ISSN: 2577-2996

PROGRESS IN MEDICAL SCIENCES, 2025
VOL 9, NO. 1, PAGE 1 – 6
DOI: doi.org/10.47363/PMS/2025(9)E172

REVIEW ARTICLE

Open Access

PrEP Therapy: Understanding the Access and Impact on HIV Incidence

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ABSTRACT

Pre-exposure prophylaxis (PrEP) as an HIV-prevention strategy has been launched in many countries around the world. The therapy is the people who are not infected but are at high risk of acquiring it. In countries with poor healthcare resources and low- and middle-income populations, the incidence of HIV is high. PrEP therapy is highly effective at preventing HIV, however, there have been challenges in implementation. Identifying the barriers that may hamper the execution and continuousness of PrEP therapy should be identified.

PrEP can significantly reduce HIV incidence in the short term provided the coverage is high and adherence to therapy is followed. Strategies for awareness of the therapy and uptake need to be implemented among populations who are at high risk of HIV infection. By increasing the number of PrEP starters and the proportion of consistent users, the effectiveness of PrEP can be significantly improved. Newer forms of PrEP developed using innovative technologies have the potential to improve adherence to therapy by reducing the frequency of administration.

This comprehensive review article highlights the effectiveness of PrEP in reducing HIV incidences from clinical trials, the obstacles in successful implementation and uptake, strategies to improve accessibility, and recent developments in long-acting injectable lenacapavir requiring fewer shots.

ARTICLE HISTORY

Received January 02, 2025
Accepted January 09, 2025
Published January 30, 2025

KEYWORDS

Pre-Exposure Prophylaxis, Accessibility, Incidence, Lenacapavir, HIV Prevention, PrEP

Introduction

Despite ongoing progress in treatment and prevention strategies, HIV infection, which targets the body's immune system, continues to be a major global public health concern. As per the global HIV statistics released in 2024, at the end of the year 2023, approximately 39.9 million people were living with HIV globally. In that 1.4 million were children of age less than 14 years. Adults population was 38.6 million. In 2023, approximately 1.3 million people acquired HIV, however, there was a 29% decline in new infections compared to the year 2010 which showed 2.1 million new infections. Though 6.3 lac patients succumbed to death in 2023, the death rate has been reduced by 51% compared to statistics of 2010 [1]. The world faces are improving, however, the HIV epidemic is still thought-provoking because the total number of people living with HIV has increased. In 1997, HIV infected people were approcximately 22 million. In 2022, the number increased to 39 million. In Southern African countries, HIV infection has reduced average life span by almost 2 decades [2]. There HIV is still one of the leading causes of mortality. The disease is treatable, however, there is no cure, and has significant health consequences.

Although the disease is spread globally, there exists geographical disparity as observed by the disease being more prevalent in African countries [3]. According to the Global HIV fact sheet of 2023, the most significant numbers of HIV infections have occurred in varipus parts of the world like Asia, Africa, Erope etc., indicating the global spread of the disease [4]. A population-based analysis has revealed that within the sub-Saharan region, the population of young women and girls infected with HIV is significantly higher than young men and boys [5]. Developed countries have lower HIV prevalence rates, but the epidemic continues to affect key population [6]. The epople are at high risk are men who have sex with men. Also the people who inject drugs are vulnerable.

As there is no preventive vaccine for HIV, it is advisable to use pharmacologic and non-pharmacological treatment to prevent the infection and transmission [7]. The use of newer effective antiretroviral medications has significantly increased the life span of people infected with HIV by avoiding the untimely deaths, and successful treatment has shown normal life expectancy. Modern antiretroviral drugs effectively suppress HIV to undetectable levels [8]. When the viral load goes below level of detection, it is indicator of reduced risk of transmission. This "treatment as prevention" approach has been pivotal in reducing HIV transmission. By educating people on safe sex practices, promoting male circumcision, and offering postexposure prophylaxis for those potentially exposed to HIV, public health efforts have made significant strides in HIV prevention. Despite this progress, HIV rates remain high in Europe and North America, especially among certain risk groups and it is crucial to continue these efforts, especially in high-risk groups, to further curb the spread of HIV.

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This review delves into the intricacies of PrEP therapy, examining its accessibility and the profound impact it has on HIV incidence rates worldwide. By exploring the barriers to widespread adoption and highlighting successful implementations, this paper aims to provide a comprehensive understanding of how PrEP can contribute to achieving global HIV prevention goals. Upcoming treatment options are also focused on.

