

ORIGINAL ARTICLE

Multicompartmental pharmacokinetic evaluation of long-acting cabotegravir in healthy adults for HIV preexposure prophylaxis

Jafar Sadik Shaik¹ | Ethel D. Weld² | Stacey Edick³ | Edward Fuchs² | Sharon Riddler³ | Mark A. Marzinke² | Ronald D'Amico⁴ | Kalpana Bakshi¹ | Yu Lou⁵ | Craig Hendrix² | Kelong Han¹ | Susan L. Ford⁶ | David Margolis⁴ | William Spreen⁴ | Parul Patel⁴

¹GlaxoSmithKline, Collegeville, PA, USA

²Johns Hopkins University School of Medicine, Baltimore, MD, USA

³University of Pittsburgh, Pittsburgh, PA, USA

⁴ViiV Healthcare, Research Triangle Park, NC, USA

⁵Precision Biosciences, Durham, NC, USA

⁶GlaxoSmithKline, Research Triangle Park, NC, USA

Correspondence

Parul Patel, PharmD, ViiV Healthcare, 5 Moore Drive, Research Triangle Park, NC 27709, USA.

Email: parul.x.patel@viihealthcare.com

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ViiV Healthcare

Aims: Cabotegravir is an integrase strand transfer inhibitor in clinical development as long-acting (LA) injectable HIV preexposure prophylaxis.

Methods: This phase I study assessed pharmacokinetics of cabotegravir in plasma and anatomical sites associated with sexual HIV-1 transmission after repeated oral and single intramuscular (IM) LA dosing in healthy adults. Following a 28-day oral lead-in period of cabotegravir 30 mg and a washout period of 14–42 days, participants were administered a single ultrasound-guided gluteal IM cabotegravir LA 600-mg injection. The study objective was to characterize cabotegravir concentrations in plasma, cervical, vaginal and rectal tissues, and cervicovaginal and rectal fluids and up to Week 12 after IM injection.

Results: Nineteen participants enrolled and 16 completed the study through Week 52. Cabotegravir was detected in plasma and all tissues and fluids. Median plasma cabotegravir concentrations exceeded the in vitro protein-adjusted 90% maximal inhibitory concentration through Week 12. Median tissue- and fluid-to-plasma cabotegravir concentration ratios across all visits were 0.32 for rectal fluid and 0.08–0.16 for other tissues and fluids. Adjusted R^2 coefficients between cabotegravir concentrations in plasma and cervical, vaginal and rectal tissues were 0.78, 0.79 and 0.90, respectively. Injection-site reactions were common (88% of participants) and were mostly grade 1 in intensity (82%). Two participants reported 11 non-drug-related serious adverse events.

Conclusion: Concentrations of cabotegravir in tissues and fluids were proportional to plasma over time, with strong correlations between tissue and plasma concentrations. Cabotegravir LA tissue-to-plasma ratios may be important for understanding its use as preexposure prophylaxis.

Jafar Sadik Shaik and Ethel D. Weld are joint first authors and contributed equally to the manuscript.

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KEYWORDS

antiretrovirals, HIV/AIDS, pharmacokinetic–pharmacodynamic

1 | INTRODUCTION

Globally, 38 million people are living with HIV, and an estimated 1.7 million people were newly infected in 2019.¹ The HIV treatment 90–90–90 targets aiming to diagnose 90% of people with HIV infection, treat 90% of those diagnosed, and achieve viral suppression in 90% of people receiving treatment by 2020 were established to help end the AIDS epidemic.² Although maintaining an undetectable viral load is effective at preventing sexual transmission of HIV, consistent access and adherence to oral antiretroviral therapy, stable retention in care, and numerous barriers to daily lifelong oral therapy are significant challenges.³ Multiple strategies to prevent HIV-1 transmission have been evaluated, including preexposure prophylaxis (PrEP).^{4,5} Two regimens approved for HIV-1 PrEP are daily oral 2-drug formulations of emtricitabine + tenofovir disoproxil fumarate and emtricitabine + tenofovir alafenamide.^{6,7} The dapivirine vaginal ring for HIV-1 PrEP in women is approved by the European Medicines Agency and prequalified by the World Health Organization.^{8,9} However, global uptake of PrEP is low in individuals who would benefit from PrEP, with 590 000 people receiving at least 1 PrEP dose in 2019—falling far short of the goal of 3 000 000 by 2020.¹⁰ Rate of PrEP uptake in the USA is low among African American men who have sex with men, despite the burden of HIV infection and likelihood of acquiring HIV being very high in this population.^{11–13} Low rates of medication adherence to daily oral therapy reduce the effectiveness of PrEP.^{14,15} Thus, PrEP with less-frequent, parenteral administration could offer an alternative to daily oral dosing or event-driven PrEP with improved compliance and longer duration of protection, which may be preferred by some people with high likelihood of acquiring HIV-1.¹⁶

