Is Emtricitabine-Tenofovir Disoproxil Fumarate Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection Safer Than Aspirin?

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Background. The safety and effectiveness studies of emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) for human immunodeficiency virus (HIV) infection pre-exposure prophylaxis (PrEP) in men and women showed that daily use reduced the risk of HIV acquisition, but there still may concerns about safety.

Methods. A narrative review was done in September 2015 comparing the 5 major studies on PrEP for HIV infection—Pre-exposure Prophylaxis Initiative (N = 2499; 3324 person-years), Partners Preexposure Prophylaxis (N = 4747; 7830 person-years), TDF2 (N = 1219; 1563 person-years), Preexposure Prophylaxis Trial for HIV Prevention among African Women (N = 2056; 1407 person-years), and Vaginal and Oral Interventions to Control the Epidemic (N = 4969; 5509 person-years)—and the 2 major studies on aspirin safety—Physicians’ Health Study (N = 22 071; over 110 000 person-years) and the Women’s Health Study (N = 39 876; approximately 400 000 person-years). The numbers needed to harm (NNH) were calculated for FTC-TDF for HIV infection PrEP and aspirin.

Results. The NNH for FTC-TDF in men who have sex with men and transgender women was 114 for nausea and 96 for unintentional weight loss; in heterosexual couples, the NNH was 68 for moderate decreased absolute neutrophil count. For aspirin, the NNH was 909 for major gastrointestinal bleeding, 123 for any gastrointestinal bleeding, and 15 for any bleeding problems in men. In women, the NNH for easy bruising was 10.

Conclusions. We conclude that FTC-TDF for PrEP for HIV infection favorably compares with aspirin in terms of user safety. Although long-term studies are needed, providers should feel reassured about the safety of short- and medium-term PrEP for HIV infection with FTC-TDF.

Keywords. emtricitabine-tenofovir disoproxil fumarate; HIV; PrEP.

In July 2012, the US Food and Drug Administration (FDA) approved a once-daily oral emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) tablet as combination therapy (FTC-TDF) for pre-exposure prophylaxis (PrEP) to prevent human immunodeficiency virus (HIV) acquisition [1]. The safety and effectiveness of FTC-TDF for HIV PrEP in men and women was reported in several studies and showed that daily use reduced the risk of HIV acquisition, a profound achievement in HIV prevention [2–4]. For example, in the Pre-exposure Prophylaxis Initiative (iPrEx) trial, it was reported that among men who have sex with men (MSM) and transgender women (N = 2499; 3324 person-years), PrEP reduced the incidence of HIV acquisition by 44% [3]. Although 44% might not seem high, that analysis was done conservatively by intention-to-treat, whereas an analysis restricted to those with adequate blood levels of medication showed a 92% reduction in HIV acquisition [3].

In another study, Partners Preexposure Prophylaxis (Partners PrEP; N = 4747; 7830 person-years), Baeten et al [2] reported on the effectiveness of antiretroviral prophylaxis for HIV prevention in heterosexual couples. When comparing the rate of acquisition among HIV-1 serodiscordant, heterosexual couples taking oral TDF and FTC-TDF with those taking a placebo, it was found that oral TDF and FTC-TDF reduced the rate of HIV acquisition by 67% and 75%, respectively [2]. Among women, the effectiveness of TDF was 71% and 61% for FTC-TDF [2]. Furthermore, Thigpen et al [4] in the TDF2 study observed 1219 heterosexuals (1563 person-years) and found that FTC-TDF conferred a 62% protective effect. Although other studies of tenofovir-based PrEP for HIV infection in women did not find reduced rates of HIV acquisition among those allocated to the active medication, such as Van Damme et al’s [5] study, Preexposure Prophylaxis Trial for HIV Prevention among African Women (FEM-PrEP; N = 2056; 1407 person-years), and Marrazzo et al’s [6] study, Vaginal and Oral Interventions to Control the Epidemic (VOICE; N = 4969; 5509
person-years), the low adherence to medications for PrEP likely explains the lack of effectiveness seen in the trials mentioned.

With the potential increased use of FTC-TDF for prevention of HIV infection, there is the potential that it could have a large impact on the HIV epidemic if use were brought to scale. However, for scale-up of FTC-TDF for the prevention of HIV infection to have a public health impact, sustainable funding and physician training are required in addition to physician and public confidence in the safety of the medication.

Therefore, it seems prudent to consider the safety of FTC-TDF for PrEP for HIV infection against a standard of chemoprophylaxis in medicine—aspirin. Aspirin is the mostly widely prescribed and used primary and secondary chemoprophylactic for cardiovascular and gastrointestinal diseases, including cancer [7]. Prophylactic aspirin (daily or every 2 days) is used by almost one fifth of all adults in the United States [8]. It is estimated that 52% of adults in the United States aged 45 to 75 years are on aspirin therapy [9]. Therefore, given the frequent use of aspirin as a prophylactic drug in the United States, it invites the question: Is FTC-TDF for PrEP for HIV infection safer than aspirin?

