CLINICAL VIGNETTE

Elevated Serum Creatinine in a Patient Taking HIV Pre-exposure Prophylaxis

George C. Yen, MD and Gregory J. Lam, MD

Case

A 44-year-old male with no significant past medical history presented with an interest in HIV pre-exposure prophylaxis, PrEP. He identified gay and is sexually active with male partners. He has never been diagnosed with a sexually transmitted infection (STI), does not engage in risky behaviors such as unprotected penetrative sex and is in what he defined to be an "open-relationship" where he and his partner have also been sexually active with other men. Although he considered himself to be low risk, he wanted the "extra layer of security" of being on a medication to reduce his risk of acquiring HIV. He does not smoke, has about two to three alcoholic drinks per week in social settings and denies the use of illicit or recreational substances.

He was counseled on the potential adverse effects of emtricitabrine/tenofovir disoproxil, Truvada (TDF-FTC) which include renal insufficiency and decrease in bone mineral density.[1] He was informed TDF-FTC can reduce the risk of acquiring HIV if taken daily when used in combination with safe-sex practices, and that TDF-FTC does not reduce the risk of acquiring other viral or bacterial STIs. He would need to return every three months for risk reassessment, STI screening, HIV testing and a basic metabolic panel to screen for renal insufficiency while taking tenofovir. He agreed to follow the recommendations and after a 4th generation HIV Ag/Ab test returned as negative, he was started on TDF-FTC.

Patient took daily TDF-FTC without missing doses or noting significant adverse effects. His baseline creatinine before initiation of TDF-FTC was 1.06 mg/dl with an eGFR $\geq$ 89. At his quarterly follow-up visits, his creatinine was initially stable but increased to 1.29 mg/dl at six months and 1.33 mg/dl, nine months after starting PrEP. Repeat testing two days later confirmed renal insufficiency with serum creatinine of 1.44 mg/dl and eGFR of 59. He was not taking NSAIDS, but occasionally takes protein supplements, which was unchanged for two years before starting PrEP. He had no changes in diet or hydration and did not take other medications including herbal or other supplements. Urine output was unchanged, without hematuria, dysuria or polyuria and he had no family history of kidney disease.

He was instructed to stop TDF-FTC and three months later, he returned for follow-up. His serum creatinine improved to near baseline at 1.14 mg/dl. He was still interested in HIV pre-exposure chemoprophylaxis and was started on Emtricitabine/ Tenofovir Alafenamide, Descovy (TAF-FTC), a similar pro-drug to TDF-FTC. Patient tolerated the medication well, and had stable renal function with three-month follow-up creatinine of 1.12 mg/dl.

Discussion

More than 38,000 new HIV diagnoses in the United States were reported in 2017. This has remained stable from 2012. The incidence has remained highest in age groups 25-34 (~33%), and in Latino and African-Americans who combined make up about 2/3 of all new HIV diagnoses.

Emtricitabrine/tenofovir disoproxil, Truvada (TDF-FTC) for PrEP was approved by the FDA in July 2012 as chemoprophylaxis against sexually acquiring HIV infection. Two large clinical clinical trials demonstrated efficacy. The Partners PrEP study in Uganda and Kenya was a post-hoc case control analysis of sero-discordant heterosexual couples with detectable plasma and intracellular drug levels and reported 90% risk reduction.[2,3] The iPREX trial examined gay, bisexual and transmen in six countries and reported risk reduction of 92%.[1] As a result, clinical guidelines have recommended TDF-FTC for PrEP as a preventive option for HIV negative individuals who are at risk. This has been included in multiple US and global heath guidelines, from the CDC, WHO, ACOG, and IAS-USA (International Antiviral Society). In 2019, the United States Preventive Services Task Force, USPSTF issued a grade A recommendation that clinicians offer PrEP to persons at risk of HIV infection, included clinical risk assessment guidelines, and recommended TDF-FTC, which was the only formulation of PrEP approved by the FDA at that time. Grade A recommendations indicate there is high evidence of certainty that the net benefit of TDF-FTC for HIV prevention is substantial.[4]

According to the CDC guidelines on population candidates for PrEP use, about 1.2 million individuals are estimated to be at high risk for acquiring HIV and should be offered PrEP. According to Gilead, less than 20% of those candidates are currently on Truvada. A comprehensive sexual history should be obtained to detect substantial risk of acquiring HIV infection and this includes men who have sex with men or heterosexual women and men who have a sexual partner with HIV, a recent bacterial STD, high number of sexual partners, a history of inconsistent or no condom use or commercial sex work. Heterosexual women and men who live in high prevalence

areas or networks of HIV are also eligible as well as injection drug users.

