



4-1-2019

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### **Recommended Citation**

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**Pre-exposure prophylaxis as a prevention strategy for HIV seroconversion in the men who have sex with men population with comparison of its effectiveness in other at-risk groups**

By

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Capstone Project

Submitted to the Faculty of the

Department of Physician Assistant Education

of University of the Pacific

in partial fulfilment of the requirements

for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

April, 2019

**Abstract**

Since the beginning of the United States AIDS epidemic in the early 1980s, the medical community has overcome significant challenges in the diagnosis and treatment of Human Immunodeficiency Virus (HIV) infections. Many advancements in suppressing HIV viral loads and maintaining healthy immune system function in HIV positive patients have been achieved with antiretroviral therapy (ART). Moreover, these drugs have been shown to be effective for preventing HIV infections. Once-daily Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) has been approved by the FDA for this purpose. The availability of this preventive therapy, commonly known as preexposure prophylaxis (PrEP), necessitates educating at-risk patient populations about its prophylactic benefits. In order to select appropriate candidates for PrEP prophylaxis, its efficacy in different at-risk populations needs to be determined. This investigation examines disparities in PrEP's efficacy among at-risk groups and proposes explanations that may guide the medical provider in offering PrEP therapy to patients who could benefit. Additionally, current clinical trials and studies with alternative PrEP options will be explored.

Keywords: HIV, HIV pre-exposure prophylaxis, HIV prevention, PrEP

## Introduction

According to the CDC's 2015 HIV surveillance data, in the United States approximately 40,000 individuals seroconverted to an HIV positive status and the prevalence of HIV reached nearly 1 million people. Notwithstanding this staggering number, the percentage of individuals who became HIV seropositive declined by eight percent from the years 2010 to 2015.<sup>1</sup> Improved preventative and therapeutic measures have played a pivotal role in reducing HIV seroconversion and infections. Despite advancements in HIV treatment and prevention, preventative strategies including preexposure prophylaxis (PrEP) are underutilized across many medical settings. Of particular concern are the stigma surrounding potential HIV exposures and the lack of awareness about PrEP, both of which can impede the clinician's efforts to educate patients who are at high risk of HIV seroconversion.

In order to select candidates for prevention of HIV seroconversion, persons at increased risk of HIV exposure need to be identified. According to the CDC, gay and bisexual men account for 67% of the approximately 40,324 new HIV diagnoses made in the United States in 2016.<sup>2</sup> Furthermore, receptive anal intercourse has a 13-fold higher risk of transmitting HIV than insertive anal intercourse.<sup>3</sup> Although male-to-male sexual contact puts gay and bisexual men as the population at the highest risk of HIV seroconversion, other populations such as heterosexuals, serodiscordant couples, and IV drug users are also at increased risk. Unprotected receptive anal intercourse accounts for approximately 138 infections per 10,000 exposures, but needle-sharing injection drug use accounts for approximately 63 infections per 10,000 exposures, while receptive and insertive penile-vaginal intercourse each account for 8 infections and 4 infections per 10,000 exposures respectively.<sup>5</sup> All of these high-risk populations may benefit from preventative measures against HIV seroconversion. Therefore, medical providers should counsel patients

accordingly. Besides educating patients about safe-sex practices, clinicians can offer preexposure prophylaxis with anti-retroviral agents.

Antiretrovirals (ARV) have been shown to suppress HIV viral loads, which results in viable CD4 T-lymphocyte counts and healthy immune system function in HIV infected patients. In addition, when used prophylactically these medications have been shown to prevent HIV infection in high-risk individuals. Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) was initially approved in 2004 by the Food and Drug Administration (FDA) to be used in combination with other ARVs in an HIV treatment regimen.<sup>4</sup> After its success in HIV therapy was demonstrated, this formulation of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) was studied and approved by the FDA on July 16<sup>th</sup>, 2012 for preexposure prophylaxis (PrEP) treatment in HIV negative patients who are at high risk of HIV seroconversion.<sup>3</sup> When taken appropriately, PrEP was shown to be effective for prevention of HIV seroconversion in at-risk populations. Experience with PrEP has primarily been in the men who have sex with men (MSM) population. Although PrEP's overall efficacy in at-risk patients has been proven, further investigation is needed to show its usefulness in specific at-risk groups such as heterosexuals, IV drug users, and serodiscordant couples. In order to optimize PrEP's effectiveness, it is important to understand its potential benefits and limitations across all at-risk populations.

