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Research Article

Multicompartmental pharmacokinetic assessment of long-acting cabotegravir for HIV preexposure prophylaxis in healthy persons

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Abstract

Objectives: In clinical development as a Long-Acting (LA) injectable HIV preexposure prophylaxis, bototregravir is an integrase strand transfer inhibitor. Techniques: In healthy people, this phase I trial evaluated the pharmacokinetics of cabotegravir following repeated oral and single intramuscular (IM) LA doses in plasma and anatomical areas associated with sexual HIV-1 transmission. Participants received a single gluteal IM cabotegravir LA 600 mg injection guided by ultrasonography after a 28-day oral lead-in period of 30 mg of cabotegravir and a 14–42 day washout period. The aim of the study was to determine the levels of cabotegravir in plasma, cervical, vaginal, and rectal tissues, as well as in cervicovaginal and rectal fluids and up to Week 12 following intramuscular injection. Outcomes: Out of the nineteen enrolled subjects, sixteen finished the study by Week 52. Plasma contained cabotegravir, which was found in all fluids and tissues. Through week 12, the 90% maximum inhibitory concentration of cabotegravir in vitro was not met by the median plasma concentration. The rectal fluid had a median tissue-to-plasma cabotegravir concentration ratio of 0.32 during all visits, while the other tissues and fluids had a median ratio of 0.08-0.16. The adjusted R2 values were 0.78, 0.79, and 0.90 for the cabotegravir concentrations in plasma and the cervical, vaginal, and rectal tissues, respectively. Eighty-eight percent of subjects experienced injection-site responses, the majority of which were grade 1 (82%). Eleven major adverse events unrelated to drug use were reported by two subjects. In summary over time, the amounts of cabotegravir in tissues and fluids were proportionate to plasma, and there were significant connections between the concentrations in tissues and plasma. The tissue-to-plasma ratios of capegravir LA may be significant in comprehending its application as preexposure prophylaxis.

INTRODUCTION

There are 38 million HIV-positive individuals worldwide, and an estimated 1.7 million new cases of the virus were reported in 2019 [1]. To aid in the end of the AIDS epidemic, the HIV treatment 90-90-90 targets were set, with the goal of diagnosing 90% of individuals infected with HIV, treating 90% of those diagnosed, and achieving viral suppression in 90% of individuals on treatment by 2020 [2]. While keeping a viral load below detection is useful in preventing HIV from being transmitted through sexual contact, maintaining stable retention in care, regular access to and compliance with oral antiretroviral therapy, and the many obstacles that stand in the way of daily, lifetime oral therapy are major obstacles [3]. Preexposure prophylaxis (PrEP) is one of the ways to prevent HIV-1 transmission that has been explored among others [4,5]. HIV-1 PrEP has two approved regimens: daily oral 2-drug combinations consisting of tenofovir disoproxil fumarate and emtricitabine with tenofovir alafenamide plus emtricitabine [6,7]. The World Health Organization has prequalified and the European Medicines Agency has approved the dapivirine vaginal ring for HIV-1 PrEP in women [8,9]. PrEP is not widely used by those who could benefit from it, with only 590 000 people worldwide taking at least one dosage in 2019-a long cry from the target of 3,000 000 by 2020 [10]. Despite the high prevalence of HIV infection and chance of contracting the virus among African American men who have sex with men, the rate of PrEP uptake in this demographic is low in the United States [11-13]. The effectiveness of PrEP is diminished by low rates of medication adherence to daily oral dosing [14,15]. Therefore, parenteral PrEP treatment less frequently could provide a longer duration of protection and better compliance compared to event-driven PrEP or daily oral dose, which may be preferred by some individuals with a high risk of HIV-1 infection [16]. A Long-Acting (LA) single medication for PrEP called capetregravir is an HIV integrase strand transfer inhibitor that is now in the late stages of development [17]. Less than 1% of cabotegravir is free to circulate in plasma due to its strong protein binding [18]. Preclinical investigations in macaques showed that plasma cabotegravir concentrations that are achievable in humans shielded against Simian-Human Immunodeficiency Virus (SHIV) and simian immunodeficiency virus challenges when cabotegravir LA was delivered as a single agent [19-21].

