RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 5(1):31-37, 2026

©RIJRMS Publications

ONLINE ISSN: 1115- 6198

Print ISSN: 1597-3107

https://doi.org/10.59298/RIJRMS/2026/513137

Long-Acting Cabotegravir Injectable Pre-Exposure Prophylaxis: Efficacy and Implementation in High-Risk Populations

Wotsomu Evasi

Clinical Pharmacology and Antimicrobial resistance Kampala International University Uganda
Email: evasi.wotsomu@stdwc.kiu.ac.ug

ABSTRACT

Human immunodeficiency virus (HIV) remained a global public health challenge despite advances in antiretroviral therapy. Oral pre-exposure prophylaxis with tenofovir-based regimens has demonstrated efficacy but faces adherence barriers that limit real-world effectiveness. Long-acting cabotegravir, an integrase strand transfer inhibitor formulated for intramuscular injection, represents a paradigm shift in biomedical HIV prevention by eliminating daily adherence requirements. This review critically evaluated the biochemical properties, clinical efficacy, and implementation challenges of long-acting cabotegravir injectable pre-exposure prophylaxis in high-risk populations. A comprehensive literature search identified peer-reviewed clinical trials, pharmacokinetic studies, implementation science research, and policy documents published between 2015 and 2025. Cabotegravir exhibited sustained plasma concentrations following bimonthly intramuscular administration, achieving four-fold higher protective efficacy than oral tenofovir disoproxil fumarate/emtricitabine in clinical trials among men who have sex with men, transgender women, and cisgender women. Phase 3 trials demonstrated 66 to 89 percent relative risk reduction compared to daily oral prophylaxis. However, implementation barriers included injection site reactions in 30 to 40 percent of recipients, prolonged pharmacokinetic tail necessitating oral bridging therapy, healthcare infrastructure requirements for injectable delivery, and substantial cost differentials compared to generic oral formulations. Emerging resistance patterns and inequitable global access remained critical concerns. Long-acting cabotegravir represented a highly efficacious prevention modality that addressed adherence challenges but required comprehensive implementation strategies addressing logistical, economic, and equity considerations to realize population-level impact.

Keywords: Cabotegravir, Pre-exposure prophylaxis, HIV prevention, Integrase inhibitors, Injectable antiretrovirals.

INTRODUCTION

Cabotegravir belongs to the integrase strand transfer inhibitor class of antiretroviral agents, characterized by nanomolar potency against HIV-1 through blockade of viral DNA integration into the host genome [1]. The compound exhibits unique physicochemical properties, including extremely low aqueous solubility and high lipophilicity, enabling formulation as a long-acting nanosuspension with sustained release kinetics following intramuscular depot injection [2]. Following injection into the gluteal muscle, cabotegravir nanocrystals undergo gradual dissolution, maintaining plasma concentrations above the protein-adjusted 90 percent inhibitory concentration for eight to twelve weeks [3]. This pharmacokinetic profile eliminates the daily adherence requirement inherent to oral prophylaxis, theoretically maximizing biological efficacy by ensuring continuous drug presence at mucosal surfaces where HIV transmission occurs [4]. The molecular mechanism involves chelation of divalent metal cations within the integrase active site, preventing catalytic activity essential for proviral integration [5].

Despite the availability of effective oral pre-exposure prophylaxis regimens [6], HIV incidence remains elevated in key populations, including men who have sex with men, transgender women, and adolescent girls and young women

in high-prevalence settings. Adherence to daily oral tenofovir-based prophylaxis proves challenging across diverse populations, with real-world effectiveness substantially lower than observed in controlled efficacy trials [7]. Behavioral, structural, and psychosocial barriers, including pill fatigue, stigma, and competing life priorities, compromise consistent medication use [8]. Suboptimal adherence translates to inadequate drug concentrations at sites of viral exposure, permitting transmission events that would otherwise be prevented [9]. Long-acting injectable formulations address this adherence gap by shifting responsibility from daily individual action to periodic clinical encounters, potentially improving prevention coverage, particularly among populations facing adherence challenges [10]. Economic modeling suggests that even modest uptake of highly efficacious long-acting prevention could yield substantial reductions in population-level HIV incidence [11]. This review aims to critically synthesize current evidence regarding the biochemical properties, clinical efficacy, safety profile, and implementation challenges of long-acting cabotegravir injectable pre-exposure prophylaxis in high-risk populations.

