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Safety of Oral Tenofovir Disoproxil Fumarate-Based Pre-Exposure Prophylaxis for HIV Prevention

Kenneth K. Mugwanya, MBChB, MS^{1,2,3} and Jared M. Baeten, MD, PhD^{1,2,4}

¹Department of Epidemiology, University of Washington, Seattle, USA ²Department of Global Health, University of Washington, Seattle, USA ³Division of disease control, school of Public Health Makerere University, Kampala Uganda ⁴Department of Medicine, University of Washington, Seattle, USA

Abstract

Introduction—Tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis is a novel HIV prevention strategy for individuals at increased sexual risk for HIV infection. For any biomedical prevention intervention, the bar for tolerating adverse effects in healthy persons is high compared to therapeutic interventions.

Areas covered—We provide a concise summary of the clinical safety of TDF-based pre-exposure prophylaxis with focus on TDF-related effects on tolerability and side effects, kidney function, bone density, HIV resistance, sexual and reproductive health. The evidence base for this review is derived from a literature search of both randomized and observational studies evaluating efficacy and safety of TDF-based PrEP, TDF alone or in combination with emtricitabine, identified from PUBMED and EMBASE electronic databases, clinicaltrials.gov and major HIV conferences.

Expert opinion—TDF-based pre-exposure prophylaxis is a potent intervention against HIV acquisition when taken which is generally safe and well tolerated. The risk of the small, non-progressive, and reversible decline in glomerular filtration rate and bone mineral density as well as the potential selection for drug resistance associated with PrEP are outweighed, at the population level and broadly for individuals, by PrEP's substantial reduction in the risk of HIV infection.

1 Introduction

Tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), reduces the risk of HIV acquisition in individuals at substantial risk of HIV infection when used as pre-exposure prophylaxis (PrEP) ¹⁻⁴. FTC and TDF are widely prescribed as part of combination antiretroviral therapy for the treatment of HIV. While generally safe and well tolerated in HIV-infected persons, TDF is infrequently associated with increased risk of some toxicities, including renal impairment (ranging from mild to occasionally severe, with higher risk among persons of African descent vs Caucasians) ^{5,6} and loss of bone mineral

density⁷. Moreover, use of antiretroviral medications, for treatment of HIV and potentially for prophylaxis as well, carries some risk of selection for HIV viruses harboring antiretroviral resistance. Thus, the use of TDF and FTC-TDF as PrEP has raised important questions about the safety of these medications for use as preventative agents. Importantly, for all biomedical prevention interventions, the bar for tolerating adverse effects must be high compared to therapeutic interventions, as the group using the preventative intervention is otherwise healthy and has only a chance of contracting the condition being prevented. For PrEP, given the epidemiology of HIV risk, the majority of persons who will be prioritized for implementation of PrEP will likely be younger, otherwise healthy, and with minimal use of concurrent medications⁸. In this article, we provide a concise review and summary of current data on the clinical safety of oral TDF-based PrEP for healthy adults for HIV prevention with focus on TDF-related tolerability and adverse effects.

2 Mechanism of action and clinical pharmacology

TDF is a prodrug for tenofovir, an acyclic nucleotide analogue reverse transcriptase inhibitor⁹. Tenofovir is a potent competitive inhibitor of HIV and hepatitis B virus reverse transcriptase that is additive or synergistic when combined with other antiretroviral agents inhibiting viral replication⁹; for both HIV and HBV, it has a high barrier for the development of viral resistance mutations. It has a long elimination and intracellular half-life (~17 and >60 hours, respectively), allowing for once-daily dosing. The oral bioavailability of TDF in fasted subjects is ~25% and following absorption, TDF is rapidly (<1 minute) converted to tenofovir which is metabolized intracellularly to the active metabolite, tenofovir diphosphate¹⁰. Maximum tenofovir plasma concentrations are achieved within 1 to 2 hours of oral administration¹⁰. TDF (and FTC) is not an inducer or a substrate for cytochrome P450 enzymes but is primarily eliminated unchanged in urine by a combination of glomerular filtration and active proximal tubular secretion¹⁰. About 20-30% of the tenofovir is actively transported across the basolateral membrane into the proximal tubular epithelial cells by organic anion transporters¹¹, with active efflux into the tubular lumen across the apical membrane via the multi-drug resistance proteins transporters¹², intrinsically making the proximal tubule epithelial cells a target for tenofovir-related kidney toxicity¹³. The pathogenesis of TDF-related toxicities is not well elucidated but may be a consequence of effects on the proximal tubule epithelial cell mitochondria^{14,15}, although tenofovir is a weak inhibitor of mammalian and mitochondrial DNA polymerases compared to the structurally similar acyclic nucleotide analogues, cidofovir and adefovir.