Cabotegravir is an HIV integrase strand transfer inhibitor in late-stage development as a long-acting (LA) single agent for PrEP.¹⁷ Cabotegravir is highly protein bound in plasma, with less than 1% free in circulation.¹⁸ Preclinical studies in macaques demonstrated that cabotegravir LA administered as a single agent protected against simian–human immunodeficiency virus (SHIV) and simian immunodeficiency virus challenges, with plasma cabotegravir concentrations that can be attained in humans.^{19–21} Plasma cabotegravir concentrations above the *in vitro* protein-adjusted 90% maximal inhibitory concentration (PA-IC₉₀) provided protection in 97% of male macaques challenged intrarectally with SHIV (half-maximal tissue culture infectious [TCID₅₀] dose, 50) and >90% of medroxyprogesterone-treated female macaques challenged intravaginally with SHIV (TCID₅₀ dose, 300).^{19,20} Female macaques had a 90% probability of protection from intravaginal simian immunodeficiency virus challenge (TCID₅₀ dose, 1000) when plasma cabotegravir concentration was above 4× PA-IC₉₀.²¹ Cabotegravir LA as PrEP was evaluated in the ECLAIR and HIV Prevention Trials Network (HPTN) 077 studies with dosing frequency of every 8 or 12 weeks to maintain target plasma

What is already known about this subject

- Long-acting cabotegravir demonstrated superior efficacy vs. emtricitabine and tenofovir disoproxil fumarate as pre-exposure prophylaxis for HIV-1 infection in 2 phase III studies and may be preferred by some individuals.
- There are limited data in humans describing cabotegravir concentrations in anatomical sites related to sexual transmission of HIV-1 following long-acting injection.

What this study adds

- After a single, long-acting intramuscular 600-mg cabotegravir dose, cervicovaginal and rectal tissue and fluid concentrations were lower but proportional to those in plasma; tissue and plasma cabotegravir concentrations were strongly correlated.
- Tissue-to-plasma ratios may be important for evaluating the effectiveness of long-acting agents as preexposure prophylaxis.

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 affording protection in animal challenge studies.^{22,23} In the ECLAIR study of men with a low likelihood of sexually acquiring HIV-1, cabotegravir LA 800 mg intramuscularly (IM) every 12 weeks for 3 doses resulted in plasma cabotegravir levels below PA-IC₉₀ in 15–31% of participants.²² These results were similar in men and women administered the same dosing schedule in the HPTN 077 study among persons with a low likelihood of acquiring HIV-1,²³ confirming that dosing every 12 weeks may be insufficient. In a second cohort of the HPTN 077 trial, cabotegravir LA 600 mg IM injection every 8 weeks for 5 doses maintained plasma concentrations above 1× PA-IC₉₀ and above 4× PA-IC₉₀ pharmacokinetic (PK) targets up to 36 weeks in all participants, regardless of sex.²³

The HPTN 083 and 084 trials, 2 separate global, phase III, double-blind, double-dummy, noninferiority studies, were unblinded early at a predefined, interim analysis when cabotegravir 600 mg LA IM injections administered every 8 weeks demonstrated superior efficacy to daily oral emtricitabine + tenofovir disoproxil fumarate for PrEP in men who have sex with men and transgender women (HPTN 083) and cisgender women (HPTN 084) at high risk of acquiring HIV-1 through sexual transmission.^{17,24} Cabotegravir LA was generally well

tolerated in phase II and III PrEP trials; therefore, it is a promising candidate for PrEP.^{17,22–24} Cabotegravir plus rilpivirine LA dosed every month or every 2 months for HIV-1 treatment is approved for maintenance of virological suppression in adults infected with HIV-1.