PHARMACOKINETICS AND PHARMACODYNAMICS OF LONG-ACTING CABOTEGRAVIR

Nanosuspension Formulation and Absorption

The long-acting cabotegravir formulation comprises drug nanocrystals suspended in an aqueous medium with polysorbate surfactant, yielding a depot injection that releases the drug over extended periods [12]. Following gluteal intramuscular administration of 600 milligram doses, cabotegravir undergoes flip-flop kinetics wherein absorption becomes the rate-limiting step rather than elimination [13]. Peak plasma concentrations occur approximately seven days post injection, followed by a gradual decline characterized by an apparent half-life of five to seven weeks, substantially exceeding the 40-hour half-life of oral formulations [14]. Steady-state concentrations are achieved after two loading doses administered four weeks apart, followed by maintenance injections every eight weeks [15]. The prolonged absorption phase results from the gradual dissolution of nanocrystals at the injection site, with particle size distribution critically determining release kinetics [16].

Distribution and Protein Binding

Cabotegravir demonstrates extensive tissue distribution with an apparent volume of distribution exceeding 12 liters, reflecting lipophilic partitioning into cellular compartments [17]. Plasma protein binding approximates 99 percent, predominantly to albumin, necessitating consideration of free drug concentrations when evaluating pharmacodynamic thresholds [18]. The protein-adjusted 90 percent inhibitory concentration against wild-type HIV-1 is 0.166 micrograms per milliliter, a benchmark consistently exceeded throughout the dosing interval at steady state [19]. Tissue distribution studies demonstrate accumulation in rectal and vaginal mucosal tissues, the primary sites of sexual HIV transmission, with tissue to plasma ratios exceeding unity [20]. This anatomical distribution pattern supports the biological plausibility of prophylactic efficacy. Cabotegravir penetrates female and male genital tract secretions, achieving concentrations capable of inhibiting viral replication in ex vivo challenge models [21]. These pharmacokinetic characteristics position cabotegravir favorably for prevention applications where sustained mucosal drug presence is paramount.

CLINICAL EFFICACY EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

HPTN 083 Trial in Cisgender Men and Transgender Women

The HIV Prevention Trials Network study 083 enrolled 4566 cisgender men who have sex with men and transgender women at elevated HIV risk across multiple international sites [22]. Participants received either long-acting cabotegravir injections every eight weeks or daily oral tenofovir disoproxil fumarate/emtricitabine in a double-blind, double-dummy design [23]. The trial demonstrated 66 percent relative risk reduction favoring cabotegravir, with incidence rates of 0.38 versus 1.21 per 100 person-years in the cabotegravir and oral arms, respectively [24]. Superiority was declared at a pre-planned interim analysis, leading to unblinding and offer of cabotegravir to all participants [25]. Notably, adherence to oral prophylaxis measured via tenofovir diphosphate in dried blood spots revealed that only 79 percent of participants in the oral arm maintained protective drug levels, whereas pharmacokinetic sampling confirmed adequate cabotegravir concentrations in 99 percent of injection recipients [26]. This adherence differential largely explains the observed efficacy gap. Breakthrough infections in the cabotegravir arm predominantly occurred during the initiation period or among individuals with subtherapeutic drug levels, underscoring the importance of adequate dosing and oral lead-in coverage [27].