### **Animal Studies and Pharmacokinetics**

Initial studies in animals and humans using tenofovir disoproxil fumarate (TDF) showed that a single ARV was inadequate for prophylactic protection,<sup>6-7</sup> although it did have a good safety profile in humans. The need for two drug combinations for HIV prophylaxis was evident since a single ARV was ineffective.

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The hypothesis of utilizing a two-drug regimen for HIV prophylaxis was promising and thus further explored in animal models. Chinese rhesus macaques were challenged with simian HIV to determine if using a two-drug combination compared to a single drug agent or no drug at all had a better prophylactic effect against HIV transmission. These monkeys were either untreated (control group) or treated; the treatment groups received tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), or a compounded TDF-FTC. The results revealed that monkeys treated with a subcutaneous dose of FTC or a human equivalent dose of TDF-FTC, had a 3.8- and 7.8-fold decreases in seroconversion rates respectively, compared to the untreated monkeys.<sup>8</sup> This evidence confirmed that two agents provided better prophylaxis than either a single agent or no ARV.

Success of the two-drug regimen in animals prompted human trials. The pharmacokinetic profiles of ARVs in humans, in particular, their tissue penetrance, are especially important with regards to using these drugs as a prophylactic option because some human tissues are exceptionally vulnerable to transmission of HIV. In 2011, male and female volunteers were studied to determine the concentrations of TDF and FTC in blood plasma as well as in mucosal tissues, particularly in vulnerable tissues like rectal and vaginal mucosa. Despite a small sample size, 100-fold higher concentrations of TDF were found in rectal tissues compared to vaginal/cervical tissues.<sup>9</sup> Given these results, PrEP use in certain groups may be more or less effective depending upon the tissue exposed to the virus. After pharmacokinetic studies, PrEP research shifted to human participants for FDA approval.

PrEP was approved after many noteworthy studies examined its safety and efficacy for preventing HIV infection in groups that are at particularly high risk of HIV seroconversion, such as the MSM population, transgender women who have sex with men, high-risk heterosexual men

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and women, and IV drug users. Clinical studies were necessary to determine PrEP's efficacy across these at-risk groups.

### **Men Who Have Sex with Men and PrEP: iPrEx Trial, ANRS Ipergay Study, PROUD study**

A multinational, double-blind placebo-controlled known as the Preexposure Prophylaxis Initiative, or the iPrEx trial, evaluated whether a once-daily compounded regimen of TDF-FTC would provide adequate chemoprophylactic protection against HIV in the MSM and transgender women who have sex with men populations. A total of 2499 HIV seronegative MSM and transgendered women who have sex with men were assigned to either the treatment group with TDF-FTC, or the placebo-control group. A comprehensive package of protection was also provided to these patients through monthly visits. These visits included information on safe-sex practices, condoms, HIV testing, and treatment of other STIs. Serum drug levels were also measured in each of the subjects to determine adherence. The subjects were followed for a total of 3324 person-years. Results showed a 44% reduction in HIV seroconversion in the treatment group compared to placebo. Although this value was lower than what the researchers predicted, the discrepancy was partly explained by low adherence. In the subjects who had detectable serum drug levels, risk of HIV seroconversion decreased by 92% compared to those subjects with poor or undetectable levels who evidently did not adhere properly to the drug regimen. These findings highlighted that PrEP compliance correlates with higher efficacy of the intended prophylactic effect.<sup>10</sup>