Globally, sexual transmission is responsible for most new acquisitions of HIV, primarily through men who have sex with men and heterosexual contact.^{1,12} Therefore, determining cabotegravir concentrations in anatomical sites associated with sexual transmission is important in the overall evaluation of cabotegravir LA as PrEP. Although cabotegravir concentrations associated with preclinical efficacy have been characterized in macaque challenge studies with SHIV,^{19,20,25} cabotegravir concentration data in sites related to sexual HIV-1 transmission following IM injection in humans are limited. The 114433 study evaluated cabotegravir concentrations following a lower 400-mg IM dose (NCT01756131); however, anatomical sites were limited to plasma and tissues in a small sample size ($n = 8$).²⁶ Herein we report the PK of cabotegravir LA in tissues and fluids associated with sexual HIV-1 transmission sites following repeat 30-mg oral daily dosing and following a single 600-mg IM dose administered under ultrasound guidance separated by a washout period between treatments.

2 | METHODS

2.1 | Design

This was a phase I, open-label study of healthy adults that assessed PK of cabotegravir in plasma and anatomical tissues and secretions associated with sexual transmission of HIV-1 following repeat oral and single LA dosing (NCT02478463). Participants received daily oral cabotegravir 30 mg for 28 days to assess safety and tolerability. Participants then underwent a washout period of 14–42 days to permit clinic scheduling of subsequent IM administration. Participants received a single, ultrasound-guided, gluteal IM injection of cabotegravir LA 600 mg administered by a physician, with confirmation of depot injection location via magnetic resonance imaging at 1 of 2 study sites. A spinal needle ≥ 9 cm was used at both sites to ensure drug deposition took place within the gluteal muscle rather than deep subcutaneous tissue, which, at times, may occur using a standard 3.8-cm needle. PK assessments were collected at the end of oral dosing and following injection through Week 12, with continued safety monitoring and quarterly PK sampling through study completion at 52 weeks postinjection. Cabotegravir LA 600 mg was selected because it is a clinically relevant dose predicted to achieve target PK concentrations in study participants associated with preclinical efficacy for prevention of SHIV infection in macaques.^{19,23}

The study was conducted at Johns Hopkins Hospital (Baltimore, MD, USA) and the University of Pittsburgh Medical Center (Pittsburgh, PA, USA) from 27 February 2017 to 25 July 2019, in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and principles of the Declaration

of Helsinki. Johns Hopkins Medicine Institutional Review Board (Baltimore, MD, USA) and Western Institutional Review Board (Puyallup, WA, USA) approved the study protocol and conduct. All participants provided written informed consent and could withdraw at any time.

2.2 | Participants

Eligible participants were healthy men and women aged 18–55 years with body weight ≥ 40 kg and body mass index (BMI) between 18.5 and 35.0 kg/m². Women were eligible if they were not pregnant or lactating and either of reproductive potential using a highly effective contraceptive method or not of reproductive potential (premenopausal with documented tubal ligation, bilateral tubal occlusion or bilateral oophorectomy). Women who consented to genital tract sampling but declined rectal sampling were also eligible. Exclusion criteria were related to medical history (e.g., history of seizure disorder, cardiovascular disease, liver disease) and diagnostic assessments, including positive test results for hepatitis B virus, hepatitis C virus, HIV or other sexually transmitted infections. Other exclusion criteria are summarized in the Supplemental Information.

2.3 | Objectives and assessments

Primary study endpoint was cabotegravir concentrations following a single 600-mg (3-mL) IM gluteal injection in plasma and rectal tissue and fluid in men and women and cervical tissue and cervicovaginal fluid in women at Days 3 and 8 and Weeks 4, 8 and 12 and in vaginal tissue in women at Day 3 and Week 8 (Table S1). Secondary endpoints included cabotegravir concentration tissue- and fluid-to-plasma and tissue-to-fluid ratios; PK parameters of cabotegravir in plasma, tissues and fluids; tissue- and fluid-to-plasma area under the concentration–time curve (AUC) ratios; and safety parameters, including those observed through Week 52 (Supplemental Table S1).

