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Pre-exposure prophylaxis of HIV: A right way to go or a long way to go?

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Abstract

Antiretroviral drugs are being tried as candidates for the pre-exposure prophylaxis (PrEP) against HIV for a considerable period, due to their potential for immediate inhibition of viral replication. Discrepancies in the findings called for a critical review of the relevant efforts and their outcomes. A systematic literature search identified 143 eligible articles of which only 5 reported complete findings while another 11 were still on-going. Observed moderate efficacy and good safety profile seemed to identify PrEP as a promising step for minimizing the spread of HIV to relatively unaffected population and controlling the epidemic among high risk population groups. But the duration of this efficacy was found to depend heavily on the availability, adherence and other related issues like cost, political commitment, ethical consideration etc. To prevent potential cultural and behavioral modifications, proper pre-administration counseling also seemed critical for the success of PrEP as a cost-effective intervention with adequate coverage.

Keywords

Pre-exposure Prophylaxis; Antiretroviral Therapy; HIV prevention; Controlling the HIV epidemic; Prevention of HIV spread

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Introduction

Despite promising global efforts to address HIV epidemic like condom promotion [1], circumcision [2 3], voluntary counseling and testing (VCT) [4], prevention of mother-to-child HIV transmission (PMTCT) [5], increased access to Anti-Retroviral Therapy (ART) [6 7] and harm reduction strategies (needle-exchange [8] and opiate-substitution for injecting drug users [9]), HIV is still a catastrophe worldwide.

During past two decades, efforts to develop a vaccine have faced difficulties due to enormous genetic diversity of HIV [10]. Only three candidate HIV vaccines (VAX 003/ VAX004, STEP, RV144) have completed clinical efficacy trials so far. The failure of STEP trial in North America added further uncertainty to this comprehensive strategy to curb HIV epidemic [11 12]. Discovery of microbicides against HIV seemed promising for controlling the epidemic. However, further research is warranted to resolve issues of discrepancies in the protective efficacy of these microbicides [13–15]. Following the failure of preventive behavioral approaches for controlling HIV, the concept of HIV prevention using ART regimens, pre-exposure prophylaxis (PrEP) gained popularity for being cost-effective, simple, safe and having biological plausibility for its use in HIV prevention [16].

PrEP and its development

Advent of highly active antiretroviral therapy (HAART) in 1996 is a landmark in the battle against HIV [17]. Prior studies have shown that ART can inhibit replication of HIV-1 [18], increase the CD4:CD8 ratio [19] and thus can prolong survival of HIV-infected persons [20]. Montaner reported a population-level association of better HAART coverage with lower viral load and reduced incidence of HIV [17]. Timely initiation of HAART was also found to reduce the amount of HIV-1 shedding in genital secretions [21] leading to lower sexual transmission [22]. Mother to child HIV transmission during pregnancy, delivery or breastfeeding was intervened with HAART and till date PMTCT remained one of the most successful HIV preventive strategies globally [23–25]. The success of ART inspired the idea that PrEP with HAART could be effective for HIV prevention.[26]. Success of trials dealing with post-exposure prophylaxis [27–29] helped in further evolution of the concept of PrEP [30–33]. The underlying hypothesis for PrEP was that prophylactic use of anti-retroviral drug(s) [25] were considered to be able to inhibit viral replication right from the entry of HIV in human body [34].

Several animal trials established the efficacy and safety of PrEP. Denton demonstrated reduced intra-vaginal transmission of HIV in humanized BLT mice after pre-treatment with a combination (TDF-FTC) of Tenofovir Disoproxil-Fumarate (TDF) and Emtricitabine (FTC) [35 36]. In some other non-human primate studies, PrEP with oral and topical tenofovir-based gel, prior to systemic or mucosal simian human immunodeficiency virus (SHIV) challenge, could provide substantial protection (70–100%) [36–40].

Evaluations of the results from studies involving human subjects thus seem to be the need of the hour to infer about the implementation of PrEP. In this systematic review of literature, we explored the concept of PrEP, its development and its protective role in HIV acquisition,

summarized the results of the completed trials on PrEP and discussed socio-cultural and ethical aspects, cost-effectiveness and public health implications of PrEP.