Given the importance of adherence to PrEP, a study to address PrEP's efficacy with on-demand use rather than once daily dosing was conducted. The ANRS Ipergay study examined whether using PrEP on-demand, which means taking the drugs only as needed for risky sexual behaviors, would still provide prophylactic protection in the MSM cohort. In this double-blind,

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randomized placebo-controlled study, on-demand use conditions were met when the treatment group took two doses of TDF-FTC 2 to 24 hours prior to sexual contact, and then took additional doses at 24 and 48 hours after the sexual contact. Risk was reduced by 86% in the treatment group compared to the placebo group.<sup>11</sup> Although these findings were promising, they were limited because the number of on-demand doses taken could not exceed the maximum total daily dose regardless of the number of sexual encounters in a day. An open-label study approximating real-life application of PrEP could correct this limitation.

PROUD was the first open-label, randomized controlled trial for PrEP, which was designed to test efficacy in real-life situations in the MSM population. Five hundred and forty-four male participants who had condom-less anal intercourse in the previous 90 days were enrolled in the study across 13 sexual health clinics in England. Initially, the study called for an immediate treatment group and a deferred treatment group, but all of those assigned to the deferred group were eventually moved to the treatment group after evidence in concurrent studies showed PrEP to be efficacious in HIV prevention. Findings confirmed that daily TDF-FTC provided the best protection against HIV seroconversion, eliminating the concerns of PrEP utilization in the MSM population in real-world settings.<sup>12</sup>

While PrEP is effective in MSM, the population at the highest risk of seroconversion, other populations are also at risk, such as heterosexuals and IV drug users. These groups could potentially benefit from PrEP, leading to additional research with PrEP in these patient populations.

### **Heterosexuals and PrEP: Partners PrEP Trial, TDF2 Study, and FEM-PrEP Study**

The Partners PrEP Trial addressed the use of antiretroviral therapy (ART) for preventing HIV in heterosexual serodiscordant couples, otherwise known as discordant serostatus, which



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means one partner was HIV positive and the other is HIV negative. A sample of 4747 couples was enrolled and then randomly assigned to treatment with TDF, TDF-FTC, or placebo. Seroconversion occurred in a total of 82 subjects. 17 subjects seroconverted in the TDF group, 13 in the TDF-FTC group, and 52 in the placebo group, equating to a 67% and 75% decrease in incidence of HIV seroconversion in the TDF and TDF-FTC groups, respectively.<sup>13</sup> These results were promising; however, further studies were needed in order to confirm that these prophylactic treatments were efficacious in this group.

Additional research in sexually active heterosexuals at risk for HIV seroconversion was assessed in the TDF2 study. This phase III, randomized, placebo-controlled clinical trial was conducted in different cities in Botswana, which has the world's second highest HIV seroconversion rate.<sup>14</sup> This trial randomly selected 1219 men and women to be assigned to either the TDF-FTC treatment group or to the placebo group. Unfortunately, due to poor retention of the subjects, it was stopped early. The researchers decided to perform a modified analysis of the data they obtained, which showed an overall efficacy of 62.2% of TDF-FTC in preventing HIV seroconversion when used in conjunction with a package of other HIV prevention tools.<sup>14</sup> Despite the poor subject retention, evidence in this study suggests that PrEP is effective. Nonetheless, further studies are necessary to confirm these findings.

Since previous studies did not show successful HIV prevention in at-risk heterosexual women, the 2012 FEM-PrEP study specifically tested PrEP's efficacy in this population. Across Kenya, South Africa, and Tanzania, 2129 women were enrolled. These women were randomly assigned to receive once daily TDF-FTC (the treatment group), or a once daily placebo (the control group). HIV seroconversion was detected in 33 women in the TDF-FTC group and in 35 women in the placebo group, with an incidence rate of 4.7% and 5.0% respectively<sup>15</sup>. This study was also

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terminated early because PrEP was not proven to be efficacious in preventing HIV infection in these women. The data did not show efficacy in once daily FTC-TDF, but detectable serum drug levels were only present 28% to 37% at the time the specimens were collected, revealing that a lack of adherence may have explained the lack of efficacy. Although adherence to prophylaxis is vital for prevention, the pharmacokinetics of TDF-FTC limit drug concentrations in vaginal and cervical tissues as compared to rectal tissues. This discrepancy in tissue drug concentration must be considered when determining whether PrEP is appropriate for use in heterosexual females who engage in unprotected coitus.