PK sampling of plasma, cervical tissue, cervicovaginal fluid and rectal tissue and fluid occurred on Day 29 of the oral dosing period and on Days 3 and 8, and Weeks 4, 8 and 12 after IM injection. Vaginal tissue was collected on Day 3 and Week 8. Additional PK plasma samples were collected predose, 4 hours after IM injection on Day 1, and on Day 5 and Weeks 24, 36 and 52 after IM injection. Cervicovaginal and rectal fluids were collected via vaginal speculum and anoscopy, respectively, using polyethylene terephthalate swabs prior to cervical or vaginal and rectal biopsies, respectively. Collection of 3 vaginal and 2 cervical tissue samples via vaginal speculum and 3 rectal tissue samples via flexible sigmoidoscopy occurred at each biopsy. Vaginal tissue samples were collected first if both vaginal and cervical tissues were obtained at the same visit.

Cabotegravir concentration ratios for tissues and fluids to plasma and tissues to fluids were calculated for samples collected after repeated oral dosing and across all visits for samples collected after IM injection. Safety and tolerability were assessed by monitoring and recording adverse events (AEs), clinical laboratory assessments,

electrocardiographic results, physical examination findings, and vital sign measurements. Blood samples were collected into potassium ethylenediaminetetraacetic acid tubes, centrifuged at 4°C to separate plasma, and stored at $\leq -80^{\circ}\text{C}$ until analysis.

Plasma, tissue, and fluid cabotegravir concentrations were analysed by the Clinical Pharmacology Analytical Laboratory at Johns Hopkins University Bayview Medical Center (Baltimore, MD, USA) via liquid chromatography with tandem mass spectrometry (LC-MS/MS). Assays were validated in accordance with the US Food and Drug Administration's Bioanalytical Method Validation Guidance for Industry.^{27,28} The plasma assay was described previously.²⁹ For cabotegravir measurement in tissue, biopsies were homogenized in 70% methanol, subjected to solid-phase extraction, and analysed via LC-MS/MS on an API 5000 mass spectrometer (SCIEX, Redwood City, CA, USA). For cabotegravir measurement in fluid, vaginal and rectal fluids were extracted from a polyethylene terephthalate swab and analysed via LC-MS/MS using an API 5000 mass spectrometer. Assay lower limits of quantification for plasma, tissues and fluids were 0.025 $\mu\text{g/mL}$, 0.05 ng/sample and 0.0625 ng/swab, respectively. Tissue and fluid concentrations were normalized to net swab or tissue weight and expressed in $\mu\text{g/mL}$, assuming a density of 1 g/mL. Data were acquired and quantified using Analyst 1.6 (SCIEX).

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.³⁰

2.4 | Data analyses

Cabotegravir PK parameters were estimated from concentration-time data using noncompartmental methods with Phoenix WinNonlin ≥ 6.3 (Certara, Princeton, NJ, USA). Relationship between plasma and tissue or fluid cabotegravir concentrations at matched timepoints was graphically assessed with log-log linear regression using R software (R Foundation, Boston, MA, USA). PK parameters were summarized using descriptive statistics. Log-transformed maximum observed concentration (C_{max}), apparent terminal phase half-life ($t_{1/2}$) and AUC from time 0 to infinity ($\text{AUC}_{0-\infty}$), the last quantifiable time point (AUC_{0-t}), Week 4 ($\text{AUC}_{0-\text{Wk4}}$), Week 8 ($\text{AUC}_{0-\text{Wk8}}$) and Week 12 ($\text{AUC}_{0-\text{Wk12}}$) were analysed by analysis of covariance using mixed-linear models with sex as a fixed effect and BMI as a continuous covariate. All ratios were individually calculated for each participant. Safety results were summarized using descriptive statistics.

3 | RESULTS

3.1 | Study population and baseline characteristics

Of 29 individuals screened, 19 were enrolled and 16 (84%) completed 52 weeks of follow-up. Of those enrolled, mean age was 33 years, mean BMI was 27 kg/m^2 ; 53% were women (Table 1).

