PRE-EXPOSURE PROPHYLAXIS (PREP), A NEW AIDS PREVENTION TOOL. WHERE ARE WE? IMPLEMENTATION STRATEGIES FROM INDIAN PERSPECTIVES.

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ABSTRACT
Pre-exposure prophylaxis is one of the new AIDS preventive tool. Rapid testing, circumcision, condom, abstinence are the other preventive strategies, which are mainly male controlled methods. Each of these strategies have their advantages and disadvantages. No single prevention strategy will be 100% effective against HIV transmission. Hence, transmission reduction will require integration of all available prevention strategies. Implementation of a newer preventive method is the biggest challenge in a country like India which is highly populated and the spread of HIV infection is rampant. It is important that we prepare strategies against the anticipated challenges of implementation while awaiting for the final report of trials and regulatory approval. This will accelerate the process of our campaign against HIV spread. An effort is made to discuss the challenges and the possible answers in implementation of newer pre-exposure prophylaxis as a preventive method in our population. Successful implementation requires the integrated efforts from the prescribers, users, policymakers, voluntary organizations and media.

KEYWORDS: Pre-exposure, implementation, prevention, strategy.
INTRODUCTION

The risk of HIV infection. PrEP can be in the form of a pill taken by mouth or a gel applied in the vagina or rectum and continued during periods of risk \(^1\).

July 2012 FDA gave approval to once daily administration of combination of emtricitabine/tenofovir for HIV prevention in men and women at risk for HIV \(^2\). In India women represent 60% of HIV infected individuals. This will be a female controlled prevention method who are unable to negotiate condom use. Hence this new concept will be useful for our population to contain HIV spread \(^1\).

PREP IMPLEMENTATION

Implementation can be discussed as core five themes \(^3\)

1. Scientific groundwork
2. Regulatory and policy groundwork
3. Stakeholders
4. Infrastructure groundwork
5. Delivery and long term monitoring

Challenges and possible answers from Indian perspective in implementing PrEP

Scientific groundwork

Guidelines: It is necessary that we should have guidelines to the prescribers and policymakers about the regimen, route, laboratory tests, suitable population and drug administration for special population. Center for disease control and prevention, department of health and human services (USA Guidelines) has already published guidelines after critically analyzing the available data by a systematic search and review of published literature which is intended for primary care physicians, health program policymakers \(^4\). To generate the guidelines we require some amount of quality clinical trial data from our population. This will give enough confidence to clinicians in their practice.

Clinical Efficacy: Studies till date have proven the efficacy of tenofovir (TDF) and or emtricitabine (FTC) as PrEP regimen both by topical and oral route. The Centre for the AIDS Programme of Research in South Africa (CAPRISA 004) trial, a double blinded randomized controlled trial of TDF vaginal gel vs. placebo in 889 HIV uninfected non-pregnant women in KwaZulu-Natal, South Africa \(^5, 6\). After 12 months of follow-up, preliminary HIV incidence rate in the treated group was 50% lower than in the placebo group irrespective of
condom use, urban or rural community, sexual behavior, or concurrent HSV-2 infection. Recently reported results of the iPrEx study of TDF/FTC (vs. placebo) for PrEP in men who have sex with men (MSM), after the intention-to-treat analysis, TDF/FTC was associated with a 44% reduction in HIV acquisition \[^{7,8}\].

Partners PrEP enrolled 4747 HIV-1 serodiscordant heterosexual couples from Uganda and Kenya found 75% (95% CI 55–87%) relative risk reduction was observed in the Truvada arm (fixed dose combination of TDF 300 mg + FTC 200 mg \[^9\]). Long acting injectables like rilpivirine an NNRTI (T1/2=84 days) and integrase strand transfer inhibitor (GSK1265744, T1/2=21-50 days) which are still in the investigatory stage can be helpful in improving the compliance \[^{10}\]. But these trial data are from a their population. There were no trials done in India to know the awareness of the regimen among people and health care personnel or its safety or efficacy in our population. Hence trials in our general and special population has to be encouraged as we are different by culture, financial status and our behaviors.

Studies have also shown that PrEP can be a component but not the replacement for the available preventive strategies. People should be educated about it being an additional measure but not a replacement \[^{11}\]. This could be a challenge to promote PrEP over condom in Indian population as the later is the most accepted and successful method of HIV prevention especially among population of south India \[^{12}\].