In 97% of male macaques given an intrarectal SHIV challenge, plasma cabotegravir concentrations greater than the in vitro protein-adjusted 90% maximum inhibitory concentration (PA-IC90) offered protection (half-maximal tissue culture infectious [TCID50]). Dose, 50) and more than 90% of female macaques receiving medroxyprogesterone intravaginally challenged with SHIV (TCID50 dose, 300) [19,20]. When the plasma cabotegravir concentration was greater than 4× PA-IC90, female macaques had a 90% chance of being protected against the intravaginal simian immunodeficiency virus challenge (TCID50 dose, 1000) [21]. In the HIV Prevention Trials Network (HPTN) 077 and ECLAIR studies, cabotegravir LA as PrEP was assessed. The drug was administered every 8 or 12 weeks to maintain target plasma cabotegravir levels above 1× PA-IC90 (0.166 µg/mL) and above 4× PA-IC90 (0.664 µg/mL) in 95 and 80% of study participants, respectively, based on concentrations that had been shown to provide protection in animal challenge studies [22,23]. In the ECLAIR trial, men who were unlikely to contract HIV-1 through sexual activity were given 800 mg of cabotegravir LA intramuscularly (IM) every 12 weeks showed that 15-31% of participants had plasma cabotegravir levels below PA-IC90 after three doses [22]. In the HPTN 077 trial, individuals with a low risk of contracting HIV-1 showed comparable outcomes in both men and women who received the same dosage schedule. This suggests that the recommended dose schedule of every 12 weeks may not be adequate. Within a second cohort of the HPTN 077 trial, all individuals, irrespective of gender, were able to maintain plasma concentrations above the 1× and 4× PA-IC90 Pharmacokinetic (PK) objectives for up to 36 weeks with cabotegravir LA 600 mg IM injection every 8 weeks for 5 doses [23]. The two distinct worldwide phase III double-blind, double-dummy, noninferiority trials, HPTN 083 and 084, were unblinded early at a predetermined interim analysis upon administration of cabotegravir 600 mg LA IM injections. In men who have sex with men and transgender women (HPTN 083) and cisgender women (HPTN 084) who are at high risk of getting HIV-1 through sexual transmission, once every eight weeks proved to be a more effective form of PrEP than daily oral emtricitabine + tenofovir disoproxil fumarate [17,24]. Betabetamerone LA is a good candidate for PrEP because it was typically well tolerated in phase II and III trials [17,22-24]. For the maintenance of virological suppression in people infected with HIV-1, capetregravir + rilpivirine LA dosed every month or every two months is approved as an HIV-1 treatment. The majority of new HIV infections worldwide are caused by sexual transmission, mostly by males who have sex with other men and through heterosexual contact.1, 12 As a result, measuring the quantities of cabotegravir in anatomical locations linked to sexual transmission is crucial to the assessment of cabotegravir LA as PrEP in its entirety. While macaque challenge trials with SHIV have defined cabotegravir concentrations associated with preclinical efficacy, there is a dearth of information regarding cabotegravir concentrations in sites related to sexual HIV-1 transmission following intramuscular injection in humans [19,20,25]. The 114433 study (NCT01756131) assessed the levels of cabotegravir after an IM dosage of 400 mg; however, the small sample size (n = 8) only included plasma and tissues as anatomical locations [26]. The PK of cabotegravir LA in tissues and fluids linked to sexual HIV-1 transmission sites is reported here after two consecutive 30-mg oral daily doses and one 600-mg intravenous dosage given under ultrasound supervision, separated by a washout interval in between treatments **(Chart)**.

METHODS

Construct

In this phase I, open-label trial involving healthy people, the PK of cabotegravir was evaluated in plasma, as well as in anatomical tissues and secretions linked to HIV-1 sexual transmission after repeated oral and single LA doses (NCT02478463). For 28 days, participants were given 30 mg of oral cabotegravir daily to gauge their tolerance and safety. In order to allow clinics to schedule the administration of further IM, participants endured a washout period ranging from 14 to 42 days. A physician used ultrasound guidance to administer a single, gluteal intramuscular injection (IM) of cabotegravir LA 600 mg to the participants. At one of the two trial sites, magnetic resonance imaging was used to confirm the position of the depot injection. To guarantee that the medicine was deposited inside the gluteal muscle rather than deeper, a spinal needle measuring less than 9 cm was utilized at both locations. Subcutaneous tissue, which can occasionally be accessed with a conventional 3.8-cm needle. PK assessments were taken at the conclusion of the oral dosage and after injection through Week 12. After that, safety monitoring and quarterly PK sampling were conducted until the study's completion, which occurred 52 weeks after injection. Because cabotegravir LA 600 mg is a therapeutically relevant dose linked with preclinical efficacy for the prevention of SHIV infection in macaques, it was chosen to attain target PK concentrations in trial participants [19,23]. From February 27, 2017, to July 25, 2019, the research was carried out at the University of Pittsburgh Medical Center and Johns Hopkins Hospital in Pittsburgh, Pennsylvania, in compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical The ideals and practice of the Helsinki Declaration. The study protocol and conduct were approved by the institutional review boards of Johns Hopkins Medicine (Baltimore, MD, USA) and Western Institutional Review Board (Puyallup, WA, USA). Each participant gave written, informed consent and was free to discontinue participation at any moment.

Participants

Men and women in good health, aged 18 to 55, who had a body weight of at least 40 kg and a body mass index (BMI) of 18.5 to 35.0 kg/m2, were eligible to participate. Women met the eligibility requirements if they were not nursing or pregnant, not of reproductive potential (premenopausal with proven tubal ligation, bilateral tubal occlusion, or bilateral oophorectomy), or of reproductive potential utilizing a very effective method of contraception. Additionally eligible were women who gave their consent for genital tract collection but refused rectal sampling.

Medical history (such as a history of seizures, heart illness, liver disease, etc.) and diagnostic evaluations (such as positive test results for HIV, hepatitis B or C virus, or other STDs) were among the exclusion criteria. The Supplemental Information contains a summary of additional exclusion criteria.

