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Oral antiretroviral therapy for the prevention of HIV-1 infection: ready for prime time?

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"Ultimately, PreP is likely to take its place among the pillars of a comprehensive prevention package including other biomedical interventions with proven efficacy."

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It has been 30 years since the first cases of HIV-related immunodeficiency were described, and HIV is now a worldwide pandemic. An estimated 33 million individuals are living with HIV/AIDS, with an estimated 22.5 million from sub-Saharan Africa alone [101]. The advent of combination highly active antiretroviral therapy (cART) has dramatically decreased HIV-related morbidity, with substantial gains in life expectancy among those able to access antiretroviral medications [1]. Despite these advances, millions of new infections occur annually. Interventions to reduce transmission have traditionally focused on risk-reduction strategies, but additional biomedical interventions intended to decrease HIV transmission and prevent new infections have been assessed in clinical trial settings including male circumcision, vaginal microbicides, HIV vaccines and therapy for concomitant sexually transmitted infections, with varied success.

It is now abundantly clear that antiretroviral therapy itself plays a key role as a means of preventing transmission. The role of HIV viral load as a driver of HIV transmission has been well-established: the higher the viral load, the higher the risk. When plasma viral load (and consequently viral load within genital secretions) is reduced with cART, transmission risk diminishes. A randomized clinical trial of cART among serodiscordant couples (HPTN 052) was recently halted due to the overwhelming benefit of early therapy for prevention, demonstrating a 96.3% risk reduction in transmission [2]. In addition, early initiation of cART was associated with a 41% decrease in the predefined morbidity end point.

Ecologic studies among injection drug users, community-based population studies and mathematical models further support the role of treatment as prevention.

Prophylaxis with antiretroviral therapy is well established as an intervention to decrease the risk of acquiring HIV infection following occupational exposure, and has been assessed in the setting of high-risk nonoccupational exposure, leading to US recommendations for use in these settings. Animal models also support the use of antiretroviral therapy prior to exposure as a means of decreasing risk of infection [3], setting the stage for clinical trials evaluating pre-exposure prophylaxis (PreP) given to HIV-uninfected individuals as a strategy to decrease HIV infection.

The iPrEx study was conducted among 2499 HIV-uninfected men who have sex with men (MSM) [4] who were randomized to receive daily the fixed-dose combination tablet of emtricitabine (FTC)–tenofovir disoproxil fumarate (TDF) or placebo in conjunction with comprehensive prevention services (as performed in all PreP trials), with a relative reduction of 44% (95% CI: 15–63%) in HIV incidence [4]. Of note, among subjects in the FTC–TDF arm, those with detectable drug levels

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in blood (a marker of high adherence to the regimen) had a relative reduction in HIV risk of 92% [4], suggesting that optimal adherence is needed to maximize the effectiveness of the intervention.

However, more recently, the Family Health International-sponsored FEM-PrePP study was halted following negative results of an interim analysis [102]. FEM-PrePP was a double-blind, placebo-controlled study of daily oral FTC–TDF in 1951 African women aged 18–35 years. In this analysis, the HIV infection end points were distributed equally between the FTC–TDF and placebo arms and continuation of the study was deemed futile [102].

This result is in direct contrast to the findings of the TDF2 study conducted by the Centers for Disease Control in Botswana [5], where young adults (aged 18–39 years) of both genders (n = 1219) were randomized to receive daily oral FTC–TDF or placebo. During follow-up an overall protective efficacy of 77.9% (95% CI: 41.2–93.6%) for the pre-exposure regimen was reported [5].

The Partners PrePP study has also found significant benefit with the use of both daily FTC–TDF and TDF alone [6,103]. Heterosexual African men and women (n = 4747) involved in serodiscordant relationships were randomized to receive daily FTC–TDF, TDF alone or placebo. Interim analysis of the trial data led to discontinuation of the placebo arm as the protective efficacy of FTC–TDF and TDF was 73% (95% CI: 49–85%) and 62% (95% CI: 34–78%) respectively, compared with placebo [6].

In addition to oral antiretroviral-based PrePP, topical applications in the form of vaginal 1% TDF gel have undergone evaluation. The CAPRISA004 trial evaluated 889 South African women, and demonstrated a 39% reduction in HIV acquisition [7]. The risk reduction was higher in women with >80% adherence to the TDF gel, where the HIV incidence was 54% lower than the placebo arm [7]. Comparison between oral and topical preparations is ongoing in the Microbicide Trial Network's VOICE trial (MTN003) evaluating the use of either TDF gel or oral FTC–TDF.