3 Clinical application of TDF for HIV prevention

PrEP involves administering antiretroviral medications to HIV uninfected, at-risk individuals to lower their risk of sexual HIV acquisition. Biological plausibility to support efficacy and safety trials of antiretroviral PrEP against HIV acquisition was derived from human studies of post-exposure prophylaxis and of use of antiretrovirals for the prevention of perinatal HIV transmission; animal studies of vaginal and rectal viral challenge provided models of PrEP efficacy¹⁶⁻²⁰. Randomized clinical trials have demonstrated that oral TDF-based pre-exposure prophylaxis is highly effective against HIV acquisition in a diverse at-risk populations and geographical regions, with protective effectiveness of 44-75% in the

randomized comparisons and >90% in persons adherent to PrEP as prescribed. However, a lack of efficacy was observed in two PrEP trials in African women^{21,22}, thought to be due to very low adherence to PrEP in those studies. In 2012, the US Food and Drug Administration approved daily oral FTC-TDF for HIV prevention in persons with heightened risk for HIV in combination with other HIV prevention strategies²³. Subsequently, the US Centers for Disease Control and Prevention has issued detailed guidelines for the delivery of PrEP in clinical settings²⁴, and, recently, the World Health Organization issued guidelines recommending PrEP be offered as a prevention options to persons at substantial risk for HIV acquisition^{8,25}. TDF alone is also effective for HIV prevention. Recent evidence from pragmatic trials has demonstrated high protective effectiveness for PrEP against HIV infection in “real world” settings²⁶⁻²⁸.

4 Safety evaluation

Evidence for this review was derived from a search of literature on PrEP efficacy and safety from randomized clinical trials, open-label extensions following randomized trials, implementation PrEP projects, and observational studies. Articles published in English between January 1, 1999 and August 15, 2015 were identified from PubMed and EMBASE electronic databases, and the clinical trials registry (www.clinicaltrials.gov) using combination search terms (preexposure prophylaxis, pre-exposure prophylaxis, PrEP, HIV, Truvada, tenofovir, antiretroviral, chemoprophylaxis, and toxicity category). Abstracts from major HIV conferences (e.g., Conference on Retroviruses and Opportunistic Infections, International AIDS Conference, and IAS Conference on HIV Pathogenesis, Treatment, and Prevention) were also considered. In addition, we reviewed reference lists of relevant papers. Toxicity signals are summarized under the following categories: general side effects, kidney, bone, HIV resistance, and sexual and reproductive health. The studies contributing to this review and the summary of evidence are provided in the Table.

4.1 General and any adverse effects

Overall, the frequency of any adverse events (i.e. any clinical or laboratory finding), both overall, grade 3/4, and serious adverse events, was no greater for persons assigned PrEP versus those assigned placebo or no PrEP in clinical trials^{1-4,21,29-32}. General gastrointestinal symptoms, commonly referred to as PrEP start-up syndrome, (primarily nausea, but also including diarrhea, vomiting, and abdominal pain), occurred in 1- 18% of participants assigned active PrEP compared to 0-10% in persons assigned placebo. PrEP start-up symptoms are generally limited to within the first month and end spontaneously^{1-4,21,27,29,30,33}.