### **IV Drug Users and PrEP: The Bangkok Tenofovir Study**

Though sexual transmission of HIV is of utmost concern, intravenous drug use and needle sharing put individuals at high-risk of HIV seroconversion. According to the Center for Disease Control, people who injected drugs (PWID) accounted for 9% of the nearly 40,000 new HIV diagnoses in 2016.<sup>16</sup> Even though this group accounts for a smaller percentage of new HIV diagnoses, PrEP could still serve as a beneficial strategy. The 2013 Bangkok Tenofovir study, a phase III, randomized, double-blind, placebo-controlled trial examined whether PrEP would reduce the risk of HIV seroconversion in PWID. The 2413 participants were enrolled across 17 drug-treatment clinics in Bangkok, Thailand; 1204 participants in the treatment group were instructed to take 300mg of once daily tenofovir disoproxil fumarate (TDF), and 1209 participants belonged in the placebo control group. Seventeen subjects in the TDF group seroconverted to an HIV positive status, while 33 seroconverted in the placebo-control group, equating to a 48.9% reduction in HIV incidence.<sup>17</sup> Whether those that seroconverted did so from their IV drug use or from sexual intercourse was a limitation of this study. Nonetheless, PWID are at significant risk of seroconverting and PrEP should be offered to this population.

### **Side Effects and Adverse Events of PrEP**

Currently, Once-daily Truvada® (emtricitabine/tenofovir disoproxil fumarate) is approved for the use of PrEP in high-risk patients. In the iPrEx study, nausea was reported in 22 patients in the treatment group compared to 10 patients in the placebo group. Additionally, unintentional weight loss of 5% or more was seen in 34 versus 19 patients of the treatment and placebo groups respectively<sup>10</sup>. However, in the Partners PrEP trial no statistical differences were found in side effects including fatigue, nausea, abdominal pain, headaches, or diarrhea<sup>13</sup>. Future research may find drugs for HIV prophylaxis that have fewer side effects. Nonetheless, PrEP currently has only limited and mostly mild adverse effects in comparison to the protective value it provides. When prescribing PrEP, not only is understanding its side effects and adverse events important in providing the proper patient education but also specific precautions should be considered.

Severe adverse reactions can occur with PrEP, for which reason cautionary measures should be instituted. Truvada®, which contains tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), requires evaluation of a patient's renal function before and during therapy. TDF is excreted extensively by the kidneys and can be nephrotoxic. Poor renal function could lead to toxic levels of the drug. Serum creatinine values can be used to determine whether a patient is an appropriate candidate for PrEP and should be monitored periodically throughout therapy.<sup>18</sup> In the iPrEx trial, only one subject was dropped from the study due to an increase in serum creatinine compared to no dropouts in the placebo group.<sup>10</sup> In the Partners PrEP trial, six subjects were dropped from the study due to an increase in their serum creatinine compared to no dropouts in the placebo group.<sup>13</sup>

Another adverse reaction of TDF is loss of bone mineral density (BMD). Over the course of a year's therapy, TDF can cause a 1-3% decreased in BMD compared to other NRTIs.<sup>19</sup> In the

iPrEx trial, 13% of the participants lost more than 5% BMD of the spine compared to 6% of the participants in the placebo group.<sup>10</sup> Bone fractures were noted in 1.7% of the treatment group in the iPrEx trial compared to 1.4% in the placebo group.<sup>10</sup> In the Partners PrEP trial, 0.8% of the treatment group experienced bone fractures compared to 0.6% in the placebo group.<sup>13</sup> Although BMD is affected, the benefits of PrEP exceed these relatively insignificant changes. Nonetheless, this adverse effect should be taken into consideration for those with small stature or preexisting osteomalacia.

