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Long-Acting Antiretroviral Therapies for HIV Treatment and Prevention: Efficacy and Implementation

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ABSTRACT

Human immunodeficiency virus (HIV) infection remained a persistent global health challenge despite significant progress in antiretroviral therapy. While daily oral antiretroviral regimens have substantially improved survival and reduced transmission, long-term adherence difficulties continue to compromise treatment and prevention outcomes. Long-acting antiretroviral therapies emerged as an innovative pharmacological approach aimed at overcoming these limitations. This review examined the biochemical rationale, clinical efficacy, and implementation considerations of long-acting antiretroviral therapies for both HIV treatment and prevention. A narrative review methodology was utilized to synthesize and critically analyze existing scientific literature on long-acting antiretroviral agents, including pharmacological studies, clinical trials, and implementation research. Evidence indicated that long-acting antiretroviral therapies achieved virologic suppression comparable to conventional oral regimens while offering advantages in adherence, patient satisfaction, and prevention efficacy. Injectable long-acting agents also demonstrated superior effectiveness in HIV prevention compared to daily oral pre-exposure prophylaxis. Nonetheless, challenges related to resistance risk, healthcare infrastructure, cost, and equitable access persist. Long-acting antiretroviral therapies represented a transformative advancement in HIV care, but their optimal impact will depend on strategic implementation and health system adaptation.

Keywords: HIV, Long-acting antiretrovirals, Antiretroviral therapy, HIV prevention, Pharmacokinetics.

INTRODUCTION

Human immunodeficiency virus (HIV) infection continues to pose a significant burden on global health systems, requiring lifelong management to suppress viral replication and prevent disease progression and transmission [1, 2]. The introduction of combination antiretroviral therapy has transformed HIV from a fatal illness into a manageable chronic condition [3]. However, the effectiveness of daily oral antiretroviral therapy remains highly dependent on consistent, lifelong adherence, which is often difficult to sustain in real-world settings.

Challenges such as pill fatigue, medication-related stigma, adverse drug effects, mental health conditions, and socioeconomic constraints contribute to suboptimal adherence and treatment interruptions [4]. These factors can result in virologic failure, drug resistance, and increased risk of HIV transmission. Consequently, there has been growing interest in alternative therapeutic strategies that reduce dosing frequency while maintaining sustained antiviral activity.

Long-acting antiretroviral therapies represent a significant innovation in HIV pharmacotherapy [5, 6]. By utilizing advanced drug delivery systems that allow medications to remain active in the body for extended periods, these therapies aim to simplify treatment regimens and improve adherence. The development of injectable and implantable formulations has expanded the scope of HIV management, offering new options for both treatment and prevention.

In addition to their role in treatment, long-acting antiretroviral agents have demonstrated substantial promise in HIV prevention, particularly as pre-exposure prophylaxis for individuals at high risk of infection. This dual application underscores their potential to address persistent gaps in HIV control strategies [7]. This review provides a comprehensive evaluation of long-acting antiretroviral therapies, encompassing their pharmacological and biochemical foundations, clinical efficacy and safety, role in HIV prevention, and key implementation challenges. The purpose of this article is to critically assess the potential of these therapies to enhance HIV treatment and prevention outcomes while identifying areas requiring further research and policy development.

Pharmacological and Biochemical Basis of Long-Acting Antiretroviral Therapies

The development of long-acting antiretroviral therapies is rooted in advances in pharmaceutical chemistry, formulation science, and pharmacokinetics [8]. Unlike conventional oral antiretroviral drugs, which require daily administration to maintain effective plasma concentrations, long-acting formulations are designed to release active compounds slowly over weeks or months. Most currently available long-acting antiretroviral agents are administered via intramuscular injection and formulated as nanosuspensions [9, 10]. These formulations consist of poorly soluble drug crystals that dissolve gradually at the injection site, resulting in sustained systemic drug exposure. This controlled release mechanism enables prolonged maintenance of drug concentrations above the inhibitory threshold required to suppress viral replication.

From a biochemical standpoint, long-acting antiretroviral therapies primarily target essential viral enzymes, such as integrase and reverse transcriptase [11]. Integrase strand transfer inhibitors prevent the incorporation of viral DNA into the host genome, while non-nucleoside reverse transcriptase inhibitors disrupt viral DNA synthesis. These targets are well-suited for long-acting delivery due to the high potency and favorable pharmacodynamic profiles of the agents involved. However, the prolonged presence of antiretroviral drugs in the body introduces unique pharmacokinetic considerations. Following discontinuation, drug concentrations decline gradually, creating a prolonged "pharmacokinetic tail" during which subtherapeutic levels may persist. This period poses a potential risk for viral replication and resistance development if not managed appropriately. Understanding these biochemical dynamics is essential for optimizing dosing schedules, patient selection, and transition strategies between long-acting and oral therapies.