4.2 Kidney toxicity

An important concern for the use of TDF for PrEP is the potential for kidney toxicity. Three secondary analyses of the Partners PrEP, iPrEx, and Bangkok Tenofovir studies provide detailed analyses of changes in estimated glomerular filtration rate (eGFR), a commonly-used measure of overall kidney function. In those studies, TDF-based PrEP was associated with a small but statistically significant decline in eGFR that was non-progressive and resolved with TDF discontinuation. In the Partners PrEP Study³⁴, with a median per-

protocol follow-up of 18 months, declines in eGFR attributed to TDF-based PrEP versus placebo were 1-3 mL/min/1.73 m² (p <0.05), a change of <1.5% from baseline that was non-progressive for 36 months and was not accompanied by a significant increase in the likelihood of a clinically relevant change in eGFR (i.e., 25% decline from baseline). Similar magnitude of decline in calculated creatinine clearance were observed in the iPrEx cohort after up to 81 weeks of observation (~2% loss in creatinine clearance from baseline) that was stable through the last on-treatment visit³⁵. In the Bangkok Tenofovir Study^{2,36}, the net decline in creatinine clearance attributable to TDF versus placebo were 1-5 mL/min significantly lower for participants assigned TDF versus placebo up to 60 months. Overall, the frequency of graded creatinine elevations were more common in PrEP arms but not statistically different from placebo and the reported kidney abnormalities resolved after TDF was discontinued^{1-4,21,22,29-32,34-37}. Detailed evaluation of proximal tubular function, was only reported by an optional sub-study of the iPrEx trial among 1137 participants (563 FTC-TDF, 574 placebo)³⁵. In that sub study, the frequency of abnormal fractional excretion of phosphorus and uric acid, glycosuria in presence of normal serum glucose, and proteinuria was rare and no more common in persons assigned FTC-TDF than placebo. Similarly, other studies reporting on the frequency of graded decreased phosphorus did not observe difference between TDF-based PrEP versus placebo.

4.3 Bone toxicity

Loss of bone mineral density (BMD) and potentially bone fractures is another concern for TDF-based PrEP, potentially as a consequence of TDF-related phosphate wasting³⁸. Overall, TDF-based PrEP appears to be associated with modest (0.4% to 1.6%) but statistically significant net loss in BMD among HIV-uninfected individuals without elevation in the risk of bone fractures^{1,2,4,22,39-41}. The observed decline resolves to baseline level after TDF is discontinued. In a sub-study of the iPrEx cohort (247 subjects receiving FTC-TDF, 251 placebo)⁴¹, 12% and 2% of participants had low BMD in the spine and the hip at baseline, respectively, and FTC-TDF PrEP was associated with a net BMD decrease versus placebo at the spine or hip of -0.6% to -0.91% at 24 weeks that was stable up to 96 weeks with no elevated risk for bone fractures. BMD decline was correlated with tenofovir plasma levels. In a sub-study of CDC TDF Safety Study among HIV-negative men who have sex with men (94 on TDF, 90 on placebo)⁴⁰, baseline low BMD (z-score) was 10% and the net mean BMD decline for TDF versus placebo were -0.7% to -1.1% at femoral neck, total hip or at the L2-L4 spine over 24 months of follow-up; 13% of participants on TDF vs. 6% placebo of participants experienced 5% BMD loss at the femoral neck at 24 months (p =0.13) with no significant difference in the risk for bone fractures (p =0.75). In a BMD sub-study of the TDF2 Study (68 on FTC-TDF, 79 on placebo)³⁹, net BMD decrease from baseline at forearm, spine, and hip was 0.8% to 1.6% lower for TDF-FTC versus placebo at month 30 (p <0.05). The proportion of participants with BMD losses of >3.0% at any anatomic site was higher for FTC-TDF vs placebo (50.0% vs 32.9%, p =0.04); no benefits for calcium supplementation for participants with a low baseline BMD were observed. Of note, completion rates were very low in that sub-study (<70%).

