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SUPPLEMENT ARTICLE

Preexposure Prophylaxis for Mitigating Risk of HIV Transmission During HIV Cure–Related Clinical Trials With a Treatment Interruption

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Analytical treatment interruption performed during human immunodeficiency virus (HIV) cure–related clinical trials exposes sex partners of participants in these trials to a risk of HIV transmission. Preexposure prophylaxis (PrEP), which emerged in recent years as a key strategy for preventing HIV transmission, is often considered a useful tool to prevent this risk. This article supports offering PrEP to participants' sex partners in stable relationships in these trials but also notes limitations that must be addressed. It concludes that PrEP cannot on its own eliminate the risk of secondary transmission in this context.

Keywords. PrEP; HIV; analytical treatment interruption; HIV transmission.

Analytical treatment interruption (ATI) remains the best way to analyze the impact of cure-related strategies during human HIV infection [1]. For the patient, the risks secondary to ATI are considered very low if clinical and biological criteria are met (eg, high $CD4^+$ T-cell count, high nadir $CD4^+$ T-cell count, and no history of an AIDS-defining event) [1]. Indeed, a recent retrospective subgroup analysis of select data from the SMART (Strategies for Management of Antiretroviral Therapy) study suggest that a short period of treatment interruption in antiretroviral therapy (ART) recipients with stable viral suppression and $CD4^+$ T-cell counts >400 cells/mL, a nadir $CD4^+$ T-cell count of >200 cells/mL, and without concomitant diseases was safe and acceptable [2]. Otherwise, treatment interruptions have been associated with secondary transmission to sex partner(s) (see the case report by Lelièvre and Hocqueloux [3] elsewhere in this supplement).

The use of preexposure prophylaxis (PrEP) has emerged in recent years as an important strategy for preventing HIV transmission. In humans, PrEP has been evaluated as topical tenofovir gel, oral tenofovir (eg, Truvada) with or without emtricitabine, and a long-acting injectable antiretroviral [4]. PrEP has proven efficacious in trials with high levels of adherence [5–7], and the World Health Organization (WHO) recommends PrEP implementation in populations at substantial risk of HIV acquisition [8]. Currently, only oral PrEP with tenofovir plus emtricitabine is recommended for HIV prophylaxis, and it will be our focal example.

How much can the use of PrEP resolve the challenge of potential HIV transmission in HIV cure–related trials with an ATI? The WHO recommendation and results of large clinical trials may support offering PrEP to participants' sex partners in stable relationships. But several points bar PrEP from eliminating the risk of secondary transmission during ATI on its own.

First, PrEP efficacy was evaluated in clinical trials only in combination with other prevention tools (condoms use) and included a strong counseling and support component, elements that should therefore also be included in HIV cure–related trials with an ATI.

Second, the effect of PrEP may differ between different populations at risk. Two recent large-scale trials, PROUD [9] and IPERGAY [5], showed very encouraging results from use of PrEP in high-risk men who have sex with men. However, in studies of serodiscordant couples (ie, Partners PrEP [6] and TD2F [7] trials), the effectiveness of PrEP seemed to be inferior (Table 1). In addition, large PrEP clinical trials that only included women (ie, the FEM-PrEP [10] and VOICE [11] trials) showed disappointing results (Table 1). Moreover, even if PrEP was found to be effective in women in the TDF2 trial [7], the level of efficacy (49%) was found to be lower than in men (80%). The difference is not significant, though, as the trial was not powered to evaluate efficacy in women alone. Nonadherence was identified as the main reason for the failure of these clinical trials. Other factors that have been identified as potential contributors to the lower efficacy of PrEP in women include socioepidemiologic characteristics (eg, transmission route, HIV

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Table 1. Efficacy of Oral Preexposure Prophylaxis (PrEP) With Truvada in Clinical Trials With a High Level of Adherence

