Question: Are there any studies or concerns for long-term use of PrEP with herpes suppressive therapy? Also, are there are any studies on the long-term effects of PrEP?

Tenofovir disoproxil fumarate (TDF) 300 mg co-formulated with emtricitabine (FTC) 200 mg (hereafter referred to as TDF/FTC) was approved by the Food and Drug Administration (FDA) in 2004 and indicated in combination with other antiretroviral agents for treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients.[1,2] In 2012, TDF/FTC received FDA approval for the additional indication of use in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. To date, TDF/FTC is the only FDA-approved medication for PrEP. The 2014 Centers for Disease Control and Prevention (CDC) clinical practice guideline for PrEP in the United States (US) recommends the TDF/FTC once daily oral regimen for all at risk populations addressed in the guideline.[3]

The TDF component of PrEP was first FDA-approved in 2001 for use in combination with other antiretroviral agents for treatment of HIV-1 infection.[4] In clinical trials in HIV-1-infected patients, small but significant changes in bone mineral density (BMD), along with increases in biochemical markers of bone metabolism, occurred with use of TDF. In addition, post-marketing cases of new onset or worsening renal impairment, including acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) have been reported with TDF use in HIV-1-infected patients. Consequently, warnings and precautions regarding potential bone effects and renal toxicity are included in both TDF and TDF/FTC product labeling.[1,4] The manufacturer notes that the effects of TDF-associated changes in BMD on long-term bone health and fracture risk are unknown but baseline assessment of BMD should be considered in patients with a history of pathologic bone fracture or risks for osteoporosis. Assessing creatinine clearance in all individuals prior to initiation of treatment and periodically during treatment as clinically warranted is also recommended. Additionally, FDA-approved labeling of TDF/FTC carries a boxed warning that states, "[TDF/FTC] used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug resistant HIV-1 variants have been identified with use of [TDF/FTC] for a PrEP indication following undetected acute HIV-1 infection. Do not initiate [TDF/FTC] for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed."[1]

PrEP with herpes suppressive therapy

Regarding the potential concern for long-term use of PrEP with herpes suppressive therapy, TDF/FTC product labeling addresses the concomitant use of other drugs that affect renal function.[1] Since both TDF and FTC are primarily excreted through a combination of glomerular filtration and active tubular secretion, coadministration with other drugs that are eliminated via active tubular secretion may lead to increased concentrations of TDF, FTC, or the coadministered drugs. In TDF/FTC product labeling and the CDC PrEP guideline, antiviral drugs acyclovir and valacyclovir are included in the list of example drugs that can potentially interact with TDF/FTC via competition for active tubular secretion.[1,3] The CDC PrEP guideline recommends monitoring patients for dose-related renal toxicity when these drugs are coadministered.[3] The most recent CDC guidelines for treatment of sexually transmitted diseases recommend acyclovir, valacyclovir, or famciclovir as suppressive therapy for recurrent genital herpes simplex virus type 2 (HSV-2).[5] Famciclovir is not specifically mentioned in TDF or TDF/FTC labeling or the CDC PrEP guideline. Famciclovir labeling describes a drug interaction study in 12 healthy volunteers that showed no impact of a single dose of famciclovir 500 mg on the pharmacokinetics of a single dose of FTC 200 mg.[6] However, after oral administration, famciclovir is rapidly and extensively metabolized into its active metabolite, penciclovir, which is primarily excreted through the kidney.[7] Active tubular secretion contributes to the elimination of penciclovir.

A search of the literature yielded no published studies that addressed use of TDF or TDF/FTC (as either PrEP or HIV treatment) concomitantly with acyclovir, valacyclovir or famciclovir. Therefore, as with acyclovir and valacyclovir, monitoring for renal toxicities is recommended if famciclovir is used for HSV-2 suppressive therapy concomitantly with PrEP.