Methods

A systematic literature search was conducted in PubMED and EMBASE databases for accessing articles relevant to PrEP. Articles published in English between January 2003 and September 2013, were included using the following key-terms in various combinations: 'Pre-exposure Prophylaxis' or 'PrEP', 'HIV' and 'trial'. Reference list of each selected article was used to identify additional literatures. After reviewing 143 eligible articles, it was revealed that globally, among several PrEP trials, complete results from only 5 were published, while another 11 were yet to be completed. Most of them assigned Truvada [a combination of TDF and FTC, licensed by U.S. Food and Drug Administration (FDA) in 2004] to treatment group.

Results

Concluded trials on PrEP included: iPrEX [41], conducted among men or transgender who had sex with men and were assigned either TDF-FTC or placebo; FEM-PrEP [42], conducted among women using either oral TDF-FTC or placebo; PIP [43], which involved HIV-1 serodiscordant heterosexual couples assigned to take oral TDF-FTC daily; TDF2 [44 45], conducted among heterosexual men and women assigned either to TDF2 or placebo and BTS[46], conducted among injecting drug users taking TDF or placebo daily (Table 1). We also summarized some undergoing/not released studies in table 2.

Efficacy

In the iPrEX trial, 100 out of 2441 participants became HIV-infected during follow-up (36 among TDF-FTC and 64 among placebo group, a relative reduction of 44% in HIV incidence, p=0.005). In the FEM-PrEP trial, 68 participants had sero-conversion (33 in TDF-FTC, 35 in placebo group, estimated hazard ratio in the TDF-FTC group was 0.94, p=0.81). In PIP study, HIV occurred among 82 participants (17 in TDF, 13 in TDF- FTC and 52 in placebo group, 67% relative reductions in HIV-1 acquisition among TDF group, $p<0.001$ and 75% among TDF-FTC group, $p<0.001$). In TDF2 trial, 33 were HIV-infected during the study (9 in TDF-FTC, 24 in placebo group, relative reduction of 61.7%, p=0.03). In the BTS, 50 participants became infected during follow-up (17 in the TDF group and 33 in the placebo group, indicating a 48.9% reduction in HIV incidence). Except FEM-PrEP, all other trials reported some reductions in HIV-risk among treatment groups.

Safety

Overall occurrence of adverse events were found to be highest in TDF2 trial (91.2% among treated vs. 88.2% among placebo group, and the difference was significant) and BTS (91% in TDF group vs. 90% in placebo group and difference was not statistically significant) followed by FEM-PrEP trial (74.1 in treated vs. 72.3% in placebo group and difference was not statistically significant), iPrEX trial (both groups reported 8%) and lowest in TDF2 trial (6.3% in both).

In iPrEX trial, serum creatinine were elevated among TDF-FTC compared to placebo group (2% vs. 1%, p=0.08). Self-reported nausea and unintentional weight loss were more in the TDF-FTC group. FEM-PrEP trial showed similar results. Gastrointestinal adverse effects were observed more among treated groups in PIP, BTS and TDF2 trials.

Adherence

Adherence was measured by pill-counts, bottles returned and self-reported pill use. However, due to social desirability bias, these measurements might not reflect the true adherence as patients might over-report their adherence [47]. On estimating the concentration of assigned drugs in blood, we observed lower adherence compared to adherence measured by pill-counts (in iPrEX 51%, in FEM-PrEP <40%, in PIP 82% and in TDF2 80%) [48]. It is worth mentioning that in BTS adherence was assessed daily at daily directly observed therapy (DOT) and monthly at non-DOT visits using a study drug diary. According to the diaries, participants took the study drug an average of 83.8% days and two groups showed no significant statistical difference.

Behavioral disinhibition

Behavioral disinhibition, also known as risk compensation, addresses the possibility that certain HIV-risk reduction measures may increase risky behaviors due to decreased self-perceived risk [49 50]. Thus, while applying the innovative “risk-homeostasis model” to HIV prevention, the main concern is that assuming protective benefits of promising interventions may be offset by increased risky behaviors. Risk compensation has been observed in several interventions including HIV vaccines [51 52], anti-retroviral drugs [53–59] and male circumcision [60]. Also, it was reported that people tend to escalate high-risk behaviors with the belief that HIV is no longer an incurable disease due to the easy availability of HAART [61].

Drug Resistance

Near about 50% of HIV patients on HAART in US developed resistance to at least one of the components. Rapid mutation of viral proteins has led to emergence of drug-resistance and transmission of drug-resistant strains [62–64] progressing to cross-resistance and slow response to available ART [65].

