



## ***PrEP Today and Tomorrow: On-Demand, Injections and Topicals***

### **Daily Oral PrEP using TDF/FTC**

Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy in which HIV-negative individuals take antiretroviral medications to reduce their risk of acquiring HIV. In 2012, the U.S. Food and Drug Administration (FDA) approved the first-ever drug combination for use as PrEP—a once daily oral formulation of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC<sup>1</sup>; commonly referred to by its brand name Truvada®, Gilead Sciences). Daily oral PrEP using TDF/FTC has been shown to reduce the risk of acquiring HIV from sex by up to 99%. Among people who inject drugs, daily oral PrEP reduces the risk of acquiring HIV by approximately 74% [1].

However, despite robust efforts to educate vulnerable populations and improve access to PrEP, uptake of this HIV prevention strategy remains low in California and across the country [2]. A recent analysis from the U.S. Centers for Disease Control and Prevention (CDC) found that an estimated 1.2 million people have indications for PrEP, but only 18.1% of these individuals were prescribed PrEP in 2018 [3]. In addition, prior research has documented disparities in PrEP uptake by race/ethnicity, gender and geography [2].

Given the low uptake of daily oral PrEP, exploration of safe alternative agents (e.g. medications) and alternative modalities to deliver PrEP (e.g. alternative dosing, injectables, topical agents, and long-acting treatment) are integral to address PrEP disparities moving forward [4]. The purpose of this brief is to provide an overview of existing and future PrEP agents and modalities.

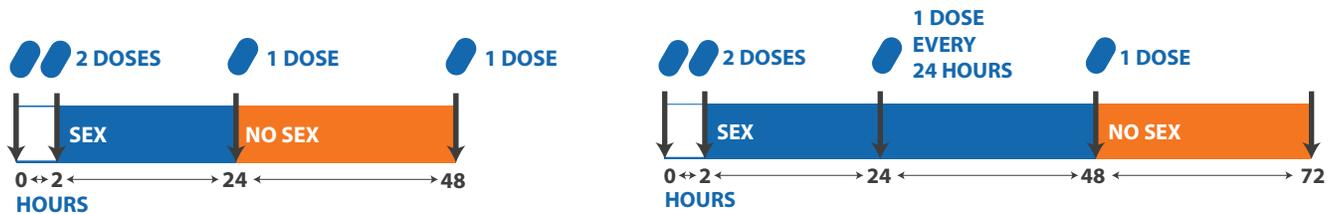
### **2-1-1 PrEP for Anal Sex using TDF/FTC**

“On-demand” PrEP – also known as 2-1-1 PrEP– is an alternative dosing strategy in which an individual takes oral TDF/FTC only before and after sex. On-demand dosing involves taking a double dose of TDF/FTC (two pills) anywhere from 2 to 24 hours before anticipated sex, and then, if sex happens, one tablet at 24 and 48 hours after the double dose. Hence the name 2-1-1 PrEP. If sex occurs several days in a row, one pill daily is continued until 48 hours after the last sexual encounter.

In a large randomized clinical trial among men who have sex with men (MSM), 2-1-1 PrEP showed to be an effective alternative to daily oral PrEP. Additional data are needed to determine if 2-1-1 PrEP works for people having vaginal sex. On-demand dosing is currently supported by guidelines of the European AIDS Clinical

<sup>1</sup>While brand names of the medications will be used here for recognition purposes, it should be noted that generic versions of these drugs will become available shortly. Thus, other companies producing these medications will not be using the same brand name.

Society as well as the national bodies in the United Kingdom, France, Canada, and Australia. In 2018, the International Antiviral Society-USA Panel (IAS-USA) also endorsed on-demand PrEP for gay and bisexual men, highlighting additional benefits related to potential cost-savings, especially for individuals who engage in infrequent sex [5,6,7]. The IAS-USA does not recommend this alternative dosing strategy for other populations due to a lack of data and daily PrEP using TDF/FTC continues to be the only dosing strategy currently recommended by the CDC [8]. 2-1-1 PrEP offers an important option for people who have less frequent anal sex or for people who are unable or prefer not to take daily PrEP, but are able to anticipate or plan their sexual activity.