4.4 HIV resistance

One concern commonly raised about the safety of TDF PrEP is the potential for selection of HIV resistance. Resistance can arise when PrEP is used by individuals with unidentified HIV infection (principally acute infection at the time of PrEP initiation) or in persons with inadequate adherence who experience breakthrough infection in the face of some drug pressure. Seven trials investigated cases of drug resistance to either FTC (the substitution mutations M184I/V) or TDF (K65R and K70E) PrEP^{1-4,21,22,26,42-44}, primarily using standard genotypic assays but with next generation ultrasensitive analyses in some cases. Overall, 9 out of 45 individuals with unrecognized acute HIV infection at randomization and assigned to either TDF or FTC-TDF had mutations that confer resistance to FTC or TDF, and so did 7 resistant HIV infections out of 271 cases of incident HIV infection post-randomization in individuals that were assigned either TDF alone or FTC-TDF^{1-4,21,22,26,42-44}. The development of resistant mutations appeared to be related to FTC more commonly than TDF, consistent with a lower bar to selection of the M184V mutation for FTC than the K65R mutation for TDF. Importantly, PrEP-related resistance faded to background levels after PrEP was stopped. These data suggest that selection for mutations that confer resistance is rare but occur primarily if PrEP is started with early HIV infection unrecognized by antibody testing done at the time of PrEP initiation. The population level effect of the PrEP-related resistance is still unclear but mathematical modeling suggest that the cumulative risk of drug resistance from PrEP could be much lower than that associated with that already known to be selected by antiretroviral treatment of persons with established HIV infection⁴⁵.

4.5 Sexual and reproductive health

Women at greatest risk for HIV are in their childbearing years exposed to both the risk for HIV infection and unintended pregnancy. PrEP and joint use of hormonal contraception could offer dual protection. Two studies reported detailed data on the effectiveness of hormonal contraception comparing participants randomized to receive active PrEP and those randomized to receive placebo. In the Partners PrEP Study, pregnancy rates and hormonal contraceptive effectiveness were statistically similar for women assigned PrEP versus placebo⁴⁶. In the same cohort, the protective effectiveness for PrEP versus placebo was similar among women using DMPA and those using no hormonal contraception, 64.7% and 75.5% respectively ($p=0.65$)⁴⁷. In the FEM-PrEP Study, pregnancy rates were not significantly different for women assigned FTC-TDF PrEP versus placebo after adjustment for age, contraception method and site [adjusted hazard ratios (95% confidence interval): 1.2 (0.9 to 1.8), $p=0.20$]^{22,48}. These data suggest that TDF-based PrEP does not appear to affect the effectiveness of hormonal contraception, nor does hormonal contraception affect PrEP efficacy.

Data on the safety for exposed fetuses are limited because in PrEP trials with heterosexual women medication was promptly discontinued for those who became pregnant, but some data are available from women who were on study drug in their first few months of pregnancy. In the Partners PrEP Study, among 288 women with first trimester (median= 35 days) TDF exposure⁴⁹, the frequency of pregnancy loss was 42.5% for women receiving FTC-TDF ($p=0.46$) and 27.7% on TDF alone ($p=0.16$) vs 32.3% on placebo. In addition,

there were no significant differences in pregnancy-related and infant adverse outcomes including preterm birth, congenital anomalies, and growth throughout the first year of life for infants born to women who received PrEP vs placebo. Similarly, pregnancy rates and related adverse outcomes were similar for women assigned FTC-TDF or TDF alone versus placebo in the VOICE trial²¹. In a Ugandan study of safety of daily/intermittent FTC-TDF PrEP versus daily/intermittent placebo³⁰, 3 pregnancies were recorded overall, resulting in one live birth (daily placebo group) and 2 losses: one spontaneous abortion at 6 weeks of pregnancy (daily active group) and a molar pregnancy (intermittent placebo group). Taken together, these data although limited by small numbers and follow-up duration suggest no clinically significant risks for poor birth outcomes or infant growth among women with early pregnancy TDF exposure and are consistent with evidence from HIV-infected women using tenofovir for treatment^{50,51} and data on pregnancy and infant outcomes in the US Antiretroviral Pregnancy Registry involving >3000 pregnancies with first trimester exposure to either FTC or TDF⁵².