Goals and evaluations

The main goal of the study was to determine the levels of cabotegravir after a single intraperitoneal injection (IM) of 600 mg (3 mL) in plasma, rectal tissue, and fluid in both men and women, as well as in cervical tissue, cervicovaginal fluid, and vaginal tissue in women on Days 3 and 8 and weeks 4, 8, and 12. PK parameters of cabotegravir in plasma, tissues, and fluids; tissue- and fluid-to-plasma Area Under the Concentration-Time Curve (AUC) ratios; tissue-to-fluid ratios; tissue-to-plasma concentration ratios; and safety parameters, including those observed through Week 52 On Day 29 of the oral dosage period, PK samples of plasma, cervical tissue, cervicovaginal fluid, and rectal tissue and fluid were taken and following IM injection on Days 3 and 8, as well as Weeks 4, 8, and 12. Day 3 and Week 8 saw the collection of vaginal tissue. Predose, Day 1, Day 5, Weeks 24, 36, and 52 following IM injection, and four hours after the injection were all times when further PK plasma samples were obtained. Prior to cervical or vaginal and rectal biopsies, respectively, polyethylene terephthalate swabs were used to collect cervical and rectal fluids using vaginal speculum and anoscopy, respectively. At every biopsy, three vaginal, two cervical, and three rectal tissue samples were obtained using flexible sigmoidoscopy and a vaginal speculum, respectively. If samples of the vaginal and cervical tissues were obtained during the same visit, the vaginal tissue samples were taken first.

Ratios of cabotegravir concentrations in tissues and for samples obtained following repeated oral dosage, as well as for samples collected after intravenous injection, the ratios of fluids to plasma and tissues to fluids were computed for each visit. By tracking and documenting Adverse Events (AEs), clinical laboratory evaluations, electrocardiogram data, physical examination findings, and vital sign readings, safety and tolerability were evaluated. Samples of blood were drawn into tubes containing potassium ethylenediaminetetraacetic acid, separated into plasma by centrifugation at 4°C, and then kept at ≤−80°C until analysis. The Clinical Pharmacology Analytical Laboratory at Johns Hopkins University Bayview Medical Center (Baltimore, MD, USA) used liquid chromatography with tandem mass spectrometry (LC–MS/MS) to analyze the quantities of capegravir in plasma, tissue, and fluid. The Bioanalytical Method Validation Guidance for Industry published by the US Food and Drug Administration was followed in the validation of the assays [27,28]. The plasma assay was already explained.29 Biopsies were homogenized in 70% methanol, put through solid-phase extraction, and then analyzed using LC–MS/MS on an API 5000 mass spectrometer (SCIEX, Redwood City, CA, USA) in order to determine the amount of cabotegravir in tissue. Vaginal and rectal fluids were removed using a polyethylene terephthalate swab and subjected to LC–MS/MS analysis using an API 5000 mass spectrometer in order to quantify the amount of cabotegravir present in the fluid. The lower limits of quantification for the assay were 0.025 µg/mL for plasma, 0.05 ng/sample, and 0.0625 ng/swab for tissues and fluids, respectively. Assuming a density of 1 g/mL, tissue and fluid concentrations were reported in µg/mL and normalized to net swab or tissue weight. Analyst 1.6 was used to collect and quantify the data (SCIEX).

Data evaluations

With Phoenix WinNonlin ≥6.3 (Certara, Princeton, NJ, USA), noncompartmental methods were used to estimate the PK parameters of capecitavir based on concentration–time data. Using R software (R Foundation, Boston, MA, USA), the relationship between plasma and tissue or fluid cabotegravir concentrations at matched timepoints was visually examined using log–log linear regression. A descriptive statistical summary was used for the PK parameters. Analysis of covariance was performed using mixed-linear models with sex as a fixed effect and BMI as a continuous covariate. The variables that were analyzed were log-transformed maximum observed concentration (Cmax), apparent terminal phase half-life (t1/2), and AUC from time 0 to infinity (AUC0-∞), the last quantifiable time point (AUC0-t), Week 4 (AUC0-Wk4), Week 8 (AUC0-Wk8), and Week 12 (AUC0-Wk12). Each participant's ratios were computed separately. Descriptive statistics were used to summarize the safety outcomes.

PK: Following many oral doses and one intramuscular injection, the concentrations of capetreavir were assessed in plasma, tissues, and fluids (Figure 1). After a single intramuscular injection of 600 mg, plasma cabotegravir concentrations were ≥4× PA-IC90 in 100% of patients by Day 3 to Week 4. After intramuscular injection, the median cabotegravir plasma concentrations were ≥4× PA-IC90 (0.664 µg/mL) at Week 8 and continued to be higher than PA-IC90 (0.166 µg/mL) at Week 12. After receiving a single 600 mg intramuscular injection, at Weeks 8 and 12, respectively, 100% and 60% of individuals exhibited plasma cabotegravir concentrations over PA-IC90. At ≥48 weeks postinjection, plasma cabotegravir concentrations were found in 2 women (12%) out of 17 individuals (BMI, 28.0 and 30.4 kg/m2). Fourteen After Week 24, 82% of subjects had no detectable plasma cabotegravir concentrations; 6 (43%) women and 8 (57%) men had the same median [range] BMI (29.0 [24.1–33.1] kg/m2) and 25.5 [21.4–29.2] kg/m2).

