproxil fumarate for a PrEP indication
- Completed the items on the Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP)

HIV-Negative Person Agreement

By signing below, I acknowledge that I have talked with my healthcare provider about the risks and benefits of emtricitabine/tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection, and I understand them clearly. Specifically, I attest to the following:

- My healthcare provider talked with me about the importance of follow-up HIV-1 testing, and I agree to have repeat HIV-1 screening tests (at least every 3 months) as scheduled by my healthcare provider
- My healthcare provider talked with me about the safety risks involved with using emtricitabine/ tenofovir disoproxil fumarate to reduce the risk of getting HIV-1 infection
- My healthcare provider talked with me about a complete prevention strategy and always practicing safer sex by using condoms correctly
- I will talk with my healthcare provider if I have any questions
- I have read the Emtricitabine/Tenofovir Disoproxil Fumarate Medication Guide

HIV-Negative Person's Signature

Date

Checklist for Prescribers:

Initiation of Emtricitabine/ Tenofovir Disoproxil Fumarate 200 mg/300 mg for Pre-exposure Prophylaxis (PrEP)

Individual Label

Instructions: Complete checklist at each visit and file in individual's medical record.

I have completed the following prior to prescribing emtricitabine/tenofovir disoproxil fumarate for a pre-exposure prophylaxis (PrEP) indication for the individual who is about to start or is taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication:

Lab Tests/Evaluation	Counseling/Follow-up					
Completed high risk evaluation of uninfected individual	Discussed known safety risks with use of emtricitabine/ tenofovir disoproxil fumarate for a PrEP indication					
 Confirmed a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication 	Counseled on the importance of scheduled follow- up every 2 to 3 months, including regular HIV-1 screening tests (at least every 3 months), while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP					
If clinical symptoms consistent with acute viral infaction are present and recent (c1 month) symptoms.	indication to reconfirm HIV-1-negative status					
infection are present and recent (<1 month) exposure is suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection. (Note:	Discussed the importance of discontinuing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if seroconversion has occurred, to reduce the development of resistant HIV-1 variants					
emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is contraindicated in individuals with unknown HIV-1 status or who are HIV-1 positive)	Counseled on the importance of adherence to daily dosing schedule					
Performed HBV screening test	Counseled that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should be used only as part of a comprehensive prevention strategy					
 Confirmed estimated creatinine clearance (CrCl) >60 mL/min prior to initiation and periodically during treatment. In patients at risk for renal dysfunction, 	 Educated on practicing safer sex consistently and using condoms correctly 					
assess estimated CrCl, serum phosphorus, urine glucose, and urine protein before initiation of emtricitabine/tenofovir disoproxil fumarate and	Discussed the importance of the individual knowing their HIV-1 status and, if possible, that of their partner(s)					
periodically while emtricitabine/tenofovir disoproxil fumarate is being used. If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/tenofovir disoproxil fumarate for a PrEP	Discussed the importance of and performed screening for sexually transmitted infections (STIs), such as syphilis and gonorrhea, that can facilitate HIV-1 transmission					
indication, evaluate potential causes and reassess potential risks and benefits of continued use	Offered HBV vaccination as appropriate					
Confirmed that the uninfected individual at high risk is not taking other HIV-1 medications or HBV medications	Provided education on where information about emtricitabine/tenofovir disoproxil fumarate for a PrEP indication can be accessed					
Evaluated risk/benefit for women who may be	☐ Discussed potential adverse reactions					
pregnant or may want to become pregnant	Reviewed the Emtricitabine/Tenofovir Disoproxil Fumarate Medication Guide with the uninfected individual at high risk					

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This document contains copy for the creation of the REMS for emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication HCP Website.

Revised: XX/1X

www.ftc-tdf-preprems.com Global Items

Area on page	Description and copy
Global Header/Utilities	REMS Information Prescribing Information and Medication Guide
	rescribing mormation and wedication duide
Global Top Navigation	0.0
	1.0 Prophylaxis therapy
	1.1 Emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication 1.2 Comprehensive Management
	2.0 Starting Individuals
	2.1 Checklist for Prescribers 2.2 Agreement Form
	3.0 <u>Support</u>
	3.1 <u>REMS Materials</u> 3.2 <u>Post-Training Review Questions</u>

Area on page	Description and copy
Global Footer	Site Map
	The information on this site is intended for audiences 18 years of age or older in the
	United States only. The content on this site may not apply to non-US audiences as
	regulatory control, legal requirements and/or medical practices may vary in other
	countries.
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Global Right Rail Callouts

Area on page	Description and copy
Header over all RR callouts	REMS Center
Right rail callout	Materials Download important materials for healthcare providers and uninfected individuals about emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
Right rail callout	Post-Training Review Questions Assess your knowledge of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication by answering a series of review questions

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Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300mg for a Pre-exposure Prophylaxis (PrEP) Indication

[Copy]

This is a **Risk Evaluation and Mitigation Strategy (REMS)** Web site.

Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication—in combination with safer sex practices—can help reduce the risk of sexually acquired HIV-1 infection as part of a comprehensive HIV-1 prevention strategy in adults at high risk. Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication does not replace existing prophylaxis strategies. Review factors that can help healthcare providers identify individuals at high risk for sexually acquired HIV-1 infection and important prescribing considerations

Review the online training for prescribers > [Launches slide show PDF or div layer]

Report completion of training for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication

[link to UBC and external database to capture name, degree, address (street, city, state, zip) and specialty]

Participate in a Knowledge, Attitude, and Behavior (KAB) survey to assess the use and understanding of emtricitabine/tenofovir disoproxil fumarate for PrEP [link to UBC for KAB pre-qualification page]

REMS Information

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

To make sure emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is prescribed and taken safely, emtricitabine/tenofovir disoproxil fumarate Sponsor(s) has worked with the FDA to develop materials for the REMS program to educate and inform healthcare providers and uninfected individuals at high risk for acquiring HIV-1.

Access REMS resources >

Slide Show/Review Questions

Area on page

Description and copy

Slide 1	Emtricitabine/Tenofovir Disoproxil Fumarate for a Pre-exposure Prophylaxis (PrEP) Indication
	Healthcare Provider Training
Slide 2	Pre-Exposure Prophylaxis (PrEP) Indication
	 Emtricitabine/tenofovir disoproxil fumarate is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.
Slide 3	Factors to Help Identify Individuals at High Risk
	Has partner known to be
	HIV-1 infected, or
	Engages in sexual activity
	within a high prevalence area or social network and one or more of the following:
	 Inconsistent or no condom use
	 Diagnosis of sexually transmitted infections
	 Exchange of sex for commodities (such as money, shelter, food, or drugs)
	 Use of illicit drugs or alcohol dependence
	Incarceration
	 Partner(s) of unknown HIV-1 status with any of the factors listed above

When Prescribing Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication, Healthcare Providers MUST:

- Prescribe emtricitabine/tenofovir disoproxil fumarate as part of a comprehensive prevention strategy because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to the recommended daily emtricitabine/tenofovir disoproxil fumarate dosing schedule because the effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels
- Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical signs or symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected,
 - delay starting PrEP for at least 1 month and reconfirm HIV-1 status or
 - use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- While using emtricitabine/tenofovir disoproxil fumarate for a PrEP indication,
 HIV-1 screening tests should be repeated at least every 3 months
 - If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, emtricitabine/tenofovir disoproxil fumarate should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection

Slide 5

BOXED WARNING

 Emtricitabine/tenofovir disoproxil fumarate used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drugresistant HIV-1 variants have been identified with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication following undetected acute HIV-1 infection. Do not initiate emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed.

BOXED WARNING (Continued)

 Emtricitabine/tenofovir disoproxil fumarate is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients infected with HBV who have discontinued emtricitabine/tenofovir disoproxil fumarate. Therefore, hepatic function should be monitored closely with both clinical and laboratory followup for at least several months in patients who are infected with HBV and discontinue emtricitabine/tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Slide 7

Why Use Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication?

- By inhibiting HIV-1 from replicating as it enters the body, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication works to prevent the virus from establishing permanent infection. However, emtricitabine/tenofovir disoproxil fumarate should not be seen as the first line of defense against HIV-1 infection
- Because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be used in combination with a comprehensive prevention strategy that includes safer sex practices, such as regular and correct condom use, regular HIV testing for themselves (and their sexual partners), and other proven HIV prevention methods to safely and effectively reduce the risk of acquiring HIV-1 infection
 - Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must only be prescribed to uninfected individuals at high risk who are confirmed to be HIV-1 negative
 - Uninfected individuals who are prescribed emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should not miss any doses.
 Missing doses may increase the risk of acquiring HIV infection

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Key Findings of the Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication Studies: The iPrEx Trial

