Pre-Exposure Prophylaxis as a Method for Prevention of Human Immunodeficiency Virus Infection

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The treatment of HIV/AIDS evolved dramatically during the last 34 years since the introduction of HAART (highly active antiretroviral therapy). Currently, people living with HIV treated with HAART are facing a treatable (although not curable) chronic disease with a life expectancy almost equal to the average life expectancy of the general population [1]. Therefore, most efforts by HIV care providers focus on four major areas: (i) antiretroviral drugs with a better safety and tolerability profile, (ii) future drugs that can potentially cure HIV, (iii) prevention and treatment of co-morbidities and metabolic complications related to HAART and HIV, and (iv) strategies to stop the epidemic using different modes for HIV prevention [2-4].

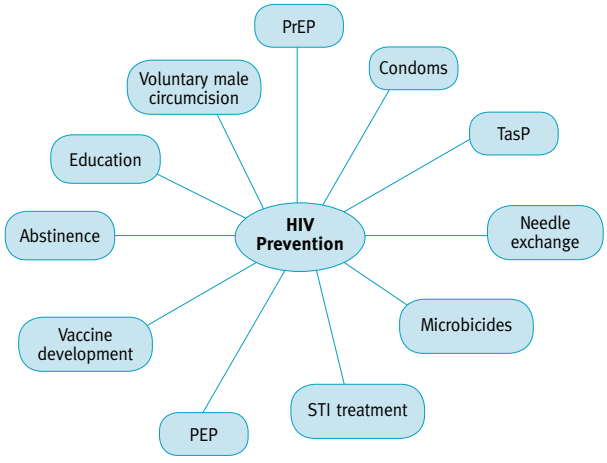
Today, HIV research focuses on better antiretroviral drugs, drugs that can potentially cure HIV, prevention and treatment of co-morbidities

Modalities for the prevention of new HIV cases are diverse and include different approaches [Figure 1]. It is clear that the best option for HIV prevention is an anti-HIV vaccine, but this is not yet available [5]. Until a preventive vaccine does become available, other methods are being explored and should be used. During the first 30 years the paradigm was based on three main modalities – a public health campaign, the use of condoms, and extensive HIV testing. Post-exposure prophylaxis (PEP) with HAART (treatment of a person who was exposed to HIV within 72 hours of exposure for 4 weeks) also became a modality for HIV prevention in some circumstances [6]. In recent years new approaches were shown to be effective, including male circumcision, HAART treatment as prevention (TasP), and antiretroviral treatment as pre-exposure prophylaxis (PrEP).

Voluntary male circumcision was shown to reduce 60% of female-to-male HIV transmission especially in areas with a high HIV prevalence [7]. Thus, male circumcision was adopted by the World Health Organization as a recommended method for HIV prevention. The concept of treatment as prevention (TasP) received its legitimacy following publication of the HTPN 052 study [8,9]. That study showed that in serodiscordant couples, treatment of the infected partner regardless of their CD4 cell counts protected the uninfected partner from HIV acquisition. The concept of TasP led to the (UNIADIS) "90 90 90" initiative, whose aim is to diagnose 90% of people living with HIV, treat 90% of them, and achieve 90% success (viral suppression) by the year 2020. It was suggested that the 90% goal achievement will end the HIV epidemic [10]. Indeed, many HIV guidelines recommend HAART treatment to all HIV patients regardless of their CD4 cell counts or clinical condition [11].

In this review we will focus on pre-exposure prophylaxis (PrEP) as the modality for HIV prevention. Several small studies previously reported the efficacy of antiretroviral drugs in healthy people for the prevention of HIV infection [12]. The first large randomized study that attempted to prove the efficacy of PrEP as a mode to prevent HIV infection was the iPrEx trial [13]. This was a phase 3, randomized, double-blind, placebo-controlled trial among men and transgender (male-to-

Figure 1. Methods for HIV prevention



PrEP = pre-exposure prophylaxis, PEP = post-exposure prophylaxis, TasP = treatment as prevention, STI = sexually transmitted infections

female) adults who reported having had sex with a man during the 6 months preceding their enrollment. Participants were randomly assigned to receive a daily oral dose of either the fixed dose combination of tenofovir (TDF) and emtricitabine (FTC) or a placebo. All participants (drug and placebo groups) were seen every 4 weeks for an interview, HIV testing, counseling about risk reduction and adherence to PrEP medications, pill count, and dispensing of pills and condoms. It was found that 36 of 1224 (2.9%) participants in the TDF/FTC group and 64 of 1217 (5.25%) in the placebo group had acquired HIV infection. Along the course of the study TDF/FTC treatment was associated with a 44% reduction in HIV acquisition. The reduction was greater (50%) in those patients with > 50% adherence (by self-report and pill count/dispensing). Moreover, the reduction in HIV acquisition was even higher (73%) in participants with at least 90% adherence to the PrEP medications [13]. Accordingly, a 92% reduction in HIV acquisition was observed in participants with detectable levels of TDF/FTC in their plasma/cells compared to those without detectable drug levels. In that study, TDF/FTC was well tolerated, although nausea in the first month was more common among participants taking medication compared to the placebo group (9% versus 5%). No differences in severe (grade 3) or life-threatening (grade 4) adverse laboratory events were observed between the active and placebo group, and no drug-resistant virus was found in the 100 participants infected after enrollment to the study. Interestingly, all study participants (active and placebo groups) represented higher rates (compared to baseline parameters) of condom use [13].