Long-term effects of PrEP

Long-term data on the safe and effective use of TDF/FTC in HIV-1-infected patients have provided ample support for the co-formulation to be recommended for the past several years in US guidelines as first-line treatment of HIV in combination with other antiretrovirals.[8] However, the incidences of sometimes irreversible renal and bone toxicities associated with TDF have led to the development and recent FDA approval of tenofovir alafenamide (TAF), a prodrug of TDF that has demonstrated comparable efficacy, with more favorable effects on renal and bone markers.[9] TAF is available in almost all of the same co-formulations as TDF with other antiretrovirals. The current HIV treatment guidelines recommend TAF over TDF primarily in patients with chronic kidney disease (estimated glomerular filtration rates (eGFR) <60 mL/min) and in patients with osteoporosis.[8] Of note, the co-formulation of TAF/FTC is not FDA-approved for use as PrEP, but a phase 3 randomized placebo-controlled trial comparing safety and efficacy of TAF/FTC and TDF/FTC for PrEP in the US is currently underway.[10] Outcome measures for safety include changes in renal biomarkers and BMD.

Studies on the long-term effects of PrEP are lacking. As mentioned above, the CDC PrEP guideline recommends the TDF/FTC once daily oral regimen as 1 prevention option for specified adult populations (sexually active men who have sex with men (MSM), heterosexually active men and women, and injection drug users) at substantial risk of HIV acquisition.[3] These recommendations were based on a review of efficacy and safety results from 8 completed phase 2/3 randomized, double blind, placebo-controlled PrEP clinical trials in healthy HIV-1-uninfected adults with normal renal function (estimated creatinine clearance (CrCl) ≥60 mL/min).[11-18] These studies are summarized in Table 1. Three of the studies (all in heterosexual African women) contributed low quality evidence because they were stopped early, 1 due to operational issues[16] and 2 due to futility of treatment attributed to very low adherence rates.[15,17] Overall, results of the other 5 studies in multiple population types demonstrated a 44%-75% reduction in risk of HIV acquisition with TDF or TDF/FTC, with a favorable safety profile over the course of 1-2 years of follow-up on average. There were no significant differences in rates of serious adverse events compared to placebo in any of the studies. However, in a few of the studies, small but statistically significant declines in some renal and/or bone biomarkers were observed.

A literature search for PrEP clinical trials evaluating long-term use and/or safety did not identify any long-term studies, but did provide additional safety information from 7 published substudies of the PrEP clinical trials that were included in the CDC guideline; 3 evaluated changes in BMD[19-21] and 4 evaluated changes in renal function.[22-25] These studies are summarized in Table 2. All 3 studies that evaluated BMD demonstrated small but statistically significant decreases in mean BMD changes measured by z-scores of the hip, lumbar spine, femoral neck, and/or forearm. Averaging 2 years of follow-up, participants in TDF or TDF/FTC study groups had mean changes from baseline in BMD that were 0.61%-1.64% lower compared to those in the placebo groups. These changes appeared within the first 6 to 12 months of treatment and stabilized or resolved thereafter. There were no differences in fracture rates between active drug and placebo during any of the studies. The substudy of renal and hepatic changes in the FEM-PrEP trial was stopped early and limited by very low adherence rates; the results are only included in Table 2 for completeness.[25] The other 3 substudies that evaluated renal function compared changes from baseline in mean estimates of CrCl and/or eGFR between TDF or TDF/FTC and placebo.[22-24] As seen with the BMD changes, changes in CrCl and eGFR were small but statistically significant. The longest of the 3 substudies followed male and female injection drug users in Thailand on treatment for

up to 5 years.[22] At month 60, the decline in CrCl was 5.2 mL/min lower in the TDF group compared to the placebo group (p=0.002), with comparable decreases in eGFR. Significant differences were observed beginning at 24 months of treatment but were shown to resolve in the subjects that were reevaluated 20 months after stopping the study drug. The substudy that evaluated changes in CrCl in MSM and transgender females in multiple countries showed similar differences in change from baseline over a mean treatment duration of 81 weeks, with the biggest difference that reached statistical significance being a 2.4 mL/min mean reduction in estimated CrCl in TDF/FTC users compared to placebo (p=0.008) at week 84.[23] Again, these differences resolved post-treatment (4-8 weeks after discontinuation). The third substudy compared changes from baseline in eGFR with TDF, TDF/FTC, or placebo in heterosexual men and women in Africa.[24] With a median treatment duration of 18 months, the mean differences from baseline in eGFR were 1.23 and 1.59 mL/min/1.73m^2 lower than placebo with TDF and TDF/FTC (p=0.004 and 0.001, respectively). The differences appeared at week 4 and began to wane after 12 months. These PrEP substudies provide corroborating evidence of reversible subclinical changes in renal and BMD biomarkers with relatively short-term use of TDF or TDF/FTC.