TABLE 1 Baseline demographics

Parameter	Participants in overall population (n = 19)	Participants in evaluable pharmacokinetic population (n = 15) ^a
Age (y)		
Mean (SD)	33.3 (9.1)	30.1 (7.0)
Range	22.0–53.0	22.0–46.0
Sex, n (%)		
Female	10 (53)	7 (47)
Male	9 (47)	8 (53)
Body mass index (kg/m^2)		
Mean (SD)	27.2 (3.3)	26.9 (2.9)
Range, min-max	21.4–33.1	21.4–31.1
Height, mean (SD), cm	171.1 (10.2)	171.8 (9.0)
Weight, mean (SD), kg	79.4 (11.5)	79.1 (9.0)
Race and ethnicity, n (%)		
Not Hispanic and not Latino	19 (100)	15 (100)
Asian	1 (5)	1 (7)
Black and African American	6 (32)	5 (33)
White	12 (63)	9 (60)

SD, standard deviation.

^aFour participants did not have evaluable pharmacokinetic data: 2 withdrew before receiving intramuscular injection; 1 had injection maladministration into the retroperitoneal cavity; and 1 was hospitalized for non-study drug-related serotonin syndrome.

Prior to receiving IM injection, 2 participants withdrew at investigator discretion due to missed study visits or lost to follow-up. A third participant withdrew consent on Day 282 following IM injection due to relocation. Two participants did not undergo PK tissue sampling because of IM injection maladministration into the retroperitoneal cavity ($n = 1$) and hospitalization for non-study-drug-related serotonin syndrome ($n = 1$).

3.2 | PK

Cabotegravir concentrations were evaluated in plasma, tissues and fluids following repeat oral dosing and after a single IM injection (Figure 1; Table 2). Plasma cabotegravir concentrations were $\geq 4\times$ PA-IC₉₀ in 100% of participants after repeat oral dosing and by Day 3 to Week 4 following a single IM 600-mg injection (Table 3). Median cabotegravir plasma concentrations were $\geq 4\times$ PA-IC₉₀ (0.664 $\mu\text{g/mL}$) at Week 8 and remained above PA-IC₉₀ (0.166 $\mu\text{g/mL}$) at Week 12 following IM injection. Following a single 600-mg IM injection, 100 and 60% of participants had plasma cabotegravir concentrations above PA-IC₉₀ at Weeks 8 and 12, respectively. Plasma cabotegravir concentrations were detected in 2 women

FIGURE 1 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 $4 \times$ PA- $IC_{90} = 0.664 \mu\text{g/mL}$ and PA- $IC_{90} = 0.166 \mu\text{g/mL}$, respectively. Plasma LLOQ = $0.025 \mu\text{g/mL}$; fluid LLOQ = $0.0000625 \mu\text{g/mL}$; tissue LLOQ = $0.00005 \mu\text{g/mL}$. D, day; LA, long-acting; LLOQ, lower limit of quantification; PA- IC_{90} , in vitro protein-adjusted 90% maximal inhibitory concentration. ^a Median rectal tissue concentration at Week 12 was less than tissue LLOQ

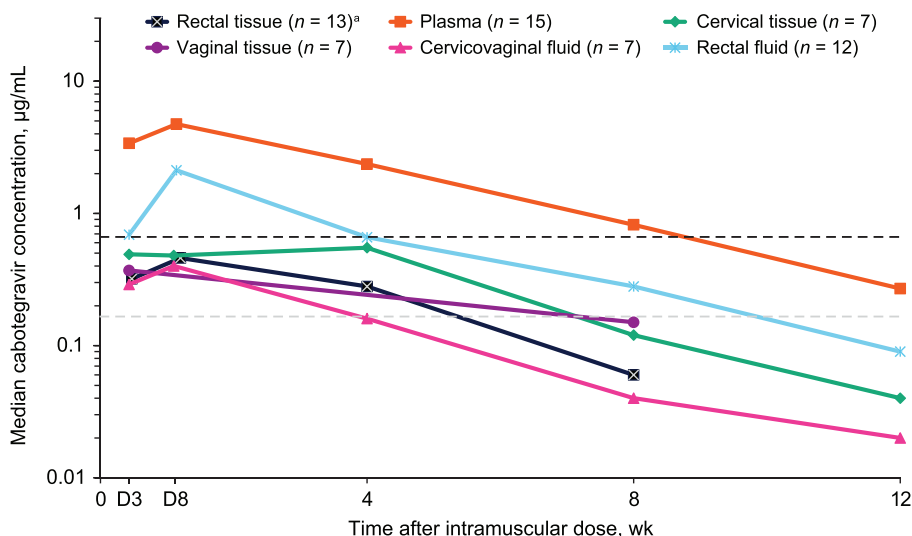


TABLE 2 Median (range) cabotegravir concentrations ($\mu\text{g/mL}$) in plasma, tissues and fluids after oral dosing and intramuscular injection