**Safety:** Till date both the drugs were found to be safe except for the mild adverse effects like headache, upper respiratory tract infection, nausea, abdominal discomfort, loose stool and fatigue \[^{11}\]. These drugs also were shown to reduce bone mineral density (BMD) \[^{13}\] and can elevate serum creatinine \[^{14}\]. It was found that creatinine elevation is reversible after stopping the drug and reduction in BMD is clinically a minor adverse event. No other adverse events that are serious in nature have been reported for both these drugs. Studies in special population is lacking.

All the trials were conducted in other countries and have emphasized on the importance of adherence for the successful PrEP implementation \[^{5,6}\]. In fact, one of the clinical trial failed to show efficacy because drug taking behavior was only 20% in both the placebo and the study drugs group \[^{10}\]. In another study after hearing about PrEP, 74% reported an interest in using it, especially if it had no side effects and was available free of cost \[^{15}\]. It reiterates that the safety of the drugs and cost plays a major role in the patient acceptability.
Cost: Cost is an important factor that has to be considered in our country. Cost-effectiveness data is an essential information for its successful implementation, since these drugs are advised for long duration. TDF/ FTC which are the approved components of PrEP is expensive [1000 (US$ 24)] per month and so, without government buy-in, it would not be feasible. In all the studies, individuals were tested for HIV infection on a monthly basis to minimize the possibility of development of resistance in the case of seroconverters - this would add to expenses [16]. Till date there is no cost-effective analysis done in India. In a study in South Africa, it was estimated that, prior to antiretroviral therapy scale-up, if PrEP was given to all 15-35 year old women, 10-25% of new infections would be averted with a savings of US$12,500-$20,000 per infection avoided [17]. Another study in South-Africa concludes that general PrEP is costly but the focused PrEP (population at high risk) is cost saving [18]. The authors also gives hint that these findings cannot be generalized to other countries. Epidemiologic research in our population will identify the target populations for the focused PrEP.

Regulatory, Policy, and Financial Groundwork

Getting regulatory approval is important for the successful implementation. Though the USFDA has approved this method of HIV prevention, we have to hope for the early approval from the DCGI. This will give enough confidence to prescribers and also insurers to cover the costs. Negotiating DCGI for approval requires clinical trial data generated from our population. Approval of clinical trials as quick as possible in turn will encourage many sponsors to carry out more trials and to generate more data. The sponsors has to be encouraged to do the trials by providing the favorable environment for conducting studies. There is drastic fall in the number of approved clinical trials recently in India. There were 500 clinical trial approvals in 2010, came down to 262 approved trials in 2012, just 107 approvals in 2013 and 76 trials approved till may in 2014 [19]. This falling trend will discourage sponsors from taking up clinical trials. Delay in the process of approval was attributed to long submission requirements (a) the sponsor’s undertaking of providing medical treatment and compensation in case of clinical trial related injury/death (b) the sponsor’s commitment that they will market the drug in India after the trial is completed (c) submission of regulatory documents for New Drug Advisory Committee (NDAC) (d) changes in the informed consent form (ICF) to include compensation related clauses and (e) changes in the investigator undertaking to include safety reporting and compensation related clauses and (f) submission of the investigator’s list containing 50% government sites [20].
These has to be addressed with clarifications so that it creates a conducive environment to conduct clinical trial.

Useful policies from the government is required for successful implementation. Providing the drugs free of cost or at subsidized rates to all the primary care centers, ensuring its delivery and availability throughout the year will be a useful initiative. Financial assistance is necessary for PrEP drug delivery, infrastructure and human resources development, training clinical providers, outreach and community education, monitoring and surveillance, safety screening, long-term HIV testing and referrals. Health care allowance in India is still meagre at 4.1% of GDP in 2012 [21]. To increase it to double digits requires a hard work from the government and private manufacturers and a strong political will. Insurance companies should be encouraged to bring in PrEP under coverage after providing essential information to the companies.

**Stakeholder and Infrastructure Groundwork**

Clinical and para-clinical personnel, PrEP users, government policy makers, voluntary groups, and media with coordinated and integrated approach is required for the implementation.

Active strategies to identify and reach the populations that are stigmatized or hidden, such as sex workers, injection drug users, racial and ethnic minorities is important. Training and supervision of clinical and non-clinical providers, structures for drug delivery and distribution, personnel and laboratory facilities for safety screening and HIV testing, mechanisms for monitoring and surveillance, education for potential users, and personnel and infrastructure for behavioral interventions is required.