The use of daily oral PrEP with Tuvada® has been shown to be safe and effective in reducing the risk of sexual HIV acquisition

Following that proof of concept trial [13], several issues regarding the use of PrEP had to be addressed. First, can the use of PrEP in gay men be extrapolated to other risk groups like intravenous drug users (IVDUs) and heterosexual men and women? Is HAART (as a chronic treatment of non-HIV infected persons), especially TDF which is known to have some degree of nephrotoxicity for long periods, safe? The possibility of emergence of HIV resistance in those patients receiving TDF/FTC as PrEP who eventually will be infected is also worrying.

To this end, the US MSM Safety Trial [14], a phase 2 randomized, double-blind, placebo-controlled HIV preventive study, investigated the clinical safety and the effects on behavior in 400 men who have sex with men (MSM). Participants were randomly assigned to receive daily oral TDF or placebo. During the study period (24 months), medication adherence was high: 92% by pill count and 77% by pill bottle openings recorded by Medication Event Monitoring System (MEMS) caps. The overall frequency of adverse events did not differ significantly between the TDF and placebo groups. In multivariate analyses, back pain was the only adverse event associated with TDF. In a subset of men (n=184) in whom bone mineral density (BMD) was assessed, TDF was associated with a small decrease in BMD (1% decrease at the femoral neck, 0.8% decrease for total hip) without any bone fractures [14]. Among the seven participants who acquired HIV during the time of the study no TDF-associated mutations were detected. Although the primary aim of this study was the safety of the treatment, it further confirmed the efficacy of PrEP in HIV prevention [14].

Several studies investigated the efficacy and safety of PrEP given to heterosexual couples (males and females) for the prevention of HIV infection. The Partners PrEP trial [15,16] was a phase 3 randomized, double-blind, placebo-controlled study of daily oral TDF/FTC or TDF (to the unprotected partner) for the prevention of HIV acquisition by the uninfected partner in 4758 HIV-discordant heterosexual couples. This research was performed in Uganda and Kenya. In 48% of couples the infected partners were males. The trial was stopped after an interim analysis that showed statistically significant efficacy in the medication groups (TDF/FTC or TDF) compared to the placebo group. All HIV-positive partners in the study were not treated with HAART. It should be noted that the adherence to study medication in that trial was very high (98% by pills dispensed, 92% by pill count, and 82% by plasma drug levels). The rate of serious adverse events and of blood laboratory abnormalities in the TDF/FTC arm was similar to those observed in the placebo group. Among participants of both sexes either TDF or TDF/FTC was shown to significantly reduce HIV acquisition (67% for TDF and 75% for TDF/FTC). PrEP in that study was effective in HIV prevention in both male and female uninfected partners. In participants with detectable plasma drug levels a 90% reduction in the risk of HIV acquisition was observed. No TDF or FTC-resistant virus was detected among participants who were infected after enrollment.

The Botswana TDF2 Trial [17] (a phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of daily oral TDF/FTC for HIV prevention) enrolled 1219 heterosexual men and women in Botswana, and follow-up of at least 12 months has been completed. Among the participants, both sexes combined, the efficacy of TDF/FTC was 62% compared to the placebo group. As was observed in other studies [13-16], TDF/FTC PrEP was not associated with significant adverse events and no resistant virus was detected in the 33 participants who seroconverted after enrollment.

On the other hand, several PrEP studies in African women failed to show significant benefit of this approach. The FEM-PrEP trial [18] (phase 3 randomized, double-blind, placebo-controlled study) investigated HIV prevention efficacy and clinical safety of daily TDF/FTC among heterosexual women in South Africa, Kenya, and Tanzania. The trial was stopped following an interim analysis which determined the lack of TDF/FTC efficacy. However, adherence was very low in this trial (the study drug was detected in plasma samples of < 50% of women

randomly assigned to TDF/FTC). The low level of adherence is most likely the cause for the lack of PrEP efficacy in that study.

