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REVIEW

**Patient-Focused Selection of PrEP Medication for Individuals at Risk of HIV: A Narrative Review**

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## ABSTRACT

Pre-exposure prophylaxis (PrEP) medication is a key component of the HIV prevention strategy in the US, with demonstrated to be highly effective in preventing HIV acquisition among individuals at risk. Two PrEP medications are currently approved: emtricitabine/tenofovir disoproxil fumarate (Truvada®; F/TDF) was approved by the US Food and Drug Administration in 2012, followed by emtricitabine/tenofovir alafenamide (Descovy®; F/TAF) in 2019. An ongoing randomized, double-blind, Phase 3 study (DISCOVER) demonstrated that F/TAF had non-inferior efficacy to F/TDF. While both medications have been found to be efficacious and well tolerated, several studies have identified that important differences exist with regards to pharmacokinetics, bone and renal safety profiles, and other factors. In this narrative review, we conducted a comprehensive evaluation of the populations at risk of HIV who may also be affected by, or at risk of, bone or renal conditions. We reviewed the safety profiles of F/TDF and F/TAF to develop an evidence-based algorithm for selecting the appropriate PrEP medication, based on biological, behavioral, and health characteristics of an individual at risk of HIV, and considered how the choice of PrEP medication may or may not compound safety concerns for these individuals. We identified that the introduction of F/TAF provides a valuable alternative to F/TDF, allowing the personalization of PrEP. F/TAF may be the preferred medication for cisgender men and transgender women at risk of HIV infection who are predisposed to, or already have, bone or renal conditions. While the approval of F/TAF is the first step in personalization of PrEP, additional options are still warranted to help accommodate the wide spectrum of individuals at risk of HIV with different lifestyles, medical histories, preferences, and requirements.

**Keywords:** Bone; Decision making; HIV prevention; Kidney; Personalized medicine; Pre-exposure prophylaxis; Preference; Renal; Tenofovir alafenamide; Tenofovir disoproxil fumarate

## PLAIN LANGUAGE SUMMARY

Pre-exposure prophylaxis (or PrEP) prevents HIV acquisition in individuals at risk of HIV infection. There are currently two approved options for PrEP in the US; both are oral medications. The first option, approved in 2012, is a combination of two drugs called emtricitabine/tenofovir disoproxil fumarate – also known as Truvada® or F/TDF. The second option, approved in 2019, is a combination of emtricitabine and a different prodrug, tenofovir alafenamide – this combination is called Descovy® or F/TAF. Both options are 99% effective in preventing HIV if taken daily. While the risk of serious side effects from taking either of the PrEP medications is low, F/TAF has demonstrated less effect on bone and kidney health, and may be the preferred option in people with bone or kidney conditions, or in those at risk of developing osteoporosis or having risk factors for kidney disease, such as people living with diabetes or high blood pressure. As the risk of HIV sometimes overlaps with risks to bone and renal health according to race/ethnicity, poverty, alcohol/substance use, smoking tobacco, and taking other medications, F/TAF as an alternative PrEP medication allows the PrEP choice to depend on the broader health conditions of the individual. ‘Personalized medicine’ means that medicines can be chosen to suit an individual’s biology, behavior, lifestyle, and overall health. The approval of F/TAF is the first step in personalization of PrEP medication, while additional options need to be researched to meet the requirements of all individuals at risk of HIV.

### Key Summary Points

- There are currently two approved options for HIV pre-exposure prophylaxis (PrEP) in the US: emtricitabine/tenofovir disoproxil fumarate (Truvada®; F/TDF) and emtricitabine/tenofovir alafenamide (Descovy®; F/TAF).
- F/TDF and F/TAF have differences in pharmacokinetics as well as renal and bone safety profiles.
- Candidates for PrEP medication, who are at risk of HIV, often have additional risks of developing bone or renal comorbidities, due to a variety of factors including race/ethnicity, diet, alcohol/substance use, tobacco smoking, concomitant medications, and/or other lifestyle factors.
- Due to its more favorable safety profile, F/TAF may be the preferred choice for cisgender men and transgender women at risk of HIV, who are also at risk of developing bone or renal conditions; F/TDF may be the preferred choice in individuals at risk of HIV who are cisgender women or are at risk of HIV through receptive vaginal sex.
- The more favorable safety profile of F/TAF is particularly advantageous during the ongoing global COVID-19 pandemic, as it may reduce the need for individuals to attend clinics in person.
- Future PrEP options are warranted to allow for improved personalization to accommodate the various needs of individuals at risk of HIV.

### DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13353098>.

## INTRODUCTION

More than a million individuals in the US are living with HIV [1]. In recent years, pre-exposure prophylaxis (PrEP) medication for individuals who are HIV negative but at risk of acquiring HIV has become an important method of HIV prevention and a key part of the US's overall plan for Ending the HIV Epidemic [2-4]. PrEP has been shown to be highly effective in preventing HIV in both clinical trials and real-world studies, with the estimated effectiveness dependent on adherence [5-8]. A positive real-world impact of PrEP on HIV transmission rates in the US has been demonstrated and a significant association between the uptake of PrEP and overall declines in HIV diagnoses was identified in a retrospective analysis of data from the National HIV Surveillance System from 2012 to 2016 [9].

Currently, there are two oral PrEP medications approved by the US Food and Drug Administration [10, 11]. Emtricitabine/tenofovir disoproxil fumarate (Truvada®; F/TDF) [5-7, 12, 13] was approved in 2012, and is indicated for PrEP to reduce the risk of sexually acquired HIV-1 in adults at risk [11]. Emtricitabine/tenofovir alafenamide (Descovy®; F/TAF) [14] was approved in 2019 for adults and adolescents at risk, excluding individuals at risk from receptive vaginal sex, a population that has not yet been studied with F/TAF [10].

Clinical and real-world studies have demonstrated the efficacy of F/TDF in adults and adolescents at risk of HIV infection; the studies included cisgender men who have sex with men (MSM), people who inject drugs (PWID), transgender women, and heterosexual couples in which one partner was living with HIV [5-7, 12, 13, 15, 16]. The efficacy and safety of F/TAF PrEP in cisgender men and transgender women who have sex with men ( $\geq 18$  years of age) has been investigated and compared with F/TDF in the Phase 3 DISCOVER study, consisting of a 96-week randomized, double-blind period (which has been completed) and a 48-week open-label extension (which is ongoing) [14]. The results of the DISCOVER study demonstrated that F/TAF was non-inferior to F/TDF for the prevention of HIV at the primary analysis (when 100% of participants reached 48 weeks of follow-up and 50% reached 96 weeks) and also when all participants reached 96 weeks, indicating that the two medications have comparable efficacy at over 99% [14, 17].