Trial	PrEP Frequency	Population	Site(s)	Protective Efficacy, % (95% CI)	Reference
PROUD	Daily	MSM	United Kingdom	86 (52–96)	[9]
IPERGAY	Intermittent	MSM	France, Canada	86 (39–99)	[5]
Partners PrEP	Daily	Serodiscordant couples	Kenya, Uganda	75 (55–87)	[6]
TD2F	Daily	MSM, women	Botswana	62 (22–84)	[7]
FEM-PrEP	Daily	Women	Kenya, South Africa, Tanzania	6 (–52–41)	[10]
VOICE	…	Women	South Africa, Uganda, Zimbabwe	–4 (–49–27)	[11]

Abbreviations: CI, confidence interval; MSM, men who have sex with men.

subtype, exposure intensity, and percentage of population in a stable serodiscordant relationship) and biological features (eg, a difference in the distribution of ART in the female genital tract, compared with sperm or the rectum, and the peculiar composition of the vaginal microbiome) [12]. The Centers for Disease Control and Prevention therefore recommends that PrEP be taken about 20 days before vaginal sex [13].

Third, no systematic data exist indicating whether PrEP is effective against viral rebound to the very high levels of viremia that might emerge, especially during long ATI performed in some clinical trials. During HIV cure–related clinical trials, patients are usually closely monitored (every week) and guidelines recommend to resume combination ART when the viral load rebounds to 1000 copies/mL (US guidelines) or 10 000 copies/mL (European guidelines). However, some patients may miss several consultations and, therefore, may resume combination ART later than recommended.

Fourth, a recent report showed the occurrence of HIV infection in a PrEP user despite high rates of adherence and the presence of a fully susceptible virus, demonstrating that good adherence and viral susceptibility to HIV drugs may not be sufficient to prevent transmission [14]. For the use of PrEP to be considered in the context of therapeutic vaccine studies with treatment interruption, it is also essential to first check that the virus that will be present at the time of viral rebound is susceptible to drugs used for PrEP. This could be done through the collection of the history of viral genotypes and ART taken by the patient.

Fifth, the use of PrEP may be associated with safety concerns [15]. The concerns are quite rare as both drugs included in Truvada have a good safety profile; however, baseline and follow-up monitoring of renal function should be performed, especially in lean subjects (weight, ≤55 kg) with baseline creatinine clearance rates <90 mL/minute and in recipients aged ≥45 years.

Sixth, there are complications stemming from policy, including a potential discrepancy between the offer of PrEP in the trial and its offer in the surrounding community. For example, the European Medicines Agency approved Truvada for PrEP in 2016 [16]. Yet each member state determines separately how it might introduce PrEP. In January 2016, France became the first and only country in Europe in which PrEP is available and reimbursed by the health system [17]. But some HIV therapeutic vaccine studies with an ATI take place in European and other countries in which PrEP is not yet available for populations outside the study. But is it fair to offer PrEP to that at-risk population when surrounding populations at high risk of HIV acquisition are denied free PrEP? As investigators, we have a primary responsibility for the safety of study participants. But the prospect of protecting only some non–study participants (in our case, sex partners in stable relationships) may be thought to create an unfair inequality, a question that could benefit from future ethics input.

Finally, when study participants have sex partners in unstable relationships, it could complicated or impossible, partly for reasons of confidentiality, to reach their partners and provide PrEP. PrEP offers reliable protection against transmission in stable sexual relationships, but its complicated use in the context of unstable sexual relationships means that it is probably not a solution to all situations in which a risk of transmission exists.

All in all, the use of PrEP for mitigating the risk of HIV transmission in HIV cure–related trials with ATI represents an interesting and helpful tool to prevent secondary transmission that should be included in all these trials. However PrEP's mechanisms of action and some of its limitations—such as the lack of impact on the occurrence of other sexually transmitted infections that have to be regularly monitored—should be clearly explained to patients and to their sex partners in stable relationships and must be combined with several additional interventions. In addition, the lack of harmonization of free PrEP within different countries may complicate its use in (international) HIV cure–related trials with ATI.

Notes

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