Another concern in the sexual and reproductive health space is the theoretical potential for increased sexual risk behaviors as a result of using PrEP, a concept referred to as risk compensation. Risk compensation could lead to a heightened risk of HIV acquisition, overwhelming PrEP's protective effects, or could expose individuals to other adverse effects (sexually transmitted infections, unintended pregnancy). However, data to date do not indicate substantive sexual behavior with PrEP. In PrEP clinical trials, risky behavior declined over time, including declines in the frequency of sex acts unprotected with condom, number of sexual partners, and sex with partners with unknown HIV status compared to baseline levels^{1,4,22,30,31,53-57}. Importantly, PrEP use and efficacy appear to map best to individuals who are not using condoms already at the time they start PrEP.

5 Comparison with safety of potential alternative PrEP drugs

Currently FTC-TDF in the US is the only medication with a label indication as PrEP against HIV acquisition. However, new PrEP drugs and formulations are currently being evaluated including other oral agents (e.g., maraviroc), intravaginal rings (dapivirine, tenofovir), and longer-acting injectable agents (rilpivirine, cabotegravir). These agents appear to have good safety profile when used for treatment of HIV infection but their efficacy and clinical safety as PrEP in HIV-uninfected persons is still unknown. Tenofovir alafenamide (TAF) a newly-developed prodrug for tenofovir that delivers 90% lower plasma tenofovir concentrations compared with standard TDF, has recently received US FDA approval for treatment of HIV infection (approval first as a coformulation with elvitegravir/cobicistat/emtricitabine). TAF, compared to TDF, appears to result in less potential for kidney and bone toxicity in HIV-infected persons. However, TAF, alone or in combination with emtricitabine, has not been formally evaluated as PrEP in HIV-uninfected populations, although its potential for offering a PrEP option with further-diminished long-term toxicity holds substantial appeal.

6 Conclusions

TDF-based PrEP is a recommended approach to prevention of HIV acquisition in combination with other HIV prevention strategies. It is highly effective against HIV

acquisition when taken. A PrEP start-up syndrome with gastrointestinal symptoms is the most common side effect but symptoms are self-limited. TDF-based PrEP is associated with modest but statistically significant declines in both eGFR and BMD but the declines are non-progressive, and not associated with clinically relevant glomerular dysfunction and bone fractures, respectively, and quickly resolved after TDF discontinuation. HIV resistance selected by PrEP is rare but can occur if PrEP is initiated with unrecognized acute HIV infection and is mostly associated with mutations that confer resistance to the FTC component. Sexual and reproductive health concerns related to PrEP have not been borne out by current data. Of note, the low adherence to PrEP reported in some of the first generation PrEP trials may limit the strength of evidence from these study populations. Limitations of low drug exposure in some studies and short follow-up notwithstanding, these data suggest that oral TDF-based PrEP may be associated with limited clinically relevant safety signals in healthy persons, but safety among subpopulations with co-morbid conditions like reduced kidney function, diabetes, hypertension or concurrent nephrotoxic medication is still unknown as does the long-term effects beyond reported study durations.