Following oral dosage and Week 8 following IM injection, the median cabotegravir cervical tissue- and vaginal tissue-to-cervicovaginal fluid concentration ratios were greater than In contrast, in Week 12, the levels of cabotegravir in cervical tissue were found to be lower than those in cervicovaginal fluid. Following oral dosage and at all time points following intraperitoneal injection, the amounts of capegravir were also lower in rectal tissue than in rectal fluid. The adjusted R2 coefficients derived from log–log linear regression were 0.78, 0.79, and 0.90 for cervical, vaginal, and rectal tissues, and 0.60 and 0.44 for cervicovaginal and rectal fluids, respectively. The concentrations of cabotegravir in plasma and time-matched tissue and fluid were measured after a single intraperitoneal injection (Figure 2).

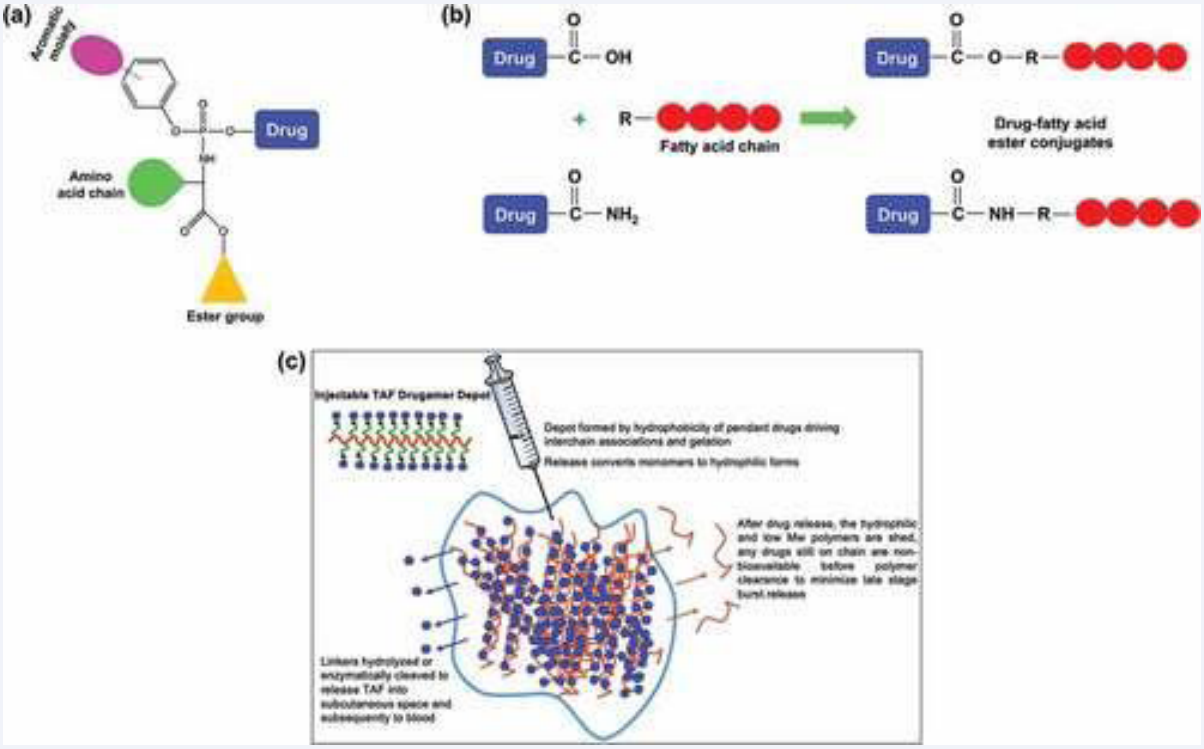


Figure 1 Schematic representation of prodrug technologies for generating Long-Acting (LA) Antiretrovirals (ARVs). (a) ProTide prodrug concept; (b) Fatty acid ester prodrug conjugates; (c) Drugamer-based prodrug approach for TAF.