Understanding the PrEP Therapy

PrEP is a novel biomedical prophylactic strategy for controlling HIV infection. The PrEP therapy is designed for people who have tested HIV negative but are at high risk of developing the disease [9]. It therapy provides an additional support to the existing HIV prevention actions, which includes encouraging safer sex practices, utilizing treatment as a preventive measure, and administering postexposure prophylaxis (PEP) following sexual exposure. PrEP therapy makes use of antiretroviral drugs for prophylactic purposes. It differs from PEP. PEP is used in emergencies, such as after unprotected sex, needle-sharing, or occupational exposure. It is a preventive medical treatment for a person who is HIV-negative but may have been exposed to virus. Such candidate have to take antiretroviral drugs within 3 days after a the exposure to HIV. It will prevent the virus from taking hold in the body. The medicines given in PEP are same as PrEp, byt additionaly few more antiretrovirals like raltegravir, or dolutegravir or a combination of darunavir and ritonavir is given by the licencer prescriber. The treatment is effective when started promptly and taken consistently for a month. Whereas, antiretroviral therapy is a lifelong treatment given to HIV-positive patients to reduce the viral titre. It also help strengthen the patient's immune system, and increase the immune cell (CD4) count in the body. Several drugs including those given in PrEP and PEP are given. The drug and treatment schedule is decided based on the health status of patient, virall load and the immune cells count. Refer figure 1 for the schematic representation of PrEP, PEP, and antiretroviral therapy.

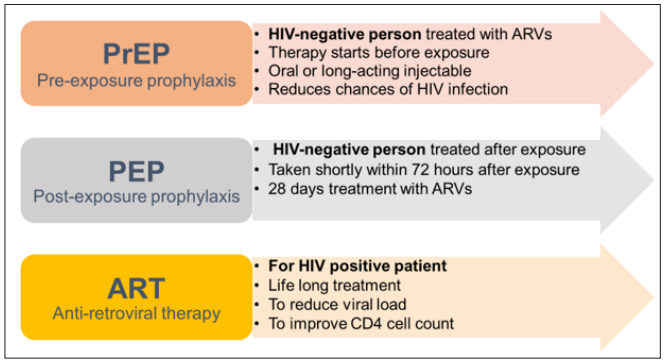

Figure 1: Schematic Representation of PrEP, PEP, and Antiretroviral Therapy

The concept of prophylaxis in HIV infection was thought of in the 1980s when zidovudine was used for prophylactic purposes by healthcare workers to protect themselves from accidental risks. Later promising results were also seen in preclinical studies for the prophylactic use of antiretrovirals [10]. Zidovudine has also demonstrated effectiveness in reducing mother-to-child transmission of the virus [11]. A clinical trial reported in 2010 demonstrated more than 40% reduction in the incidence of HIV [12]. This trial involved more than 2000 HIV-seronegative men. Study participants also included transgender women who have sex with men. Treatment involved combination of emtricitabine and tenofovir disoproxil fumarate. Subsequently few more clinical trials supported the prophylactic use of antiretrovirals prompting the US FDA to approve PrEP therapy in 2012, which is now followed all over the world [11]. PrEP therapy involves the use of antiretrovirals. The two antiretroviral medications that are given orally in PrEP therapy are tenofovir and emtricitabine which are inhibitors of an enzyme; reverse transcriptase. The HIV uses this enzyme for multiplication. Once the medication is administered orally, it gets systemically distributed including mucosas of the vagina and rectum which are the sites of virus entry into the human body through sexual intercourse. Once this enzyme gets inhibited viruses cannot convert their RNA into DNA and thus cannot replicate. Oral antiretroviral medications like tenofovir and emtricitabine are available in 2 different forms. The first one is Truvada® which is a combination of emtricitabine and tenofovir disoproxil fumarate. It is for all people at risk for HIV through sex or injection drug use. There are several generic formulations available, so that poor-income people can afford it. The second form is Descovy® which contains emtricitabine and tenofovir alafenamide. It is indicated for sexually active men. Transgender women at risk of getting HIV are also treated with this formulation. However, it is not indicated for those who were considered female at birth and can acquire HIV infection through receptive vaginal sex. These two antiretroviral medications are inhibitors of an enzyme; reverse transcriptase which the HIV virus uses for its multiplication. Oral therapy is effective provided the person adheres to the therapy plan and takes the medication as prescribed. The dose of the drugs is high and needs to be taken daily which may lead to patient non-compliance. Though this therapy significantly reduces the chances of HIV incidence, it can adversely change the functions of the kidney. There are chances of reduction in bone mineral density too.