**Delivering PrEP**

Introducing the successful strategies like the one with tuberculosis-Directly observed treatment short course can ensure the adherence. But this demands a lot of human resources and financial support. Setting up the HIV prevention clinics attached to all the primary health care centers and utilizing communication technology like text messaging, telephonic follow-up calls can be a useful alternative to overcome man power to some extent.

Mechanisms may be necessary to coordinate different aspects of PrEP implementation for individual users, to ensure that each user receives the necessary HIV testing, follow-up care,
and behavioral support in addition to PrEP drugs. Separate PrEP setups attached to the primary health care will maximize the accessibility of testing and treatment services to hard-to-reach populations.

**Long-Term Monitoring**

Periodic drug safety reports, monitoring PrEP failures, PrEP uptake, acceptability, checking periodically for the spread of HIV resistance, and regular adherence assessment will strengthen the development of implementation strategies. Monitoring and evaluating PrEP’s cost-effectiveness will also present resourcing and information infrastructure needs to policy makers. The sustainability of PrEP on a longer run as a population-level prevention strategy will depend on the success of these monitoring efforts.

**Limitations of PrEP implementation in India:**

1) **False sense of security**: Introduction of this newer preventive strategy may have negative impact on the use of condom which is the highly successful in reducing the HIV spread in India. Fall in HIV level in India is primarily due to the high levels of condom use during commercial sex in Southern India that have resulted in a steeply decreasing HIV trend since 2000 [22]. Easy accessibility, lower cost may be the reasons for its popularity. In such a situation it is a big challenge to convince the risk population to use this orally taken, more costly and additional method of prevention. Authors from the literature warn that if PrEP would even slightly decrease current condom use levels in India, its impact would be negative. Thus, in India introduction of new prevention methods such as PrEP must be done very carefully in order not to compromise the benefits gained through condom use [22]. However, condom use has its own disadvantages. Non-condom use may be seen as a gesture of intimacy, and both men and women may complain of the decreased sensation of pleasure with condom use. Condom usage decreases with intoxication-induced behavioral disinhibition [23]. Male condoms may be made of latex, polyurethane or (in the USA) treated animal tissue. This may be allergic to some people. It is also important that both partners are taught how to use condoms properly to reduce the risk of slippage or breakage of the condom.

Nevertheless, CDC states that “no single prevention strategy will be 100% effective against HIV transmission, abstinence and mutual monogamy with an HIV-negative partner will remain the only 100% effective ways to prevent infection”. Hence, reducing transmission will
require determining how best to integrate all available prevention strategies—both biomedical and behavioral [24].

2) Development of resistance: If PrEP was promoted as a strategy in India, any person who thinks he/she might be at the risk of HIV acquisition might procure TDF/FTC from the pharmacies over the counter. This might result in HIV-infected individuals who are unaware of their status taking dual-therapy (TDF/FTC) or monotherapy (TDF) and thereby develop resistance [16].

3) Safety: Long term safety data for these two drugs in Indian population is not known. So safety data is required for its use for longer period.

4) Cost: Can we spend money for purchasing drugs for a PrEP program, when funds are short for purchasing drugs for already HIV infected patients?

5) Social acceptability: PrEP carries social stigma. India is a land of diversity with people of multiple cultures. Population may not easily accept this method which requires regular intake of drugs with frequent laboratory tests before and after taking it. This consumes lot of time and is perceived as uncomfortable to many. Combating PrEP stigma requires multi-faceted approach by stigma reduction campaigns, education for health care providers and a broad recognition of PrEP users as individuals proactively using proven prevention strategies [2]. This could change the attitude of society towards PrEP users.

**Advantages of PrEP**
- More gender neutral
- Covert use feasible
- Coitally independent
- May work for more than one type of exposure (for example, for an injecting drug user who has unprotected sex)
- Can discontinue PrEP during periods where individuals are not engaging in activities that place them at risk for HIV infection
- Opportunity to link men as well as women to preventive care.
- Circumcision is considered as one of the proven preventive strategies of HIV infection [25].
Yet, circumcision in male is not an intervention commonly promoted in India. Circumcision has been historically linked with particular religion in India and therefore, there may be some hesitation in the adoption of this method by other communities. Hence, PrEP can be an acceptable method in such population.

CONCLUSION
PrEP is a newer preventive method in HIV prevention. Like other methods, PrEP also has its advantages and disadvantages. This method is not a replacement but an effective component of preventive strategies. Reducing transmission will require determining how best to integrate all available prevention strategies. Successful implementation of PrEP in our population requires the integrated approach from clinical and para clinical personnel, PrEP users, government policy makers, voluntary groups, and media.

REFERENCES