Clinical Efficacy and Safety in HIV Treatment

Clinical studies evaluating long-acting antiretroviral therapies have demonstrated that these regimens are highly effective in maintaining viral suppression among individuals with stable HIV infection [12, 13]. Injectable long-acting combinations administered monthly or bimonthly have shown non-inferior efficacy compared to standard daily oral regimens in achieving and sustaining undetectable viral loads.

Safety profiles of long-acting antiretroviral therapies are generally favorable. The most frequently reported adverse events are injection-site reactions, including pain, swelling, and induration [14]. These reactions are typically mild to moderate in severity and tend to decrease with repeated dosing. Systemic adverse effects are comparable to those observed with oral formulations of the same agents. Importantly, patient-reported outcomes indicate high levels of satisfaction and preference for long-acting regimens, particularly among individuals who experience challenges with daily pill-taking or concerns about inadvertent disclosure of HIV status [15]. Reduced dosing frequency and greater convenience contribute to improved treatment acceptance and perceived quality of life. Despite these advantages, long-acting therapies may not be suitable for all individuals. Patients with inconsistent access to healthcare services, untreated co-morbidities, or prior drug resistance may require careful evaluation before initiation. Additionally, missed injections can compromise therapeutic effectiveness, underscoring the importance of structured follow-up and adherence support within healthcare systems.

Role of Long-Acting Antiretroviral Therapies in HIV Prevention

Long-acting antiretroviral therapies have expanded beyond treatment to play a pivotal role in HIV prevention strategies. Long-acting injectable agents used as pre-exposure prophylaxis have demonstrated exceptional efficacy in preventing HIV acquisition among populations at substantial risk [16]. One of the primary limitations of daily oral pre-exposure prophylaxis has been inconsistent adherence, which reduces protective effectiveness [17]. Long-acting injectable prevention strategies address this challenge by providing sustained protective drug levels independent of daily pill-taking behavior. Clinical evidence indicates significantly lower HIV incidence rates among individuals receiving long-acting injectable prophylaxis compared to those using oral regimens.

The potential public health impact of long-acting HIV prevention is substantial, particularly for populations facing structural, social, or behavioral barriers to daily medication adherence [18, 19]. Adolescents, mobile populations, and individuals experiencing stigma may benefit disproportionately from these approaches. However, implementation challenges mirror those observed in treatment settings, including the need for regular clinic visits, healthcare infrastructure for injections, and monitoring for adverse effects. Integrating long-acting prevention strategies into existing HIV programs will require coordinated planning, community engagement, and sustained investment.

Implementation Challenges and Future Directions

Despite their clinical promise, the widespread adoption of long-acting antiretroviral therapies faces multiple implementation challenges. Healthcare systems must adapt to accommodate injectable administration, including training healthcare personnel, ensuring reliable supply chains, and maintaining appropriate storage conditions [20]. These requirements may pose significant barriers in resource-limited settings.

Cost considerations also represent a major challenge. Long-acting formulations are often associated with higher upfront costs compared to oral therapies, raising concerns about affordability and long-term sustainability [21, 22]. Equitable access will depend on pricing strategies, policy support, and integration into national HIV programs [23, 24].

Patient education and engagement are critical components of successful implementation. Individuals must understand the importance of maintaining scheduled dosing and the implications of missed injections. Clear clinical guidelines are also needed to manage transitions between long-acting and oral therapies and to mitigate resistance risks associated with discontinuation.

Future research should focus on expanding the range of long-acting antiretroviral agents, including implantable and ultra-long-acting formulations, as well as evaluating their use in diverse populations. Continued innovation and evidence-based policy development will be essential to maximize the global impact of these therapies.

CONCLUSION

Long-acting antiretroviral therapies represent a major advancement in the management of HIV, offering effective alternatives to daily oral regimens for both treatment and prevention. By addressing longstanding challenges related to adherence, stigma, and treatment burden, these therapies have the potential to improve virologic outcomes and enhance quality of life for people living with or at risk of HIV. Evidence supports their efficacy and safety, while their application in HIV prevention marks a significant step forward in reducing new infections. Nevertheless, challenges related to cost, infrastructure, resistance management, and equitable access must be carefully addressed to ensure sustainable and widespread implementation. Coordinated efforts involving clinicians, researchers, policymakers, and communities will be essential to fully realize the benefits of long-acting antiretroviral therapies. It is therefore recommended that long-acting antiretroviral therapies be incorporated into HIV treatment and prevention programs through context-specific, evidence-based implementation strategies supported by robust health system strengthening.

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