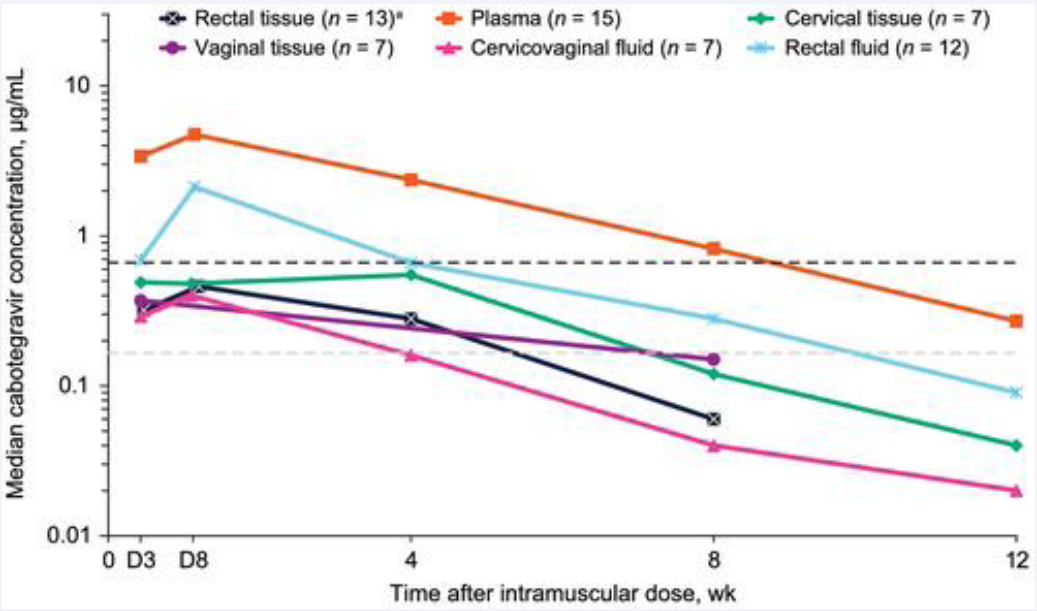


Figure 2 Median cabotegravir concentration–time profiles presented by matrix following a single, ultrasound-guided cabotegravir LA 600-mg intramuscular gluteal injection. Black and grey dashed lines indicate 4× PA-IC90 = 0.664 µg/mL and PA-IC90 = 0.166 µg/mL, respectively. Plasma LLOQ = 0.025 µg/mL; fluid LLOQ = 0.0000625 µg/mL; tissue LLOQ = 0.00005 µg/mL. D, day; LA, long-acting; LLOQ, lower limit of quantification; PA-IC90, in vitro protein-adjusted 90% maximal inhibitory concentration. a Median rectal tissue concentration at week 12 was less than tissue LLOQ.

In every matrix, the peak concentrations of cabotegravir were detected at a median time of maximum observed concentration (tmax) of 7 days after injection. The participant who had injection maladministration into the retroperitoneal cavity had lower plasma PK values for Cmax, AUC0-Wk4, AUC0-Wk8, and AUC0-Wk12 (1.26 µg/mL, 736 µg*h/mL, 1513 µg*h/mL, and 2130 µg*h/mL, respectively) compared to those who received IM injection into the gluteal muscle. Additionally, this participant had a longer overall exposure to plasma cabotegravir, showing increased values for tmax (21 days), t1/2 (124 days), AUC0-t (4697 µg*h/mL), and AUC0-∞ (5502 µg*h/mL). Comparing rectal fluid to cervical tissue, rectal tissue, and cervicovaginal fluid revealed shorter t1/2 and larger exposures (Cmax and AUC0-Wk12) (Figure 3).

Security

There were 86 recorded Adverse Events (AEs); every participant had at least one AE. During the oral lead-in phase, ten participants reported Adverse Events (AEs); none were thought to be drug-related. After receiving an IM injection, 17 individuals experienced adverse events. When Injection-Site Reactions (ISRs) were taken out of the equation, the most commonly reported Adverse Events (AEs) were pyrexia, depression, headaches, sleeplessness, and palpitations (two individuals per event [12%]). 60% of AEs had a grade of 1 or 33% had an intensity of 2, and none resulted in study withdrawal. Following IM injection, 15 participants reported drug-related Adverse Events (AEs) as judged by the investigator. These included ISRs of pain (14 people, or 82%), erythema (two participants, or 12%), and induration, pruritus, muscular cramps, and edema (one person for each event, or 6%). Most ISR Adverse Events (AEs) associated with drugs were grade 1 in severity; all resolved (median duration, 6 c) and none resulted in a withdrawal from study. Due to missing study visits and loss to follow-up, two participants withdrew early, prior to receiving an IM injection, at the discretion of the investigator. There were no discernible patterns in the clinical laboratory abnormalities found (Figure 4).

Over the course of the trial, two patients reported 11 Serious Adverse Events (SAEs). During the trial, there were no fatalities. At her Week 52 visit, a participant who had previously experienced repeated miscarriages disclosed her pregnancy and, little more than two days later, she was suspected of having a spontaneous abortion. Nine weeks after receiving the injection, the second individual experienced serotonin syndrome, which was linked to the concurrent administration of four serotonergic medications during the trial. The participant was withdrawn from the study but continued to be followed up for a long time until Week 52 due to a prolonged stay that followed and complications that led to more hospital-related SAEs, such as deep vein thrombosis in the upper extremities, extensive intraparenchymal hemorrhage following anticoagulation for deep vein thrombosis, aphasia, dysphagia, and urinary tract infection with leucocytosis. This