Patients are clinically eligible to begin TDF-FTC with a documented negative 4th generation HIV Ag/Ab test, a serum creatinine clearance greater than or equal to 60, and a hepatitis B screen. If there is no documented immunity to hepatitis B, the patient should be vaccinated based on their clinical risk. Severe exacerbations of hepatitis B have been reported in HBV-infected patients who have discontinued TDF-FTC. Furthermore, if there is a clinical suspicion of acute retroviral syndrome, initiation of TDF-FTC should be held. A HIV viral nucleic acid amplification test may be helpful in these situations. In clinical trials, resistance to tenofovir or emtricitabine occurred when TDF-FTC for PrEP was given to individuals with unrecognized acute infections.

After initiation of PrEP, patients should be followed every three months for HIV testing and every 3 to 6 months for assessing renal function and screening for bacterial STI. Two pivotal randomized double blinded placebo-controlled trials in the iPREX and Partners PrEP study showed that discontinuation rates due to adverse events with TDF-FTC were comparable to placebo. For example, in the iPREX study vs placebo, headache (7% vs 6%), abdominal pain (4% vs 2%) and a decrease in weight (3% vs 2%) were common.[1,3] This syndrome called "the start-up syndrome" is often times mild, self-limiting and resolve even while continuing PrEP.[4] Frequent laboratory abnormalities in the study included an elevated serum creatinine and low serum phosphorous.

Tenofovir-associated nephrotoxicity is rare with an incidence ranging from 1% to 6%. Secondary analyses of three large PrEP trials demonstrated small but statistically significant declines in eGFR or calculated creatinine clearance in participants assigned to active PrEP.[5] The clinical significance of the declines in kidney function is unclear as most were mild and self-limited or resolved after stopping PrEP.[6,7] Given the increased risk of nephrotoxicity, patients should avoid concurrent use with nephrotoxic agents including but not limited to NSAIDS. The substantial reduction in risk of HIV infection should be weighed with the small increase in the relative and absolute risk of kidney injury with daily oral PrEP.

In addition to the risk of acute kidney injury, tenofovir has also been shown to cause Fanconi Syndrome, a rare renal disorder characterized by proximal tubular cell dysfunction. This leads to altered absorption and inappropriate urinary losses of amino acids, glucose, bicarbonate, and phosphate, resulting in hypokalemia, hypophosphatemia, and hyperchloremic metabolic acidosis.[8,9] Although baseline urinalysis is not generally recommended by expert guideline panels, a baseline and follow up urinalysis may be useful when monitoring patients on PrEP.

TDF-FTC for PrEP is not recommended for individuals with a creatinine clearance less than 60. Most expert guidelines recommend stopping TDF-FTC if estimated GFR falls below that cutoff. Until recently, there were no chemoprophylaxis options for individuals at risk for HIV with kidney dysfunction. The FDA recently approved Emtricitabine/tenofovir alafenamide, TAF-FTC, Descovy in 2019 as an additional option for PrEP. TAF-FTC is similar to TDF-FTC and can be used in patients with a CrCl greater than or equal to 30. DISCOVER, a randomized controlled trial of TAF-FTC demonstrated noninferiority in preventing HIV infection in high risk cis MSM and transgender women. Tenofovir alafenamide (TAF) is a novel prodrug with improved properties relative to tenofovir disoproxil fumarate (TDF). TAF produces higher levels of intracellular TFV diphosphate, the pharmacologically active metabolite. Effective therapy can be achieved at approximately 90% lower systemic exposure to TFV, the pharmacologically active metabolite, translating to better bone and renal safety outcomes compared with TDF-FTC. Both drugs are well tolerated with low rates of adverse events related discontinuations.[10]

Conclusion

Primary care physicians will be at the frontline in HIV prevention and should familiarize themselves with guidelines for PrEP initiation and maintenance. Descovy (TAF-FTC) is new FDA approved chemoprophylaxis option for individuals at risk for HIV infection who may not tolerate TDF-FTC, who have coexisting kidney disease or who have experienced kidney dysfunction from TDF-FTC. Guidelines for PrEP initiation are the same for both drugs. Close monitoring with HIV testing and a serum creatinine every three months is still indicated despite the improved renal and bone profiles seen in MSM or transgender men taking TAF-FTC.

Summary of Guidance for PrEP Use

	Men Who Have Sex With Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection:	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • Lives in high-prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)
Clinically eligible:	• Documented negative HIV test before prescribing PrEP • No signs/symptoms of acute HIV infection • Normal renal function, no contraindicated medications • Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doeses of TDF/FTC (Truvada), ≤90 day supply		
Other services:	• Follow-up visits at least every 3 months to provide: • HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STD symptom assessment • At 3 months and every 6 months after, assess renal function • Every 6 months test for bacterial STDs		
	• Do oral/rectal STD testing	• Assess pregnancy intent • Pregnancy test every 3 months	• Access to clean needles/ syringes and drug treatment services

Source: US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States —2014: a clinical practice guideline.

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