To overcome the disadvantages of oral therapy, long-acting injectables are developed that need to be taken less frequently [13]. The first approved long-acting injectable is of cabotegravir. Several studies are done in macaque models. Researchers experiemented various routes of exposure like rectal, vaginal, penile, and parenteral. Results demonstrated promising outcomes for the development of long-acting cabotegravir as a PrEP agent. It was approved by the FDA in 2021 for PrEP [14,15]. The advisory guideline also indicated that the therapy for adults and adolescents weighing at least 35 kilograms who are at the risk of infection, The therapy will reduce the risk of sexually acquired HIV. It is an intramuscular injection containing 600 mg of active given in gluteal muscles every month for the first two months followed by every two months [16]. Cabotegravir inhibits enzyme integrase strand transfer. This mechanism of action prevents the integration of viral genome into the host's DNA. A multicentre, double-blind, randomized, placebo-controlled, phase 2a trial was conducted at 10 different locations in the USA. Healthy men assessed as being at low risk for acquiring HIV-1, were administered with long-acting injection of cabotegravir. Researchers reported a injection-site reactions [13]. The incidences were high, but the reactions were mild-to-moderate and lasted for short duration. The overall treatment was well tolerated. The safety aspects were acceptable. From the pharmacokinetic profiling, an 800 mg dose every 12 weeks was found to be suboptimal, and therefore researchers

suggested the need for alternative dosing strategies. Later, a global clinical trial (HPTN 077) of this injectable was conducted to check the safety and tolerability in low-risk individuals who were HIV-negative. Pharmacokinetics were also studied for at 2 different dosage regimens and concluded that targets are better achieved at a dose of 600 mg every 8 weeks than for 800 mg every three months [17]. Later in 2023, it was approved for PrEP therapy in European countries.

Further studies on prolonging the duration of action have led to the development of ultra-long-acting cabotegravir. Preclinical evaluations were performed in primates. Results showed complete protection against repeated rectal SHIV challenges. Phase 1 study of such ultra-long acting injection showed promising results allowing the dose of new formulation to be injected every four months which could potentially reduce the frequency of clinic visits for patients and improve compliance [18].

Impact of PrEP Therapy

Oral PrEP Therapy

The impact of oral PrEP therapy has been assessed in several trials at different locations and on various populations and found to have mixed results [19]. A study of prophylaxis (iPrEx) was conducted at 11 sites in six countries on more than 2400 candidates. The participants were HIV-seronegative men or transgender women who have sex with men. The participants were divided into two groups and received either placebo or oral combination PrEP therapy [20]. The HIV incidences were noted in 36 and 46 participants from the treatment and placebo groups respectively. Thus there was more than 40% reduction in the incidence of HIV infection showing the effectiveness of oral PrEP therapy. This study was further extended and it was open label; iPrEx OLE. It was 72-week study in which HIV incidence among men and transgender women who have sex with men was analyzed. Participants having condomless receptive anal intercourse showed higher uptake of therapy [21]. For those who followed the therapy as suggested, the HIV incidence was 49% lower. When the therapy was given free of charge, the uptake was more leading to a higher impact of therapy during the periods of high risk. When the same therapy was followed in HIV serodiscordant heterosexual couples from Kenya and Uganda, researchers observed a 75% reduction in HIV incidence [21]. Two large phase 3 trials (VOICE and FemPrEP) conducted in African women showed no effectiveness of therapy and the adherence to therapy was also poor [22]. Oral therapy involves daily administration of the medication which often leads to poor compliance and less adherence to the recommended dosage regimen [23,24]. Therefore, researchers further conducted a follow-up study on 88 participants of the FemPrEP study to understand the participant's reasons and explanations. It was concluded that personal motivations like reduction in risk and positive outcomes of the research can improve therapy adherence [25,26]. External cues, reminders, and community engagement programs can facilitate adherence to the therapy. An integrated analysis of 11 different studies of PrEP effectiveness conducted in cisgender women indicated that low HIV incidence was associated with high therapy adherance.

