Important Safety Information About Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for HIV-1 Pre-exposure Prophylaxis (PrEP)

For Healthcare Providers

About Emtricitabine/Tenofovir Disoproxil Fumarate for HIV-1 PrEP

INDICATION AND PRESCRIBING CONSIDERATIONS

The combination of emtricitabine and tenofovir disoproxil fumarate is indicated in combination with safer sex practices for HIV-1 pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. Individuals must have a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP.

- If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting HIV-1 PrEP for at least 1 month and reconfirm HIV-1 status or use a test cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection

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

- Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and has additional risk factors for HIV-1 acquisition, such as:
  - 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 HIV-1 PrEP:

- Only prescribe emtricitabine/tenofovir disoproxil fumarate as part of a comprehensive prevention strategy because emtricitabine/tenofovir disoproxil fumarate is not always effective in preventing 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), the importance of virologic suppression in their partner(s) with HIV-1 and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis, chlamydia, and gonorrhea)
- While using emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP, HIV screening tests should be repeated at least every 3 months, and upon diagnosis of sexually transmitted infections. Some individuals, such as adolescents, may benefit from more frequent visits and counseling
- Do not initiate emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed

The following points should also be considered when prescribing emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP in adolescents:

- Use of emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP as part of a comprehensive HIV prevention strategy for adolescents should include consideration of the ability of the individual to understand the importance of adherence to daily dosing, the need for frequent HIV testing, the need for frequent sexually transmitted infection testing, and the continued risk of pregnancy
- In a clinical study in adolescents, the percentage of subjects with protective levels of drug declined markedly after subjects switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits and counseling

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 HIV-1 PrEP, 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 HIV-1 PrEP.

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 HIV-1 PrEP IN UNDIAGNOSED EARLY HIV-1 INFECTION

- **Emtricitabine/tenofovir disoproxil fumarate used for HIV-1 PrEP 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 HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed**
- **Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients 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 HBV-infected patients who discontinue emtricitabine/tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted**

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Contraindications

- **Emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP 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 and development of HIV-1 resistance**

  Use emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP 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, including:
    - Using condoms consistently and correctly
    - Knowing their HIV-1 status and that of their partner(s)
    - The importance of virologic suppression in their partner(s) with HIV-1
    - Being regularly tested for other sexually transmitted infections that can facilitate HIV-1 transmission (eg, syphilis, chlamydia, and gonorrhea)
  - Inform uninfected at-risk individuals about and support their efforts to reduce sexual risk behavior

- Use emtricitabine/tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 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. Therefore, care should be taken to minimize drug exposure in HIV-1 infected individuals:
    - Confirm a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP. 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 HIV-1 PrEP, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (eg, fever, fatigue, myalgia, skin rash) and ask about potential exposure events (eg, unprotected, or condom broke during, sex with an HIV-1 infected partner) 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 HIV-1 PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved or cleared 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 HIV-1 PrEP, HIV-1 screening tests should be repeated at least every 3 months, and upon diagnosis of any sexually transmitted infections. Some individuals, such as adolescents, may benefit from more frequent visits and counseling
    - If a screening test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared 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 HIV-1 PrEP
  - 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, as demonstrated by measurable drug levels in clinical trials

- **New onset or worsening renal impairment:** Can include acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia). Prior to initiating and during use of emtricitabine/tenofovir disoproxil fumarate, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients. Emtricitabine/tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDS]). Cases of acute renal failure after initiation of high-doses or multiple NSAIDS have been reported. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction
  - **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 HIV-1 PrEP, evaluate potential causes and reassess potential risks and benefits of continued use**
- **HBV infection:**
  - All patients should be tested for chronic hepatitis B virus (HBV)
  - HBV-uninfected individuals should be offered vaccination
  - HBV-infected individuals should be monitored closely for exacerbations of hepatitis B for at least several months after discontinuing emtricitabine/tenofovir disoproxil fumarate (see **BOXED WARNING** above)

- **Lactic acidosis/severe hepatomegaly with steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Discontinue treatment in any patient who develops clinical 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 adults 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 HIV-1 PrEP in Specific Populations

- **Pregnancy:**
  - Data on the use of emtricitabine/tenofovir disoproxil fumarate during pregnancy from observational studies have shown no increased risk of major birth defects. There are insufficient human data on the use of emtricitabine/tenofovir disoproxil fumarate during pregnancy to inform a drug-associated risk of miscarriage
  - Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother-to-child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV, including continuing or initiating emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP, during pregnancy
  - A pregnancy registry is available. Enroll pregnant women exposed to emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263
- **Lactation:**
  - It is not known if the components of emtricitabine/tenofovir disoproxil fumarate (emtricitabine and tenofovir disoproxil fumarate) affect milk production or have effects on the breastfed child
  - In HIV-1–uninfected women, the developmental and health benefits of breastfeeding and the mother's clinical need for emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from emtricitabine/tenofovir disoproxil fumarate and the risk of HIV-1 acquisition due to nonadherence and subsequent mother-to-child transmission
  - Women should not breastfeed if acute HIV-1 infection is suspected because of the risk of HIV-1 transmission to the infant
- **Pediatrics:**
  - Safety, adherence, and resistance were evaluated in a single-arm, open-label clinical trial (ATN 113) of 67 HIV-1 uninfected at-risk adolescent men who have sex with men and received emtricitabine/tenofovir disoproxil fumarate once daily for HIV-1 PrEP
  - In the ATN 113 trial, HIV-1 seroconversion occurred in three subjects. Tenofovir diphosphate (DP) levels in dried blood spot assays indicate that these subjects had poor adherence
  - Adherence to study drug, as demonstrated by tenofovir DP levels in dried blood spot assays, declined markedly after Week 12 once subjects switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits and counseling

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 200 mg/300 mg for HIV-1 Pre-exposure Prophylaxis (PrEP) and the Agreement Form for Initiating Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg for HIV-1 Pre-exposure Prophylaxis (PrEP) to help manage and counsel individuals about the safe use of emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP.

For more information about emtricitabine/tenofovir disoproxil fumarate and its indication for HIV-1 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 HIV-1 PrEP, 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 HIV-1 PrEP at 1-800-625-7471.

Notes

Reference: TRUVADA [package insert]. Foster City, CA: Gilead Sciences, Inc; 2018.

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