HIV Pre-Exposure Prophylaxis: Current Controversies and Questions

In most areas around the world, HIV transmission continues unabated, particularly among the groups already most-affected by this virus; e.g., men who have sex with men (MSM), persons who engage in injection drug use (IDU), and individuals who reside in or emigrate from regions where HIV is endemic.[1] To prevent such transmission, clinicians, policy workers, and prevention specialists have trialled and implemented many strategies, including behavioural counselling, treatment for sexually transmitted infections (STI), access to HIV testing, HIV viral load suppression, and, recently, the use of antiretroviral medications as pre-exposure prophylaxis (PrEP).[2] This new intervention, however, is not without controversy.

First, questions arise about what PrEP is, and the answer is simple: PrEP is a novel HIV prevention strategy that employs the well-established practice of having susceptible persons initiate anti-infective medication before exposure to a communicable disease to prevent acquisition of the targeted infection. This practice is used, for example, for influenza (Oseltamivir) or malaria (Chloroquine).[3] PrEP is thus not a new strategy; it is just a novel HIV prevention approach that allows HIV-negative persons to use HIV medications (specifically, single tablet fixed-dose Emtricitabine 200mg + Tenofovir DF 300mg [FTC/TDF]) so that, after exposure to HIV, the virus cannot replicate and cause irreversible infection in the person using PrEP.[4]

Second, questions abound about if PrEP works. The short answer is that PrEP is efficacious, but with varying effectiveness, likely because it requires that people take FTC/TDF one tablet per os (PO) daily. To explain further, in the iPrEx study, which involved 1224 MSM, a meagre 44% reduction in HIV transmission was observed in the FTC/TDF arm, compared to control arm, when all participants were analyzed.[5] When HIV transmission outcomes were stratified based on whether or not persons had detectable TDF in plasma, however, efficacy rose to 92%.[5] This suggests that while efficacious, PrEP is limited by the need to take daily medication.[5] Other studies have shown similar results,[6-8] supporting the conclusion that while PrEP can prevent HIV transmission, its ability to do so depends on daily medication use, and all of the complications and life circumstances that can undermine so-called perfect adherence.

One recent trial (IPERGAY),[9] consequently, explored if FTC/TDF could be taken only when required, rather than continuously. This research allotted participants to receive either placebo or FTC/TDF using the following schedule: two tablets 2 to 24 hours before sex, followed by one tablet every 24 hours for two days; if sexual contact occurred on consecutive days, participants were to take one tablet daily for the days they had sex, followed by one tablet every 24 hours for two days after the last sexual contact.[9] The study found an 86% reduction in seroconversion in the FTC/TDF arm, compared to placebo.[9] The IPERGAY participants, however, took a median of 15 FTC/TDF pills per month,[9] which is the same number of pills found to correspond with maximal HIV prevention outcomes in prior pharmacokinetic analyses of PrEP.[10] The IPERGAY authors thus cautioned that their "results cannot be extrapolated to persons taking a lower number of pills per month".[9 p2245] As such, while event-driven, or what the authors called "On Demand", PrEP may work, current data do not support it.[11] Research needs to explore if a lower pill number and/or frequency or a different dosing regimen could yield prevention outcomes that match continuous PrEP use with at least 15 tablets per month.[11]