In addition to the proven efficacy of F/TDF and F/TAF, clinical studies have demonstrated well-tolerated safety profiles for the two medications when used as PrEP [12-14]. There are nevertheless important differences between F/TDF and F/TAF in terms of bone and renal safety [14]. The use of F/TDF has been associated with notable decreases in bone mineral density (BMD) and renal function (as measured by estimated glomerular filtration rate [eGFR]) both in individuals with HIV and in individuals who were HIV negative using PrEP [19-21]. F/TAF has been associated with improved maintenance of bone and renal safety parameters versus F/TDF in individuals with HIV [22].

Likewise, this was a key area for investigation in the DISCOVER trial, which compared F/TDF and F/TAF for PrEP. In that study, F/TAF was associated with improved maintenance of BMD and renal function versus decreases in both BMD and eGFR in the F/TDF arm at the end of the 96-week treatment period [14].

The lipid profile and body weight of participants were monitored throughout the DISCOVER trial [17]. In both the F/TDF and F/TAF study arms, decreases were seen from baseline in low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) at 96 weeks. Triglyceride levels were increased at 96 weeks in the F/TAF arm, although the increase from baseline, while statistically significant, is unlikely to be clinically meaningful. No significant differences were seen between the study arms in the ratio of TC to high-density lipoprotein cholesterol (HDL-C) or LDL-C:HDL-C, both of which have greater predictive value for cardiovascular disease than the individual parameters in isolation [23]. Among participants receiving F/TDF at baseline, 3% of those who switched to F/TAF started a lipid-modifying agent versus 0.9% of those who remained on F/TDF ( $p=0.03$ ) [24]. Among PrEP-naïve individuals, however, there was no significant difference in the rates of lipid-modifying agent initiation between the arms (1.3% vs 1.0%,  $p=0.27$ ) [25].

Weight gain was seen in both the F/TAF and F/TDF groups at week 96 in DISCOVER and was greater in the F/TAF arm (F/TAF: +1.7 kg; F/TDF: +0.5 kg). The weight gain observed in the F/TAF arm was similar to that seen in longitudinal studies of young adults in the US who were not taking PrEP [26, 27].

In this narrative review, we examine the overlap between populations at risk of HIV and those at risk of bone and/or renal conditions, with a particular focus on the US. We also review the clinical dataset for F/TDF and F/TAF to develop an evidence-based algorithm for selecting an appropriate PrEP option for an individual at risk of HIV, based on the biological, behavioral, and health characteristics of the candidate.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## **INDIVIDUALS AT RISK OF HIV**

The relative risk of acquiring HIV varies depending on the type of exposure and sexual risk behaviors. At an individual level, the risk of acquiring HIV is multifactorial. However, some factors are considered to increase risk. MSM who have condomless sex or who have had a bacterial sexually transmitted infection, for example, are considered a group at substantial risk of HIV and are recommended to use PrEP by the Centers for Disease Control and Prevention (CDC) [28]. MSM have been shown to have the highest lifetime risk of HIV (around 1 in 6) of all groups in the US (**Table 1**) [29], and in 2018, ~70% of new HIV diagnoses in the US were among MSM [1]. HIV has a

disproportionately high impact on racial and ethnic minorities, with Black/African American people, for example, accounting for 42.8% of HIV diagnoses in the US in 2018, compared with 25.5% for White people [1]. Black/African American MSM have the highest overall lifetime risk of HIV (around 1 in 2) [29]. Hispanic/Latino MSM have a 1 in 5 lifetime risk, compared with a 1 in 11 lifetime risk among White MSM [29].

Transgender people are particularly at risk of HIV, with estimated prevalence rates in the US of 14.1% and 3.2% among transgender women and transgender men, respectively [30]. The lifetime risk of HIV increases with age [29], although the rates of diagnosis are highest in the 25- to 34-year age group [1]. Individuals living in the Southern states in the US have been shown to have the highest lifetime risk of HIV [29], and prevalence is higher among individuals who have a lower socioeconomic status [31]. Finally, PWID have an increased lifetime risk of HIV, which is higher in females than males (1:26 vs 1:42, respectively) [29].

## **INDIVIDUALS AT RISK OF HIV AND RENAL CONDITIONS**

### **Renal Disease in the US**

Approximately 15% (37 million) of people in the US are estimated to have chronic kidney disease (defined as an eGFR <60 ml/min/1.73 m<sup>2</sup> for ≥3 months) [32, 33]. Furthermore, diabetes and hypertension are common, with prevalence rates in the US of ~13% and ~46%, respectively [34, 35]. Rates of kidney disease, diabetes, and hypertension are generally more common in males versus females, and the risk increases with age [34-36].

### **Risk Factors**

#### ***Race/Ethnicity***

Black/African American and Hispanic/Latinx individuals (particularly MSM) are disproportionately affected by HIV [29] and also have a high prevalence of conditions such as hypertension, diabetes, and obesity [36, 37], which may be associated with the elevated prevalence of kidney failure and end-stage renal disease [35-38].

#### ***Age***

Aging is associated with changes to the renal system, gradually leading to declines in renal function and overall renal health [39]. While chronic kidney disease is more prevalent in the elderly, physiological declines in kidney function can begin as early as 30–40 years of age depending on many factors, some of which are listed below [39, 40].

### ***Alcohol/Substance Use Disorder***

Individuals with alcohol and/or substance use disorders (e.g. methamphetamines) are more likely to engage in sexual behaviors that place them at risk of HIV [42, 43]. Studies have found that people who identified as gay or bisexual have a high likelihood of lifetime substance use disorders [44, 45]. Methamphetamines, cocaine, opioids, marijuana, and alcohol have all been shown to have a negative effect on renal health. These risk factors should be discussed with individuals and taken into consideration when individualizing PrEP medication selection.

### ***Tobacco Use***

Gay, bisexual, and transgender populations have been reported to have high tobacco use rates [35]. Tobacco use has numerous negative effects that may cause tubular dysfunction and glomerulosclerosis leading to the progression of chronic kidney disease [49]. Notably, the use of e-cigarettes has increased in recent years, particularly among younger populations [50], which may also reduce renal function as has been shown in mice exposed to e-cigarette vapor [51].