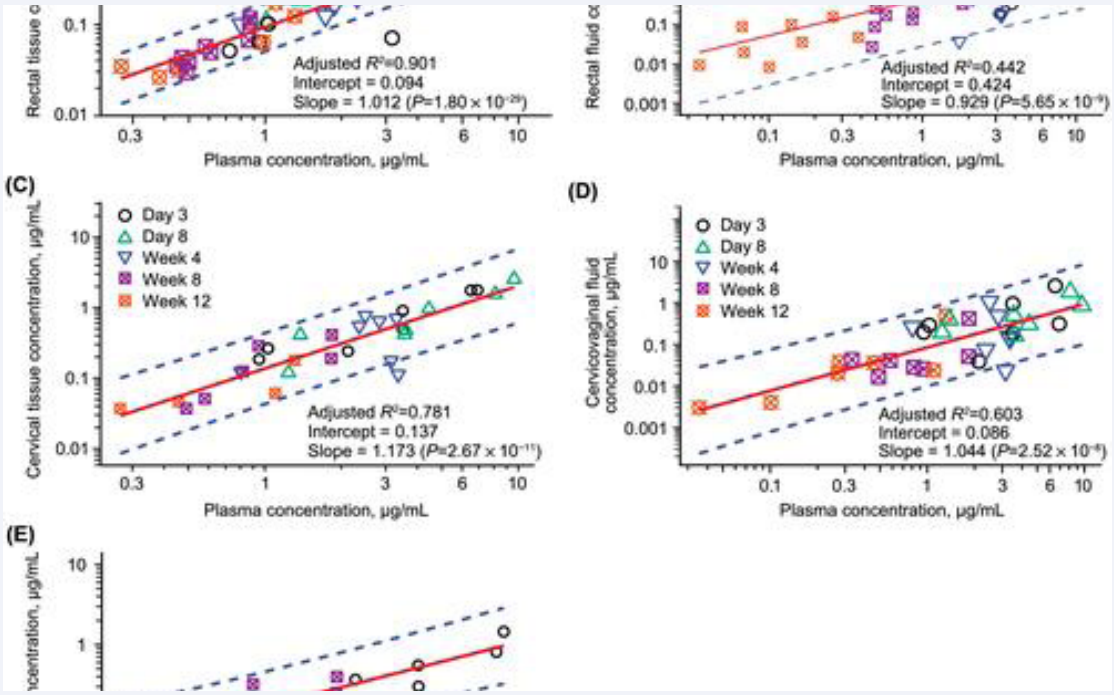


Figure 3 Cabotegravir concentration following cabotegravir 600 mg IM injection in plasma vs. time matched samples from (A) rectal tissue, (B) rectal fluid, (C) cervical tissue, (D) cervicovaginal fluid, and (E) vaginal tissue. Log–log linear regression assessed the relationship between plasma and time-matched tissue and fluid concentrations. IM, intramuscular.

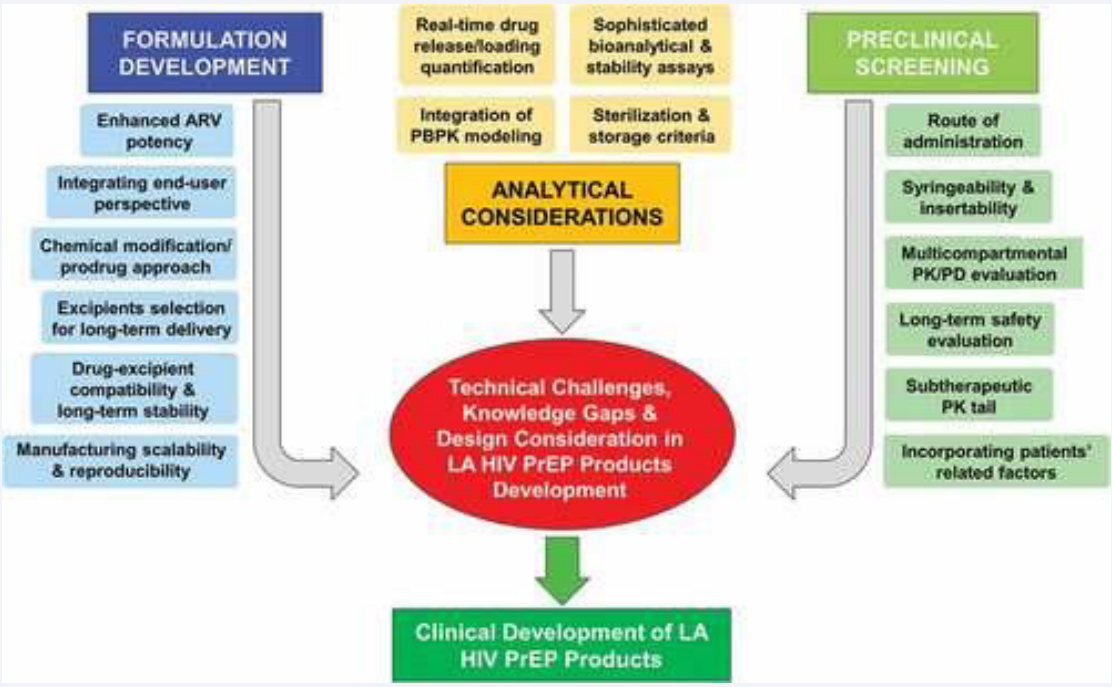


Figure 4 Technical challenges, design considerations, and knowledge gaps in the development of Long-Acting (LA) HIV products.

participant also reported two further SAEs that were connected to two later hospitalizations: one for a brief period of time due to dyspnea and the other for post-traumatic stress disorder. The participant's antianxiety drugs were adjusted after discharge, and after that, the participant's psychological functioning roughly recovered to what it was before the first SAE was reported. With the exception of intracerebral hemorrhage, which was still healing at the most recent clinical follow-up visit, all SAEs disappeared. No SAEs recorded in any trial participant were thought to be connected to the study medication.