METHODS

A narrative review was done in September 2015 comparing the 5 major studies on PrEP for HIV infection—iPrEx, Partners PrEP, TDF2, FEM-PrEP, and VOICE—and the 2 major studies on aspirin safety—the Physicians’ Health Study (PHS; N = 22 071; over 110 000 person-years) and the Women’s Health Study (WHS; N = 39 876; approximately 400 000 person-years). PubMed was used as the search platform for the literature review using the search words “Emtricitabine Tenofovir Disoproxil Fumarate” OR “Pre-Exposure Prophylaxis for HIV” OR “Aspirin Safety” OR “Aspirin Physicians Health Study” OR “Aspirin Women Health Study”. The studies on PrEP for HIV infection were conducted in outpatient settings globally, whereas aspirin was studied in outpatient settings in the United States. The studies on PrEP for HIV infection were conducted in patients over 18 years old at high risk of HIV acquisition; studies in women limited ages to 18 to 35 or 18 to 45 years of age. The PHS recruited male physicians aged 40 to 84 years, and the WHS followed female health professionals aged 45 years or older. The numbers needed to harm (NNH) and excess risk were calculated for FTC-TDF for PrEP for HIV infection and aspirin. Numbers needed to harm is a common method used in cost-benefit analyses to normalize harmful events in studies with varying populations and study durations. We restricted reporting the number of excess events to statistically significant associations found in the studies.

RESULTS

The published studies on the prophylactic use of FTC-TDF and aspirin showed they were both associated with an excess risk of a particular set of adverse events (Table 1) [2–6, 10, 11]. In the iPrEx trial of FTC-TDF for HIV prevention, 0.8 excess events of unintentional weight loss and 0.7 excess events of moderate nausea per 100 FTC-TDF user-years were reported [3]. In the Partners PrEP study, investigators observed 0.9 excess cases per 100 FTC-TDF user-years of moderate decreased absolute neutrophil counts [2]. The TDF2 study investigators reported excess rates of nausea (8.9 excess events per 100 FTC-TDF user-years), vomiting (3.3 per 100), and dizziness (3.1 per 100) among those taking FTC-TDF [4]. The FEM-PrEP study observed excess rates of mildly elevated liver enzymes (4.1 excess events per 100 FTC-TDF), vomiting (3.6 per 100), and nausea (2.6 per 100), whereas the VOICE study only observed 1.3 excess events per 100 FTC-TDF user-years of mildly elevated serum creatinine levels [5, 6].

In both men and women, investigators of the iPrEx, Partners PrEP, TDF2, FEM-PrEP, and VOICE studies reported no serious irreversible events and no FTC-TDF-associated hospitalizations or deaths [2–6]. Further reversible adverse effects included a mild decrease in creatinine clearance (a marker for renal function) and a small decrease in bone mineral density, both of which reversed after FTC-TDF discontinuation [12, 13]. It should be noted that FTC-TDF prophylaxis for HIV infection has not been associated with any bone fractures, adverse pregnancy-related events, or permanent renal failure [3, 14, 15].

Comparatively, aspirin was associated with bleeding disorders in men and women (Table 1) [10, 11]. In the final report on aspirin, the PHS, for the prevention of cardiovascular disease in men published in 1989, investigators reported excess rates of bleeding problems (1.3 excess events per 100 aspirin user-years), easy bruising (1.0 per 100), epistaxis (0.4 per 100), other bleeding problems (0.2 per 100), melena (0.2 per 100), other noninfectious disorders of the digestive tract (0.1 per 100), and duodenal ulcers (0.03 per 100) [10]. The WHS, published on aspirin and the prevention of cardiovascular disease in women, reported an excess number of cases of easy bruising (1.0 excess events per 100 aspirin user-years), epistaxis (0.2 per 100), hematuria (0.1 per 100), peptic ulcers (0.1 per 100), and gastrointestinal symptoms (0.1 per 100), with some bleeding events requiring transfusion (0.02 per 100) [11].

How do physicians weigh the risks and benefits of prophylactic medication? One key consideration is the NNH: the number of treated patients per year needed to possibly result in a harmful outcome. For FTC-TDF in the iPrEx study in MSM and transgender women, the NNH was 114 for nausea and 96 for unintentional weight loss (Table 1). In the Partners PrEP Study, the NNH was 68 for moderate decreased absolute neutrophil count; for other adverse events, the NNH was 166 for decreases in creatinine clearance and 5 for a 1% average decrease in bone density in the spine and approximately one half of 1% in the hip over a period of 24 weeks; all of which were reversible.
More substantial changes in bone density were not observed [12].