Third, questions about behavioural dis-inhibition have arisen: Will PrEP lead to less condom use? A meta-analysis of 18 studies found this may be true: "the use of PrEP for HIV infection was associated with increased risk of STI acquisition among MSM".[12 p2251] The maxim, *correlation does not equal causation*, however, is important here because at least three factors likely contributed to the identified association: (1) it is possible that people who use PrEP truly do use condoms less, increase their number of partners, and/or engage in more anal sex, etc., suggesting in this case that the risk for STIs might actually increase after PrEP initiation due to behavioural disinhibition; (2) it is equally possible that PrEP is used by persons who, before starting this intervention, were already at higher risk for STIs, meaning that increased STI diagnoses were simply the outcome of providing PrEP to appropriate target populations, which, as per the United States Centers for Disease Control (CDC), would be individuals with a "history of inconsistent or no condom use"[4 p11]; and/or (3) it may also be that more STI diagnoses among PrEP users is an artefact of frequent STI testing among such persons, which is possible because clinical practice guidelines[4] recommend STI testing at least every 6 months to obtain refills of FTC/TDF. Interestingly, option two is perhaps most likely, as, within the PrEP trials,[5,9,10,13,14] elevated rates of STIs were diagnosed among PrEP users before FTC/TDF initiation, and differences in STI diagnosis rates were usually not identified either after PrEP initiation or between the control and experimental arms of the PrEP trials. Nonetheless, these data irrefutably highlight that people who use PrEP should receive routine STI testing.[4]

Another important discussion point about PrEP and condoms is that, to date, all but the PROUD study[14] compared PrEP plus condoms and behavioural counselling *versus* condoms and behavioural counselling.[4] Most data about PrEP, therefore, do not arise from, to describe it colloquially, *bareback trials*, but from studies wherein the reported rates of condom use was often very high.[4] Notably, PROUD – as an open label study involving MSM who reported condomless anal sex in the previous 90 days – observed an 86% reduction in HIV seroconversion in the study arm, compared to the control arm.[14] However, some of the prevention benefits may have related to post-exposure prophylaxis: 12 participants receiving FTC/TDF used post-exposure prophylaxis a total of 14 times during the study.[14] Conversely, suggesting that PrEP may have been more effective than the published estimate is that, of the 3 participants who seroconverted and had been randomised to receive FTC/TDF, none had used the medication.[14] Until this study is replicated, however, it is likely best to follow the product monograph for FTC/TDF, which indicates that PrEP should only be considered "as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices … that includes consistent and correct use of condoms".[15 p13] Although it is possible that future studies will support that PrEP can effectively prevent HIV transmission in the absence of condoms, in the meantime, only one study has demonstrated this relationship.

Fourth, questions have arisen about the adverse effects associated with FTC/TDF use. Indubitably, these concerns are valid. In the available trials, while side effects were usually transient (often resolving in the first month) and uncommon (frequencies less than 10% compared to placebo), side effects were mostly gastrointestinal (abdominal cramping, nausea, emesis, diarrhea), neurological (headaches), and musculoskeletal (arthralgia).[4] Elevated serum creatinine levels (signalling potential decreases in renal function) also occurred among less than 8% of PrEP participants using FTC/TDF.[4] While infrequent and reversible after FTC/TDF discontinuation, the combination of these changes in serum creatinine, the ease of screening for creatinine elevations, and the potential sequelae of diminished renal function was sufficient to have the United States Centers for Disease Control (CDC) clinical guidelines recommend serum creatinine testing every three to six months during PrEP use, with FTC/TDF discontinuation (or non-initiation) in the event of a creatinine clearance less than 60mL/min.[4] Importantly, this creatinine clearance value was an exclusion criterion from the extant PrEP studies, meaning that no data exist about PrEP efficacy, side effects, or complications in persons with lower creatinine clearance.[4] These short-term effects should be discussed with patients before PrEP initiation.

Discussions about the long-term sequelae of PrEP should also occur. In contrast to the short-term issues, however, these are not well established, as PrEP studies have all been less than four

years in duration.[4] As such, we can only speculate about what could occur based on data dating back to the year 2000 about the effects of these medications in HIV treatment trials and from post-marketing adverse event tracking of FTC and TDF (both as independent medications and in fixed-dose combination form).[16] According to the product monograph,[15] observed adverse events for TDF/FTC have included lipodystrophy, lactic acidosis and hepatomegaly (both more common among women), and pancreatitis. Whether or not these outcomes would occur among HIV-negative persons who use FTC/TDF for PrEP is unknown, and, as with short-term side effects, needs to be discussed with patients prior to PrEP initiation.