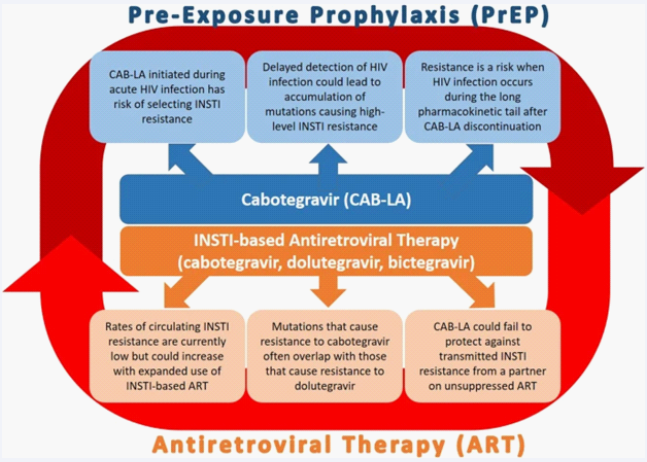
Conversation

A single 600 mg intramuscular injection of cabotegravir under ultrasonography guidance resulted in detectable drug concentrations in plasma and the majority of tissue and fluid samples 12 weeks after injection from anatomical regions linked to sexual HIV-1 acquisition. Through Week 8, median plasma cabotegravir concentrations were ≥4× PA-IC90, a clinical threshold linked to efficacy in HIV-positive study participants in phase II and III treatment trials and predicted to be linked to efficacy when employing the same regimen for HIV-1 PrEP. By week 12, PA-IC90 was above. Every subject had plasma cabotegravir concentrations that were above PA-IC90 through Week 8 and ≥4× PA-IC90 from Day 3 to Week 4. 52 weeks following the final treatment, 12% of subjects had measurable plasma cabotegravir concentrations. Injection, a result that is comparable to what was seen in men 52–60 weeks after the last injection in HPTN 077 (23%), and after the last injection in ECLAIR (17%) [22,29]. Nonetheless, 24 weeks after injection, 82% of trial participants had no detectable plasma cabotegravir concentrations, which is comparable to what was seen following the last injection in ECLAIR (81%). Botogravir LA 600 mg every 8 weeks produced plasma cabotegravir trough concentrations at or above 1× and 4× PA-IC90 targets in 95 and 80% of participants, respectively, for 8 weeks following the last injection in the HPTN 077 study; therefore, regardless of absorption kinetics, dosing every 8 weeks is probably enough to cover the majority of participants.23 Among the sampled anatomical sites, median cabotegravir The largest quantities were found in rectal fluid, which was followed by cervicovaginal fluid, cervical tissue, vaginal tissue, and rectal tissue. Peak concentrations were reached in all tissues and fluids after around 7 days. After a single 600-mg intraperitoneal injection, the median cabotegravir concentrations in cervical and rectal tissues through Week 4 and in rectal fluid through Week 8 were higher than PA-IC90. At Week 12, the median cabotegravir concentrations in all tissue and fluid samples were lower than PA-IC90. In cervical and rectal tissue, at Week 4, 71 and 77% of participants, respectively, exhibited cabotegravir concentrations over PA-IC90. This finding is in line with a previous study that showed lower absolute tissue concentrations in comparison to plasma [26]. By Week 12, very few individuals had cervical and rectal cabotegravir concentrations higher than PA-IC90 tissue as well as cervical fluid. The slopes of the median concentration-time profiles in plasma, tissues, and fluids were similar. The amounts of cabotegravir in time-matched cervical, vaginal, and rectal tissue exhibited strong associations (adjusted $R2 > 0.75$). On the other hand, there was less correlation between plasma and rectal fluid (adjusted $R2 = 0.44$), and between plasma

and cervicovaginal fluid (adjusted R2 = 0.60). This could be attributed to participant variability in fluid concentration as well as differences in the active and passive transport of drugs from cells into fluid. The decreased correlation coefficient may have been caused by the rectal fluid cabotegravir concentrations, which were >30× median concentration (0.66 µg/mL) in week 2 of the study (1 man, 1 woman). For all tissues and fluids, the slope of the log–log linear regression was close to 1, suggesting a direct link with plasma concentrations. Rectal fluid cabotegravir concentrations varied the greatest between subjects overall, followed by plasma and cervicovaginal fluid. Tissues showed significantly less variability.