HPTN 084 Trial in Cisgender Women

The companion study HPTN 084 enrolled 3224 cisgender women in sub-Saharan Africa, employing an identical trial design comparing cabotegravir injections to oral tenofovir disoproxil fumarate/emtricitabine [28]. Results demonstrated even greater relative efficacy, with 89 percent risk reduction and incidence rates of 0.21 versus 1.79 per 100 person-years favoring cabotegravir [29]. The marked superiority in this population likely reflects lower adherence to daily oral prophylaxis in the comparator arm, with only 65 percent of participants maintaining protective tenofovir diphosphate concentrations [30]. Young women aged 18 to 25 years exhibited particularly low oral adherence but achieved similar protection with injections as older participants, suggesting that long-acting modalities may preferentially benefit populations facing adherence challenges [31]. Acceptability assessments revealed high satisfaction with the injectable regimen, with 93 percent of participants expressing preference for

continuing injections over switching to oral prophylaxis [32]. These findings established cabotegravir as a highly effective prevention option for cisgender women in high-incidence settings where oral prophylaxis uptake and persistence have proven inadequate.

SAFETY PROFILE AND ADVERSE EVENT CONSIDERATIONS

Injection Site Reactions

The most common adverse events associated with long-acting cabotegravir are injection site reactions, occurring in 30 to 40 percent of recipients across clinical trials [33]. These reactions manifest as pain, induration, swelling, pruritus, or nodule formation at gluteal injection sites, typically resolving within seven days but occasionally persisting for several weeks [34]. Severity is generally mild to moderate, with fewer than one percent of participants discontinuing due to injection site tolerability [35]. Pathophysiologically, these reactions reflect local inflammatory responses to depot nanocrystals and muscular trauma from injection volume, as each dose requires three milliliters administered via a large-bore needle [36]. Strategies to minimize discomfort include proper injection technique with the Z-track method, gluteal muscle massage post injection, and alternating injection sites between doses [37]. Importantly, injection site reactions do not predict subsequent adverse events and typically diminish in frequency and severity with repeated administrations as participants acclimate to the regimen [38].

Systemic Adverse Events and Safety Signals

Beyond injection site reactions, the systemic safety profile of cabotegravir proves comparable to oral tenofovir-based prophylaxis, with no unexpected serious adverse events attributable to study drug [39]. Hypersensitivity reactions have been reported rarely, including one case of post-injection reaction requiring hospitalization, though causality remains uncertain [40]. Laboratory abnormalities occur at rates similar to oral comparators, with no clinically significant effects on renal function, bone mineral density, or hepatic transaminases observed during prophylactic use [41]. Weight gain has emerged as a signal in treatment cohorts receiving integrase inhibitors, but prophylactic trials have not demonstrated significant differences between cabotegravir and comparator arms [42]. Neuropsychiatric symptoms, including depression, anxiety, and sleep disturbances, were reported by approximately five percent of cabotegravir recipients, rates comparable to oral prophylaxis, though temporal associations with injections warrant ongoing surveillance [43]. The prolonged pharmacokinetic tail presents theoretical concerns regarding persistent low-level drug exposure following discontinuation, potentially increasing vulnerability to resistant virus exposure during the tail phase [44].

IMPLEMENTATION CHALLENGES AND REAL-WORLD CONSIDERATIONS

Healthcare Delivery Infrastructure Requirements

Successful implementation of long-acting cabotegravir requires substantial healthcare system adaptations compared to oral prophylaxis delivery models [45]. Injectable administration necessitates clinical encounters every eight weeks, demanding reliable appointment systems, trained personnel, and cold chain maintenance for drug storage [46]. Many community-based HIV prevention programs lack infrastructure for injectable delivery, potentially limiting access particularly in resource-constrained settings where HIV burden is greatest [47]. Injection administration requires clinical space, adequate staffing, and waste disposal systems for needles and syringes [48]. Task-shifting strategies permitting nurses or community health workers to administer injections may expand access but require training investments and regulatory authorization [49]. Telemedicine models that reduce visit frequency for clinical assessments while maintaining injection schedules represent one adaptation strategy being piloted [50]. Geographic accessibility poses barriers for populations facing transportation challenges, potentially necessitating mobile clinics or decentralized service delivery points [51].