7 Expert opinion

Oral TDF-based PrEP is an effective and FDA approved novel strategy to reduce risk of HIV acquisition. Normative agencies have issued guidelines for use of PrEP in clinical settings as a prevention option to persons at substantial risk for HIV acquisition. Clinical experience has been accumulated from randomized clinical trials and observational studies involving more than 10,000 HIV-uninfected adults from diverse geographies and at-risk groups, exposed to TDF-based PrEP ranging from 6 months to 5 years. These data suggest that oral TDF-based PrEP is generally safe and well-tolerated in healthy HIV-uninfected populations. TDF-based PrEP carries a small but statistically significant risk for renal and bone toxicity, somewhat limited data for safe use in pregnancy and lactation, as well as potential to select for HIV resistance to PrEP medications, if PrEP is used by persons with established HIV infection. Renal and bone effects of TDF-based PrEP appear to resolve on drug discontinuation. The US CDC recommends monitoring of renal function at 3 months and bi-annually based on creatinine clearance after initiating PrEP but given that clinically relevant renal toxicities are rare and appear to resolve quickly after stopping TDF, less renal monitoring may be sufficient. Tubular renal toxicity from PrEP appears to be very rare and active screening is not recommended. Although the clinical significance of the observed bone loss on future risk for fragility fractures is not clear, current evidence does not support radiologic assessments of bone health before the initiation of PrEP or for the monitoring of persons while taking PrEP. A new formulation of tenofovir, tenofovir alafenamide (TAF), has recently been developed and appears to demonstrate favorable renal and bone safety profile compared to TDF but efficacy and safety as PrEP is yet to be proven in HIV-uninfected populations. Regarding safety during pregnancy and breastfeeding, current data from first trimester exposure TDF PrEP and collaborated with data from the US Antiretroviral Pregnancy Registry (sufficient enough to rule up to 2 fold increase in risk of birth defects associated with TDF exposure) do not cause concern for PrEP use during early pregnancy, but effects of TDF-based PrEP used the entire pregnancy and early postpartum are essentially unknown. Selection for mutations that confer resistance to TDF and FTC is

rare but risk exist primarily when PrEP is initiated with unrecognized HIV infection; mathematical modeling studies suggest that the cumulative risk of drug resistance from PrEP is expected to be low. In addition, PrEP breakthrough infections are rare and this risk must be weighed against the number of new HIV infections averted by PrEP. Importantly, the observation that resistant mutations faded to background level after stopping PrEP is reassuring suggesting that the risk of compromising subsequent combination treatment options for a minority of individuals with PrEP breakthrough infections might be low and of limited public health consequence. In summary, TDF-based PrEP is a highly potent HIV prevention strategy for which the observed risks arguably are outweighed, at the public health level and for at-risk individuals, by its HIV prevention benefits.

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* of importance, ** of considerable importance.

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Summary of clinical safety of oral tenofovir disoproxil fumarate-based pre-exposure prophylaxis for HIV prevention