For aspirin, major gastrointestinal bleeding is expected once per 909 person-years of prophylaxis; any gastrointestinal bleeding is expected to occur once per 123 person-years [16]. The NNH for aspirin was 15 for any bleeding problems in men (Table 1) [10]. In women, the NNH for easy bruising was 10.

A meta-analysis of 16 aspirin and cardiovascular disease prevention trials with a total of 55,462 participants estimated that there would be 1 hemorrhagic stroke in every 833 persons treated prophylactically [17]. A more recent study estimated that 1 hemorrhagic stroke was expected for every 5000 patients treated with aspirin who were diagnosed with coronary heart disease [18]. Given the large number of people taking aspirin, the number of potential aspirin-related adverse events is not inconsequential.

The other side of the balance of determining when to initiate prophylaxis is the benefit and the severity of the condition being prevented. Although HIV infection is currently treatable in places where medication is available and the life expectancy of treated HIV-infected patients approaches that of HIV-uninfected patients [19], HIV infection remains highly stigmatized, treatment is very costly and requires regular medical visits. HIV is still potentially transmissible to others, and current treatments have their own short- and long-term toxicities [20]. However, PrEP for HIV infection also has associated financial costs, requires regular medical visits, and may have stigma attached to it in some communities [21].

Cardiovascular disease is the leading cause of premature life lost in the United States, and an estimated 85.6 million persons are living with some form of cardiovascular disease [22]. One study found that the number needed to treat (NNT) with aspirin to avoid 1 nonfatal myocardial infarction event was 27 per year, and the NNT to avert 1 cardiovascular disease-related event over the same period of time was 20 [23].

Using FTC-TDF for PrEP for HIV infection, it was demonstrated that the NNT to avoid 1 HIV infection was 13 in the PROUD study, a randomized trial conducted in England with MSM who had reported having recent anal intercourse without [2, 12, 13].

### Table 1. The Number of Excess Cases per 100 Intervention User-Years Observed by Study and the Number Needed to Harm in Emtricitabine-Tenofovir Disoproxil Fumarate vs Aspirin

| Adverse Events by Gender by Study | FTC-TDF for PrEP for HIV | Aspirin |
|-----------------------------------|--------------------------|---------|
|                                   | Excess Cases per 100 FTC-TDF User-Years | Number Needed to Harm | Excess Cases per 100 Aspirin User-Years | Number Needed to Harm |
| **Men**                           |                         |         |                                    |                      |
| Pre-exposure Prophylaxis Initiative |                         |         |                                    |                      |
| Unintentional weight loss (>5%)   | 0.8                     | 96      | 1.3                                | 15                   |
| Nausea                            | 0.7                     | 114     | Easy bruising                      | 1.0                  |
| **Women**                         |                         |         |                                    |                      |
| Pre-exposure Prophylaxis Trial for HIV Prevention Among African Women |                          |         |                                    |                      |
| Mildly elevated liver enzymes     | 4.1                     | 36      | Melena                            | 0.2                  |
| Vomiting                          | 3.6                     | 41      | Other noninfectious disorders of the digestive tract | 0.1               |
| Nausea                            | 2.6                     | 56      | Upper gastrointestinal ulcers     | 0.1                  |
| Vaginal and Oral Interventions to Control the Epidemic |                          |         | Duodenal ulcer                    | 0.03                |
| Mildly elevated serum creatinine  | 1.3                     | 72      |                                    |                      |
|                                 |                          |         |                                    |                      |
| **Women**                         |                         |         |                                    |                      |
|                                    |                          |         |                                    |                      |
|                                    |                          |         |                                    |                      |
| Women's Health Study              |                          |         |                                    |                      |
| Easy bruising                     | 1.0                     | 10      |                                  |                      |
| Epistaxis                         | 0.2                     | 41      |                                  |                      |
| Hematuria                         | 0.1                     | 124     |                                  |                      |
| Peptic ulcer                      | 0.1                     | 154     |                                  |                      |
| Any gastrointestinal symptoms     | 0.1                     | 125     |                                  |                      |
| Gastrointestinal symptoms         | 0.02                    | 553     |                                  |                      |