PrePP with oral antiretrovirals has now been shown to be effective in the prevention of HIV-1 infection. However, practical issues regarding implementation must be further evaluated. At present there are a number of ongoing and planned clinical trials that will help to refine possible interventions [104], and no doubt will add to the complexity of interpreting current results. For instance, the MTN VOICE trial recently announced early discontinuation of its oral TDF arm due to futility [105]. Further information is required to more clearly understand the differences in the positive findings of CAPRISA, the TDF2 and Partners PrePP studies and those of FEM-PrePP and VOICE. The results may in part be explained by differences in drug concentrations obtained within genital tissues when an oral compared with topical product is used [8]. Adherence is clearly vital in achieving adequate drug concentrations, but whether other differences in terms of gender-specific concerns, sexual behaviors, concurrent sexually transmitted infections or other factors explain these differences remains to be determined. In this context, further data are also needed regarding the possible negative impact of hormonal contraception use that has been implicated in increasing the risk of HIV acquisition among women in some studies [9].

The target populations for PrePP remain to be well defined. The results of iPrEx support consideration of use in sexually active MSM, and mathematical models have suggested benefit if this intervention were to be scaled up in this population [10,11]. Similarly, mathematical models suggest benefit when interventions are targeted to sex trade workers and their clients [12], and also more generally to heterosexual young women in South Africa at high risk of HIV infection [13]. Further evaluation among specific populations such as sex-trade workers and injection drug users is urgently required.

In addition to concerns regarding efficacy, current trials have also evaluated safety of oral TDF-based strategies. No major differences in metabolic safety profile (with particular focus on renal abnormalities) for both oral TDF and FTC–TDF have been noted in the TDF2 and Partners PrePP studies. Nonsignificant changes in renal function were observed in iPrEx; however, a substudy has identified small but significant differences in bone mineral density in those receiving FTC–TDF [4,14]. As TDF also provides activity against hepatitis B, concerns regarding the potential for hepatitis B flares upon drug discontinuation have been raised.

The development of resistance among individuals who have unrecognized baseline HIV infection, or who become infected while taking prophylaxis, remains a concern. In the TDF2 study a single individual with unrecognized acute HIV infection at baseline initiated FTC–TDF with development of high-level M184V and K65R mutations conferring resistance to both agents [5]. Mathematical modeling suggests that the use of PrePP could lead to significant increases in the proportion of new infections with evidence of primary resistance in both the MSM setting and within the context of the sub-Saharan epidemic [11,15]. The development of rigorous routine monitoring for HIV infection during use of PrePP will be essential, and adherence not only to medication schedules, but also monitoring programs for both seroconversion and metabolic safety will be required for individuals undertaking prophylactic strategies. Strategies using

intermittent dosing schedules of FTC–TDF and also alternate agents such as maraviroc, which has a differing metabolic and resistance profile, are currently under evaluation [104].

An additional potential concern with the use of any form of prophylaxis is that of behavioral disinhibition leading to increased risk behaviors, which could compensate for the protective effect of the intervention [12]. These concerns have also been raised, but are not supported by current data in the setting of cART therapy programs. Of note, reported unprotected sexual intercourse actually diminished over time in the Partners PreP and CAPRISA studies.

Implementation of PreP will require significant commitments from programs to scale-up HIV testing, engage populations who may benefit from prophylaxis, and provide access to care for both therapy and monitoring. At a program level, decisions regarding funding for prophylaxis in at-risk individuals will need to be balanced against the need to provide care for those known to be HIV infected. Achieving appropriate regulatory approval for the use of antiretroviral agents for prophylaxis and providing funding for both prevention and therapeutic programs will take robust global commitment.

Ultimately, PreP is likely to take its place among the pillars of a comprehensive prevention package including other biomedical interventions with proven efficacy. However, the use of PreP may have limited utility: in the South African mathematical model [13], cost–effectiveness diminishes relative to large-scale roll out of antiretroviral therapy for those in need. Early treatment of those infected, as demonstrated in the landmark HPTN 052 trial, should thus remain a cornerstone of the HIV and AIDS control strategy. Early treatment markedly decreases mortality, simultaneously decreases morbidity – particularly extrapulmonary tuberculosis, and secondarily has a dramatic effect on decreasing HIV transmission.

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