Table

Safety signal	Reference contributing to evidence	Summary/range of effects for TDF-based PrEP vs placebo or no PrEP	Current recommendation
PrEP start-up syndrome	1, 2, 3, 4, 21, 22, 27, 28, 29, 30, 31, 32,33	Mild gastrointestinal symptoms (primarily nausea but also vomiting, diarrhea, abdominal pain) are the most common side effects associated with PrEP occurred 1-18% of participants assigned PrEP vs 0-10% of participants assigned placebo in clinical trials but end spontaneously within limited 1-2 months.	Counsel clients on potential side effects
Kidney toxicity	34, 35,36	1-5 mL/min/1.73m ² net mean eGFR decline associated with PrEP vs placebo with no clinically relevant eGFR decline from baseline observed up to 5 years. Declines resolve with drug discontinuation. Limited data on tubular dysfunction but no evidence of difference in prevalence for PrEP vs placebo seen in the iPrEx sub-study. Study specific net eGFR/CrCl decline attributable to PrEP Partners PrEP Study (CKD-eGFR): -1.23 to -1.59 mL/min/1.73m ² over 1.8 per-protocol months. Proportion of persons with 25% eGFR decline at 12 months: 1.3-1.8% for PrEP vs 1.3% for placebo. iPrExStudy (CrCl): -1.3 at 4 weeks and -1.5 mL/min -1.5 mL/min at last-on treatment visit , observed over 81 weeks (p=0.02). No differences in markers of proximal tubular dysfunction between PrEP and placebo. Bangkok Tenofovir Study (CrCl): -2.5 mL/min at 24 months and -5.2 mL/min at 60 months.	During PrEP use, current CDC guideline are: a) Initiate PrEP in person with CrCl ≥60mL/min, and no contraindicated medications. b) Monitor renal function at 3 month and then bi-annually using CrCl not serum creatinine alone
Bone toxicity	39,40,41	Overall, 1.6% net loss in BMD associated with PrEP vs placebo over 1-2 years with no elevation in risk for bone fractures has been reported. Decline resolves to baseline with TDF discontinuation. Study specific net BMD decline attributable to PrEP vs placebo/no PrEP iPrEx Study (at week 24): Hip: -0.61% (p=0.001); lumbar spine: -0.91% (p=0.001) TDF2 Study (at month 30): Forearm: -0.86% (p=0.008); Spine: -1.64% (p<0.001) Hip: -1.55% (p=0.001); Proportion of persons with 3% bone loss at any site: 50% vs 32.9%; p=0.04. CDC Safety Study: Femoral neck: -1.1% (p=0.004); Total hip: -0.8% (p=0.003); Lumbar spine L2-L4: -0.7% (p=0.11); Proportion of persons with 5% bone loss at any site at 24 month: 13% vs 6% (p=0.1)	Laboratory or radiologic assessments of bone health is not recommended before the initiation of PrEP or for the monitoring of persons while taking PrEP
Antiretroviral Resistance	1, 2, 3, 4, 22, 21, 26, 27, 42, 43, 44	HIV mutations that confer resistance to FTC (M184I/V) or TDF (K65R and K70E) are rare but can occur, principally with unrecognized acute infection at the time of PrEP initiation. In all reviewed studies, resistant mutation were observed in 9/45 and 7/271 of persons with unrecognized acute HIV infection at PrEP initiation and PrEP breakthrough HIV infection (i.e. persons who were HIV uninfected at the initiation of PrEP), respectively. Mostly affects FTC component than TDF and appeared to fade to background levels after PrEP was stopped	Documented negative HIV test result before prescribing PrEP, and no signs/symptoms of acute HIV infection. HIV test every 3 months.
PrEP-hormonal contraception interaction	46, 47, 48	No evidence that PrEP affects hormonal contraception effectiveness and vice versa	PrEP can be used among women using contraception for pregnancy prevention.
Pregnancy adverse events	30, 48, 49	Limited data from first trimester TDF exposure suggest no increased risk for poor birth outcomes and no delays in infant growth during the first year of life. Eg. Pregnancy loss in Partners PrEP study (n=288 pregnancies): 42.5% for FTC-TDF (p=0.16) and 27.7% for TDF group (p=0.46) vs 32.3% placebo	US FDA labeling information permit PrEP use for preconception and during pregnancy by the uninfected partner as it may offer an additional tool to reduce the risk of sexual HIV acquisition, recognizing that the amount of data is limited. Assess pregnancy data is limited. Assess pregnancy intent while on PrEP and counsel based on available data.

<i>Safety signal</i>	<i>Reference contributing to evidence</i>	<i>Summary/range of effects for TDF-based PrEP vs placebo or no PrEP</i>	<i>Current recommendation</i>
Behavior risk compensation	1, 2, 3, 4, 21, 22, 26, 27, 29, 30, 31, 32, 33, 53, 55, 56, 57	Evidence of substantial behavior risk compensation is limited. Current data generally show declines in sex acts unprotected with condom, number of sex partners, having sex with partners of unknown status during follow-up and no difference in objective indicators of unprotected sex like incident STI infections and pregnancy compared to placebo or no PrEP (including baseline)	Consider the epidemiologic context of the sexual practices reported by the individual. Provide behavioral risk reduction support, medication adherence counseling, and STI symptom assessment at start and while on PrEP.