Until more robust data become available to assess the effects of long-term PrEP use, in addition to closely monitoring HIV status at least every 3 months to avoid development of TDF/FTC resistance, the CDC PrEP guideline recommends assessing renal function in all individuals at baseline and at least every 6 months during PrEP.[3] Consistent with prescribing information, PrEP should not be initiated in patients with estimated CrCl <60 mL/min (using Cockcroft-Gault formula) and should be discontinued if renal failure begins to develop.[1,3] The guideline notes that since the decreases in BMD seen in PrEP clinical trials were small and either stabilized or resolved without increased risk of fractures, neither baseline nor routine monitoring of bone health during PrEP are recommended at this time unless individuals have a history of pathologic or fragility bone fractures or significant risk factors for osteoporosis.[3]

Summary

In summary, while TDF/FTC has demonstrated a favorable risk-benefit profile with long-term use in the treatment of HIV infection, studies evaluating long-term PrEP use are lacking. Current guidelines are based on safety and efficacy evidence from relatively short-term phase 2 and 3 clinical trials. Documented cases of renal toxicity associated with TDF use in HIV-infected patients warrant baseline assessment and continuous monitoring of renal function throughout use for PrEP to help identify early signs of renal impairment and prevent long-term complications. Data on concurrent use of PrEP with HSV-2 suppressive therapy are not available. However, coadministration of TDF/FTC with either acyclovir, valacyclovir, or famciclovir may result in elevated concentrations of each agent due to competition for the same renal elimination pathways. Therefore, close monitoring for renal toxicities is especially warranted in patients using PrEP while receiving herpes suppressive therapy.

Table 1: Evidence summary from CDC 2014 PrEP clinical practice guideline[3]

Study	Design	Primary Endpoint(s)	Duration	Location	Population	Agent	Control	Efficacy HR [%] (95% CI)	Safety	Limitations	Evidence Quality*
iPrEx[11]	Phase 3 RCT	HIV incidence (modified intent-to-treat analysis)	Followed quarterly for a median 1.2 years, max 2.8 years	Peru; Ecuador; Brazil; Thailand; South Africa; US	MSM and male to female transgender adults who have sex with men	TDF/FTC (n=1251)	Placebo (n=1248)	0.56 [44%] (0.37-0.85)	No significant differences in overall AE or serious AE compared to placebo; moderate nausea & weight loss was more frequent in TDF/FTC group. 1 subject in TDF/FTC group discontinued due to elevated Scr, 1 due to low phosphorus.	Adherence: reduction in risk of HIV acquisition was 50% when adherence was >50%, and 73% when adherence was >90%.	High
US MSM Safety Trial[12]	Phase 2 RCT	Clinical safety of PrEP (incidence of AE & lab abnormalities)	Followed quarterly for 2 years	San Francisco; Boston; Atlanta	MSM	TDF (n=201)	Placebo (n=199)	HR not reported; 7 seroconversions occurred (none on TDF)	97% of AE were grade 1 or 2; no AE occurred significantly more in TDF compared to placebo.	Minimal. (Adherence rates were 92% by pill count and 77% by MEMS.)	High
Partners PrEP[13]	Phase 3 RCT	Seropositivity in partners previously seronegative	Followed monthly for 3 years	Kenya; Uganda	Heterosexual men and women (HIV-1 serodiscordant couples with HIV-1 positive partner not receiving ART)	TDF (n=1589) or TDF/FTC (n=1583)	Placebo (n=1586)	TDF 0.33 [67%] (0.19-0.56) TDF/FTC 0.25 [75%] (0.13-0.45)	No significant differences compared to placebo, including serious AE, serum creatinine or phosphorus abnormalities; 6 subjects in TDF groups discontinued due to elevated Scr, 0 in placebo group.	Minimal. (Adherence rates were 98% by pills dispensed, 92% by pill count, 82% by random plasma drug level testing.)	High
TDF2[14]	Phase 3 RCT	Difference in rates of HIV infection (modified intent to treat analysis)	Followed monthly for median 1.1 years, max 3.7 years	Botswana	Heterosexual men and women, age 18-29 years	TDF/FTC (n=611)	Placebo (n=608)	0.38 [62%] (15.9-82.6)	No significant differences between study groups in rates of serious clinical or laboratory AE; Small but significant decline in BMD in TDF/FTC group	High loss to follow-up: 35% in TDF/FTC group vs. 32% in placebo group did not complete follow-up; though 90% and 88% respectively had	Moderate