### ***Concomitant Medications***

Many medications can contribute to declines in renal function, which include several first-line agents for the treatment of mental health conditions [52]. Notably, some mental health conditions can be associated with a higher likelihood of acquiring HIV, as they may be linked to high-risk sexual behavior, alcohol use before sex or reduced adherence to PrEP [54].

A variety of other medications may also affect renal health. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [55, 56], antibiotics (methicillins/penicillins, cephalosporins, aminoglycosides) [55], and chemotherapies (cisplatin, ifosfamide, gemcitabine, mitomycin) [57] are just a few examples; the list of drugs with potential nephrotoxicity is extensive [58, 59]. As a result, an individual's medical history, including the use of concomitant medications that may affect renal health, should be considered before selecting the appropriate PrEP medication.

### ***Diet***

Data suggest that MSM have significantly higher estimated rates of eating disorders than heterosexual men [60]. Eating disorders, such as anorexia or bulimia nervosa, can contribute to the development of kidney disease [61]. Careful assessment of diet and symptoms of eating disorders should be considered in MSM.



## Renal Disease Rates in PrEP Users: Clinical Studies and Real-World Studies

Evidence suggests that a substantial proportion of individuals who were eligible for PrEP in clinical studies had mildly reduced renal function at baseline. A large implementation cohort study in Australia included individuals with an eGFR of  $\geq 60$  ml/min/1.73 m<sup>2</sup> and found that 28.5% had mildly reduced renal function at baseline (eGFR  $\geq 60$  to  $< 90$  ml/min/1.73m<sup>2</sup>), and that these individuals had an increased risk of further renal impairment (eGFR  $< 60$  ml/min/1.73m<sup>2</sup>) [63]. Similarly, a prospective cohort study of PrEP in the US identified that 16.6% of MSM and transgender women in the study had mildly reduced kidney function at baseline (eGFR  $\geq 60$  to  $< 90$  ml/min/1.73 m<sup>2</sup>) [64].

A variety of other conditions that may affect renal health can be found in some individuals at risk of HIV using PrEP medication, with the CDC recommending frequent renal monitoring (at least every 6 months or more frequently if risk factors are present) for F/TDF users [28]. **Table 2** summarizes the prevalence of mildly reduced renal function and conditions affecting renal health at baseline among PrEP users in clinical studies [63-66]. Collectively, these data challenge the perception that PrEP users only consist of healthy individuals without pre-existing renal impairment or conditions that impact renal health.

## INDIVIDUALS AT RISK OF HIV AND BONE CONDITIONS

### Osteoporosis and Low Bone Mass in the US

In the US, a society with an aging population, a large proportion of individuals  $\geq 50$  years of age have osteoporosis or low bone mass, which is estimated to reach 64 million by 2020 [67]. Young adults and adolescents are highly sensitive to changes in bone health before they achieve peak bone mass [68]. If bone health is disturbed during this time and peak bone mass is diminished, younger individuals might be at increased risk of osteoporosis later in life [69].

### Risk Factors

#### *Race/Ethnicity*

As noted earlier, Hispanic/Latinx individuals are at a high lifetime risk of HIV. In one study, Mexican Americans also had the highest prevalence of osteoporosis (13.4%) compared with groups defined as 'non-Hispanic White' (10.2%) and 'non-Hispanic Black' (4.9%) [67].

#### *Age*

Osteoporosis and bone loss are generally associated with aging, with rates being higher in older populations [67]. However, bone health is also an important consideration in younger individuals, as

bones grow rapidly during adolescence until they reach peak mass, typically by 30 years of age [68, 70]. Lifestyle factors and medication choices that affect bone growth during these years and result in an inadequate peak bone mass may lead to low bone density and skeletal fragility later in life [69]. Efforts should therefore be made to avoid disrupting osteogenesis if at all possible.

### ***Diet and Physical Activity***

Dietary deficiencies in calcium; vitamins D, C, and K; manganese; potassium; and zinc can contribute to poor bone health, as can low physical activity [71]. Lactose intolerance is associated with reduced bone density, which may be related to avoidance of dairy foods that are high in calcium [72]. Notably, lactose intolerance rates are higher in Black/African Americans (who are disproportionately affected by HIV) than Whites [73]. Individuals living in poverty or underserved neighborhoods are more likely to have less access to nutritional foods and have lower physical activity [74]. Discussions between healthcare professionals and candidates for PrEP are therefore warranted to ascertain information on lifestyle factors, such as diet and physical activity, which could help in the personalization of PrEP medication.

Eating disorders may also contribute to dietary deficiencies. Individuals with anorexia or bulimia often have reduced BMD and increased risk of bone conditions such as osteoporosis and osteopenia [75, 76].

### ***Alcohol/Substance Use Disorder***

As noted previously, individuals with alcohol use disorder or who use methamphetamines are more likely to engage in behaviors that place them at risk of HIV. Excessive alcohol intake has been associated with a significant increase in osteoporotic and hip fracture risk [77]. Similarly, the use of methamphetamines has been associated with a decrease in BMD [80]. Notably, a small clinical study in the Republic of Korea found that 22% and 76% of hospitalized methamphetamine users had osteoporosis and osteopenia, respectively, indicating a high incidence in this population [80].

### ***Tobacco Use***

Smoking tobacco has been shown to lower BMD and increase the risk of osteoporosis and fracture [82]. Tobacco use may therefore have a negative impact on bone health in individuals at risk of HIV, particularly in gay, bisexual, and transgender populations in which smoking rates are high [35]. As noted earlier, the use of e-cigarettes is on the rise in younger populations, who are also sensitive to factors that affect peak bone mass.

### ***Other Concomitant Medications***

Concomitant medications, particularly the use of corticosteroids, are a key consideration for bone health in individuals at risk of HIV. Short- and long-term use of corticosteroids has been associated with bone loss, while long-term use may increase fracture risk [88-90]. A wide variety of other medications can affect bone health, including antidepressants, medications for diabetes, and proton pump inhibitors [93]. Consequently, careful assessment of concomitant medications that may affect bone health should be performed to help guide the appropriate choice of PrEP medication.

### **Evidence of Osteoporosis, Osteopenia, and Low BMD among PrEP Users in Clinical Studies**

As described above, there is potential for considerable overlap between individuals at risk of HIV and those who may have (or be at risk of) conditions impacting bone health. When we examine PrEP studies, we see that this has actually translated into a substantial proportion of the study populations reporting BMD-related conditions at baseline (**Table 3**) [94-98]. Most significantly, in the largest clinical PrEP study to date, the DISCOVER study found that ~24–29% of all individuals in the BMD subanalysis had either osteopenia or osteoporosis in the spine and/or hip at baseline [94].

