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Long-Acting Cabotegravir Pre-Exposure Prophylaxis in Adolescent and Young Adult Populations: Efficacy and Adherence

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ABSTRACT

The ongoing HIV epidemic disproportionately affected adolescent and young adult populations worldwide, underscoring the urgent need for effective prevention strategies. Long-acting injectable cabotegravir (CAB-LA) has emerged as a novel pre-exposure prophylaxis (PrEP) modality designed to overcome adherence challenges associated with daily oral regimens. This review synthesized recent literature on CAB-LA's molecular mechanisms, clinical efficacy, safety, and adherence patterns specifically in adolescents and young adults. A systematic literature search of PubMed, Embase, and Web of Science was conducted for studies published from 2017 to 2025 using keywords including "cabotegravir," "long-acting PrEP," "adolescents," "young adults," and "HIV prevention." Evidence demonstrated that CAB-LA inhibits HIV integration via integrase strand transfer inhibition, with clinical trials showing superior efficacy compared to daily oral tenofovir/emtricitabine in preventing HIV acquisition in high-risk youth. CAB-LA's extended dosing interval (every two months) improved adherence and persistence, critical factors in this demographic facing stigma and pill fatigue. Safety profiles were favorable, with minimal injection site reactions and no adverse effects on bone mineral density. Notwithstanding, mental health considerations and tailored counseling remain essential for optimizing outcomes. Despite promising efficacy, challenges persisted regarding long-term safety data, cost-effectiveness, and ensuring equitable access. In conclusion, long-acting cabotegravir offers a transformative HIV prevention tool in adolescents and young adults, with adherence advantages that could markedly reduce HIV incidence in this vulnerable group. Further pragmatic studies and implementation research are needed to address outstanding gaps and maximize population health impact.
Keywords: Cabotegravir, Pre-exposure prophylaxis, Adolescents, HIV prevention, Adherence

INTRODUCTION

Despite global efforts, HIV infection remains a significant public health challenge, especially among adolescents and young adults [1, 2]. In 2021, approximately 1.5 million new HIV infections occurred worldwide, with youth aged 16–24 years accounting for a disproportionate number of these cases [3, 4]. This demographic is particularly vulnerable due to biological, behavioral, and social factors including stigma, inconsistent condom use, and challenges adhering to daily oral pre-exposure prophylaxis (PrEP) regimens. The HIV epidemic's persistence underlines an urgent need for innovative prevention modalities that align with the lifestyles and sociopsychological realities of young populations [5].

Historically, oral PrEP using tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) demonstrated robust efficacy but is hindered by adherence challenges in adolescents due to pill burden, stigma, and privacy concerns [6]. Long-acting injectable cabotegravir (CAB-LA), an integrase strand transfer inhibitor formulated for intramuscular administration every eight weeks, has emerged as a promising alternative with potential to enhance adherence and reduce HIV acquisition risk. CAB-LA's biochemical mechanism targets HIV integration, a critical step in viral replication, thus effectively preventing infection establishment by blocking viral DNA integration [7]. This review aims to critically examine the molecular basis, clinical efficacy, safety, adherence patterns, and implementation

challenges of CAB-LA as PrEP among adolescent and young adult populations. Emphasis is placed on synthesizing contemporary evidence from clinical trials, cohort studies, and real-world assessments to clarify CAB-LA's role within this high-risk group and to identify future research directions.

METHODOLOGY

A systematic search was conducted in PubMed, Embase, and Web of Science databases covering the period January 2017 to September 2025. Search terms included "cabotegravir," "long-acting injectable," "PrEP," "adolescents," "young adults," and "HIV prevention." Inclusion criteria were original research studies, clinical trials, systematic reviews, and meta-analyses focused on CAB-LA use for HIV prevention, particularly in adolescent or young adult populations. Exclusion criteria comprised studies not directly related to PrEP, animal studies, and reports without data on adherence or efficacy.

Data synthesis prioritized high-quality evidence including Phase II/III clinical trials, large cohort studies, and systematic reviews. Key outcome measures analyzed were HIV incidence reduction, adherence rates, safety profiles, and factors influencing acceptability. Evidence was critically appraised for methodological rigor, population representativeness, and relevance to adolescent contexts.

MOLECULAR AND BIOCHEMICAL BASIS

Mechanism of Action

Cabotegravir is an integrase strand transfer inhibitor that targets HIV-1 integrase, the viral enzyme essential for integration of viral DNA into the host genome a pivotal step for productive infection [8]. By binding to the integrase active site, CAB blocks strand transfer, effectively preventing viral replication. Unlike reverse transcriptase inhibitors used in oral PrEP, this molecular target offers a direct blockage of viral chromosomal integration, thereby enhancing potency [9].

Pharmacokinetics and Dosing

CAB-LA is formulated for intramuscular injection, providing sustained plasma drug concentrations above the inhibitory threshold for approximately eight weeks per dose. This long-acting profile is suitable for adolescent populations where adherence to daily pills is challenging. Pharmacokinetic studies demonstrate predictable drug release kinetics without significant accumulation or toxic metabolites. Importantly, CAB-LA lacks the bone mineral density reduction observed with tenofovir-containing oral PrEP, a critical consideration for adolescents undergoing bone development [10].

