Safety and Tolerability of Tenofovir for Preexposure Prophylaxis Among Men Who Have Sex With Men

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Efforts to reduce HIV incidence among men who have sex with men (MSM) have been disappointing.[1–18] The iPrEx clinical trial found that tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) prescribed as a single pill (Truvada) for daily use among MSM in North and South America were associated with a modest 44% decline in HIV seroincidence.[19,20] However, the protection among men who actually adhered to the daily drug regimen was far higher, suggesting a new paradigm for HIV protection for motivated at-risk MSM.[21] Safety is a paramount consideration for any prophylactic medical intervention, whether a diagnostic procedure, chemoprevention, or immunization. Despite the mixed efficacy results in clinical trials,[19,22–28] the prospect of widespread and prolonged use of oral or topical (eg, microbicide) pre-exposure prophylaxis (PrEP) has generated an interest in further evaluation of safety, particularly of TDF, given U.S. Food and Drug Administration approval and Centers for Disease Control and Prevention and WHO guidelines for PrEP use by MSM using FTC/TDF.[29–36]

Grohskopf et al[37] in this issue of *JAIDS* describe a large U.S. multicenter study of the clinical safety of daily TDF among HIV seronegative MSM, in anticipation of its use for PrEP. In this 4-arm randomized placebo-controlled trial, neither participants nor their evaluators knew whether they were assigned 300 mg TDF orally per day or placebo. In a clever approach to assessing whether taking the pills might be associated with changes in risk behavior over time, each of the TDF and placebo groups had an immediate or 9-month delayed dosing arm.

The authors are thorough in their evaluation of safety, and no events differed significantly between the 186 TDF and 187 placebo recipients (55% of the 679 MSM screened for the study). An impressive 87% (n = 325) of men completed the final study visit. Fully, 90% of MSM participants reported at least 1 adverse event, only 3% of whom were deemed severe. While a multivariable analysis found that back pain was significantly more likely among TDF recipients ($P = 0.04$), no objective evidence of back disorders could be found. Nor can we be sure that this finding is not spurious, a possible consequence of multiple comparisons of outcomes.

A principal finding is that no evidence of TDF-associated renal disease was seen, compared with the placebo group. Among 3 men who had either persistent elevation of serum creatinine $\geq$0.5 mg/dL over baseline or had confirmed grade 4 hypophosphatemia, all were assigned to placebo. Nonetheless, it is well known that TDF is associated with renal side effects when in widespread clinical use among HIV-infected persons.[38,39] Whether the longer term and more widespread use of TDF for PrEP will result in more TDF-associate renal disease is not known.

It will be helpful in future subanalyses for the investigators to examine drug users apart from nonusers, particularly, in the context of adherence. Users of stimulants are at higher risk for seroconversion and also may be less adherent to PrEP. Alcohol use is of importance for any such study for the same reasons. Age may also interact with drug side effects in substantial ways.

A caveat in any PrEP study is the measure of adherence used, as well as measurement of risk behavior. Both reports are subject to social response bias and trial participants may have known that their reports could be important for policy making.

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Persons who know that they are not supposed to increase risk behavior may tell us investigators what we want to hear. The accuracy of self-reported adherence is poor, and use of the Medication Event Monitoring System (MEMS) bottle caps/microprocessors to estimate medication usage are perhaps just a small improvement. Far superior are assessments of plasma or tissue drug levels, and this would give a more definitive assessment of adherence.

Dual energy x-ray absorptiometry (DEXA) scans were done (at the San Francisco study site only) to assess for bone mineral density (BMD). DEXA was performed among both a subset of HIV-seronegative MSM who were screened but not enrolled (n = 210, none on TDF at the time) and those who subsequently enrolled in the prospective trial (n = 184 with ≥1 scan; 94 receiving TDF and 90 not receiving it). These data are not reported in the Grohskopf et al study because they were reported previously by Liu et al.[40] At baseline, 20 participants (10%) had low BMD (Z score ≤ −2.0 at the L2–L4 spine, total hip, or femoral neck). In the clinical trial, the specifics of the BMD losses, as noted in the TDF vs. the placebo group or the group that had not yet received treatment at the femoral neck (as treated analysis), were: 1.1% decrease [95% confidence interval (CI): 0.4% to 1.9%] in mean BMD at the femoral neck; 0.8% decline at the total hip (95% CI: 0.3% to 1.3%); and 0.7% decline at the L2–L4 spine (95% CI: −0.1% to 1.5%). In the full 24-month follow-up, 13% of TDF recipients vs. 6% of other men experienced >5% BMD loss at the femoral neck (P = 0.13). Low BMD was associated strongly with drug use, either amphetamines [odds ratio (OR) = 5.9, 95% CI: 1.7 to 20.2 or inhalants (OR = 4.6, 95% CI: 1.3 to 15.8). In contrast, men who took multivitamins, calcium, or vitamin D were less likely to have low BMD at baseline (OR = 0.26, 95% CI: 0.10 to 0.71).[40]