### **CHOOSING A PREP MEDICATION**

At PrEP initiation, an accurate assessment of the HIV risk of an individual should be performed. HIV risk-prediction models, such as SexPro for MSM in the US (developed to be inclusive of Black MSM), may help assess risk and target PrEP [99]. Key groups that are recommended for PrEP (if they are at risk of HIV acquisition) include sexually active MSM, transgender women, and PWID [28].

Collectively, evidence suggests that there is a substantial population of individuals at risk of HIV who also either have, or are at risk of developing, bone or renal impairments. This population may particularly benefit from taking F/TAF versus F/TDF for PrEP, due to its improved bone- and renal-related safety profile [17]. Notably, when considering PrEP, a careful evaluation of all concomitant illnesses and medications should be performed before initiation. Herein, we present an algorithm outlining the key steps in the decision to prescribe either F/TAF or F/TDF in individuals who have, or are at risk of developing, bone or renal impairments (see **Figure 1**).

#### **Consideration #1**

An assessment of the type of sexual activity that the PrEP candidate participates in is an important first step. If the PrEP candidate is at risk of HIV through receptive vaginal sex (e.g. a cisgender woman), then F/TDF should be prescribed as it is the only PrEP medication currently approved for this population [10, 11].

### ***Supporting Evidence***

The approval of F/TDF for use by individuals at risk from receptive vaginal sex has been based on randomized clinical trial data from the Partners PrEP study, which demonstrated its efficacy and safety [100]. In this study, HIV incidence rates were 0.5 and 1.99 per 100 person-years in the F/TDF and placebo groups, respectively, which translated to a 75% risk reduction with F/TDF versus placebo. Additionally, the incidence of serious adverse events (AEs) were similar between the two treatment groups. F/TAF has not yet been investigated in individuals at risk of HIV from receptive vaginal sex [10].

### **Consideration #2**

On-demand PrEP dosing (two tablets 2–24 hours before sex, one tablet 24 hours later, and another tablet 24 hours after that) may be considered in a subset of MSM. Although no PrEP medication is currently approved for on-demand dosing, the use of on-demand F/TDF has been shown to be highly effective at preventing HIV in some MSM [101–103]; however, these studies were conducted in a principally White population. High levels of once-daily F/TDF PrEP initiation have been demonstrated among at-risk Black MSM [104], but no studies have examined on-demand dosing in principally Black MSM populations to date. As such, the World Health Organization recommends that F/TDF could be considered in a limited population of MSM who have infrequent sex, are able to plan for sex at least 2 hours in advance, and do not have chronic hepatitis B infection [105]. In this subset of MSM, on-demand F/TDF could be an option depending on the preferences of the individual; F/TAF has not yet been investigated for on-demand PrEP.

### ***Supporting Evidence***

Most studies of PrEP to date have been of daily dosing; however, a randomized clinical study investigating on-demand PrEP for MSM at high risk of HIV infection demonstrated a statistically significant 86% reduction in infection risk with F/TDF versus placebo [102]; the study population was mostly White. An open-label extension of this study demonstrated long-term effectiveness (median follow-up 18.4 months) of on-demand F/TDF in this population [101]. Finally, a post-hoc subanalysis from this study in individuals having infrequent sex (median of five times per month) demonstrated a 100% reduction in HIV infection risk with F/TDF versus placebo [103].

### **Consideration #3**

F/TDF and F/TAF have different drug–drug interaction considerations noted in their prescribing information that could impact the choice of PrEP medication (Table 4) [10, 11]. For example, people

receiving F/TDF and some hepatitis C antiviral agents (sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or ledipasvir/sofosbuvir) should be monitored for AEs associated with TDF [11]. In contrast, the use of F/TAF should be avoided in combination with some anticonvulsants (some of which may be being used as mood stabilizers) (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antimycobacterials (rifabutin, rifampin, rifapentine), and St John's wort [10].

#### **Consideration #4**

If the PrEP candidate is at risk of sexually acquired HIV and an appropriate candidate for F/TAF, then renal health should be considered next. Key criteria for renal health considerations include being >40 years of age, evidence of chronic kidney disease or declining renal function, use of concomitant medications with known renal AEs, a history of having a condition that may impact renal health (e.g. diabetes, hypertension, or a family history of cardiovascular disease), or use of stimulants. F/TAF should be considered in any PrEP candidate with one or more of the above key criteria.

#### **Supporting Evidence**

Clinical studies have identified differences in the effects of F/TAF and F/TDF on kidneys, based on renal biomarkers. There is a well-documented association between F/TDF and modest declines in measures of renal function, such as estimated creatinine clearance (eCrCl) and eGFR, when used for HIV treatment and prevention [19, 20, 106-108]. Given the known effects of F/TDF on renal function, the CDC has recommended that serum creatinine (Cr) is measured at baseline and any individual with an eCrCl of <60 ml/min should not be prescribed F/TDF [28]. Renal health must be evaluated either before or when prescribing PrEP medications, to avoid administration to individuals with renal impairment or those at risk of declining renal function [63, 64, 66].

The available evidence indicates that F/TAF is not associated with a significant decline in renal function when used for PrEP [14]. F/TAF can be prescribed to individuals with lower renal function in comparison with F/TDF, and is recommended in individuals with an eCrCl  $\geq 30$  ml/min or with an eCrCl <15 ml/min and who are on chronic hemodialysis [10]. The DISCOVER study demonstrated that significant eGFR changes were not identified in the F/TAF arm, with significant eGFR decreases ( $-4.1$  ml/min) observed in the F/TDF group at 96 weeks ( $p < 0.001$ ) [17]. Importantly, these difference in eGFR between F/TAF and F/TDF were evident at 96 weeks among older individuals ( $\geq 50$  years of age) ( $p < 0.001$ ) (**Figure 2**) [17], who have been shown to have a higher risk of developing renal dysfunction when taking F/TDF [63]. Two biomarkers have been shown to be associated with proximal renal tubule dysfunction when elevated: retinol binding protein (RBP) to Cr ratio and  $\beta 2$  microglobulin ( $\beta 2M$ ) to Cr ratio [109, 110]. In the DISCOVER study, there were no significant changes in urine

RBP:Cr and  $\beta$ 2M:Cr from baseline in the F/TAF group, while levels were significantly higher in the F/TDF group at 96 weeks ( $p < 0.001$ ), which was again evident in individuals  $\geq 50$  years of age ( $p < 0.001$ ) (**Figure 2**) [17].