PATHOPHYSIOLOGY AND TRANSLATIONAL EVIDENCE

HIV Acquisition Risk in Adolescents

The immunobiology of HIV acquisition in adolescents includes mucosal vulnerabilities and behavioral risks associated with sexual debut and experimentation. Adolescents face enhanced transmission risks due to immature immune defenses, co-infections, and high-risk sexual behaviors compounded by social determinants such as stigma [11].

Translational Evidence from Clinical Trials

HPTN 083 and HPTN 084 trials were pivotal Phase III studies demonstrating CAB-LA's superiority to oral TDF/FTC PrEP in preventing HIV among high-risk populations including young adults and adolescents. HPTN 084 specifically enrolled adolescent girls and young women in sub-Saharan Africa, a critical demographic with high HIV prevalence. CAB-LA reduced HIV incidence by approximately 89% compared to oral PrEP, largely attributed to improved adherence facilitated by bimonthly injections [12].

Translational research also shows that CAB-LA maintains effective drug levels irrespective of vaginal or anal sexual exposure routes, supporting its broad applicability. Safety analyses indicate minimal systemic toxicity and low incidence of injection site reactions, which were generally mild and transient [13].

DIAGNOSTIC AND BIOMARKER IMPLICATIONS

Biomarkers for Adherence and Drug Levels

Assessment of adherence in adolescents remains challenging, hindered by self-report biases and privacy concerns. Plasma cabotegravir concentrations serve as pharmacokinetic biomarkers reliably quantifying adherence, with levels correlating to HIV protection efficacy. These objective measures facilitate monitoring beyond self-report or pill count strategies used for oral PrEP [14].

Limitations and Emerging Biomarkers

While plasma CAB concentrations provide direct assessment, the pharmacokinetic tail phase period of waning drug levels post-injection poses a risk of subtherapeutic exposure, fostering resistance if HIV exposure occurs. Novel biomarkers under investigation include hair and dried blood spot assays, facilitating long-term adherence monitoring. However, these require validation in adolescent cohorts [15].

THERAPEUTIC STRATEGIES AND BIOCHEMICAL TARGETS

Current Implementation of CAB-LA in Adolescents

CAB-LA is administered as an intramuscular injection every eight weeks after an initial oral lead-in phase to assess tolerability. This regimen reduces pill burden and aligns with adolescent developmental needs for discretion and

convenience. Implementation requires integrated counseling addressing injection site management, mental health, and stigma reduction [16].

Successes and Failures

Clinical trials report high acceptability and retention among adolescents, with most completing scheduled injections on time. Improved adherence compared with oral PrEP is a major success, reducing HIV incidence and offering an alternative for youth with pill fatigue. However, failures include logistic challenges in regular clinic visits for injections, possible injection site discomfort, and limited data on use during pregnancy [17].

Emerging Interventions

Investigational ultra-long-acting formulations aim to extend dosing intervals beyond two months, potentially to four months, enhancing convenience. Alternative delivery modalities, such as implants, are in development but not yet clinically available. Combination strategies integrating CAB-LA with behavioral interventions and digital adherence support may optimize outcomes [18].

FUTURE DIRECTIONS AND RESEARCH GAPS

Technological Advances

Advances in pharmacology may yield injectable formulations with longer half-lives and improved tolerability, potentially expanding to younger adolescents and key populations. Development of point-of-care adherence biomarkers could streamline monitoring in resource-limited settings [19].

Unmet Needs in Adolescent Populations

Key gaps include paucity of long-term safety data, particularly during pregnancy and lactation, and lack of robust real-world effectiveness studies across diverse sociocultural contexts. Economic evaluations to ensure cost-effectiveness in low-income countries and strategies to overcome structural barriers, such as stigma and healthcare access, are urgently needed [20].

Implementation Science

Future research must focus on optimized service delivery models integrating CAB-LA into adolescent health services. Tailored mental health support, peer counseling, and integration with other sexual and reproductive health services are critical to maximize adherence and persistence. Additionally, understanding adolescents' preferences and behavioral dynamics is vital for effective scale-up [21].

CONCLUSION

Long-acting cabotegravir represents a paradigm shift in HIV prevention for adolescents and young adults by addressing critical adherence barriers inherent with daily oral PrEP. Its potent integrase-inhibitory activity, combined with a sustainable dosing regimen, offers superior efficacy and favorable safety profiles validated in pivotal clinical trials. CAB-LA's pharmacological advantages are complemented by high acceptability in youth populations facing pronounced stigma and social challenges with oral regimens. Nonetheless, pragmatic challenges remain, including maintaining injection adherence, ensuring equitable access, and accruing long-term safety data, especially in pregnant adolescents. Multi-disciplinary and culturally sensitive implementation strategies are imperative to harness the full potential of CAB-LA in reducing HIV burden among youth globally. Continued research into optimizing dosing intervals, adherence biomarkers, and integration with comprehensive adolescent health services will be critical. This body of evidence endorses CAB-LA as a transformative advancement in HIV prevention with substantial promise for impacting the epidemic in adolescent populations. Long-acting cabotegravir should be prioritized in adolescent HIV prevention programs, coupled with targeted support measures to optimize adherence and address psychosocial barriers.

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