The findings of Grohskopf et al[37] are reassuring in that the risk of renal disease from TDF in seronegative MSM is not high in 2-years of follow-up, acknowledging that the sample size is only 187 men on TDF. That more than double the TDF recipients had a BMD loss of >5% at the femoral neck is a concern,[40] although larger studies would be needed to confirm this trend. In summary, renal disease may not be as prominent a concern with PrEP as BMD loss is, although larger studies are needed to ensure that this is truly the case. The BMD data alone suggest that TDF-based PrEP is not benign. Lower dosing regimens, as with event-driven use (ie, not using PrEP when not sexually active), are being investigated in such studies as the HIV Prevention Trials Network (HPTN) 067 protocol (The ADAPT study), with HPTN 066 assessing pharmacokinetics of intermittent dosing approaches. New drugs that show promise for PrEP and that are not associated with BMD loss are also being studied. For example, HPTN 069 is assessing the safety and tolerability of maraviroc with and without FTC/TDF. Complementing the rectal microbicide studies of the Microbicides Trials Network, the HPTN focuses on oral PrEP development and testing.[41–45]

Assessing adherence was a major goal of the study reported by Grohskopf et al; much has been written about PrEP, which has good protective efficacy in men or women only with high adherence. The authors state that "daily oral TDF was well tolerated, with reasonable adherence." However, drug interruptions were frequent, with 178 temporary drug interruptions documented among the 373 participants [the authors do not make clear whether these are 178 persons with one (or more) interruptions each or whether this was an unspecified smaller number of persons with ≥1 interruption each]. The median length of TDF interruptions was 37 days, with a range of 2–428 days. Some men (17.6% of participants) stopped taking TDF altogether. For real world applications, a minimum estimate of those who might stop is necessary, especially under conditions in high-income countries where DEXA scanning might be provided to all.

The data on behavior change over time are not reported here by Grohskopf et al but have been published recently by Liu et al.[46] But Grohskopf et al do report seroconversions during the study. Among all 400 enrolled participants including 27 persons who never were dispensed study drug or placebo, 7 seroconversions were noted, none among participants taking TDF. Viral load performed on a stored specimen from 1 man's enrollment visit showed him to be in the window period; he had 1770 viral copies per milliliter, but only seroconverted at a later date such that he was infected at enrollment.[37] Data are not presented to calculate a person-time incidence rate nor do the authors speculate what the protective efficacy might have been. This is how it should be. The study was not designed as an efficacy trial, and to present it as such would do a disservice to the participants and to the science of the trial.

In summary, the work of the San Francisco, Boston, and Atlanta investigators suggests that renal disease will not be common, although some persons terminated their PrEP use once renal warning signs emerged. The BMD data have been presented earlier, but suggest the need for safer options to TDF. While the rate of adverse events for PrEP has been low, monitoring of drug side effects is needed in seronegative persons on PrEP much as it is needed in persons with HIV-infection being treated for their disease. This is suggested by the reasons for discontinuation of drug from this study of Grohskopf et al. Although side effects are uncommon, they could be important, and clinical follow-up is needed. How PrEP gets translated into real-world prevention practice is a challenge given the need for clinical services for screening, drug administration, and monitoring of toxicity.[29–36] It remains an open question whether enough MSM will use PrEP, adhere to it, and tolerate it to make a difference in the high HIV incidence that beleaguers the MSM community worldwide.[47–54] A new paradigm for men's health services may be necessary for integrated clinical and prevention services to truly make a difference in the global epidemic.[54]

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