Review Article

Zero transmission of HIV – “Still a long way to go”
An Update on TasP: PrEP and PEP of HIV infection

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Abstract
AIDS emerged as one of the most important public health issues of the late twentieth and early twenty-first centuries and is now one of the leading causes of global morbidity and mortality. The AIDS epidemic has prompted wide-reaching changes in public health, clinical practice, and scientific research, and has had a great impact upon societies throughout the world. This review article gives an insight into updates on TasP (Treatment as prevention), PrEP (pre-exposure prophylaxis) and PEP (Post-exposure prophylaxis) of HIV infection.

Keeping in view the ABC policy (Abstinence, behavioral change, condoms) and all the updates on TasP, PrEP, PEP and Test & Treat policy, and the scenario of implementation of zero transmission of HIV, probably we will find an answer with more intense research (RCTs) in near future.

Keywords: AIDS, HIV infection, Antiretroviral

1. Introduction
AIDS emerged as one of the most important public health issues of the late twentieth and early twenty-first centuries and is now one of the leading causes of global morbidity and mortality. The AIDS epidemic has prompted wide-reaching changes in public health, clinical practice, and scientific research, and has had a great impact upon societies throughout the world. HIV is transmitted from person to person. Each infected person interacts with other individuals in a variety of relationships, is a member of at least one cultural group, belongs to some type of community, and lives in specific social and economic environments. Thus, the conditions under which individuals transmit HIV to others vary in a highly complex manner across individuals, families, groups, neighbourhoods, regions, and countries. Such variation, when combined with the issues of transmission through sexual contact and drug use, presents a compelling challenge to the design and implementation of effective public health measures to control the AIDS epidemic.

Antiretroviral therapy has transformed a once universal fatal illness to that of chronic stable infection. As ART has to be started life long, with a high degree of resistance, patient readiness is of paramount importance. Goals of ART are to ensure maximal and durable suppression of the virus, to reconstitute and preserve immunologic quantity and function, to improve quality of life and to reduce morbidity and mortality due to HIV infection.

2. Antiretroviral treatment as prevention (TasP)
As per WHO suggestion, with the right prevention and interventions delivered within a human rights framework, HIV can be controlled and possibly even eliminated. WHO, UNAIDS and the United Nations General Assembly have called for 15 million people to be on ART by 2015. ART has considerable benefit, both as treatment and in preventing HIV and TB.

Treatment as prevention (TasP) is a term used to describe HIV prevention methods that use ART in HIV-positive persons to decrease the chance of HIV transmission independent of CD4 cell count. There is enough evidence to suggest that once you treat HIV infected patients, their ability to transmit the infection is minimized. The Rakai study from Uganda demonstrated that plasma viral load is the main predictor of heterosexual HIV transmission, and that transmission is rare when plasma viral load is < 1500 copies/ml. Spanish study of serodiscordant couples showed no HIV transmission in the sexual partners of HAART-experienced patients, and that HAART was associated with a substantial reduction (80%) in HIV transmission. Observational studies among diverse patient populations have provided data regarding the immune restorative effects of HAART as well as the role of HAART in decreasing HIV transmission to uninfected individuals. Donnem et al in a prospective cohort analysis in African population showed that lower CD4 counts and higher viral loads are associated with increased transmission of HIV and provision of ART to HIV-1 infected patients could be an effective strategy to achieve population-level reductions in HIV-1 transmission. The vertical transmission of HIV has been reduced to < 2% in developed countries due to HAART.

It is certain that TasP needs to be considered as a key element of combination HIV prevention and as a major part of the solution to ending the HIV epidemic. In the short and medium term, while countries are concentrating their efforts on scaling up treatment according to the eligibility criteria recommended by WHO, it is expected that they will concurrently identify opportunities to maximize the use of ART for prevention purposes (TasP).

The focus should be on specific populations in whom the prevention impact is expected to be greatest (e.g. serodiscordant couples, pregnant women, key populations). WHO is working with countries to address programmatic and operational challenges in order to derive the consolidated guidelines which are to be released.
3. Pre-exposure prophylaxis for HIV (PrEP)

PrEP refers to preventative treatment before exposure to an infectious agent i.e. HIV. It is not a new concept. It is similar to malaria prophylaxis commonly given for travelers who proceed to endemic areas. PrEP involves prevention of acquisition in HIV-negative persons. Pre-exposure prophylaxis, or the use of antiretroviral drugs by HIV negative people to prevent infection, is an emerging biomedical approach to HIV prevention. Several studies have been presented at scientific conferences including National and International AIDS conferences or reported in peer-reviewed journals, with somewhat differing results

3.1 Why antiretroviral drugs for PrEP?

Data suggesting that ARV prophylaxis may be effective as indicated by effectiveness of ARVs for prevention of parent to child transmission (PPTCT), post-exposure HIV prophylaxis in HCWs (needle-stick), monkey models for SHIV transmission with the available ARVs which are safe and which can be used once daily like - TDF (tenofovir disoproxil fumarate: Viread), – FTC: emtricitabine: Emtriva, – TDF/FTC: Truvada.

Ideal antiretroviral chemoprophylaxis should have a long half life, low toxicity, high tolerability, inexpensive, stable in heat and humidity, there should be no food requirements, safe in pregnancy, minimal drug interactions and should have highest barrier to resistance.

Various RCTs were carried out in different parts of the country. In West Africa Phase II PrEP Trial was carried out with daily TDF 300mg and placebo on women (n=936) in Ghana, Cameroon and Nigeria during June 2004 - March 2006 with no evidence of increased clinical or laboratory adverse effects, no evidence of risk compensation, inadequate power to assess efficacy which included 8 HIV seroconversions: 2 TDF, 6 placebo (p=0.24).