The DISCOVER study also found a numerically lower number of study drug-related renal AEs in the F/TAF and F/TDF groups (14/2694 vs 26/2693, respectively) [14]. Similarly, renal AEs leading to discontinuation were 2/2694 and 6/2693 in the F/TAF versus F/TDF groups, respectively [14]. The overall number of AEs leading to discontinuation was low in both groups at 96 weeks [14]. Notably, F/TAF showed a lack of impact on glucose levels and fasting lipids at 96 weeks, suggesting little effect on metabolic health [17].

The efficacy of F/TAF and F/TDF in transgender women from DISCOVER, which included those taking gender-affirming hormones, was evaluated at the primary analysis. Although sample sizes were small, no HIV infections were found for any transgender women using F/TAF or F/TDF [111]. Importantly, the incidence of AEs and renal safety outcomes in the two treatment groups were similar [111]. Additionally, intracellular drug levels of tenofovir diphosphate were higher in transwomen who had received F/TAF versus those receiving F/TDF [111].

#### **Consideration #5**

Bone health should also be considered. Key criteria include the following:  $< 25$  or  $> 50$  years of age, occurrence of bone-related conditions such osteoporosis or osteopenia, previous or current corticosteroid use, lifestyle factors that have a negative impact on bone health (e.g. history of tobacco smoking, sedentary lifestyle, poor diet, alcohol use disorder, use of methamphetamines), eating disorders, vitamin D deficiency, or low body mass index. F/TAF should be considered in any PrEP candidate meeting one or more of these criteria.

#### **Supporting Evidence**

F/TDF may be associated with declines in BMD when used for PrEP or HIV treatment, in comparison with F/TAF, which showed no effect on BMD [21]. A systematic review and meta-analysis included a mixed group of studies wherein F/TDF was used as PrEP, HIV treatment, and hepatitis B virus treatment [21]. When taken as PrEP, F/TDF was associated with a minor BMD decrease in the lumbar spine and total hip (mean differences of  $-0.82\%$  and  $-0.81\%$ , respectively), although a larger decrease in BMD was seen in the HIV treatment studies [21]. Importantly, two open-label studies from the Adolescent Trials Network of PrEP evaluated BMD changes in young adult/adolescent MSM [16, 112]. One study in individuals 18–22 years of age identified modest but significant decreases in BMD in the hip and whole body (median differences of  $-0.44\%$  and  $-0.61\%$ , respectively) with F/TDF at week 24 [112]. The other study included individuals 15–17 years of age and found a significant

decrease in the total body BMD Z-score at week 48 [16]. A subsequent extension study showed that BMD Z-scores in the spine and whole body remained below baseline in individuals 15–19 years of age 48 weeks following discontinuation of PrEP [113]. Despite the potential effects of F/TDF on bone health, the CDC does not currently recommend BMD assessment before initiation of F/TDF, although individuals with a history of fractures, or at significant risk of osteoporosis, are recommended to be referred for appropriate consultation and management [28]. Although not specifically recommended by the CDC, BMD measurement may provide additional clinically important information to guide decision making before initiating F/TDF for PrEP and could be considered by clinicians.

Unlike F/TDF, F/TAF has not been associated with a decline in BMD when used for PrEP [14]. In a prespecified subgroup analysis, the DISCOVER study demonstrated BMD increases among individuals in the F/TAF group, with levels significantly higher than F/TDF in the spine and hip at 48 and 96 weeks (**Figure 3**) [14, 17]. Similar effects on BMD were seen between individuals <25 and ≥25 years of age at both time points [14, 17]. F/TAF was associated with a significantly lower rate of osteoporosis and osteopenia in the spine than F/TDF after 48 weeks of medication, with low and similar fracture rates (2%) in both PrEP groups [114].

#### **Consideration #6**

Finally, F/TAF should be considered in candidates who prefer a smaller tablet size or blister packaging.

#### **Supporting Evidence**

Candidate preferences about tablet size are a key consideration as F/TAF is about one-third of the size of F/TDF (249 vs 767 mm<sup>3</sup>, respectively). In general, larger tablets are harder to swallow, which may act as a barrier to medication adherence and reduce long-term adherence [115, 116]. A study conducted in the US identified that many individuals reported or anticipated difficulty in taking PrEP tablets (F/TDF), with aversion to size being a common theme [117]. Additionally, almost all individuals stated that reducing the size of the PrEP tablet would increase their willingness to take medication [117]. Collectively, these data indicate that F/TAF may be a preferred option for individuals at risk of HIV, especially those who prefer a smaller tablet or who struggle to swallow a larger tablet.

F/TDF is supplied in a bottle, whereas F/TAF is also available in a DayTracker™ perforated blister pack [118, 119]. Blister packaging may increase medication adherence and avoid errors, by helping the individual self-monitor medication consumption [120]. Some individuals may find separate blister packs less conspicuous, which can be important given the high level of stigma that remains around HIV and PrEP use. Given the importance of daily PrEP adherence for the optimal

effectiveness in preventing HIV, the candidate's preferences should be considered, and the DayTracker™ blister pack for F/TAF could be particularly useful for individuals who are at risk of forgetting to take their medication. Improving adherence to PrEP is essential for ensuring that real-world effectiveness matches the efficacy levels achieved in clinical trials. Any factors that reduce an individual's willingness or ability to use PrEP correctly – such as large tablet size or inconvenient packaging – risk compromising clinical outcomes.

## **NOVEL MEDICATIONS FOR PREP IN DEVELOPMENT**

A number of alternative strategies for PrEP are in development, including the use of implants or long-acting injections to achieve sustained dosing. A recent double-blind placebo-controlled phase I trial found that implant-based release of the investigational nucleoside reverse transcriptase translocation inhibitor, MK-8591 (islatravir), for example, was generally welltolerated [121]. Moreover, an interim analysis of data from the HIV Prevention Trials Network 083 study reported that the investigational drug cabotegravir was superior to F/TDF in MSM and transgender women in preventing HIV acquisition when injected once every 8 weeks [122]. Additionally, the HIV Prevention Trials Network (HPTN) 084 study recently reported on the HPTN website that a regimen containing cabotegravir injected once every eight weeks was superior to daily oral F/TDF at preventing HIV acquisition in cisgender women – we await to see these results published in a peer-reviewed journal [123]. These long-acting agents have the potential to further revolutionize the choice of PrEP for individuals at risk.