In an active-controlled phase 3 DISCOVER trial, two forms of tenofovir either alafenamide or (25 mg) or disoproxil fumarate (300 mg) were administered daily [27]. The treatment was in combination with emtricitabine (200 mg) and also involved a matched placebo group. HIV incidences were reported seven and fifteen in the alafenamide and disoproxil fumarate group, respectively [28]. The alafenamide form of tenofovir showedcomparable efficacy to the daily disoproxil fumarate form of tenofovir when given in combination with emtricitabine for HIV prevention. Both the therapies were well tolerated. There were low adverse events for both dosage forms. The participants who were admnistered alafenamide derivative had more favorable effects on bone mineral density and kidney functining compard to the those who had taken disoproxil fumarate derivative of tenofovir.

Long-Acting Injectable PrEP Therapy

Many survey-based analytical studies conducted in various countries like China, Malaysia, Uganda, etc. have indicated that participants are aware of oral PrEP therapy and very few participants knew about long-acting injectable PrEP [28]. After knowing the description of injectable therapy, a large majority of the participants expressed their willingness to opt for injectable therapy [29-31]. Apart from the convenience of less frequent dosing, the significant variables responsible for preference for injectable PrEP were younger age, low income, multiple sex partners, having a higher chances of acquiring of HIV infection. Also the people who have taken PrEP therapy earlier also showed inclination towards injectable.

A clinical study (HPTN 077) was done for long-acting cabotegravir [29]. Its aim was to observe the safety, tolerability, and acceptability. It was a phase 2a trial conducted at several locations that also compared the safety and tolerability of the injection [32]. Acceptability was quantitatively estimated using scores given to parameters like pain at the site of injection, any inflammatory reaction or rash at the injection site. Side effects experienced following the previous injection were also covered. Participants from non-US regions showed more acceptability whereas preference for injection over oral therapy was more in US male participants and non-US female participants.

A randomized, double-blind, double-dummy, multinational trial (HPTN 083) compared long-acting injectable cabotegravir (600 mg, IM, every 2 months), with daily oral tenofovir disoproxil fumarate-emtricitabine. This was phase 2 and 3 interventional study [33]. It was done to compare the efficacy of both the treatments. It involved analysis of the prevention of HIV infection in at-risk cisgender men who have sex with men. Participants also included at-risk transgender women who have sex with men. The incidence of HIV infection was observed in 52 participants, of which 13 were in the injectable group and the rest were from the oral therapy group. Therefore, researchers concluded that a long-acting injection of cabotegravir is superior to oral PrEP therapy for the selected category of participants.

Recently the data from the clinical trial (HPTN 084) was published in the journal The Lancet [33]. This was a phase 3 study conducted in females from 7 different countries in sub-Saharan Africa [34]. There were more than 3200 participants half of which were in the cabotegravir group. There were only 2 HIV incidents in this

group where whereas 36 HIV incidences were observed in the oral PrEP group. Both the PrEP therapies were safe, effective, and well tolerated, however, injectable was superior in preventing HIV infection.

A recent survey-based analysis has identified the population groups that would benefit from long-acting injectables. The conclusion of this survey showed that young people, child-bearing women, people having multiple sex partners, people with psychological issues in adhering to therapy, and homeless people are the potential ones to benefit from injectable PrEP [35].

Recent Updates in PrEP Therapy

Lenacapavir is a novel and highly potent drug. It selectively inhibits HIV capsid protein and therefore interferes with several stages in the viral replication process. Iy was tested in a phase 3, double-blind, randomized trial [36]. The participants were adolescent girls and young women. More than 2300 participants in South Africa and Uganda completed the study. The injection was given subcutaneously. Injection frequency was every 26 weeks. No participant acquired HIV infection. This was PURPOSE 1 trial [37]. Thereafter, PURPOSE 2 trial is being conducted on more than 3200 cisgender men who have sex with men and transgender people. The study also had participants which are non-binary and who have sex with male partners. In this study only 2 HIV incident cases in the lenacapavir group among 2,180 participants [38]. 99.9% of participants who received lenacapavir remained protected. Refer figure 2 for the overview of lenacapavir clinical trials.