Study	Design	Primary Endpoint(s)	Duration	Location	Population	Agent	Control	Efficacy HR [%] (95% CI)	Safety	Limitations	Evidence Quality*
									compared to placebo with no difference in fracture rates.	known HIV status at study exit. Adherence rates were 84% by pill count, 94% by self-report for preceding 3 days.	
FEM-PrEP[15]	Phase 3 RCT	Incidence of HIV-1 or 2; incidence of clinical and laboratory abnormalities (AST, ALT, creatinine, phosphorus)	Followed monthly up to 1 year	Kenya; South Africa; Tanzania	Heterosexual women	TDF/FTC (n=1062)	Placebo (n=1058)	0.94 [6%] (0.59-1.52) Result not statistically significant. See limitations.	With the exception of higher rates of nausea/vomiting associated with TDF/FTC in the early weeks of the study and higher rate of any ALT elevation, no significant difference between study groups in rates of clinical or laboratory adverse events.	Stopped at interim analysis due to futility; limited follow-up time; very low adherence to drug regimen (<40% by drug level analysis); 13% of subjects lost to follow-up	Low
West African Trial[16]	Phase 2 RCT	Incidence of HIV-1 or 2; incidence of grade 2 or higher Scr elevations; grade 3 or 4 elevations in AST or ALT; grade 3 or 4 phosphorus reductions	Followed monthly for up to 1 year	Ghana; Cameroon; Nigeria	Heterosexual women	TDF (n=469)	Placebo (n=467)	0.35 [65%] (0.03-1.93) Result not statistically significant. See limitations.	No significant differences in safety endpoints between groups. See limitations.	Stopped early for operational concerns; small sample size; insufficient power to assess efficacy safety endpoints; limited follow-up time on assigned drug	Low

Study	Design	Primary Endpoint(s)	Duration	Location	Population	Agent	Control	Efficacy HR [%] (95% CI)	Safety	Limitations	Evidence Quality*
VOICE[17]	Phase 2B RCT	Incidence of HIV-1 infection	Followed monthly for 2.5 years	South Africa; Uganda; Zimbabwe	Heterosexual women	TDF (n=1007) TDF/FTC (n=1003	Placebo (n=1009)	TDF 1.49 [-50%] (0.97-2.3) TDF/FTC 1.04 [-4%] (0.73-1.5) Results not statistically significant. See limitations.	Rate of elevated Scr in participants in TDF/FTC group was 1.3% vs. 0.2% in placebo group (p=0.004); all mild except 1 case. No other significant differences in safety outcomes.	TDF arm stopped at interim analysis (futility); very low adherence to drug regimen in both TDF and TDF/FTC arms (<40% of plasma samples with detectable drug in all groups).	Low
BTS[18]	Phase 3 RCT	Incidence of HIV-1 infection (modified intention-to-treat analysis)	Followed monthly for mean of 4.0 years, max 6.9 years	Bangkok, Thailand	Injection drug users	TDF (n=1204)	Placebo (n=1207)	0.51 [49%] (9.6-72.2)	Nausea/vomiting was more common in TDF group in first month of follow-up; no significant differences in rates of serious AE between groups.	Minimal. (Mean adherence was 84% based on drug diaries.)	High

* Based on GRADE quality ratings: High=further research is very unlikely to change our confidence in the estimate of effect; Moderate=further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low=further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very Low=any estimate of effect is very uncertain

AE=adverse event; ALT=alanine aminotransferase; ART=antiretroviral therapy; AST=aspartate aminotransferase; CI=confidence interval; FTC=emtricitabine; HIV=human immunodeficiency virus; HR=hazard ratio; max=maximum; MSM=men who have sex with men; PrEP=preexposure prophylaxis; RCT=randomized controlled trial; Scr=serum creatinine; TDF=tenofovir disoproxil fumarate; US=United States