Five concluded PrEP trials reported moderate risk of induce mutation. Six of the total seven reported drug-resistant cases were infected at enrollment in iPrEX, PIP and TDF2 trials. Of the six, four showed resistance to FTC, one to TDF and another one had K65R, M184V and A62V mutations. In the FEM-PrEP study, five persons developed mutations (4 in TDF-FTC group, and 1 in placebo group).

Cost-effectiveness

Based on two mathematical prediction models of cost-effectiveness of daily ART [66 67], it was observed that:

1. Efficacy of PrEP if increased from 50% to 90%, the cost of per quality-adjusted life-year (QALY) gain would decrease from US $298,000 to US $107,000 per QALY [66].
2. PrEP may diminish HIV infection with substantial cost-effectiveness in high-risk populations.
3. 50% reduction of the cost of PrEP would result in a cost of per QALY gain of US $114,000 instead of US$298,000

It was estimated that PrEP among high-risk behavior groups, may avert approximately 3 million new HIV-infections in southern sub-Saharan Africa by 2017 [67], while depending on the extent of ART coverage and baseline HIV incidence, prevention of one HIV infection was found to save $12,500–$20,000 [68].

Discussion

This paper described the concept and development of PrEP, summarized major findings of five published PrEP trials and further discussed some important factors required to be considered for successful implementation.

Observed differences in safety between trials might be due to the application of different measures of occurrence of adverse events. Prior studies indicated that TDF and FTC could affect renal and bone mineral density [69 70]. Researchers found a decline in scores for mineral density of bones in the forearm, hip and lumbar region among 221 participants in TDF2 study. There were no significant differences across study groups relating to mortality or serious clinical adverse events. Although most of these trials reported short-term effects, evaluation of the long-term effects is needed before declaring the safety of PrEP. WHO guidelines also define the clinical contraindications of PrEP with caution [21].

Another major side-effect was hepatic flare [71 72]. Prior research indicated that 23% patients might have post-treatment exacerbation of hepatitis-B infection [73]. In all five studies, an eligible participant required to have a negative test result for hepatitis-B virus surface antigen. Only in the PIP trial and the BTS hepatitis B vaccination was done. No tests for hepatitis-B were performed in any of these trials.

Five completed trials did focus on different risk-groups having risk-behaviors reflecting different routes of HIV-transmission. Early research indicated that the concentration of drug varied according the types of mucosal tissue [74]. Compared to rectal tissue, higher concentrations of assigned drugs in the vaginal and cervical tissues might partly explain the higher risk reduction showed in PIP and TDF2 trials over iPrEX trial. Secondly, difference in adherence also might contribute to this inconsistency. In the five trials, participants were reported to have high rates of adherence (>90%).

In the absence of HIV preventive vaccine or cure, initiation of PrEP may be helpful in controlling HIV epidemic among high-risk population. PrEP is one of the most innovative and promising HIV prevention approaches discovered till date but its implementation is limited. Overall, it is evident from the published trials that PrEP is effective and safe [41–

44]. However, the duration of this efficacy is strongly related to the coverage of ART, adherence of the participants, use of other harm reduction interventions (condom use etc.), toxicity and other related issues like cost, political commitment, ethical consideration etc.

Adherence is essential for assessing optimal treatment and is influenced by many factors. Previous studies indicated that individuals suspecting the efficacy of ART showed poor compliance [75]. A survey on adherence to both PEP and PrEP suggested that approximately 67% would take daily pills to prevent HIV given the evidence of efficacy and safety of the prescribed drug. Among all trials, iPrEx study indicated excellent safety and moderate efficacy, while FEM-PrEP trial reported lack of efficacy due to low adherence determined by drug levels in blood. The inter-relationship between self-reported adherence and adverse effects is very complex and further research is needed to apprehend this.

These trials clearly indicated that for enhancing adherence, accurate identification of the correlates of non-compliance and continuous monitoring of adverse events are required. Experiences from ART proved that adherence was strongly associated with safety and drug-resistance [76 77]. However, improvement of adherence is a challenge and identified correlates include education [78], social support [79], socio-demographic and psychological factors [80], misconceptions, cultural beliefs, switching to combination therapies, history of addiction, inconvenient dosing frequency, dietary restrictions, pill-burden and side effects [78].

With regard to PrEP, mathematical model predicted that behavioral disinhibition could invalidate the PrEP strategies if not reversed it [81]. Another concern is the promotion of sexually transmitted infections (STIs) by behavioral disinhibition as ARTs have no effect on them. No such risk compensation was observed in these five PrEP trials. iPrEX trial demonstrated that proportion of participants practicing receptive anal intercourse declined and there was an increase in condom use. In the PIP study, the proportion of HIV-negative partners reporting unprotected sex decreased from 27% at enrollment to 9% during follow-up. In both FEM-PrEP and TDF2 trials, participants reported having less partners during follow-up. In BTS, reports of injecting drugs during the previous 3 months, sharing needles and sex with more than one partner decreased during follow-up.