Visit	Median (range) ^a					
	Plasma (n = 15)	Cervical tissue (n = 7)	Vaginal tissue (n = 7)	Cervicovaginal fluid (n = 7)	Rectal tissue (n = 13)	Rectal fluid (n = 12)
Oral 30 mg						
Day 28	5.98 (2.19–8.78)	1.10 (0.56–2.12)	0.54 (0.22–1.56)	0.45 (0.16–2.75)	0.59 (0.20–1.17)	3.36 (0.91–22.70)
Intramuscular 600 mg						
Day 3	3.39 (0.72–6.9)	0.49 (0.19–1.77)	0.37 (0.06–1.46)	0.29 (0.04–2.63)	0.32 (0.05–0.67)	0.69 (0.00–6.63)
Day 8	4.74 (1.01–11.2)	0.48 (0.12–2.54)	–	0.40 (0.17–1.86)	0.46 (0.11–0.95)	2.12 (0.77–9.6)
Week 4	2.36 (0.80–5.12)	0.55 (0.11–0.77)	–	0.16 (0.02–1.10)	0.28 (0.10–0.45)	0.66 (0.04–21.4)
Week 8	0.82 (0.33–3.10)	0.12 (<LLOQ to 0.41)	0.15 (<LLOQ to 0.40)	0.04 (0.02–0.43)	0.06 (0.00–0.31)	0.28 (0.03–0.77)
Week 12	0.27 (0.04–1.31)	0.04 (<LLOQ to 0.18)	–	0.02 (<LLOQ to 0.50)	<LLOQ (<LLOQ to 0.17)	0.09 (0.01–6.12)

LLOQ, lower limit of quantification.

^aLLOQs were 0.025, 0.0000625 and 0.000050 $\mu\text{g/mL}$ for plasma, fluids and tissues, respectively.

among 17 participants (12%) at ≥ 48 weeks postinjection (BMI, 28.0 and 30.4 kg/m^2 , respectively; Figure S1). Fourteen (82%) participants had no measurable plasma cabotegravir concentrations after Week 24; of these, 6 (43%) were women (median [range] BMI, 29.0 [24.1–33.1] kg/m^2) and 8 (57%) were men (median [range] BMI, 25.5 [21.4–29.2] kg/m^2).

Following repeat oral dosing at Day 28, median cabotegravir concentrations were $\geq 4 \times$ PA- IC_{90} in cervical tissue and rectal fluid and more than PA- IC_{90} in vaginal tissue, rectal tissue and cervicovaginal fluid (Table 2). Cabotegravir concentrations were above PA- IC_{90} in 100 and 86% of participants in all tissues and cervicovaginal fluid, respectively, after oral dosing (Table 3). Following a single 600-mg IM injection, median cabotegravir concentrations were greater than PA- IC_{90} in cervical and rectal tissues through Week 4 and rectal fluid through Week 8 (Figure 1; Table 2). Median cabotegravir concentrations in all tissues and cervicovaginal fluid were below PA- IC_{90} at Week 8 after IM injection. Following IM injection, cabotegravir concentrations were above PA- IC_{90} in 77, 83, 71 and

43% of participants in rectal tissue, rectal fluid, cervical tissue and cervicovaginal fluid, respectively, at Week 4 and 43% of participants in vaginal tissue at Week 8 (Table 3). Cabotegravir concentrations in cervical and vaginal tissues were higher than in cervicovaginal fluid after oral dosing and at Week 8 following IM injection (Table 2). Median cabotegravir concentrations for the entire study population in rectal tissue at Week 12 were below the lower limit of quantification because $>50\%$ of participants had non-quantifiable values.