- In one clinical trial of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, emtricitabine/tenofovir disoproxil fumarate was shown to reduce the risk of HIV-1 acquisition by 42% for high risk men who have sex with men who also received comprehensive prevention services, including monthly HIV-1 testing, condom provision, counseling, and management of other sexually transmitted infections
- In a post-hoc case control study of plasma and intracellular drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir.
 Efficacy was therefore strongly correlated with adherence
- Because of the intensive risk reduction counseling provided as part of the trial, self-reported risk behavior among the subjects in this clinical trial declined overall during the trial, both in terms of decreases in the number of sexual partners and increases in condom use

Slide 9

Key Findings of the Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication Studies: The Partners PrEP Trial

- In another clinical trial of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, emtricitabine/tenofovir disoproxil fumarate was shown to reduce HIV-1 acquisition by 75% in uninfected individuals in stable heterosexual serodiscordant relationships who also received comprehensive prevention services, including monthly HIV testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations
- In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence. Risk reduction increased further in subjects with detectable plasma tenofovir

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1 Infection

- Prescribe emtricitabine/tenofovir disoproxil fumarate for PrEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection
 - Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea)
 - Inform uninfected individuals about and support their efforts in reducing sexual risk behavior

Slide 11

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1 Infection

- Prescribe emtricitabine/tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-negative
 - HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine/tenofovir disoproxil fumarate, because emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete regimen for HIV-1 treatment; therefore, care should be taken to minimize drug exposure in HIV-infected individuals
 - Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month

Important Safety Information: Comprehensive Management to Reduce the Risk Slide 12 of Acquiring HIV-1 Infection Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical signs or symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection While using emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection Important Safety Information: Comprehensive Management to Reduce the Risk Slide 13 of Acquiring HIV-1 Infection Counsel uninfected individuals to strictly adhere to the recommended daily emtricitabine/tenofovir disoproxil fumarate dosing schedule. The effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels Important Safety Information: Additional Warnings and Precautions Slide 14 New Onset or Worsening Renal Impairment Can include acute renal failure and Fanconi syndrome Assess estimated creatinine clearance (CrCl) before prescribing treatment with emtricitabine/tenofovir disoproxil fumarate and periodically during therapy with emtricitabine/tenofovir disoproxil fumarate In individuals at risk of renal impairment, assess estimated CrCl, serum phosphorus, urine glucose and urine protein before prescribing emtricitabine/tenofovir disoproxil fumarate and periodically while emtricitabine/tenofovir disoproxil fumarate is being used

Important Safety Information: Additional Warnings and Precautions

New Onset or Worsening Renal Impairment

- Avoid administering emtricitabine/tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy have been reported after initiation of high dose or multiple NSAIDs in patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients.
- Do not use emtricitabine/tenofovir disoproxil fumarate for a PrEP indication in HIV-1 uninfected individuals with an estimated CrCl below 60 mL/min
 - If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/tenofovir disoproxil fumarate for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use

Slide 16

Important Safety Information: Additional Warnings and Precautions Lactic acidosis/severe hepatomegaly with steatosis:

 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

Bone effects

- Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir disoproxil fumarate. Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss
- Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients

Slide 17

Important Safety Information: Additional Warnings and Precautions HBV Infection

- It is recommended that all individuals be tested for the presence of chronic HBV before initiating emtricitabine/tenofovir disoproxil fumarate
- HBV-uninfected individuals should be offered vaccination
 Coadministration with other products
 - Do not use emtricitabine/tenofovir disoproxil fumarate with drugs containing emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide, with drugs containing lamivudine, or with adefovir dipivoxil

Important Safety Information: Use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication in Specific Populations

Pregnancy

- There are no adequate and well controlled trials in pregnant women.
- emtricitabine/tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.
- If an uninfected individual becomes pregnant while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, careful consideration should be given to whether the use of emtricitabine/tenofovir disoproxil fumarate should be continued, taking into account the potential increased risk of HIV infection during pregnancy*
- A pregnancy registry is available. Enroll pregnant women taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication by calling 1-800-258-4263

*Gray RH, et al. Lancet. 2005;366(9492):1182-1188.

