Review Article

A Review on HIV Vaccine & limitations of long-acting PrEP with a focus on Lenacapavir

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Abstract: This review examines the current state of HIV prevention, comparing the advancements and limitations of long-acting PrEP, with a focus on lenacapavir, and the persistent need for an effective HIV vaccine. Lenacapavir represents a significant improvement in PrEP due to its high efficacy and less frequent dosing schedule, which enhances adherence. However, its high cost, the necessity for a robust healthcare infrastructure, the potential for drug resistance, and concerns about long-term safety present challenges. Despite the effectiveness of lenacapavir in preventing individual infections, an HIV vaccine is still vital for achieving global control and potential eradication of HIV. Vaccines offer advantages in terms of accessibility, scalability, and the potential to provide sterilizing immunity. Yet, the development of an HIV vaccine is hindered by the virus's high mutation rate, the absence of a natural immunity model, effective immune evasion mechanisms, and difficulties in conducting clinical trials. The review concludes that PrEP and vaccines are complementary strategies. PrEP can serve as an effective interim solution while efforts to develop a vaccine continue. A balanced approach that prioritizes both PrEP and vaccine research, along with careful consideration of economic, ethical, and social factors, is essential for successful HIV prevention.

Keywords: HIV Vaccine, long-acting PrEP, Lenacapavir

1. INTRODUCTION

The landscape of HIV prevention has been fundamentally reshaped by the emergence of pre-exposure prophylaxis (PrEP). Recent progress, marked by the development and approval of long-acting injectable PrEP, most notably twice-yearly lenacapavir, signifies a major leap forward [1]. Lenacapavir's high efficacy and infrequent dosing schedule offer a stark contrast to traditional daily oral PrEP regimens. Clinical trials have consistently demonstrated lenacapavir's remarkable ability to prevent HIV acquisition, with efficacy rates that often surpass those of its daily counterparts. The PURPOSE trials, for instance, showcased near-complete protection in cisgender women and robust protection in other populations, highlighting its potential to significantly curb new infections. This long-acting convenience addresses a critical challenge in HIV prevention: adherence [2]. By eliminating the need for daily pill-taking, lenacapavir simplifies PrEP uptake and maintenance, potentially mitigating the stigma associated with carrying and taking daily medication and offering a practical solution for individuals who struggle with consistent oral dosing. The reduced dosing frequency could translate to greater PrEP uptake, as individuals may find the twice-yearly injections more manageable and less intrusive into their daily lives. Furthermore, the discreet nature of an injection, compared to a daily pill regimen, may also contribute to its acceptability among certain populations [3].

2. LENACAPAVIR PrEP: BENEFITS AND CHALLENGES

However, despite these advantages, lenacapavir PrEP is not without its challenges. A significant concern is cost, as the price of lenacapavir may pose a substantial barrier to widespread access, particularly in low- and middle-income countries where the burden of HIV is concentrated. Pharmaceutical companies often set high prices for new medications to recoup research and development costs, but this can limit accessibility for those who need them most [4]. Efforts to negotiate lower prices, implement tiered pricing structures, and explore generic manufacturing options will be crucial to ensure equitable access. Effective implementation of lenacapavir PrEP also necessitates a well-established healthcare infrastructure. Trained personnel and adequate facilities are required for administering the injections and providing necessary follow-up care. This may strain resources in settings with limited healthcare capacity, where healthcare systems are already overburdened [5]. The need for regular clinic visits for injections could also be a barrier for some individuals, especially those in rural areas or with limited mobility. While currently considered low, the potential for drug resistance is another factor to consider. The long half-life of lenacapavir, while beneficial for PrEP, means that any breakthrough infections could lead to prolonged drug exposure, potentially complicating future treatment options. It is essential to monitor individuals on lenacapavir PrEP for any signs of resistance and to develop strategies to minimize this risk. Additionally, clinical trials have reported injection-site reactions, although generally mild, and the long-term effects and overall safety profile of lenacapavir are still under investigation, given its relatively recent introduction. Ongoing research is needed to fully understand the potential long-term consequences of lenacapavir use and to identify any rare but serious side effects [6].

3. The Enduring Need for An HIV Vaccine

In light of these considerations, the pursuit of an effective HIV vaccine remains a crucial long-term goal. Vaccines offer several key advantages over PrEP, particularly in terms of global accessibility and scalability. Vaccines are generally more cost-effective and easier to distribute on a large scale, making them a more viable option for widespread prevention, especially in resource-limited settings [7]. The infrastructure required for vaccine delivery, while significant, is often less demanding than that needed for the ongoing administration of injectable PrEP. Importantly, while PrEP primarily prevents infection, a sterilizing HIV vaccine holds the potential for viral eradication. By preventing not only infection but also the establishment of viral reservoirs within the body, a vaccine could offer a pathway to eliminating the virus altogether. This is a crucial distinction, as PrEP requires continuous use to remain effective, while a vaccine could provide long-lasting protection with a finite intervention [8]. Furthermore, a vaccine would overcome the challenges associated with PrEP adherence. Instead of requiring ongoing individual action, a vaccine could provide long-term protection with a finite intervention. This would eliminate the need for individuals to remember to take medication or attend regular clinic visits, simplifying HIV prevention efforts. In the long run, the cost-effectiveness of a successful HIV vaccine is likely to surpass that of widespread, lifelong PrEP administration [9]. The initial investment in vaccine development could yield significant long-term savings by reducing the need for ongoing treatment and prevention efforts. Finally, a vaccine that effectively prevents infection would also prevent the development of drug resistance, a growing concern with the increasing use of antiretroviral drugs, including those used for PrEP [10].