Another approach under development is the use of broadly neutralizing antibodies (bnAbs). These have been shown to reduce the risk of simian HIV infection in non-human primates [124]. While no single bnAb would be able to neutralize all strains of HIV in humans, cocktails of multiple bnAbs could provide effective protection [125]. Two large phase IIb trials of VRC01, a bnAb that targets the conserved CD4 binding site of the HIV envelope, are currently under way in humans. Modeling suggests that the overall prevention efficacy of VRC01 may be between 37% and 82% [126], suggesting that the antibody therapy, while valuable, will not be an immediate substitute for pharmaceutical approaches.

## **CONCLUSIONS**

The implementation of PrEP has had significant success in reducing the transmission of HIV in the US, and helps to mitigate risk in groups disproportionately affected by HIV [9, 12, 13, 17, 111, 127], including PWID [12]. While F/TDF has been demonstrated to reduce the risk of HIV infection in PWID [12], modeling suggests that both regimens could provide rapid and lasting protection in this population [128] although we note that F/TAF and F/TDF are not yet approved for this indication.



PrEP update rates are suboptimal. There are many reasons behind low PrEP uptake rates, but one barrier cited by individuals has been concern over its long-term safety effects [129]. Adherence to daily PrEP medication may also be impacted by long-term safety concerns or experience of AEs [130]. Lack of adherence may explain why the real-world effectiveness of PrEPs does not always match the efficacy levels observed in clinical trials. Due to adherence concerns, some PrEP users and providers have turned to off-label alternatives to daily dosing, such as on-demand PrEP regimens [101]. Although not appropriate for all patients, on-demand PrEP could be an option allowing further choice for some MSM.

Compounding barriers around safety, the evidence shows that current PrEP users are not all 'young, otherwise healthy' individuals: many are older, have pre-existing medical conditions, or have behavioral risk factors affecting renal and bone health. While for some patients the long-established F/TDF and the newer F/TAF may both constitute safe and effective PrEP options, for other groups the introduction of F/TAF, with its improved bone and renal safety profile, provides a valuable alternative. It represents an additional step toward personalization of PrEP depending on the individual's broader health status and preferences. As such, F/TAF may help to begin to address the disproportionately low uptake of PrEP among certain populations such as ethnic minorities. In particular, F/TAF may be the medication of choice for populations of cisgender men and transgender women at risk of HIV who are also at risk of developing osteoporosis or renal disease.

The robust safety profile of F/TAF compared with F/TDF may be advantageous in settings where access to in-person visits is limited (e.g. in rural areas, or due to COVID-19- related safety guidelines) [131]. PrEP programs, as well as HIV testing and treatment, have faced considerable disruption as a result of the pandemic, and telemedicine has gained more attention as having an important role. Notably, the safety profile of F/TAF for individuals with renal and bone-related risk factors may reduce the need for patients to attend clinics in person (although HIV testing would still be necessary). Clinicians should thus consider whether F/TAF may be a safer option when implementing PrEP in a virtual setting.

Age, comorbidities, tobacco smoking, substance use, concomitant medications, race/ethnicity, mental health, family history, and lifestyle should all be considered before initiating any medication, including PrEP. While each factor individually may be insufficient to drive choice of a PrEP medication, taken together, these factors should be considered as part of the 'bigger picture' of the individual's current health, lifestyle, and medical history. It is possible that cost differences among the PrEP options described could be a consideration for HIV prevention programs, and cost-effective analyses should be investigated for current and emerging PrEP options in future studies.

Nevertheless, with HIV prevention, as with many other biomedical interventions, providers should

consider how the choice of a medication could contribute to or exacerbate other risk factors in a patient's life. As a result, the approach to PrEP should become increasingly individualized and patient centered as more options become available.

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**Table 1** Estimated lifetime risk of HIV by risk group and race/ethnicity [29]

Risk group	Estimated lifetime risk of HIV	
	Male	Female
Total	1 in 68	1 in 253
Risk group		
MSM	1 in 6	NA
Heterosexual	1 in 524	1 in 266
PWID	1 in 42	1 in 26
Race/ethnicity		
American Indian/Alaska Native	1 in 131	1 in 403
Asian	1 in 176	1 in 943
Black/African American	1 in 22	1 in 54
Hispanic/Latinx	1 in 51	1 in 256
Native Hawaiian/other Pacific Islander	1 in 95	1 in 432
White	1 in 140	1 in 941

*MSM* men who have sex with men, *NA* not applicable, *PWID* people who inject drugs

**Table 2** Prevalence of mildly reduced renal function and conditions affecting renal health at baseline in clinical studies of PrEP

Population	Sample size, <i>N</i>	Baseline prevalence, %				References
		Suboptimal eGFR levels (≥60–<90 ml/min/1.73 m <sup>2</sup> )	Hyperlipidemia	Hypertension	Diabetes	
MSM and transgender women in a multinational study <sup>a</sup>	5387	NA	12	10–11	3	[65]
MSM and transgender women in the USA	557	16.6	NA	11.3	1.6	[64]
MSM and transgender women in a multinational study <sup>b</sup>	1224	NA	NA	2	NA	[66]
Individuals at high risk of HIV in Australia	5868	28.5	NA	NA	NA	[63]

*eGFR* estimated glomerular filtration rate, *MSM* men who have sex with men, *NA* not applicable, *PrEP* pre-exposure prophylaxis

<sup>a</sup> Includes USA, Canada, UK, Italy, Spain, Netherlands, Germany, France, Austria, Ireland, and Denmark

<sup>b</sup> Includes USA, Thailand, South Africa, Brazil, Ecuador, and Peru

**Table 3** Prevalence of osteoporosis or osteopenia and low BMD at baseline in clinical studies of PrEP

Population	Sample size, <i>N</i>	Region	Prevalence, %	References
Osteoporosis or osteopenia				
MSM and transgender women in a multinational study <sup>a</sup>	375 <sup>b</sup>	Spine Hip	27–29 24–25	[94]
Low BMD <sup>c</sup>				
MSM in the USA	210	Spine Hip Femoral neck ≥1 of the above	8.1 2.4 0.5 9.5	[95]
MSM and transgender women in a multinational study <sup>d</sup>	498	Spine Hip	12 2	[96]
Heterosexual men and women in Botswana	220	Spine Arm ≥1 of the above	3.6 4.5 6.8 <sup>e</sup>	[97]
Heterosexual women in Uganda and Zimbabwe	518	Spine Hip	5.8 0.6	[98]