Slide 19

Important Safety Information: Use of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication in Specific Populations

Nursing Mothers

 The components of emtricitabine/tenofovir disoproxil fumarate are excreted in breast milk. Because the risks to the infant are not known, mothers taking emtricitabine/tenofovir disoproxil fumarate for PrEP should be instructed not to breastfeed. If an uninfected individual acquires HIV-1 infection, it is recommended that she not breastfeed to avoid risking postnatal transmission of HIV-1

Pediatrics

 emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is based on trials in adults

Slide 20

Important Safety Information: Confirming and Regularly Reconfirming Negative HIV-1 Status

- Emtricitabine/tenofovir disoproxil fumarate should be used to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-1 negative
 - A negative HIV-1 status should be confirmed before prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Individuals should be regularly tested (at least every 3 months) while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication to reconfirm that they are HIV-1 negative
 - If symptoms consistent with acute HIV-1 infection develop following a
 potential exposure event, PrEP should be discontinued until negative
 infection status is confirmed using a test approved by the FDA as an aid
 in the diagnosis of HIV-1, including acute or primary HIV-1 infection

Important Safety Information: Confirming and Regularly Reconfirming Negative HIV Status

Potential for Resistance in Undetected Acute HIV-1 Infection

- It is important to be alert to the signs of potential acute HIV-1 infection when prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. These include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and cervical and inguinal adenopathy
- HIV-1 resistance mutations may emerge in individuals with undetected HIV-1 infection who are taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Although emtricitabine/tenofovir disoproxil fumarate is active against HIV-1, emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete treatment regimen for HIV-1 infection
 - HIV-1 infected patients taking emtricitabine/tenofovir disoproxil fumarate must take it with other antiretroviral agents to fully suppress virus replication and avoid the development of resistance

Slide 22

Important Safety Information: Drug Interactions and Common Adverse Events Drug Interactions

- Coadministration of emtricitabine/tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir.
- For further details about emtricitabine/tenofovir disoproxil fumarate drug interactions, please see the <u>Prescribing Information [link to PDF of PI]</u> for emtricitabine/tenofovir disoproxil fumarate

Common Adverse Reactions

 In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of emtricitabine/tenofovir disoproxil fumarate subjects and more frequently than by placebo subjects were headache, abdominal pain and decreased weight.

Additional Educational Materials

- Agreement Form for Initiating emtricitabine/tenofovir disoproxil fumarate for Preexposure Prophylaxis (PrEP)
 - Designed for prescribers to use with uninfected individuals to facilitate discussion of appropriate use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Form covers safety risks associated with use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, the importance of adherence to the recommended daily dosing regimen, regular assessment of HIV-1 test results, and screening for sexually transmitted infections
- Checklist for Prescribers: Initiation of emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP)
 - Checklist of key components for prescribers to consider before starting an uninfected individual on emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
 - Checklist items include confirming a negative HIV-1 test result, screening for signs or symptoms of acute HIV-1 infection, counseling on safety risks and importance of adherence, and other components to ensure a comprehensive prevention strategy
- Copies available from www.ftc-tdf-preprems.com or by filling out the postage paid, business reply card at the back of the Training Guide for Healthcare Providers

Slide 24

Additional Educational Materials

- Additional educational materials can be reviewed and downloaded at www.ftc-tdfpreprems.com
- Please confirm completion of training by going to www.ftc-tdf-preprems.com or by filling out the postage paid, business reply card at back of the Training Guide for Healthcare Providers
- A survey is being conducted to fulfill an FDA-required Risk Evaluation and Mitigation Strategy (REMS) program to assess prescribers' knowledge regarding important safety information associated with the use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. To participate, please go to www.ftc-tdfpreprems.com.

Post-training screen

Assess Your Knowledge of Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication

[Buttons]

Go to review questions [Advances to questions page/launches question 1]
No thanks [Advances to input screen for specialty/degree]

Report completion of training for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication

[link to UBC and external database to capture name, degree, address (street, city, state, zip) and specialty]

Participate in a knowledge, attitude, and behavior (KAB) survey to assess the use and understanding of emtricitabine/tenofovir disoproxil fumarate for PrEP [link to UBC for KAB pre-qualification page]

Question 1

Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP indication should be used only:

Correct answer: D

- a) As part of a comprehensive HIV-1 prevention strategy that includes other preventive measures, since emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection
- b) In individuals who have been counseled to strictly adhere to their emtricitabine/tenofovir disoproxil fumarate daily dosing schedule, since the effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels
- In individuals who have a confirmed negative HIV-1 test prior to initiating and routinely while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication
- d) All of the above

Correct	Incorrect. Please try again.
<u>Next</u>	Try again
[Advances to next screen]	[Greys out selected wrong answer]