In US (CDC) also a clinical and behavioral safety trial of Tenofovir was conducted on 400 HIV-ve MSM (Atlanta, San Francisco and Boston) in two arms (immediate: Oral TDF vs. placebo, 1:1) and the study was completed in 2009/10. Preliminary analyses suggest no serious safety concerns and no increased risk in men taking a study pill, compared to those not taking a study pill during their first nine months of study participation. These were randomized, double-blind, placebo-controlled and assessed safety and efficacy in preventing HIV infection.

Similarly, various studies were carried out by CDC (CDC 4940, CDC 4370), NIH, BMGF (IPREX), USAID (CAPRISA 004), Bangkok Tenofovir Study (BTS), Botswana TDF-2 Study which showed the effectiveness of tenofovir (Tab and gel) with incidence rate ratio: 0.61 (CI: 0.4 to 0.94); p = 0.017. 39% lower HIV incidence in tenofovir gel group8. The iPrEx trial, a study of PrEP in men who have sex with men (MSM) and transgender women, found an overall 44% reduction in HIV infections for people taking tenofovir/emtricitabine (Truvada) compared to placebo. In people with detectable drug in their blood, a strong indicator of adherence, the efficacy was over 90%.11

Various studies were also carried out showing efficacy of intermittent PrEP (IAVI) in Kenya and Uganda in 2009. Fixed doses of PrEP, either daily dosing or fixed Monday and Friday dosing (intermittent), had similar and relatively high adherence rates among the study populations. Regimens of one tablet of FTC/TDF, administered daily or intermittently also had good safety profiles. Intermittent dosing is feasible in important at-risk populations in Africa. However, post-coital adherence was low12. There are many issues to work out around the implementation and use of PrEP. All of the PrEP studies fully analyzed to date have found significant differences in efficacy based on treatment adherence. PrEP works for people who are able to take it regularly. Adherence education and support will be critical in any efforts to implement PrEP13 and also there are various questions to be answered namely, Who will use it? Who will pay for it? Will it get to the people who need it most? Can we afford to give antiretroviral drugs to HIV negative people when millions of HIV positive people worldwide do not have access to treatment?. Looking at all these as well as interaction with HIV/AIDS experts and review of literature, PrEP can be possibly implemented in a closed and smaller population, where finance is not a problem but it still requires accurate RCTs to overcome benefits viz harms.

We now know that condoms, clean needles, male circumcision and prophylaxis to prevent mother-to-child transmission have worked well in preventing infection. It is known that PrEP works for men who have sex with men and transgender women, and there is conflicting but generally positive evidence of its effectiveness for heterosexuals. Vaginal and anal microbicides are another promising approach currently being studied.

Having a diverse array of effective prevention options can go a long way to controlling and possibly halting the HIV/AIDS pandemic. While more research is needed to better understand the new approaches of PrEP and treatment as prevention, drug companies, policymakers, and communities affected by HIV must do even more work to meet the challenges presented by these recent advances and to maximize their impact. As UNAIDS Executive Director Michel Sidibe said at the IAS meeting, “We have to remember that history will judge us not by our scientific breakthroughs, but how we apply them.”14

3.2 “Test and Treat” Policy

This policy advocates testing of individuals and treating all those who are positive so that it acts as prevention to others while controlling the infection in positive ones. Studies showed that early treatment, when compared to standard guidelines would lead to 0.75% reduction in death rates and 0.50% reduction in incidence of active TB16.

Increasing evidence suggests that insidious damage occurs during “asymptomatic” HIV infection which underscores the potential benefit of ART. The prominence of non-AIDS events as a major cause of morbidity and mortality in those with ongoing HIV replication suggests that early ART initiation may further improve the quality and length of life for persons living with HIV17.

3.3 Early Initiation of ART (CD4 < 500)**?

Benefits are significant - 94% reduction in mortality, >70% reduction in hospitalization, ~ 70% reduction in TB. Minimizing the risk of non AIDS defining events and malignancies18. However a debatable issue with pros and cons. WHO now recommends starting of ART at CD4 count at 500.

4. Weighing the options Prevention Viz Treatment

Prevention - Target audience is 1 billion. Various methods which include use of condom, circumcision, safe blood transfusion, etc. 2400 crore already spent to create awareness (88.6 % of HIV transmission has happened because of unprotected sex) Is this strategy really working?

Treatment- 2 million people are left untreated (~15% Tx rate). Patients on effective treatment can minimize the risk of transmission, we spent only ~ 120 crore, could treatment to all be a possible way forward?, Door steps are opened but it will be the future research which will provide definitive findings

In 1996, Brazil granted free universal access to antiretroviral therapy to all of its HIV-infected citizens, regardless of socioeconomic status, and rates of new HIV infections have since stabilized19. An ecological study from Taiwan provided evidence of the dramatic impact of HAART in curbing a regional epidemic and reported a 53% reduction in individuals testing positive for HIV following the availability of free access to HAART20. Granich et al published in Lancet a mathematical model which showed that universal HIV testing coupled with immediate HIV treatment and prevention strategies regardless of the disease stage could lead to elimination of the epidemic21. If we treat all infected patients, there is a chance of significant reduction in incidence, significant reduction of prevalence and probable elimination and hopefully eradication22.
Keeping in view of ABC policy (Abstinence, behavioral change, condoms) and all the updates on TasP, PrEP, PEP and Test & Treat policy, and the scenario of implementation of zero transmission of HIV, probably we will find a answer with more intense research (RCTs) in near future.

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