Despite the current adverse effects of PrEP on the kidneys and bone mineral density, healthy individuals typically tolerate the regimen well and do not require discontinuation due to these adverse effects. Other antiretrovirals and regimens are being investigated for the purpose of limiting the number of adverse events and removing the daily pill burden while still providing prophylactic HIV protection.

### **The Future of PrEP**

Descovy<sup>®</sup> (emtricitabine/tenofovir alafenamide fumarate) is currently FDA approved for the treatment of HIV. Similar to Truvada<sup>®</sup>, it contains two NRTIs and should be used in combination with other HIV medications to achieve viral suppression and maintain healthy CD4 counts. The differences between the two antiretrovirals are that Descovy<sup>®</sup> contains the NRTI known as tenofovir alafenamide fumarate (TAF) and Truvada<sup>®</sup> contains an NRTI known as tenofovir disproxil fumarate (TDF). Compared to TDF, TAF has less adverse renal effects and leads to less bone mineral density loss.<sup>19</sup> Given that less adverse effects are observed with Descovy<sup>®</sup> compared to Truvada<sup>®</sup>, the DISCOVER study was initiated to determine if Descovy<sup>®</sup> could provide prophylactic protection similar to Truvada<sup>®</sup>.

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DISCOVER, a current phase III randomized double-blind study that began in September 2016, is comparing Descovy<sup>®</sup> against Truvada<sup>®</sup> for safety and efficacy in preventing HIV seroconversion in the MSM population. This study has 5400 participants who were randomized into a group that is either being treated with Truvada<sup>®</sup> (TDF-FTC) plus a placebo pill or treated with Descovy<sup>®</sup> (TAF-FTC) plus a placebo pill<sup>20</sup>. The participants will be blinded for at least 96 weeks, after which they will have the option to be unblinded and decide whether to continue in an open label extension of the Descovy<sup>®</sup> regimen for another 48 weeks. HIV status, bone mineral density, serum creatinine, and side effects that the subjects experience will be monitored. This trial is expected to be completed in July of 2021. If proven to be efficacious, Descovy<sup>®</sup> could be the new first-line therapy for PrEP. However, it still bears the pill-burden of a once-daily regimen.

In order to improve medication adherence issues and decrease overall pill burden, other routes of PrEP administration are being investigated. Injectable routes of administering PrEP using Cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), are being tested. CAB showed excellent safety, tolerability, and acceptable pharmacokinetics in the HPTN 077 trial, a phase 2a clinical trial to assess the safety and efficacy of the injectable long-acting CAB.<sup>21</sup> Common side effects in this study were a mild injection site reaction which caused some patients to drop out of the study. The drug reached the appropriate drug levels in the treatment group that received an injectable regimen of 600mg every 8 weeks after an initial 4 week loading dose<sup>21</sup>. Currently, the HPTN 083 trial is underway that is comparing injectable CAB to the currently FDA approved PrEP, oral Truvada<sup>®</sup>, in the MSM population.<sup>22</sup> Recruitment for this study is currently ongoing and its completion date is yet to be determined. If the injectable CAB is proven to be as efficacious as Truvada<sup>®</sup>, it could become an option for at-risk individuals, especially those who have difficulty with adhering to a daily regimen.

### **Conclusion**

Evidence shows that Truvada<sup>®</sup> for PrEP is efficacious if used in high-risk populations for preventing HIV seroconversion, particularly in the MSM population. Although some studies did not confirm its efficacy, a lack of adherence to PrEP could have explained the low prophylactic effect. Less efficacy in certain populations, such as heterosexual women, may be explained by a combination of noncompliance and also by the difference in tissue concentrations of PrEP. For these reasons, the importance of adherence should be stressed when prescribing PrEP. Despite the facts that PrEP is new to the medical community and its long-term efficacy is still being investigated, it should be considered as part of the preventative package offered to at-risk populations. In the future, research could reveal alternative drug options that would likely improve patient's adherence to PrEP and could offer drugs with less adverse effects than those in the currently approved regimen.

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