Which of the following statements is false? Question 2 a) Emtricitabine/tenofovir disoproxil fumarate should be used for a PrEP indication only in individuals confirmed to be HIV-1 negative b) Emtricitabine/tenofovir disoproxil fumarate has been found to be safe and effective for pre-exposure prophylaxis to reduce the risk of acquiring HIV-1 Correct answer: B infection through injection drug use c) Women taking Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should not breastfeed their babies d) Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is not always effective in preventing HIV-1 infection Correct Incorrect. Please try again. Next Try again [Greys out selected wrong answer] [Advances to next screen] Which of the following items are not included on the Checklist for Prescribers Question 3 for initiating Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP indication? a. Perform HBV screening test Correct answer: B b. Perform testing for TB c. Confirm negative HIV-1 status of the individual d. Confirm creatinine clearance is ≥60 mL/min Correct Incorrect Next Try again [Advances to next question] [Greys out selected wrong answer]

Hepatic function should be monitored closely in: Question 4 a. HBV-infected individuals who discontinue emtricitabine/tenofovir disoproxil Correct answer: A fumarate b. All people taking emtricitabine/tenofovir disoproxil fumarate c. All people who discontinue emtricitabine/tenofovir disoproxil fumarate d. None of the above Correct Incorrect. Please try again. Next Try again [Advances to next screen] [Greys out selected wrong answer] In clinical trials evaluating emtricitabine/tenofovir disoproxil fumarate for a Question 5 PrEP indication, which of the following adverse reactions was not common? Correct answer: c a) Abdominal pain b) Headache c) Dizziness d) Decreased weight Correct Incorrect. Please try again. Next Try again [Greys out selected wrong answer] [Advances to next screen] Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is indicated only Question 6 for: a) Men who are at high risk for sexually acquired HIV-1 infection Correct answer: D b) Adults who are at high risk of acquiring HIV-1 infection by any means c) Adults who are at high risk of acquiring HIV-1 infection through injection drug use d) Adults who are at high risk for sexually acquired HIV-1 infection Correct Incorrect. Please try again. Next Try again [Advances to next screen] [Greys out selected wrong answer]

Question 7

The Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP) provides which of the following information:

Correct answer: D

- a. A list of activities that put individuals at risk for sexually acquired HIV-1 infection
- b. A confirmation that the prescriber has discussed the risks and benefits of using emtricitabine/tenofovir disoproxil fumarate for a PrEP indication with the uninfected individual
- c. A signature from the individual asserting that the prescriber has explained the risks and benefits of taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, including the need for adherence and a comprehensive prevention strategy, which includes safer sex practices
- d. All of the above

Correct	Incorrect
[Auto advances to resolve screen]	Try again [Greys out selected wrong answer]

Input screen

To help emtricitabine/tenofovir disoproxil fumarate Sponsor(s) and the FDA understand who has viewed this training, please tell us the following

Your Specialty:

[drop down menu]
Internal medicine
Family practice
General medicine
Infectious diseases
Obstetrics/gynecology
Addiction medicine

Other

Profession:

[drop down menu]

MD PA NP Other

Zip Code: [insert box to capture 5 digit zip code]

[Buttons]

<u>Submit</u> [Advances to thank you screen] No thanks [Closes div layer]

[one time error state if user misses a field on "Submit" only] Please provide this information.

Report completion of training for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication

[link to UBC and external database to capture name, degree, address (street, city, state, zip) and specialty]

Participate in a Knowledge, Attitude, and Behavior (KAB) survey to assess the use and understanding of emtricitabine/tenofovir disoproxil fumarate for PrEP [link to UBC for KAB pre-qualification page]

Thank you screen

[H1]

Thank you

Close [Closes div layer]

1.1, About Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP Indication

Area on page	Description and copy	
Headline	About emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication	
	Emtricitabine/tenofovir disoproxil fumarate is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. The following factors may help to identify individuals at high risk:	
	Has partner(s) known to be HIV-1 infected, or	
	Engages in sexual activity within a high prevalence area or social network and one or more of the following:	
	 Inconsistent or no condom use 	
	 Diagnosis of sexually transmitted infections 	
	 Exchange of sex for commodities (such as money, shelter, food, or drugs 	
	 Use of illicit drugs, alcohol dependence 	
	Incarceration	
	 Partner(s) of unknown HIV-1 status with any of the factors listed above 	
Сору	When prescribing emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis, healthcare providers must:	
	 Prescribe emtricitabine/tenofovir disoproxil fumarate as part of a comprehensive prevention strategy because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection 	
	Counsel all uninfected individuals to strictly adhere to the recommended emtricitabine/tenofovir disoproxil fumarate daily dosing schedule because the effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection was strongly correlated with adherence and measurable drug levels	
	 Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofoving disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection 	
	 Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for PrEP 	
	Be sure to not prescribe emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if signs or symptoms of acute HIV-1 infection are present	