Table 2: Summary of additional published safety data from PrEP clinical trials

Study	Design	Primary Endpoint(s)	Duration	Location	Population	Agent	Control	Baseline	Change from Baseline	Comments
BMD substudy of US MSM Safety Trial[19]	Phase 3 RCT	Change in BMD measured by z-scores of lumbar spine, total hip and femoral neck (intent-to-treat analysis)	2 years (DXA scan at baseline, 9 or 12 months and 24 months)	San Francisco	MSM	TDF (n=100)	Placebo (n=100)	Overall, 10% of subjects had low BMD (z-score ≤ -2.0). No significant difference between TDF and placebo groups in longitudinal cohort.	Mean net decrease in BMD with TDF vs. placebo: Femoral neck=1.1% (p=0.004) Total hip=0.8% (p=0.003) L2-L4 spine=0.7% (p=0.11)	The small but statistically significant declines in BMD associated with TDF occurred during the first 12 months of TDF use, with no further decline at 24 months. There was no difference in fracture rates between study groups.
BMD substudy of TDF2 Trial[20]	Phase 3 RCT	Change in BMD measured by z-scores of hip, spine and forearm	30 months (DXA scan at baseline and 6-month intervals)	Botswana	Heterosexual men and women, age 18-29 years	TDF/FTC (n=109)	Placebo (n=112)	Overall, 6.8% of subjects had low BMD (z-score ≤ -2.0); No significant difference between TDF/FTC and placebo groups.	Mean net decrease in BMD with TDF/FTC vs. placebo at month 30: Forearm=0.86% (p=0.01) Spine=1.64% (p=0.0002) Hip=1.51% (p=0.003) At month 30, 50% in TDF group vs. 33% in placebo group (p=0.04) experienced >3.0% decline in BMD at any site or time point (no difference between males and females).	Limitation: only 42 TDF/FTC subjects and 52 placebo subjects completed the study.
BMD substudy of iPrEx Trial[21]	Phase 3 RCT	Change in BMD measured by z-scores of lumbar spine and total hip (intent-to-treat analysis)	96 weeks (DXA scan at baseline and 24 week intervals)	Peru; Brazil; Thailand; South Africa; US	MSM and male to female transgender adults who have sex with men	TDF/FTC (n=247)	Placebo (n=251)	Overall, 12% and 2% of subjects had low spine and hip BMD, respectively. No significant difference between TDF/FTC and placebo groups.	Mean net decrease in spine BMD with TDF/FTC compared to placebo at week 24=0.91% (p=0.001); further net decrease for weeks 48, 72, and 96 averaged 0.12% and were not statistically significant. Mean net decrease in total hip BMD at week 24=0.61% (p=0.001) at week 48=0.92% (p<0.001) but not	Declines in both hip and spine BMD were significantly steeper during the first 24 weeks compared to those after 24 weeks. No significant differences between groups in fracture rates during the study.