Standardization of the first-line and second-line treatment regimen is required to prevent the emergence of drug-resistance based on potency, duration of efficacy, toxicity, cost and availability. Acute retrovirus syndrome (ARS) often associated with acute HIV infection is a diagnostic challenge due to the non-specific symptoms and negative or inconclusive HIV serological test results. Thus, many HIV sero-converters may be missed as observed in iPrEX trial, where among 10 participants who had been HIV-infected at enrollment, five presented ARS. According to some researchers HIV clinical case definition should include ARS [82] to address HIV-induced immunodeficiency better. Viral RNA-testing before PrEP initiation, just as PEP, could be used to detect acute infections if possible.

Majority of resistance occurs due to irregular intake of medicines or treatment interruptions [83] which may be prevented by simpler dosing schedules containing fewer pills, use of effective first-line drugs having less toxicity and assurance of social support. WHO has

established a global program for monitoring and surveillance of HIV drug-resistance with support from a network of accredited laboratories for detecting resistance at its early stage [84].

Although PrEP may be relatively cost-effective based on the designed models [67 68], the budget for its successful implementation is still a big challenge. Even if the lower bound of the expected cost for preventing one new infection is considered, it will amount to $12,500 [68], thus to prevent 3 million new infections in southern sub-Saharan by 2017, it would cost $37.5 billion, which is about 3% of the GDP of southern sub-Saharan in 2011 (www.worldbank.org/afr/stats). PrEP promotion requires raised awareness regarding HIV through health education, minimizing risk behaviors, improvement of ART coverage, commitment of resources from donors, co-ordination and cooperation of government/ funding agencies, substantial allocation of budget and a well-designed guideline.

Valid estimation of effectiveness of PrEP and its efficient implementation requires identification of appropriate target population. It has been observed that PrEP can avert considerable amount of new HIV infections provided the intervention targets appropriate population with high risk of acquisition of HIV [68]. The impact of PrEP may vary substantially across populations with different risk behaviors [81]. Populations with higher risk of HIV seem to be the appropriate target for PrEP while appropriateness of implementation of PrEP in general population is largely questionable [66 68 81].

A study among MSM in New York City during 2006 demonstrated that none were aware of PrEP and they had limited knowledge regarding microbicides and PEP. Participants showed willingness of using other non-condom biomedical HIV prevention products like microbicides, vaccine, PEP except PrEP [85]. Another survey of HIV sero-negative gay/ bisexual men in California reported that nearly half were aware of PEP and <16% had knowledge regarding PrEP [86]. For optimum utilization of PrEP in any healthcare setting, it was pertinent to take care of the components like choosing PrEP drugs, screening for safety, repeated HIV testing, sustaining other ongoing behavioral interventions, maximizing adherence, minimizing risk compensation and establishment of a strict monitoring and surveillance at population level [87]. Community education was an important tool to raise willingness among volunteers [88].

As we mentioned earlier, the cost-effectiveness of PrEP depends on the coverage of the intervention program, HIV testing and accessibility to ART [68] which in turn require strong coordination from social support systems involving Government, NGOs, institutions, communities, families and individuals [89]. However, getting the intended social support from different sectors for treating HIV is a threat to public health globally [90].

HIV-related discrimination and stigma are major barriers to access HIV/AIDS care [91] and treatment opportunities [92–94], which thus affect adherence and success of PrEP [87]. A qualitative study among female sex workers (FSW), men who have sex with men (MSM) and transgenders identified stigma/social discrimination and negative attitudes of healthcare providers as important determinants of acceptability [95 96] and efficacy of PrEP [97].

Over past 30 years, researchers and policy-makers tried to reduce the discrimination and stigma, by implementing programs like “Four Free and One Care” program in China [98] and governors around the world have been praised for addressing stigma surrounding HIV/AIDS, but there still remains a long way to go on this issue [99].

Interrelationship of social structure, cultural beliefs and gender discrimination are critical for success of PrEP [100 101]. Premature closure of PrEP trials by governments in Cameroon and Cambodia following emergence of negative advocacy highlighted the importance of following issues like appropriate conduct of research, selection of target population, involvement of community leaders, provision of treatment during and after trial, assuring access to PrEP if it is useful, sustenance of PrEP in poor countries, influence of cultural beliefs and political commitment [102]. For designing an effective preventive trial, implementation of a decentralized program and avoiding conflict of interest need to be addressed [103].