H2	Mechanism of action for pre-exposure prophylaxis
Сору	By inhibiting HIV-1 from replicating as it enters the body, emtricitabine/tenofovir disoproxil fumarate for a PrEP indication helps prevent the virus from establishing permanent infection. Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication does not replace existing HIV-1 prevention strategies.
Next page callout	Next: Comprehensive Management

1.2, Comprehensive Management

Area on page	Description and copy
Headline	Comprehensive Management
Сору	Prescribe emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1 infection. • Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, limiting the number of sexual partners, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea) • Inform uninfected individuals about and support their efforts in reducing sexual risk behavior
	Prescribe emtricitabine/tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine/tenofovir disoproxil fumarate, because emtricitabine/tenofovir disoproxil fumarate alone does not constitute a complete treatment regimen for HIV-1 treatment; therefore, care should be taken to minimize drug exposure in HIV-1 infected individuals.
	 Evaluate for signs or symptoms of acute HIV-1 infection prior to prescribing and while taking emtricitabine/tenofovir disoproxil fumarate You must confirm a negative HIV-1 test immediately prior to prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting emtricitabine/tenofovir disoproxil fumarate for at least 1 month and reconfirm HIV-1 negative status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
	Screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection
	Counsel uninfected individuals to strictly adhere to the recommended emtricitabine/tenofovir disoproxil fumarate daily dosing schedule. The effectiveness of emtricitabine/tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels.

Bold copy	It's important to remember that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is contraindicated in individuals with unknown or positive HIV-1 status. Emtricitabine/tenofovir disoproxil fumarate should only be used in HIV-1 infected patients in combination with other antiretroviral agents.
Сору	Access tools that can help you manage and counsel individuals on the correct and safe use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. Checklist for Prescribers > Agreement form >

Next page callout	Next: Checklist for Prescribers	

2.1, Checklist for Prescribers

Area on page	Description and copy Checklist for Prescribers		
Headline			
Сору	Before prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, it's important that you complete the Checklist for Prescribers: Initiation of Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-Exposure Prophylaxis (PrEP) with uninfected individuals and file in the individual's medical record. On each visit with an uninfected individual, complete the following steps:		
Сору	Complete high risk evaluation of uninfected individual onfirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. o If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposure is suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection (Note: emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is contraindicated in individuals with unknown HIV-1 status or who are HIV-1 positive) Discuss known safety risks with use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Counsel on the importance of scheduled follow-up every 2 to 3 months including regular HIV-1 screening tests (at least every 3 months) while taking emtricitabine/tenofovir disoproxil fumarate for PrEP to reconfirm HIV-1 status Discuss the importance of discontinuing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication if seroconversion has occurred, to reduce the development of resistant HIV-1 variants Counsel on the importance of adherence to daily dosing schedule Counsel that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should be used only as part of a comprehensive prevention strategy Educate on practicing safer sex consistently and using condoms correctly Discuss the importance of the individual knowing their HIV-1 status and, if possible, that of their partner(s) Discuss the importance of and perform screening for sexually transmitted infections (STIs), such as syphilis and gonorrhea, that can facilitate HIV-1 transmission		

Perform HBV screening test. Offer HBV vaccination as appropriate Confirm estimated creatinine clearance (CrCl) ≥ 60 mL/min prior to initiation and periodically during treatment. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiation of emtricitabine/tenofovir disoproxil fumarate and periodically while emtricitabine/tenofovir disoproxil fumarate is being used. If a decrease in estimated CrCl is observed in uninfected individuals while using emtricitabine/tenofovir disoproxil fumarate for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use Confirm that the uninfected individual at high risk is not taking other HIV-1 medications or hepatitis B medications Provide education on where information about emtricitabine/tenofovir disoproxil fumarate for a PrEP indication can be accessed Discuss potential adverse events Review the emtricitabine/tenofovir disoproxil fumarate Medication Guide with the uninfected individual at high risk Evaluate risk/benefit for women who may be pregnant or may want to become pregnant Next: Agreement Form Next page callout

2.2, Agreement Form

Area on page	Description and copy
Headline	Agreement Form
Сору	As part of helping uninfected individuals understand the commitment in taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, the Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate for Pre-exposure Prophylaxis (PrEP) has been created. It's important that you use the form to review the factors that may help to identify uninfected individuals at high risk. These include:
Сору	 as partner(s) known to be HIV-1 infected, or Engages in sexual activity within a high prevalence area or social network and one or more of the following: Inconsistent or no condom use Diagnosis of sexually transmitted infections Exchange of sex for commodities (such as money, shelter, food, or drugs) Use of illicit drugs, alcohol dependence Incarceration Partner(s) of unknown HIV-1 status with any of the factors listed above
Сору	After you review the risks and benefits with the individual, you must both sign and date the form and file in the individual's medical record. This will help to reinforce the importance of understanding the risks involved with emtricitabine/tenofovir disoproxil fumarate for a PrEP indication. Download a printable version of the Agreement Form .
Next page callout	Next: REMS Materials