*BMD* bone mineral density, *MSM* men who have sex with men, *PrEP* pre-exposure prophylaxis

<sup>a</sup> Includes USA, Canada, UK, Italy, Spain, Netherlands, Germany, France, Austria, Ireland, and Denmark

<sup>b</sup> BMD substudy included 375 participants out of the total number of 5387

<sup>c</sup> Defined as a Z-score below –2.0

<sup>d</sup> Includes USA, Thailand, South Africa, Brazil, and Peru

<sup>e</sup> Men, 11.3%; women, 2.6%

**Table 4** Established and potentially significant drug interactions with F/TDF and F/TAF [10, 11]

Concomitant drug class <sup>a</sup> : drug name	Effect on drug concentration	Clinical comments
F/TDF		
Nucleoside reverse transcriptase inhibitors		
Didanosine	Increased didanosine	Monitor patients closely for adverse reactions
HIV-1 protease inhibitors		
Atazanavir	Decreased atazanavir	Atazanavir 300 mg should be given with ritonavir 100 mg
Lopinavir/ritonavir	Increased TDF	Monitor patients closely for adverse reactions
Atazanavir/ritonavir	Increased TDF	
Darunavir/ritonavir	Increased TDF	
Hepatitis C antiviral agents		
Ledipasvir/sofosbuvir	Increased TDF	Monitor patients closely for adverse reactions. In patients receiving F/TDF concomitantly with ledipasvir/sofosbuvir and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy
F/TAF		
HIV-1 protease inhibitors		
Tipranavir/ritonavir	Decreased TAF	Coadministration not recommended
Anticonvulsants		
Carbamazepine	Decreased TAF	Consider alternative anticonvulsants
Oxcarbazepine	Decreased TAF	
Phenobarbital	Decreased TAF	
Phenytoin	Decreased TAF	
Antimycobacterials		
Rifabutin	Decreased TAF	Coadministration with rifabutin, rifampin, or rifapentine not recommended
Rifampin	Decreased TAF	
Rifapentine	Decreased TAF	
Herbal products		

St John's wort (*Hypericum perforatum*)

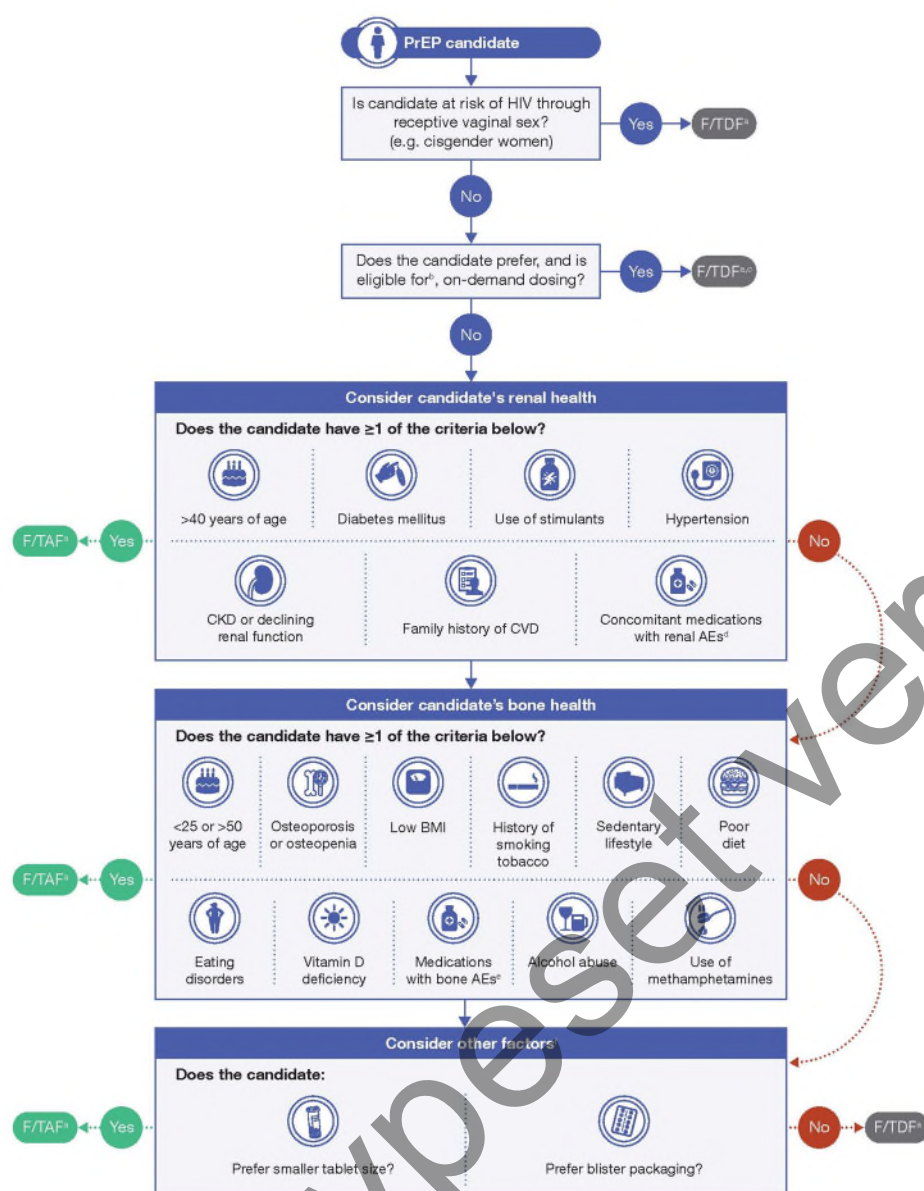
Decreased TAF

Coadministration not recommended

*F/TAF* emtricitabine/tenofovir alafenamide, *F/TDF* emtricitabine/tenofovir disoproxil fumarate, *HCV* hepatitis C virus, *NSAID* non-steroidal anti-inflammatory drug

<sup>a</sup> Coadministration of TDF or TAF with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, TDF, or TAF, and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, adefovir, dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g. gentamycin), and high-dose or multiple NSAIDs

Pre-typeset version



**Fig. 1** Algorithm for choosing PrEP

*ACEi* angiotensin-converting enzyme inhibitor, *AE* adverse event, *ARB* angiotensin receptor blocker, *BMI* body mass index, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *F/TAF* emtricitabine/tenofovir alafenamide, *F/TDF* emtricitabine/tenofovir disoproxil fumarate, *MSM* men who have sex with men, *NSAID* non-steroidal anti-inflammatory drug, *PrEP* pre-exposure prophylaxis