Economic Considerations and Cost-Effectiveness

The price differential between long-acting cabotegravir and generic oral tenofovir-based prophylaxis represents a critical implementation barrier, particularly in low and middle-income countries [52]. Initial pricing in high-income settings approached 3000 to 4000 United States dollars per person annually for drug costs alone, orders of magnitude higher than generic oral options costing less than 100 dollars annually [53]. Cost-effectiveness modeling suggests that at current pricing, cabotegravir may be economically justifiable only in populations with extremely high HIV incidence and low oral adherence, where incremental efficacy justifies added costs [54]. Voluntary licensing agreements negotiated for resource-limited settings have established substantially reduced pricing, though access remains contingent on country-specific negotiations and regulatory approvals [55]. Beyond drug acquisition costs, implementation expenses, including healthcare worker time, cold chain infrastructure, and injection supplies, add further economic burden [56]. Comparative cost-effectiveness against oral prophylaxis varies substantially by setting, with greater favorability in contexts where oral adherence is particularly poor, and HIV incidence is elevated [57]. Achieving equitable global access will require continued price negotiations, technology transfer enabling generic manufacturing, and innovative financing mechanisms including donor support for prevention programs [58].

Resistance Emergence and Pharmacokinetic Tail Implications

Following discontinuation of long-acting cabotegravir, detectable plasma concentrations persist for nine to twelve months due to continued absorption from the injection depot [59]. This prolonged tail creates a window during which individuals remain exposed to subtherapeutic drug levels that could select for integrase resistance mutations if HIV acquisition occurs [60]. Clinical trial protocols mandated oral cabotegravir or alternative prophylaxis during the tail period to mitigate this risk, but real-world adherence to such bridging therapy may prove suboptimal [61]. Breakthrough infections during cabotegravir prophylaxis have been associated with integrase resistance mutations, particularly Q148R/K accompanied by secondary mutations, in approximately half of cases with available genotyping [62]. These resistance patterns retain susceptibility to other integrase inhibitors such as dolutegravir or bictegravir, preserving second-line treatment options, though cross-resistance can occur with higher-level mutations. Mathematical modeling suggests that population-level resistance emergence depends critically on tail management strategies, with substantial increases in transmitted resistance possible if tail coverage is inadequate. Resistance testing at the time of confirmed breakthrough facilitates appropriate treatment selection and contributes to surveillance of resistance epidemiology. The balance between the substantial prophylactic benefits of long-acting cabotegravir and potential resistance implications requires ongoing monitoring as implementation expands, with particular attention to populations at highest risk of HIV acquisition during the pharmacokinetic tail.

CONCLUSION

Long-acting cabotegravir injectable pre-exposure prophylaxis represents a transformative advancement in biomedical HIV prevention, demonstrating superior efficacy to oral tenofovir-based regimens in randomized controlled trials among diverse high-risk populations. The pharmacokinetic advantages of sustained drug exposure through depot formulation eliminate daily adherence requirements, translating to 66 to 89 percent relative risk reduction compared to oral prophylaxis in clinical trial settings. However, the realization of cabotegravir's prevention potential at the population scale requires addressing multifaceted implementation challenges. Injection site reactions, while generally manageable, affect substantial proportions of recipients and may influence acceptability in some populations. Healthcare system requirements for injectable delivery, including infrastructure, training, and cold chain logistics, exceed those of oral prophylaxis and may limit accessibility, particularly in resource-constrained settings. Economic barriers pose perhaps the greatest challenge to equitable global access, with current pricing differentials favoring generic oral formulations despite cabotegravir's superior efficacy. The prolonged pharmacokinetic tail necessitates bridging strategies to prevent resistance emergence, adding complexity to discontinuation protocols. Despite these challenges, long-acting cabotegravir addresses critical adherence barriers that have limited oral prophylaxis effectiveness, offering new prevention options for populations unable to maintain daily medication routines. Successful implementation will require adaptive service delivery models, continued price negotiations to enhance affordability, and robust pharmacovigilance systems monitoring resistance emergence. Implementation programs should prioritize populations demonstrating low oral prophylaxis adherence and high HIV incidence, while establishing robust systems for tail period management, resistance monitoring, and equitable access through tiered pricing and service delivery innovations.

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CITE AS: Wotsomu Evasi (2026). Long-Acting Cabotegravir Injectable Pre-Exposure Prophylaxis: Efficacy and Implementation in High-Risk Populations. RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 5(1):31-37. https://doi.org/10.59298/RIJRMS/2026/513137