3.1, REMS Materials

Area on page	Description and copy		
Headline	REMS Materials		
Сору	You will need Ado	On this page, you'll find downloadable resources for you and uninfected individuals. You will need Adobe Acrobat installed on your computer to view these resources. If you do not have it and would like to download it, please click here .	
H3	Dear Health Care	Provider Letter	
Download box	FOR POSITION ONLY	Information for healthcare providers on the new emtricitabine/tenofovir disoproxil fumarate indication for pre-exposure prophylaxis (PrEP) Download	
H3	Training Guide for Healthcare Providers		
Download box	FOR POSITION ONLY	A comprehensive overview of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Download	
H3	Important Safety Information for Healthcare Providers		
Download box	FOR POSITION ONLY	Important safety information about TRUVADA for a PrEP indication Download [Links to PDF download]	
H3	Safety Information Fact Sheet		
Download box	FOR POSITION ONLY	A detailed overview of the safety information for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Download	

H3	Prescriber-Individual Agreement Form		
Download box	FOR POSITION ONLY	Form that should be reviewed with an individual considering/taking emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Download	
H3	Checklist for Prese	cribers	
Download box	FOR POSITION ONLY	Tool for facilitating appropriate prescribing of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Download	
H3	Medication Guide		
Download box	FOR POSITION ONLY	A comprehensive guide for uninfected individuals getting started on emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Download	
H3	Important Safety Information Brochure for Uninfected Individuals		
Download box	FOR POSITION ONLY	An easy-to-understand guide on the most important safety information about TRUVADA for a PrEP indication Download [Links to PDF download]	
H3	Prescribing Information		
Download box	FOR POSITION ONLY	Prescribing Information for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Download	
Next page callout	Next: Post-Trainin	g Review Questions	

3.2, Post-Training Review Questions

Description and copy	
Post-Training Review Questions	
If you are a healthcare provider considering prescribing emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, assess your knowledge about the safe use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.	
Go to review questions Report completion of training for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication Participate in a knowledge, attitude, and behavior (KAB) survey to assess the use and understanding of emtricitabine/tenofovir disoproxil fumarate for PrEP	

Div layer for first time visit

Area on page	Description and copy
Сору	The information on this site is intended for adult residents of the United States.
Buttons	OK [Continues to site]

5.0, Site Map

Area on page	Description and copy
Headline	Site Map
Сору	Home Prophylaxis Therapy Emtricitabine/tenofovir disoproxil fumarate for a PrEP Indication Comprehensive Management Starting Individuals Checklist for Prescribers Agreement Form Support REMS Materials Post-Training Review Questions

$\underline{6.0 \ Report \ completion \ of \ training \ for \ emtricitabine/tenofovir \ disoproxil \ fumarate \ for \ a \ PrEP}_{\underline{indication}}$

[link to UBC and external database to capture name, degree, address (street, city, state, zip) and specialty]

https://itookthetraining.com/#Home/!Prescriber

Area on page	Description and copy Emtricitabine/tenofovir disoproxil fumarate Prescriber Training	
Headline		
Сору	Have you completed the training for emtricitabine/tenofovir disoproxil fumarate for a PrEP indication? O Yes O No [If no, 6.1. If yes, 6.2]	

[6.1-If no]:

All prescribers of <u>emtricitabine/tenofovir disoproxil fumarate</u> for a PrEP indication are encouraged to review the training material available at www.ftc-tdf-preprems.com. After reviewing material, please return to this site to acknowledge completion of training.

[6.2- If yes]:

Medical Specialty:	v
Degree:	
Prescriber First Name:	
Prescriber Middle Name:	
Prescriber Last Name:	
Street Address:	
City:	
State:	
Zip:	

7.0 Participate in a Knowledge, Attitude, and Behavior (KAB) survey to assess the use and understanding of emtricitabine/tenofovir disoproxil fumarate for PrEP

Emtricitabine/tenofovir disoproxil fumarate for a PrEP Pre-registration

Thank you for your interest in the emtricitabine/tenofovir disoproxil fumarate for Pre-Exposure Prophylaxis (PrEP) survey! Please click the button that best describes you.