<sup>a</sup> If no significant drug–drug interactions

<sup>b</sup> Eligibility is limited to MSM who have infrequent sex, are able to plan for sex at least 2 hours in advance, and do not have chronic hepatitis B infection

<sup>c</sup> F/TDF is currently not approved for on-demand dosing

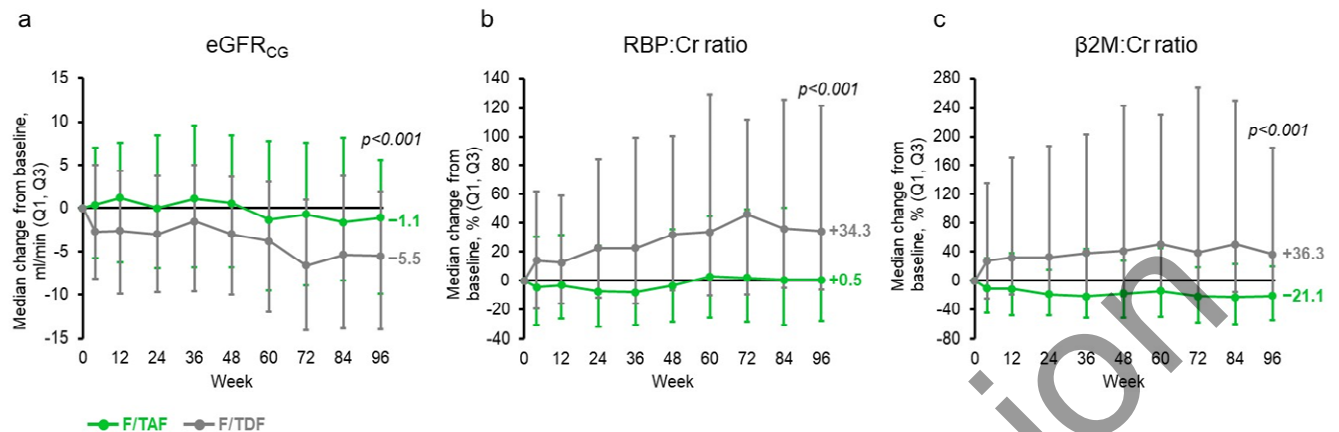
<sup>d</sup> Including psychotropic medications, NSAIDs, ACEi/ARBs, certain antibiotics, certain chemotherapies

<sup>e</sup> Including corticosteroids

<sup>f</sup> Weight gain may be slightly higher with F/TAF versus F/TDF, so this could be considered as an additional factor when discussing options with PrEP candidates



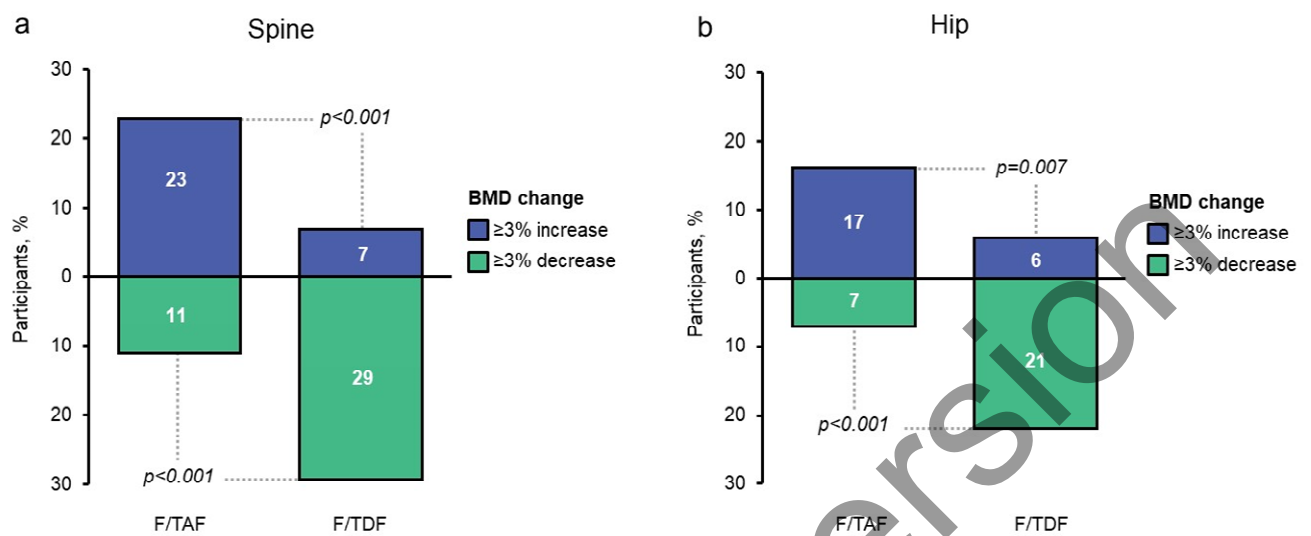
**Fig. 2** Markers of renal function in individuals  $\geq 50$  years of age using F/TAF or F/TDF for PrEP (DISCOVER study) (reproduced with permission from [17])



Cr creatinine,  $eGFR_{CG}$  estimated glomerular filtration rate (based on the Cockcroft–Gault equation), F/TAF emtricitabine/tenofovir alafenamide, F/TDF emtricitabine/tenofovir disoproxil fumarate, PrEP pre-exposure prophylaxis, RBP retinol binding protein, β2M β2 microglobulin

Median changes from baseline in (a)  $eGFR_{CG}$  and (b–c) proximal tubular protein to Cr ratios: (b) RBP:Cr ratio and (c) β2M:Cr ratio. P-values at 96 weeks are derived from the Van Elteren test stratified by baseline F/TDF for PrEP to compare the two study arms

**Fig. 3** BMD at 96 weeks in individuals using F/TAF or F/TDF for PrEP (DISCOVER study) (reproduced with permission from [17])



BMD bone mineral density, F/TAF emtricitabine/tenofovir alafenamide, F/TDF emtricitabine/tenofovir disoproxil fumarate, PrEP pre-exposure prophylaxis

Proportion of participants with  $\geq 3\%$  change in BMD from baseline in (a) spine and (b) hip. All  $p$ -values are based on dichotomized response from Cochran–Mantel–Haenszel test for nominal data (general association statistic), adjusting for baseline F/TDF for PrEP