**Prophylactic Medication**

**FTC-TDF for PrEP for HIV**

| Adverse Events by Gender by Study | Excess Cases per 100 FTC-TDF User-Years | Number Needed to Harm |
|-----------------------------------|------------------------------------------|-----------------------|
| Nausea                            | 0.7                                      | 114                   |
| Unintentional weight loss (>5%)   | 0.8                                      | 96                    |
| Women                             |                                          |                       |
| Pre-exposure Prophylaxis Initiative |                                       |                       |
| Epistaxis                         | 0.4                                      | 50                    |
| Other bleeding                    | 0.2                                      | 86                    |
| Mildly elevated liver enzymes     | 4.1                                      | 36                    |
| Vomiting                          | 3.6                                      | 41                    |
| Nausea                            | 2.6                                      | 56                    |
| Vaginal and Oral Interventions to Control the Epidemic | 1.3 | 72 |

**Aspirin**

| Adverse Events by Gender by Study | Excess Cases per 100 Aspirin User-Years | Number Needed to Harm |
|-----------------------------------|------------------------------------------|-----------------------|
| Nausea                            | 0.7                                      | 114                   |
| Unintentional weight loss (>5%)   | 0.8                                      | 96                    |
| Women                             |                                          |                       |
| Pre-exposure Prophylaxis Trial for HIV Prevention Among African Women | 1.3 | 15 |
| Epistaxis                         | 0.4                                      | 50                    |
| Other bleeding                    | 0.2                                      | 86                    |
| Mildly elevated liver enzymes     | 4.1                                      | 36                    |
| Vomiting                          | 3.6                                      | 41                    |
| Nausea                            | 2.6                                      | 56                    |
| Vaginal and Oral Interventions to Control the Epidemic | 1.3 | 72 |

Abbreviations: FTC, emtricitabine; HIV, human immunodeficiency virus; NNH, number needed to harm; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate.

The excess cases per 100 FTC-TDF user-years were calculated with the following equation: (((number of cases with adverse event in intervention group/total number of participants in the intervention group × average numbers of years followed) × 100 users)) − (((number of cases with adverse event in control group/total number of participants in the control group × average numbers of years followed) × 100 users))). The NNH was calculated with the following equation: NNH = 1/((number of cases with adverse event in intervention group/total number of participants in the intervention group) − (number of cases with adverse event in control group/total number of participants in the control group)). The data were adapted from 4 randomized studies [3, 5, 6, 10, 11].

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a condom [24]. Using models, it was estimated that the NNT to avoid 1 HIV infection in the typical man who has sex with men in the United States was 64; however, with high adherence, the NNT dropped to 30 [25]. In a high-risk area with a 35% prevalence of HIV infection, the estimated NNT was 35, and the NNT dropped to 17 with high adherence [25].

**DISCUSSION**

Based on the current evidence, we conclude that FTC-TDF for PrEP for HIV infection favorably compares with aspirin in terms of user safety. By comparing the NNH—the number of people given an intervention to observe 1 adverse outcome—for PrEP for HIV infection versus aspirin for cardiovascular disease, fewer numbers of individuals taking PrEP will have adverse outcomes when compared with those taking aspirin. The safety of FTC-TDF as a component of combination antiretroviral therapy is well studied among people living with HIV infection. Careful monitoring of renal function and bone metabolism is recommended due to FTC-TDF-associated effects on kidney function and bone density [12, 13]. However, given that the approval by the FDA of FTC-TDF for PrEP for HIV infection was in 2012, the long-term safety of FTC-TDF use is unknown among people who are not infected with HIV.

**CONCLUSIONS**

Although there is an increasing awareness and uptake of FTC-TDF for PrEP for HIV infection among some persons in high-risk groups, additional measures are needed to identify at-risk individuals and ensure they are offered PrEP for the prevention of HIV infection [26–28]. There are still clear barriers to the uptake of PrEP for HIV infection, such as access, cost, acceptability, adherence, and acceptance among medical providers [21, 29, 30]. However, given (1) that in some areas the number of people needed to treat to avoid 1 HIV infection can be as low as 13, (2) the favorable cost- and risk-benefit analyses in high-risk populations, and (3) new efforts to implement PrEP programs for HIV prevention, the future looks optimistic, at least in some parts of the country [21, 29, 31]. In San Francisco, it was reported that participants in the iPrEx trial had good adherence due to client-centered counseling, education, and strong relationships with healthcare staff [29]. Furthermore, after being educated about the potential of PrEP for the prevention of HIV infection, a large majority of high-risk MSM reported intending to use PrEP to prevent HIV infection, if available [21, 29]. Soon, newer pharmacologic formulations of PrEP for HIV infection are expected, including those with even better toleration, safer metabolic profile, and longer duration of action [30, 34]. Given the observed safety and efficacy of FTC-TDF for PrEP for HIV infection and intent of the majority of high-risk MSM to use PrEP, physicians should now actively look for patients who may benefit from it [35]. A “duty to prevent” suggests that physicians should identify patients in their practice with behaviors that might put them at risk for HIV infection and offer PrEP routinely.

**Acknowledgments**

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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