CLINICAL VIGNETTE

The "Start-Up Syndrome" of HIV Pre-Exposure Prophylaxis

Sheila Naghshineh, MD and Daniel Puneky, MD

Case

A 33-year-old man presented for consultation regarding starting pre-exposure prophylaxis for HIV (PrEP). A year prior to his presentation he had an episode of condomless receptive anal intercourse with a male partner. He was started on non-occupational Post-Exposure Prophylaxis (nPEP) with fixed dose combination tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) 300-200mg po Daily and raltegravir (RAL) 400mg po twice Daily for 28 days. He described nausea and vomiting while on this regimen, which he cited as a reason that he did not subsequently start PrEP. One month prior to his presentation, he had another episode of condomless intercourse. Approximately 2 weeks prior to presentation, he had routine sexually transmitted infection (STI) testing at an outside facility. Chlamydia/Gonorrohea PCR rectal swab was positive for chlamydia infection and negative for gonorrhea. Fourth generation HIV Ag/Ab testing and RPR were negative. He was treated with azithromycin 1g by mouth. He was not started on nPEP because it was greater than 72 hours since his exposure.

At presentation, he denied fever, dysuria, urethral discharge, constipation, diarrhea, anorectal pain and discharge, tenesmus, and rectal bleeding. He also denied influenza-like syndrome and lymphadenopathy. There were no sexual encounters since his chlamydia diagnosis two weeks prior to presentation. He was anxious regarding his recent chlamydia diagnosis and concerned about the possibility of HIV infection. He reported that he typically used condoms for all sexual encounters, but that there was a moment of indiscretion during the most recent episode as well as the year prior. He planned to continue using condoms but requested initiation of PrEP as an additional layer of protection. He reported drinking 1-2 alcoholic beverages most nights with occasional binge drinking less than monthly. He used cannabis products 1-2 times per week but denied any other drug use. He used propranolol 10mg tablets as needed for performance anxiety but was not taking any daily prescription or over the counter medications. His physical examination, including vital signs, HEENT, cardiac, pulmonary, abdominal and neurologic components, was normal. There was no cervical, supraclavicular, axillary or inguinal lymphadenopathy. Laboratory testing including 4th generation HIV Ag/Ab and HIV RNA PCR, Hepatitis C Antibody, Urinalysis, GFR and Liver Function Tests were unremarkable. Hepatitis B Surface Antigen and Core Antibody were negative. Hepatitis B Surface Antibody and Hepatitis A IgG were present. Chlamydia/ Gonorrhea PCR of oropharyngeal and rectal swabs and urine as well as RPR were negative. After extensive counseling on medication adherence, condom use, and need for regular clinical and laboratory monitoring, the patient was deemed an appropriate candidate for PrEP with TDF-FTC 300-200mg po Daily. He was advised to return in 1 month for follow up.

One week later, he returned with intractable nausea, vomiting and loose, watery diarrhea after starting TDF-FTC. He denied fever, chills, abdominal pain, hematochezia, and melena. Other pertinent negatives include cough, myalgias, arthralgias and lymphadenopathy. He denied sick contacts, travel and any sexual encounters since his last visit. He was well-appearing and his exam was benign. Complete blood counts, comprehensive metabolic panel and stool bacteria, clostridium difficile and parasite PCR were unremarkable. TDF-FTC was stopped and the patient's symptoms resolved over several days. He still desired PrEP and was initiated on fixed dose combination tenofovir alafenamide-emtricitabine (TAF-FTC) 25-200mg without any adverse events.

Discussion

In 2016, the global prevalence of HIV infections was about 36.7 million, including adults and children.[1] In the United States, there are approximately 1.2 million people aged 13 or older with HIV.[2] While there has been tremendous progress in the treatment of HIV, at this time, neither an effective vaccination nor a clinically feasible cure has been developed. Prior to 2012, the only method of HIV prevention was through behavioral risk reduction strategies.[3] In 2010, Grant et al. reported that PrEP reduces the transmission of HIV in patients at risk for acquiring HIV.[4] The U.S. Food and Drug Administration (FDA), in 2012, approved the fixed-dose combination of TDF-FTC as PrEP for adults at risk of sexually acquired HIV.[5] Seven years later, FDA approved TAF-FTC as PrEP for HIV prevention among cisgender men who have sex with men and transgender women (≥35kg) at risk through sex.[6] Multiple studies have shown that the efficacy of PrEP is highly dependent on adherence. When taken daily or consistently (at least 4 time per week), the risk of HIV transmission among men having sex with men (MSM) is reduced by up to 99%.[7-9] Such a reduction of HIV risk is an strong motivating factor for patient adherence.

Mechanism of Action

TDF and TAF are nucleotide analogues of adenosine monophosphate. Intracellularly, they are converted to tenofovir by

hydrolysis, and subsequently phosphorylated to the active form tenofovir diphosphate. FTC is a nucleoside analogue of cytosine, which is phosphorylated intracellularly to its active form, emtricitabine triphosphate. The above agents interfere with HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication.