The distribution of cabotegravir between oral dosage and intramuscular injection into tissues and fluids was comparable. Moreover, tissue-to-plasma ratios following a single 600 mg IM injection matched those found after 400 mg IM split or nonsplit injections of capetecribavir in the 114433 research [26]. When considered collectively, these findings imply that cabotegravir distribution, independent of dosage, dose splitting, or administration, stays constant and decreases in a parallel manner in tissues linked to HIV-1 sexual transmission sites. After a single 600-mg injection of cabotegravir, tissue-to-plasma ratios were generally low, with values ≤0.16 in all tissues. Begin taking 600 mg of cabotegravir every 8 weeks on 4 weeks following a first loading injection showed efficacy for PrEP in HPTN 083 and HPTN 084, [17,24] indicating that sufficiently high quantities of cabotegravir in tissues, plasma, or both, as seen here, confer a high rate of protection. Direct comparisons to HPTN 083 and HPTN 084 for plasma alone are possible because they did not use segregated collections. Interpreting the success of PrEP would be made easier with a knowledge of the cabotegravir PK and pharmacodynamics inside the genital tract compartments of research participants. Cabotegravir LA flip-flop kinetics are absorption-limited [30,31]. The plasma cabotegravir PK values matched the findings of earlier investigations. Despite the lower dose and nonsplit administration in the current study, plasma PK exposures (Cmax and AUC0-Wk12) were comparable to those after cabotegravir 800 mg IM split injection in ECLAIR research [22,23]. The current study's geometric mean of the cabotegravir LA absorption constant (0.0014) and ECLAIR's (0.0011) observed in subjects with higher absorption rates were similar [32]. The present study's findings of lower t1/2 and higher Cmax, which indicate absorption rate, in men compared to women were in line with the varying sex-specific PK parameter results found in HPTN 077 [23,33]. Using an every-8-week dosing regimen of the same dose used in this study, cabotegravir LA for PrEP demonstrated superior efficacy among men and transgender women in HPTN 083 and cisgender women in HPTN 084. This suggests that the observed sex-specific PK differences are unlikely to impact the rate of protection [17,24]. It's unclear if employing a larger needle for ultrasound-guided intramuscular cabotegravir administration can guarantee. The rate of drug absorption from the injection site may have been altered by deep gluteal IM injection in this study as opposed to usual free-hand IM gluteal injection in clinical investigations, which uses needle lengths of 3.8 or 5.1 cm. It is difficult to achieve genuine intramuscular injection, even with direct ultrasound guidance. All subjects, however, continued to have plasma cabotegravir concentrations ≥4× PA-IC90 for four weeks after receiving a single intramuscular injection of 600 mg. In a phase IIIb HIV-1 treatment study, 95% of participants achieved cabotegravir trough concentrations >4× PA-IC90 when using a loading dose strategy with every-8-week dosing [34]. This same regimen would be expected when using HIV-1 PrEP. Participants receive initial loading injections at Weeks 0 and 4, followed by maintenance injections every 8 weeks beginning at week 12.

In comparison to subjects who got injections into the gluteal muscle, those who received an injection into the retroperitoneal cavity showed plasma exposures that decreased during Week 12 postinjection but were greater overall, with a prolonged



Causes and potential consequences of cabotegravir resistance for HIV prevention and treatment.

t1/2. Nevertheless, it is improbable that, in typical situations, the clinical practice recommendation of administering an IM injection with a shorter needle (usually 3.8 cm) would achieve the depth necessary for unintentional drug deposition into the retroperitoneal cavity. Information on cabotegravir LA PK after injection maladministration has been verified is scarce. There are several restrictions on this study. Due to three dropouts and two participants who chose not to have tissue PK collection, the already small sample size was even less. The study population was constrained to a narrow range in general of BMI (18.5-35.0 kg/m2) in order to lessen PK variability and enhance the interpretability of the findings. It may be challenging to extrapolate these findings to people with greater BMIs as a result. It is likely that blood contamination occurred during sample collection, leading to an overestimation of cabotegravir concentrations in tissues and fluids. The amounts of tissue cabotegravir were assessed subsequent to tissue homogenization and might not be indicative of the concentrations in the entire tissue. The tissue and fluid cabotegravir concentration ratios are not corrected for protein binding since cabotegravir protein binding data are only available for plasma. The cabotegravir PK in plasma, tissues, and fluids after an ultrasound-guided injection is shown in these data; the PK may vary when the injection is given as a free-hand gluteal injection without imaging guidance, as is the case in clinical settings.

CONCLUSION

Botogravir was found in the tissues and fluids of anatomical locations linked to sexual HIV-1 transmission after a single intramuscular lethal injection. Time-matched tissue concentrations showed a significant correlation with plasma concentrations, and tissue and fluid cabotegravir concentrations were proportional to plasma throughout time. The tissue-to-plasma ratios and plasma PK characteristics matched those found in earlier research. Given that cabotegravir appears to be sufficiently distributed into mucosal tissues and fluids associated with sexual HIV-1 transmission, the results of this investigation can be used to guide the design and interpretation of future cabotegravir PrEP studies.

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