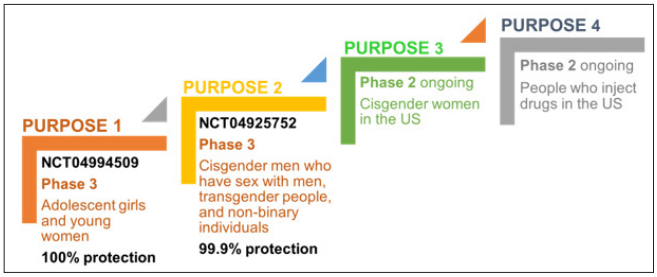

Figure 2: Status of Long-Acting Lenacapavir Clinical Trials

As of now, lenacapavir has not received approval by the FDA for PrEP therapy for HIV. However, Gilead Sciences filed the New Drug Application to the FDA on December 19, 2024, seeking approval for Lenacapavir as a twice-yearly injectable PrEP. The Science Magazine named lenacapavir as the Breakthrough Therapy. This medicine may be a promising alternative to the existing standard of care for HIV prevention [39]. Twice-yearly injection offers a significant advantage over daily oral treatment [40]. Adherence to therapy will be more and participants privacy will be maintained as it does not require daily oral dosing. UNAIDS has welcomed the results of these trials but expressed the concerns about ensuring equitable access, especially in low- and middle-income countries. Additional trials are ongoing in various countries like the United States, Argentina, and Brazil. Few more sites from Mexico, Peru, South Africa, and Thailand are also included.

The high price of lenacapavir injection is a concern that may become a barrier to its broader adoption in the clinical setting. To produce low-cost lenacapavir injection, Gilead Sciences has planned to give licenses to six manufacturers to make generic versions.

Clinical Relevance of PrEP Therapy

Centers for Disease Control and Prevention has an ambitious project to end the HIV epidemic [41]. The objective of this campaign is to reduce new infections by 90% in 2030. In this regard, PrEP is an effective approach for reducing the chances of getting HIV infection and it should be expanded to effectively reach the susceptible population. However, it is underutilized due to several hindering factors [42]. The accessibility of the PrEP program is often influenced by a multitude of factors, including the availability of medication facilities, cost of the therapy, awareness of the program, stigma, and overall healthcare infrastructure. Identifying the areas where PrEP coverage is not sufficient and expanding the services to such areas will overcome the spatial disparity [43].

For instance, financial constraints and lack of insurance coverage can make PrEP unaffordable for many individuals because the therapy is long-term [44]. Additionally, limited awareness and understanding of PrEP among both healthcare providers and potential users can reduce its uptake. The stigma associated with HIV and PrEP usage can also deter individuals from seeking out the medication. Furthermore, disparities in healthcare access, particularly in low-income and marginalized communities, can limit the availability of PrEP. Efforts to improve PrEP accessibility include increasing funding for PrEP programs, reducing medication costs, and conducting educational campaigns to raise awareness and reduce stigma. Addressing these barriers is crucial for enhancing the effectiveness of HIV prevention strategies.

Bolstering the trust between vulnerable populations and healthcare providers is key to improving program effectiveness. A positive relationship between the patient and the healthcare provider will enhance the reach of the program and will help overcome the barrier of medical mistrust. Accordingly, the treating nursing propessionals and other involved responsible staff must be educated to deliver their services and support in a nonjudgemental way. Community-based programs should implement comprehensive service packages that include screening tests, medication supply, education, counseling, follow-up, and other related activities.

Long-acting injectable PrEP therapy holds significant promise for enhancing the success of PrEP access among individuals in areas with limited healthcare access [45]. However, the high cost of the injection still remains as an anxiety about its reach to poor vulnerable populations. There is a need to update the health plans accordingly which may increase the burden on public health programs.

Concluding Remarks

As there is no effective and safe HIV vaccine, the need to employ PrEP, a biomedical HIV prevention strategy remains critical. Successful implementation of the PrEP program is critical for advancing public health efforts to combat the HIV epidemic. PrEP has demonstrated substantial efficacy in preventing HIV infection and reducing the incidence as low as possible when taken as prescribed. However, its full potential can only be realized by addressing the multifaceted barriers to accessibility. Adherence to PrEP therapy is one of the strongest predictors of its effectiveness in reducing the incidence of infection. Several studies in different

groups of populations have established that daily use of oral pills of a combination of emtricitabine and tenofovir is highly effective provided the user follows consistent administration. Several other barriers include financial constraints, lack of awareness, and stigma, as well as disparities in healthcare infrastructure, particularly in marginalized communities. Strengthening PrEP programs through increased funding, educational initiatives, and policy changes can enhance accessibility and uptake. By overcoming these challenges, PrEP therapy can play a transformative role in controlling the incidence and spread of HIV infections and ultimately accomplishing the goal of ending the HIV epidemic. Continued research and collaboration among stakeholders are essential to ensure that PrEP therapy is accessible to all who could benefit from it.

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