4. Challenges in HIV Vaccine Development

However, HIV vaccine development has been hampered by several formidable challenges. HIV's high rate of mutation results in significant genetic diversity, making it difficult to develop a vaccine that can effectively target all circulating viral strains. The virus constantly evolves, making it a moving target for the immune system [11]. This necessitates the development of vaccines that can elicit broadly

neutralizing antibodies or other immune responses that can recognize and neutralize a wide range of HIV variants. The lack of a natural model of immunity further complicates vaccine development. Unlike many other viral infections where natural recovery is common, natural recovery from HIV is rare, and the immune responses that do occur are often ineffective. This makes it challenging to identify the specific immune responses that a vaccine should aim to elicit [12]. Researchers are still working to understand the complex interplay between HIV and the immune system and to identify the correlates of protection against HIV infection. HIV also possesses sophisticated mechanisms for evading the host's immune system, including the ability to hide within latent reservoirs and downregulate the expression of viral antigens. These mechanisms allow the virus to persist in the body despite the presence of an immune response [13]. Developing an effective vaccine likely requires eliciting a complex immune response, encompassing both neutralizing antibodies and cellular immunity. Both arms of the immune system are believed to be important for controlling HIV infection, and a successful vaccine may need to stimulate both types of responses. Finally, conducting large-scale vaccine trials is complex and expensive, particularly in light of the declining incidence of HIV in some populations. It can be challenging to recruit enough participants who are at high risk of HIV infection to adequately assess the efficacy of a vaccine candidate [14].

5. PrEP AND VACCINES: COMPLEMENTARY STRATEGIES

It is crucial to recognize that PrEP and vaccines are not mutually exclusive; rather, they represent complementary approaches to HIV prevention. PrEP can serve as a vital bridge, providing a highly effective means of preventing new infections while the search for an effective vaccine continues. In this context, PrEP can be strategically targeted toward individuals and populations at the highest risk of HIV acquisition. This targeted approach can help to maximize the impact of PrEP and to reduce the overall number of new infections [15]. Meanwhile, vaccine development efforts can focus on creating a broadly effective vaccine suitable for global deployment. The development of such a vaccine would be a game-changer in the fight against HIV, offering the potential for long-term control of the epidemic. Ultimately, a vaccine remains the long-term solution for achieving lasting control and potential eradication of HIV, offering the possibility of population-level immunity and eliminating the need for ongoing individual interventions [16]. It is also conceivable that PrEP and vaccines could be used in combination in the future, potentially offering synergistic effects and even greater protection. For instance, PrEP could be administered during the initial period following vaccination to provide immediate protection while the vaccine-induced immune response develops. This combined approach could offer a more comprehensive strategy for HIV prevention [17].

6. ECONOMIC, ETHICAL, AND SOCIAL CONSIDERATIONS

The question of prioritizing an HIV vaccine versus PrEP also raises important economic, ethical, and social considerations. Decisions regarding resource allocation for HIV prevention research and programs must weigh the cost-effectiveness of each approach, their potential impact on different populations, and the urgency of addressing the epidemic. It is essential to consider not only the direct costs of each intervention but also the potential long-term benefits and savings. Equity and access are also paramount [18]. Ensuring that both PrEP and future vaccines are accessible to all who need them requires addressing issues of affordability, availability, and cultural acceptability across diverse settings. This is particularly important in low- and middle-income countries, where the HIV epidemic disproportionately affects marginalized and vulnerable populations. The HIV epidemic disproportionately affects low- and middle-income countries, and a vaccine could help to mitigate these global health disparities by providing a more affordable and scalable prevention tool. A vaccine could be a powerful tool for achieving health equity and reducing the burden of HIV in resource-limited settings [19]. Finally, individuals should have access to a range of prevention options, including PrEP

and potential future vaccines, empowering them to make informed choices about their own health and well-being. It is important to respect individual autonomy and to provide people with the information and resources they need to make informed decisions about HIV prevention. Social and cultural factors also play a significant role in shaping HIV prevention efforts. It is crucial to address stigma, discrimination, and other social barriers that may hinder access to PrEP and other prevention tools [20].

4. CONCLUSIONS

In conclusion, while long-acting PrEP, such as twice-yearly lenacapavir, represents a significant advancement in HIV prevention, it does not obviate the need for an effective HIV vaccine. Lenacapavir PrEP offers a powerful tool for preventing individual infections, but an HIV vaccine remains essential for achieving long-term control, global eradication, and greater equity in access to prevention. Both PrEP and vaccines have unique strengths and weaknesses. PrEP excels at preventing individual infections but necessitates ongoing adherence and access to healthcare. A vaccine holds the promise of population-level immunity and the elimination of ongoing interventions, but its development has proven to be a formidable challenge. Therefore, a balanced strategy is essential. Continued investment in both PrEP research and development, and the pursuit of a broadly effective, safe, and affordable HIV vaccine, must remain a top priority in the global effort to combat the HIV/AIDS pandemic. The ultimate solution will likely involve a multifaceted approach, combining both preventative and therapeutic strategies to address the diverse needs of individuals and populations worldwide. This comprehensive approach will require collaboration among researchers, healthcare providers, policymakers, and communities to ensure that the benefits of both PrEP and future vaccines are realized by all who need them.

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