PrEP raises many ethical concerns. Main concerns include role of Government and industry in providing PrEP, actual distribution of resources, standard of care in trials and monitoring the basis of prioritization. Many of these issues were raised by the closure of PrEP trials in Cameroon and Cambodia following emergence of dispute and opposition [104]. Another important ethical concern is the possibility that PrEP may promote risk behaviors especially among FSWs, drug users, MSM and other high-risk groups.

Evidence from the published trials suggested that PrEP is safe, efficacious and cost-effective. To deliver a culturally appropriate and cost-effective program for providing PrEP in a successful manner, uninterrupted drug delivery with good infra-structural support is critical. Identification of the appropriate target population and specific implementation seem to be of paramount importance for the success of PrEP. Adequate care should be taken for monitoring adverse effects of individuals on PrEP so adherence is ensured. Individual should be counseled by trained health-workers regarding risk-behaviors, informed about drug-availability and its use to maximize compliance. PrEP should not be regarded as a separate preventative approach but should be integrated with existing HIV prevention programs.

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Table 1

Salient features of prior studies on pre-exposure prophylaxis of HIV

Trial name	Study site	Intervention	Study population	Protection
iPrEx	North and South America, Thailand, South Africa	daily oral TDF-FTC[a]	2499 HIV sero-negative men or transgender women who have sex with men	44% (15% – 63%)
FEM-PrEP	Kenya, South Africa, Tanzania	daily oral TDF-FTC	2120 HIV negative women	halted early for lack of efficacy
PIP	Kenya and Uganda	daily oral TDF-FTC or TDF[b]	4747 HIV-1 serodiscordant heterosexual couples	67% (44% – 81%) TDF 75%(55%–87%) TDF-FTC
TDF2	Botswana	daily oral TDF-FTC	1219 HIV sero-negative men and women	62.2% (21.5% –83.4%)

[a] TDF-FTC: Tenofovir and Emtricitabine combination

[b] TDF: Tenofovir disoproxilfumarate

Table II

Salient features of ongoing PrEP trials (from http://data.avac.org/OngoingPrEPTrials.aspx)

Trial name	Phase	Start date	Locations	Sponsor/funder	Population	Intervention arms	Results expected
iPREX OLE	Open Label	June 2012	Brazil, Ecuador, Peru, South Africa, Thailand, United States	NIAID	1500 Men	Daily oral TDF-FTC	November 2013
CDC 494 (TDF2 Follow-Up Open Label Extension)	Open Label	November 2012	Botswana	Botswana Ministry of Health, CDC, Gilead	1200 Women, Men	Daily oral TDF-FTC	November 2013
CDC 4370 (Bangkok Tenofovir Study)	III, II	June 2005	Thailand	CDC, Bangkok Metropolitan Administration (BMA)	2400 Injecting drug users	Daily oral TDF-FTC	December 2012
Partners PrEP	III	July 2008	Kenya, Uganda	BMGF	4700 Women, Men, Heterosexual, Serodiscordant	Daily oral TDF-FTC, Oral TDF	January 2013
ANRS IPERGAY	III	January 2012	Canada, France	ANRS	1900 MSM	Intermittent oral TDF-FTC	December 2016
HPTN 069/ACTG 5305 (NEXT-PrEP)	II	February 2012	United States	ACTG, HPTN, NIAID	400 Gay men and other men who have sex with men, Men	MVC 300 mg, MVC 300 mg + TDF 300 mg, MVC 300 mg + FTC 200 mg, TDF 300 mg + FTC 200 mg	January 2014
HPTN 067 (ADAPT)	II	January 2011	South Africa, Thailand	DIADS, Gilead, HPTN, NIMH	360 Heterosexual women, MSM	Intermittent oral TDF-FTC	September 2012
HPTN 066	I	January 2011		HPTN	32 Women, Men	Different dosing schedules of TDF-FTC	October 2011
SSAT 040 (TMC278LA)	I	January 2011	United Kingdom	St Stephen's AIDS Trust	66 Men, Women	TMC278 LA	February 2012
MTN 003B	Other	November 2009	Uganda, Zimbabwe	Gilead, MTN, NIAID	518 Women	Daily oral TDF-FTC, Oral TDF	January 2013