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Descovy: New Indication for HIV Pre-exposure Prophylaxis

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Abstract

Human Immunodeficiency Virus (HIV) is a viral infection spread by contact with bodily fluids. If untreated, it results in severe immunodeficiency and ultimately death. In the 1990's, treatments to enhance the duration and quality of life were developed, and more recently, treatments have been designed to help prevent HIV infection. Currently, there is no cure for HIV infection; therefore, prevention is key to maintaining a healthy lifestyle in high risk patients. This article features a new indication for Descovy (emtricitabine and tenofovir alafenamide), which was approved by the FDA for HIV pre-exposure prophylaxis (PrEP).

Human Immunodeficiency Virus (HIV) is a viral infection spread through contact with bodily fluids.[1] There is no cure for HIV, although there are many treatment and prevention options. HIV, if not treated, can lead to Acquired Immunodeficiency Syndrome (AIDS). AIDS develops as a result of the HIV infection which reduces the number of CD4 T cells in the body, which causes an immunodeficiency. This lowers the individual's ability to fight off infections. Opportunistic infections and/or cancer can result from the bodies reduced ability to fight off infection.[1]

HIV exposure causes include unprotected sexual intercourse or sharing needles with an infected partner, mother to child during vaginal birth, and least commonly through blood transfusion.[1] Similarly, people at higher risk for contracting HIV include individuals who have unprotected anal sex, patients who participate in intravenous drug use sharing needles, uncircumcised heterosexual men, and people who have a sexually transmitted infection (STI) with open sores, allowing easier access for HIV to enter the body.[2]

Signs and symptoms vary within the different stages of HIV infection. Common signs when someone is initially infected (acute phase) include fever, headache, muscle/joint pain, rash, swollen lymph nodes, sore throat or painful mouth sores. If these symptoms are reported, the patient should be tested for HIV infection.[2]

Although there is currently no cure, there are treatments that when taken correctly, can decrease a person's HIV viral load to an undetectable level in their blood.[3] These HIV treatments are abbreviated "ART" which stands for antiretroviral therapy. According to the 2019 update from AIDS info and the National Institute of Health, it is recommended that ART therapy should be started immediately after diagnosis, on the same day if possible.[3] There are many first line treatment regimens which consist mostly of integrase inhibitors and reverse transcriptase inhibitors. These drugs work to inhibit the integration of the viral genome into the human genome and reverse transcription of the RNA to DNA, which is the mechanism that HIV uses to infect humans and cause immunodeficiency.[3] Treating HIV positive patients and getting their viral load to an undetectable level is a very effective way of preventing the spread of the infection.

There are multiple other methods for preventing the spread of HIV including abstinence, correct condom usage, and prophylactic drug therapy. Pre-exposure prophylaxis (PrEP) with Truvada (emtricitabine and tenofovir disoproxil fumarate) and the more recently approved, Descovy (emtricitabine and tenofovir alafenamide), are indicated for people who are HIV negative but at high risk of contracting the virus.[1] These individuals should take PrEP daily to reduce the risk of infection. PrEP should be combined with the

previously mentioned prevention methods for maximal reduction of risk.[1]

According to the 2017 CDC Pre-exposure Prophylaxis for the prevention of HIV guidelines, Truvada is the recommended first line therapy.[4] Truvada consists of two antiretroviral medications combined into one pill. These two medications and their strengths are emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg. The dosing is once daily for Truvada, and common side effects include nausea, flatulence, rash, and headache.[4] Adverse effects of Truvada include decreased bone mineral density and renal toxicity.[5] While on Truvada, it is recommended to assess the patient at least every three months for HIV infection.[4] This is due to the fact that if an individual does get infected, the drug should be discontinued to reduce the risk of resistance and anti-retroviral treatment therapy should be initiated.[4] Renal function should be assessed at three months, then every six months after due to the risk of nephrotoxicity. STI testing should also be completed at least every six months for sexually active individuals who are asymptomatic due to these patients being at high risk of contracting a STI.[4]

On October 3rd, 2019, the Food and Drug Administration (FDA) approved Descovy for PrEP.[6] Descovy has been on the market (originally approved in 2016) for HIV treatment. However, it was recently approved for a new indication, which makes it only the second drug to be approved for PrEP.[6] The study that led to the approval of Descovy for PrEP is the DISCOVER trial. Gilead Sciences is sponsoring the clinical trial to evaluate both safety and efficacy of Descovy as a daily oral HIV PrEP medication in comparison to Truvada.[7] The trial was a randomized (1:1), double blind, and active-controlled study that was carried out in North America and Europe. The study included 5000 participants, which looked at men and transgender women who have sex with men. Each participant ingested two pills: either Truvada or Descovy and one placebo look-alike pill for the medication they were not receiving.[7] Although the study is not scheduled to be complete until September 2021, the preliminary data demonstrated Descovy to be noninferior to Truvada in regard to efficacy, which led to its approval by the FDA for PrEP.[8] Given that this is preliminary data, limitations have not been well defined. A potential limitation is that this study only looked at men and transgender women, leading to the drug only being approved for this population. However, since this is only preliminary data and the study is not complete, we cannot be sure that they are not investigating this drug in other populations.

Descovy contains a different salt form of tenofovir (TFV), tenofovir alafenamide (TAF) as compared to Truvada, which contains tenofovir disoproxil fumarate (TDF).[9] TAF is a second-generation analog of TFV that is potentially less nephrotoxic based on its metabolism. The first-generation TFV molecule, TDF, undergoes rapid

metabolism in the plasma after oral administration. Subsequently, TFV is brought intracellularly and phosphorylated into its active molecule.[9] Due to the high rate of metabolism, higher dosing of TDF is required for the molecule to be internalized into the cells and be effective. TAF does not undergo rapid metabolism in the plasma allowing more drug to be brought intracellularly and activated into the active metabolite. Comparing the plasma concentrations of patients taking TDF or TAF, TAF was 91% lower and delivered 5.3 times as much TFV intracellularly.[7] Limiting plasma degradation of TFV allows there to be a 30-fold reduction in dosing which is hypothesized to be why there are fewer renal side effects and end organ damage reported.[9]

In a randomized phase 2 study published by Sax P et al. on September 1st, 2014, TAF showed similar viral replication suppression in infected individuals while having an improved renal safety profile compared to TDF.[9] In this study, 170 patients in total received treatment, 58 received TDF while 112 were treated with TAF.[9] Sax P. et al also reported less changes in the median serum creatinine in patients on TAF versus TDF however, these changes were not statistically significant. Significant changes were seen in renal tubular proteinuria/creatinine ratio with patients on TDF compared to TAF. Additionally, changes in bone mineral density were seen significantly less in patients on TAF compared to TDF.[9]

In conclusion, Descovy has been approved by the FDA for PrEP only in men and transgender women. However, these changes are not reflected in the most recent PrEP guidelines by the CDC in 2017. Currently, the recommended dosing of Descovy for PrEP is emtricitabine 200mg and tenofovir alafenamide 25mg once daily compared to the recommended dose of Truvada, emtricitabine 200mg and tenofovir disoproxil fumarate 300 mg once daily. [5] Based on the research that is available, TAF, the salt form of tenofovir in Descovy, may be safer for patients compared to TDF in Truvada, the current recommended therapy. Descovy may be a useful agent in the future that could impact future guideline updates.

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