Another randomized, double-blind, placebo-controlled trial of TDF for HIV prevention was conducted among heterosexual women in West Africa [19]. The study was designed to assess the safety and efficacy of daily TDF in HIV prevention. Two study sites (Cameroon and Nigeria) were closed prematurely due to operational obstacles. Analysis of trial safety data from Ghana and Cameroon found no statistically significant differences in grade 3 or 4 adverse events between the TDF and placebo groups. Eight HIV seroconversions occurred among women in the trial: 2 among women in the TDF group (rate = 0.86 per 100 person-years) and 6 among women receiving placebo (rate = 2.48 per 100 person-years), showing a significant reduction of 65% for HIV acquisition in the TDF-treated group.

The VOICE trial (MTN-003) [20] was a phase 2B randomized, double-blind study comparing oral (TDF or TDF/FTC) and topical vaginal (tenofovir) antiretroviral regimens with corresponding oral and topical placebos among 5029 heterosexual women enrolled in eastern and southern Africa. Of those women, 3019 were randomly assigned to daily oral medication (TDF/FTC 1003, TDF 1007, oral placebo 1009). The lack of adherence (TDF was detected in only 30% of plasma samples) and the high dropout of participants is most likely the main cause for lack of TDF efficacy in that study.

PrEP was shown to prevent HIV transmission in men who have sex with men, heterosexually active men and women, as well as in intravenous drug users

In summary, all trials found PrEP to be safe and well tolerated. Low adherence and operational issues precluded reliable conclusions regarding efficacy in three trials: VOICE [17], FEM-PrEP [18], and the West African trial [19]. On the other hand, four prevention trials – iPrEx [10], US MSM Safety Trial [14], Partners PrEP [15,16], and TDF2 [17] – that achieved a high medication adherence rate provided substantial evidence of PrEP efficacy among MSM as well as heterosexual men and women.

Only a few studies found HIV prevention in high risk groups for HIV acquisition not through sexual intercourse. The BTS study [21] (a phase 3 randomized, double-blind, placebo-controlled study) investigated the safety and efficacy of daily oral TDF for HIV prevention among 2413 intravenous drug users in Bangkok, Thailand. At each monthly visit, participants could choose to receive either a 28 day supply of pills or daily medication by directly observed therapy. Study clinics (n=17) provided condoms, bleach (for cleaning injection equipment), methadone (when needed), primary medical care, and social services free of charge. Participants were followed for a mean period of 4.6 years and received daily directly observed therapy 87% of the time. The intent-to-treat analysis (excluding two participants with evidence of HIV infection at enrollment) revealed significant efficacy of TDF (48.9% reduction compared to placebo). A post-hoc modified intent-to-treat analysis (removing two additional participants in whom HIV infection was identified within 28 days of enrollment), that included only participants on directly observed therapy who took their study pills at least 71% of days and missed no more than two consecutive doses with detectable levels of tenofovir in their blood, demonstrated a 73.5% reduction in HIV acquisition in the TDF compared to placebo. The rates of clinical and laboratory adverse events did not differ significantly between the TDF and the placebo groups. As was shown in previous trials, no TDF-associated mutations were detected in participants who acquired HIV despite PrEP.

Data reported at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) held in Seattle in February 2015 reinforced the knowledge gathered on PrEP. The Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis (The PROUD Study) [22] investigated PrEP efficacy in the "real world" setting and not in controlled trials. To this end, the PROUD team enrolled MSM from 13 sexual health clinics in England which were randomized 1:1 to receive open-label daily TDF/FTC either immediately or after a deferral period of 12 months, and followed quarterly for 48 weeks; 545 MSM were randomized (276 immediately, 269 deferred). During the study period, three HIV infections were observed in the immediate group (1.3/100 person-years); 19 infections were observed in the deferral group (8.9/100 person-years) despite 174 prescriptions of post-exposure prophylaxis (PEP). This yields a rate difference of 7.6/100 person-years and a relative reduction rate of 86%. The latter "real world" study clearly demonstrated efficacy of TDF/FTC in preventing HIV acquisition in high risk populations.

Recently, Molina et al. [23] in the Ipergay Trial demonstrated the efficacy of TDF/FTC "on demand" PrEP in preventing HIV acquisition in a very high risk group (condomless anal sex) of MSM. A total of 400 participants were randomized (double-blinded placebo-controlled) to either TDF/FTC or placebo groups. The medications were taken 2 to 24 hours before (two pills) and 24 hours and 48 hours (one pill each time) after each sexual intercourse (four pills per each sexual intercourse). After a median follow-up of 8.8 months the incidence of new HIV infection was 6.75 per 100 person-years in the placebo arm (14 patients) and 0.94 per 100 person-years in the TDF/FTC arm (2 patients) (reduction of 86%). The rate of serious adverse events was low (9%) and similar across the two study arms.