Study	Design	Primary Endpoint(s)	Duration	Location	Population	Agent	Control	Baseline	Change from Baseline	Comments
									significantly lower at weeks 72 or 96.	
Renal function substudy of BTS Trial[22]	Phase 3 RCT	Difference in cross-sectional mean estimate of CrCl (Cockcroft-Gault) and eGFR (MDRD and CKD-EPI)	60 months	Bangkok, Thailand	Injection drug users	TDF (n=1204)	Placebo (n=1209)	TDF vs. placebo CrCl=100.8 vs. 98.5 mL/min (p=0.03) MDRD eGFR= 95.8 vs. 95.1 mL/min/1.73m^2 (p=NS) CKD-EPI eGFR= 106.0 vs. 105.4 mL/min/1.73m^2 (p=NS)	At month 60: CrCl=5.2 mL/min lower with TDF vs. placebo (p=0.002) MDRD eGFR=3.4 mL/min/ 1.73m^2 lower with TDF vs. placebo (p=0.003) CKD-EPI eGFR=3.3 mL/min/ 1.73m^2 lower with TDF vs. placebo (p=0.002)	All 3 estimates of renal function were significantly lower in TDF group at months 24, 36, 48 and 60. Posttrial assessment of CrCl in 749 (31%) of subjects that had been off study drug for a median of 20 months showed the differences had resolved.
Renal function substudy of iPrEx Trial[23]	Phase 3 RCT	Mean net differences in estimated CrCl (Cockcroft-Gault)	144 weeks	Peru; Ecuador; Brazil; Thailand; US	MSM and male to female transgender adults who have sex with men	TDF/FTC (n=563)	Placebo (n=574)	TDF/FTC vs. placebo mean CrCl=118.4 vs. 119.5 mL/min (p=NS)	At week 4: CrCl=2.4 mL/min lower with TDF/FTC vs. placebo (p=0.02) Range over 144 study weeks: CrCl=2.7 mL/min lower to 0.038 mL/min higher with TDF/FTC. Net differences were statistically significant as late as week 84.	Mean treatment duration was 81 weeks. Scr measures at 4 and 8 weeks post-treatment showed that differences between groups in estimated CrCl resolved. A substudy of incidence of proximal tubulopathy measured by urine glucose, protein, uric acid and phosphorus revealed no differences between TDF/FTC and placebo.
Renal function substudy of Partners PrEP Trial[24]	Phase 3 RCT	Mean eGFR change and a ≥25% eGFR decline from baseline (CKD-EPI)	36 months	Kenya; Uganda	Heterosexual men and women (HIV-1 serodiscordant couples with HIV-1 positive partner not receiving ART)	TDF (n=1548) TDF/FTC (n=1545)	Placebo (n=1547)	eGFR similar among groups: 130 vs. 129 vs. 129 mL/min/1.73m^2 TDF vs. TDF/FTC vs. placebo	During median 18 months of treatment, mean change in eGFR compared to placebo: TDF: -1.23 mL/min/1.73m^2 (p=0.004) TDF/FTC: -1.59 mL/min/1.73m^2 (p<0.001) Confirmed eGFR decline of ≥25% with active treatment was rare and did not differ	Differences in eGFR change from baseline translated to a 0.9% and 1.2% decline in eGFR with TDF and TDF/FTC, respectively, compared to placebo. Differences appeared by 4 weeks, were stable at 12 months and gradually waned thereafter.

Study	Design	Primary Endpoint(s)	Duration	Location	Population	Agent	Control	Baseline	Change from Baseline	Comments
									from placebo. Adjusted relative hazard for confirmed decline of ≥25% in eGFR was 1.33 (95% CI, 0.71-2.48, p=0.37) with TDF and 1.45 (0.79-2.64, p=0.23) with TDF/FTC.	
Renal and liver toxicity substudy of FEM-PrEP Trial[25]	Phase 3 RCT	Incidence of grade 1+ creatinine, AST, ALT or grade 2+ phosphorus toxicities. Exploratory evaluation of association with HBsAb.	Hepatic and renal parameters measured at weeks: 4, 12, 24, 36, 52, 56	Kenya; South Africa; Tanzania	Heterosexual women	TDF/FTC (n=1062)	Placebo (n=1058)	ALT, AST, creatinine and phosphorus levels were comparable to average at respective sites. 20.8% in TDF/FTC group and 21.4% in placebo group were HBsAb positive	Cumulative probabilities of grade 1+ creatinine or grade 2+ phosphorus toxicity did not differ between the groups. Cumulative probabilities of grade 1+ ALT and AST toxicities were higher in the TDF/FTC arm than in the placebo arm (p = 0.03 for both). In TDF/FTC arm, proportions of ALT or AST toxicities were significantly higher in participants who were HBsAb positive than in those who were HBsAb-negative: Grade 1+, 31.6 vs. 22.4% respectively, p<0.007 Grade 2+, 5.6 vs. 2.6% respectively, p<0.047	None of the observed lab toxicities was associated with renal or hepatic clinical symptoms. Quality of evidence is low due to low adherence rates in this study.

ALT=alanine aminotransferase; ART=antiretroviral therapy; AST=aspartate aminotransferase; BMD=bone mineral density; CI=confidence interval; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CrCl=creatinine clearance; DXA=dual-energy X-ray absorptiometry; FTC=emtricitabine; eGFR=estimated glomerular filtration rate; HBsAb=hepatitis B surface antibody; HIV=human immunodeficiency virus; MDRD=Modification of Diet in Renal Disease equation; MSM=men who have sex with men; NS=not significant; PrEP=pre-exposure prophylaxis; RCT=randomized controlled trial; TDF=tenofovir disoproxil fumarate; US=United States

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