Please click the button that best do	Please click the button that best describes you.		
I am an HIV-1 Uninfected Individual	I am a Healthcare Provider		

7.1 HIV-1 Uninfected Individual

Please answer the following questions to determine if you pre-qualify to take the emtricitabine/tenofovir disoproxil fumarate survey. The emtricitabine/tenofovir disoproxil fumarate survey will help the manufacturers of this medicine know if HIV-1 uninfected individuals understand important information about taking emtricitabine/tenofovir disoproxil fumarate. If you pre-qualify, we will ask for your contact information so that we can provide you with additional information about how to participate in the emtricitabine/tenofovir disoproxil fumarate survey. Participation is voluntary and the information you provide will be kept confidential. Your contact information will be stored securely and will not be shared with any third parties or with emtricitabine/tenofovir disoproxil fumarate Sponsor(s), the manufacturers of emtricitabine/tenofovir disoproxil fumarate.

The questions below are not part of the emtricitabine/tenofovir disoproxil fumarate survey. The emtricitabine/tenofovir disoproxil fumarate survey will take approximately 20 minutes and will ask questions about important safety information about emtricitabine/tenofovir disoproxil fumarate. You will receive a \$25 gift card if you qualify for and complete the emtricitabine/tenofovir disoproxil fumarate survey or if you do not complete the emtricitabine/tenofovir disoproxil fumarate survey or if you do not complete the emtricitabine/tenofovir disoproxil fumarate survey, you will not receive the \$25 gift card. You may not register to take this survey twice. If you qualify and take the survey more than once, you will only receive one \$25 gift card. Please note, only residents of the United States may participate in the survey.

If you would like to see if you pre-qualify to participate in the emtricitabine/tenofovir disoproxil fumarate survey, please answer the following questions.

1. Are you at least 18 years old?
C Yes
C No
2. Are you a resident of the United States?
C Yes
C _{No}
3. Are you currently taking emtricitabine/tenofovir disoproxil fumarate to prevent getting infected with
HIV-1?
C Yes
C No
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[If no to any one question]

Thank you for your interest in the <u>emtricitabine/tenofovir disoproxil fumarate</u> survey. Unfortunately, based on your answers you do not pre-qualify to participate in the <u>emtricitabine/tenofovir disoproxil fumarate</u> survey.

If yes to all:

First Name:	Last Name:	
Please select your preferred	I method of contact:	
Please select a secondary m	nethod of contact:	▼

7.2 I am a Healthcare Provider

If you would like to see if you pre-qualify to participate in the emtricitabine/tenofovir disoproxil fumarate for a PrEP survey, please answer the following questions.

1. Have you prescribed emtricitabine/tenofovir disoproxil fumarate for any indication (e.g., for treatment
of HIV-1 and/or for PrEP)?
C Yes
C No
2. Are you a resident of the United States?
C Yes
C No

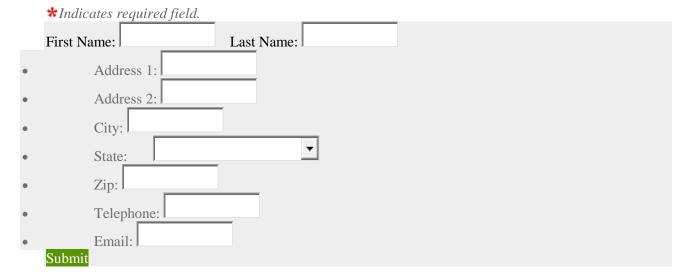
[If no]

Thank you for your interest in the <u>emtricitabine/tenofovir disoproxil fumarate</u> for a PrEP survey. Unfortunately, based on your answer you do not pre-qualify to participate in the <u>emtricitabine/tenofovir disoproxil fumarate</u> for a PrEP survey.

[If yes]

Thank you for your interest in the emtricitabine/tenofovir disoproxil fumarate for a PrEP survey. At the end of this pre-qualification process, you will have the opportunity to go directly to the emtricitabine/tenofovir disoproxil fumarate for a PrEP survey. If you qualify and you complete the full emtricitabine/tenofovir disoproxil fumarate for a PrEP survey, you will receive a \$125 honorarium for your time. Your contact information will be stored securely and will not be shared with any third parties or with emtricitabine/tenofovir disoproxil fumarate Sponsor(s), the manufacturers of emtricitabine/tenofovir disoproxil fumarate for a PrEP.

We would like to collect your contact information for our records before you leave the pre-qualification website. Please provide your contact information below.





Digitally signed by Heidi Lee
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