Taken together, the data from all PrEP studies in different settings suggest that daily oral PrEP with TDF/FTC is as safe and effective as an HIV prevention mode option for sexually active MSM, heterosexually active men and women, and IV drug users who have a substantial risk of HIV acquisition [Table 1], especially in those who adhere to treatment [24]. Given the data from all the above studies, currently the only available treatment combination for PrEP is once daily TDF/FTC (300 mg/200

Table 1. Summary of PrEP efficacy in major clinical trials*

	Study population	No. of participants	% of blood samples with tenofovir detected	HIV protection efficacy in comparison to placebo	HIV protection of participants with high drug adherence
Partners PrEP [15]	Heterosexual men and women	4758	82%	75%	90%
TDF2 [17]	Heterosexual men and women	1219	79%	62%	78%
BTS [21]	IVDUs, men and women	2413	67%	49%	70%–84%
iPrEx [13]	MSM	2441	51%	44%	92%
FEM-PrEP & VOICE [18,20]	Heterosexual women	2120, 5029	‹ 30%	No HIV protection	NA

*In all the studies the participants (drug and placebo groups) were seen on a regular basis during the studies and were consulted about risk reduction, use of condoms and post-exposure prophylaxis (PEP)

PrEP = pre-exposure prophylaxis, IVDUs = intravenous drug users, MSM = men who have sex with men

mg); other antiretrovirals like maraviroc and raltegravir are still being tested for PrEP, thus their use is not yet recommended.

Following the accumulation of PrEP supporting data, the Centers for Disease Control (CDC) and the European AIDS Clinical Society (EACS) recommended the use of PrEP in certain populations [11,25-27]. According to the published guidelines, PrEP should be offered to persons with substantial risk of acquiring HIV infection: in men who have sex with men (MSM) who have a HIV-positive sexual partner, MSMs with recent bacterial sexually transmitted infections (STI), MSMs who have a high number of sex partners and MSMs with a history of inconsistent or no condom use, and commercial MSM sex workers. In the case of heterosexual women and men, PrEP should be offered to those who have a sexual partner with HIV, to those who experienced recent bacterial STI, to persons who have a high number of sex partners, to those with a history of inconsistent or no condom use, to sex workers, and to those who live in an area of high HIV prevalence. PrEP could be offered also to IV drug users, especially those who have an HIV-infected partner or who share injection equipment.

All persons offered PrEP are eligible for that treatment only if they test negatively to HIV before PrEP is started, have no signs of acute HIV infection, and whose kidney function test is normal. Hepatitis B infection status (antigen, antibodies) should be determined prior to PrEP initiation. For persons who start PrEP it is recommended that they have a follow-up visit at least every 3 months. It is recommended that PrEP (TDF/FTC) drug supply be given for not more than 3 months. During clinic visits it is important to provide the following: HIV testing, medication adherence counseling, behavioral risk reduction support, side effect assessment, and STI symptom assessment. At 3 months and every 6 months thereafter renal function tests should be assessed. Every 6 months, testing for bacterial STIs is mandatory. In addition, women on PrEP should receive contraceptive consultation and have a pregnancy test every 3 months. Intravenous drug users should also receive access to clean needles/syringes. Discontinuation of PrEP medication is indicated for several reasons: personal choice, changed life situations resulting in lowered risk of HIV acquisition, intolerable toxicities, chronic non-adherence to the prescribed dosing regimen despite efforts to improve daily pill taking, or acquisition of HIV infection. Upon discontinuation for any reason, HIV status at the time of discontinuation, reason for PrEP discontinuation and recent medication adherence and reported sexual risk behavior should be documented in the health record. Special consideration should be given to persons with active hepatitis B infection because patients should continue treatment and follow-up. Any person who wishes to resume taking PrEP medications after having stopped should again undergo pre-prescription evaluations

In summary, the use of daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adult MSM, heterosexual men and women, and in IDUs. Acute and chronic HIV infection must be excluded by HIV testing immediately before PrEP is prescribed. The implementation of PrEP for HIV prevention may be costly, but evidence shows the efficacy of this method to be cost-effective.

In Israel, between 1981 and 2014 [28], 8449 new cases of HIV/AIDS were notified. Subtracting fatalities and those who left Israel, 6847 individuals are registered as living with HIV/AIDS in Israel. Based on epidemiological trends among each subgroup, it is estimated that 8935 individuals are presently living in Israel with the virus. In the year 2014, 468 new cases were notified. The incidence of HIV/AIDS in Israel in 2014 was 56.4 new cases per million people (based on population data at the end of 2014 from the Israel Central Bureau of Statistics). Currently, PrEP is not commonly used (for high risk population) and it is not included in the Israeli health basket as a means for HIV prevention. In our opinion, PrEP should be implemented in Israel, as it was implemented by the CDC, and offered to persons at high risk for HIV acquisition.

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