## TAF/FTC PrEP

In October 2019, the FDA approved the second drug combination for use as PrEP – a once daily formulation of tenofovir alafenamide and emtricitabine (TAF/FTC; commonly referred to by its brand name Descovy®, Gilead Sciences). TAF/FTC was approved for all routes to exposure other than vaginal exposure. At the time of regulatory approval, the FDA requested that supportive data for vaginal protection from carefully conducted clinical trials be submitted by 2025.

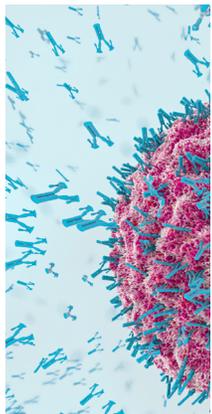
In the DISCOVER study, a randomized, active controlled study of TDF/FTC vs. TAF/FTC for HIV prevention in men who have sex with men (MSM) and transgender women (TGW), sensitive research markers of kidney function and bone densitometry (DXA scanning) suggest an improved safety profile for TAF/FTC in terms of kidney and bone health out to 96 weeks of follow-up; however the clinical significance of these changes remains unclear. TAF/FTC may offer an important PrEP alternative for individuals who have compromised kidney function, bone health issues, or who have side effects on TDF/FTC. However, TAF/FTC causes more weight gain in people taking it for PrEP or in combination with other drugs for HIV treatment than does TDF/FTC. Also, TAF/FTC treatment results in greater increases in LDL cholesterol compared to those taking TDF/FTC. Importantly, TAF/FTC was similarly effective as TDF/FTC in preventing HIV infection – but was not superior. TDF/FTC remains the preferred agent for PrEP in all clinical guidelines. Additionally, there have been no studies of 2-1-1 PrEP using Descovy®, so people preferring 2-1-1 dosing should continue using TDF/FTC exclusively. There are no data currently available for non-daily use of other PrEP agents. TDF/FTC is expected to be available as a generic formulation in 2020, at which point, TDF/FTC, an extremely safe and effective PrEP medication, will also have significant cost-effectiveness advantages.

## PrEP Tomorrow



### Long-acting injectable drugs

Long-acting medicines are medications that can be taken less frequently than on a daily basis. Injectables are medications that are taken as shots. Long-acting injectables have the potential to prevent HIV infection without relying on taking a pill every day. Cabotegravir is currently in development for HIV prevention (PrEP) as a long acting injectable medication.



### Antibodies

Antibodies are a type of protein that help the body fight infections and disease. Broadly Neutralizing Antibodies (bNAbs) are a type of antibody that can recognize and block many types of HIV from entering healthy cells. These bNAbs are being “engineered” from individuals who have unusually delayed HIV disease progression including those who have undetectable viral loads despite the absence of any treatment. Studies are still ongoing, but bNAbs are expected to have favorable safety outcomes and allow for longer periods of time between doses, potentially improving overall adherence [9]. The majority of bNAbs require intravenous administration, but studies now are testing subcutaneous injection where a short needle is used to inject the medicine under the skin.



### Vaginal rings

The vaginal rings currently in advanced development are inserted every four weeks and provide a sustained and controlled release of an antiviral drug (dapivirine) over time. Efficacy appears in the 30-50% range [10]. Vaginal rings are currently under review at the European Medicines Agency (EMA), and longer lasting formulations and formulations that include hormonal contraceptives in the same ring are in development.



### Other topical PrEP agents

Topical microbicide gels contain an antiretroviral medication that is applied to either the vagina or rectum in either on-demand or daily dosing strategies. Topical gels may be preferred because they can be dosed intermittently, can act as a lubricant during sex, may be more discreet and have different side effects when compared to oral PrEP. However, the drawback of topical gels is that they only provide protection where they are applied.



### Subdermal implants

Subdermal implants work like implanted hormonal contraception rods, providing a sustained and controlled release of drugs. These implants may work towards improving adherence while providing a longer duration of protection when compared to oral PrEP products. Unlike long-acting injectables, implants can be removed in case of side effects. Nevertheless, implants are more expensive to manufacture and require a minor surgical procedure to insert and, in many cases, to remove [12]. These are in clinical development for PrEP.



### Transdermal drug-delivery systems

Transdermal solutions, gels, and patches aim to provide a sustained and controlled release of drugs from the skin into the body. These routes of delivery can prove useful in overcoming many barriers people may face in taking oral (pill) medication. Transdermal patches have not yet begun human trials, but are currently in the early stages of exploration [13].

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