Indications for PrEP

It is critical to take a thorough medical and sexual history when considering initiating PrEP. The following are acceptable indications to start PrEP with TDF-FTC in HIV uninfected individuals at risk for contracting HIV[5,10]:

- Individuals who engage in condomless sex with partners who have an unknown HIV status, untreated HIV infection or who have unsuppressed virus while on treatment for HIV
- Individuals who are involved with partners who may have multiple or anonymous sex partners
- Individuals who are involved, or have partners who are involved, in transactional sex (e.g., sex for money, food, drugs or housing)
- Individuals who engage in sexual activity at parties and other high-risk venues or have sex partners who do so
- Individuals who report use of recreational mind-altering substances during sex (including, but not limited to: alcohol, methamphetamine, cocaine, MDMA/ecstasy, cannabis products or gamma hydroxybutyrate)
- Individuals who report injecting substances or having sex partners who inject substances including but not limited to: illicit drugs, hormones or silicone
- Individuals who are receiving non-occupational Post-Exposure Prophlyaxis (nPEP) and anticipate ongoing risk or have used multiple courses of nPEP
- Individuals who are attempting to conceive with a partner who has HIV
- Individuals who have had a bacterial STI in the past 12 months
- Individuals who self-identify with being at risk without disclosing specific risk behaviors
- Individuals who request protection of PrEP even if their sex partners have an undetectable HIV viral load

TDF-FTC is the preferred regimen in all populations listed above. TAF-FTC is approved for use for PrEP to prevent sexual transmission of HIV in men who have sex with men (MSM) and transgender women who meet the above indications. It has not been studied in cis-gender heterosexual men and women or individuals who inject drugs and is not approved for PrEP in these populations.

Precautions, Warnings, and Adverse Reactions

TDF, TAF and FTC all treat HBV infection. Prior to initiation of either agent, the individual should be tested for hepatitis B as withdrawal of the drug can result in severe acute exacerbation in patients with HBV infection.[5,11] Chronic HBV infection is not an absolute contraindication to PrEP, but patients with chronic HBV infection should be closely monitored for viremia in conjunction with a liver specialist if PrEP is discontinued. It is also critical to assess the patient for the acute retroviral syndrome and screen the patient for HIV given that both TDF-FTC and TAF-FTC alone are incomplete HIV treatment regimens, and can result in HIV viral resistance. Emtricitabine and tenofovir are primarily cleared by the kidneys and TDF has been associated with both acute and chronic renal failure as well as Fanconi syndrome, which generally resolve on discontinuation of the drug. Providers must confirm that a patient's creatinine clearance is ≥60mL/min prior to starting TDF-FTC. TAF-FTC can be started in MSM and transgender women who have a confirmed creatinine clearance ≥30mL/min. In addition, lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside and nucleotide analogs, like FTC and TDF. Any symptoms or laboratory evidence consistent with lactic acidosis or hepatoxicity should result in immediate discontinuation of PrEP.

It has been shown that TDF is associated with slight decreases in bone mineral density (BMD), although the clinical significance of this is unclear. Patients should be assessed for history of osteoporosis, pathologic fractures, or osteoporosis risk factors.[12] In MSM and transgender women whose bone health is at risk or compromised, TAF-FTC is preferred as it is not associated with a significant impact on BMD, as shown in the DISCOVER trial.

TDF-FTC has not been shown to have a significant metabolic impact. However, there is some evidence that TAF-FTC may cause a mild increase in weight and dyslipidemia.[13] The clinical significance of this is unknown.

Headache, abdominal pain and decreased weight are the most commonly observed adverse effects in HIV-negative adults on TDF-FTC.[11] In HIV negative adults who are started on TAF-FTC, the most common side effect is diarrhea in greater than or equal to 5% of patients.[6] According to Glidden et al, patients on Tenofovir-based PrEP report a self-limited *start-up syndrome*, which is associated with gastrointestinal and non-gastrointestinal symptoms.[14] Those on TDF-FTC report nausea (5-19%), abdominal pain (5-13%), vomiting (4-8%), dizziness (15%) and fatigue (11%). These symptoms typically resolve with 1-3 months. Frequently, this *start-up syndrome* is mild to moderate in nature. However, in the case of our patient, it was intolerable and prohibited further adherence. Switching to TAF-FTC did not result in a significant *start-up syndrome* for this patient, and he was able to continue the daily regimen as prescribed.

Which is the Preferred PrEP Agent: TDF-FTC or TAF-FTC?

TDF-FTC is the preferred regimen for PrEP in all individuals, and TAF-FTC is an alternative in MSM and transgender women with underlying renal disease, bone mineral concerns or severe side effects. Although it received its approval for PrEP from the FDA in 2012, TDF-FTC was first approved in 2004 for treatment of HIV infection as part of multi-drug regimen. It

remained under patent until September of 2020. It is expected that generic formulations will soon become available, and will likely result in significant decreases in the cost of drug. TAF-FTC was approved for treatment of HIV in 2016 as part of a multi-drug regimen and for PrEP in 2019. At present, it remains under patent. In our clinical experience, this has already led to an increase in requests for prior authorizations for TAF-FTC for PrEP by third party payers, and an increase in denials in the absence of clear documentation of underlying renal disease, decreased bone mineral density or prohibitive side effects. It is yet to be seen what impact these changes will have to health care costs.

It is important to consider switching to an alternative PrEP agent in the setting of adverse effects, especially given the importance of adherence in this patient population. If a patient experiences a start-up syndrome with one agent, it does not necessarily indicate that they will have similar set or severity of symptoms with another PrEP agent. If the patient meets criteria for starting PrEP, it is critical to discuss the alternative PrEP agent with the patient and implement shared-decision-making regarding switching their drug regimen.

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