Similarly, bone mineral density should be considered. Studies involving HIV-positive persons who received FTC/TDF for HIV treatment observed 3-4% decreases in bone mineral density among some study participants.[4] Notably, the HIV-positive participants in these studies received combination therapy that included other antiretroviral agents, obfuscating the applicability of these results to HIV-negative persons using FTC/TDF as PrEP. Two PrEP trials[5,17] have since observed that (1) the decreases in bone mineral density among participants receiving FTC/TDF for PrEP were only approximately 1%, (2) this decline "during the first few months of PrEP either stabilized or returned to normal",[5 p39], and (3) there were no fragility fractures during the study periods. Based on these findings, the United States Centers for Disease Control (CDC) did not recommend bone mineral density screening as part of PrEP management, unless a patient had independent risk factors that would suggest bone mineral density screening.[4] As above, it might still be prudent to inform patients about this possible risk, noting that the observational periods used to assess fragility fractures in these two studies was only one to two years.

Fifth, important questions have been raised asking if PrEP is equitable. The simple answer is that PrEP is unattainable for many persons who require it the most.[18] While physicians and nurse practitioners in many jurisdictions have authority to prescribe antiretroviral medication, high costs associated with ongoing FTC/TDF use make PrEP unattainable for many. At $29.08 (CAD) per tablet, the base cost of TDF/FTC is approximately $873 per month, which rises to $975 per month, or $11,700 per annum, with pharmacy mark-up and dispensing fees.[19] At this cost, only patients with public or private insurance plans can generally access PrEP. While, in many areas of Canada, individuals with government plans (social assistance, disability, etc.) receive 100% coverage, those with private insurance may only receive partial coverage (approximately 80-90%), resulting in high monthly out-of-pocket expenses ($100-200); alternatively, people who are good candidates for PrEP may have low yearly maximum coverage (e.g., less than $5,000), or have high yearly deductibles, which could further limit accessibility. Consequently, regarding equity, it appears that PrEP is a luxury of the rich. It could thus, rather than decreasing

HIV transmission at the population level, exacerbate inequities and leave many socially disadvantaged persons without access to an efficacious strategy that is available to those with more resources. That those who are affluent can use HIV medications to remain HIV-negative is even more ethically tenuous in light of the fact that, internationally, millions of people who are already HIV-positive are unable to afford HIV medications for lifesaving purposes.[20]

In closing, as the newest addition to the HIV prevention armamentarium, PrEP holds great promise to change the landscape of HIV transmission internationally. Available data suggest it can reduce HIV transmission by up to 92%, and that, despite often minor and transient side effects, it is overwhelmingly tolerable as a therapy.[4] This is not to say, however, that PrEP is without issue.[16] Adverse events have been reported, and the long-term negative sequelae of TDF/FTC use are unknown among HIV-negative persons.[4,16] Medication use is also problematic, as current regimens require daily pill use, which corresponds with decreased efficacy as many trial participants were unable to follow this regimen notwithstanding biweekly to monthly counselling.[4] How this will play out over a longer time period with less follow-up is uncertain, as current evidence suggests that upwards of 40% of persons who take medications have discontinued within one year of use.[21] Lastly, and most importantly, the cost of TDF/FTC makes it unattainable for many, particularly those of lower socioeconomic status who already bear the burden of many health problems, including HIV infection. This shortcoming cannot be overlooked, and warrants advocacy by nurses, frontline HIV prevention and policy workers, and the general public. An historical cornerstone of HIV prevention has been that this virus can affect everyone. It is time to ensure our prevention strategies are equally inclusive, and do not occur at the expense of the many persons who are either (1) at-risk but unable to afford PrEP and (2) presently unable to obtain HIV medications for treatment and lifesaving purposes. This is an ethical duty that, in light of available scientific evidence, applies to us all.

Patrick O'Byrne RN(EC) PhD

Production Editor / Associate Professor
Aporia – La revue en sciences infirmières /
University of Ottawa
School of Nursing

Lauren Orser RN BScN

Research Assistant
University of Ottawa
School of Nursing

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