Median cabotegravir fluid- and tissue-to-plasma concentration ratios were highest for rectal fluid and cervical tissue, respectively, on Day 28 following repeat oral dosing (Table 4). Despite absolute tissue and fluid cabotegravir concentrations being higher following repeat oral dosing than after IM injection, median cabotegravir fluid- and tissue-to-plasma concentration ratios were proportionally similar between dosing regimens. One participant had an increased rectal fluid-to-plasma concentration ratio of 10.4 following repeat oral dosing because of a high rectal fluid cabotegravir concentration (22.7 $\mu\text{g/mL}$). Similarly, median cabotegravir fluid- and tissue-to-

TABLE 3 Proportion of participants with cabotegravir concentrations $>PA-IC_{90}$ and $\geq 4 \times PA-IC_{90}$ in plasma, tissues and fluids after repeat oral dosing and after a single 600-mg intramuscular injection across sexes

Visit	Proportion, % ^a					
	Plasma (n = 15)	Cervical tissue (n = 7)	Vaginal tissue (n = 7)	Cervicovaginal fluid (n = 7)	Rectal tissue (n = 13)	Rectal fluid (n = 12)
Oral 30 mg						
Day 28						
>PA-IC ₉₀	100	100	100	86	100	100
$\geq 4 \times PA-IC_{90}$	100	71	29	43	23	100
IM 600 mg						
Day 3						
>PA-IC ₉₀	100	100	71	86	69	92
$\geq 4 \times PA-IC_{90}$	100	43	29	29	8	50
Day 8						
> PA-IC ₉₀	100	86	–	100	92	100
$\geq 4 \times PA-IC_{90}$	100	43	–	29	39	100
Week 4						
>PA-IC ₉₀	100	71	–	43	77	83
$\geq 4 \times PA-IC_{90}$	100	29	–	14	0	50
Week 8						
>PA-IC ₉₀	100	43	43	14	23	67
$\geq 4 \times PA-IC_{90}$	53	0	0	0	0	8
Week 12						
>PA-IC ₉₀	60	14	–	14	8	33
$\geq 4 \times PA-IC_{90}$	20	0	–	0	0	17

IM, intramuscular; PA-IC₉₀, in vitro protein-adjusted 90% maximal inhibitory concentration.

^aPA-IC₉₀ = 0.166 µg/mL and 4 × PA-IC₉₀ = 0.664 µg/mL.

TABLE 4 Median cabotegravir tissue- and fluid-to-plasma ratios after oral dosing and IM injection across all visits vs. 114433 study results

Study	Treatment	Ratio (range)				
		Cervical tissue to plasma (n = 7)	Vaginal tissue to plasma (n = 7)	Cervicovaginal fluid to plasma (n = 7)	Rectal tissue to plasma (n = 13)	Rectal fluid to plasma (n = 12)
201767 (present) ^a	Oral 30 mg	0.18 (0.11–0.25)	0.14 (0.03–0.18)	0.13 (0.02–0.36)	0.10 (0.07–0.17)	0.45 (0.15–10.40)
	IM 600 mg	0.14 (<LLOQ–0.31)	0.16 (<LLOQ–0.34)	0.08 (0.01–0.44)	0.09 (<LLOQ–0.16)	0.32 (<LLOQ–11.38)
114433 ²⁶ (previous)	IM 400 mg (unsplit) ^b	0.20 (<LLOQ–0.40)	0.28 (<LLOQ–0.70)	–	<LLOQ (<LLOQ–0.10)	–
	IM 400 mg (split) ^c	0.16 (<LLOQ–0.40)	0.19 (<LLOQ–0.70)	–	0.08 (<LLOQ–0.20)	–

IM, intramuscular; LLOQ, lower limit of quantification.

^aLLOQs were 0.025, 0.0000625, and 0.000050 µg/mL, for plasma, tissues, and fluids, respectively.

^bAdministered as a single injection. Samples were collected on Weeks 2 and 8.

^cAdministered as 2 200-mg injections. Samples were collected on Weeks 4 and 12.

plasma concentration ratios were also highest for rectal fluid and cervical and vaginal tissues, respectively, across all visits following IM injection.

Median cabotegravir cervical tissue- and vaginal tissue-to-cervicovaginal fluid concentration ratios were >1 after oral dosing and at Week 8 after IM injection (Table S2). By contrast, cabotegravir

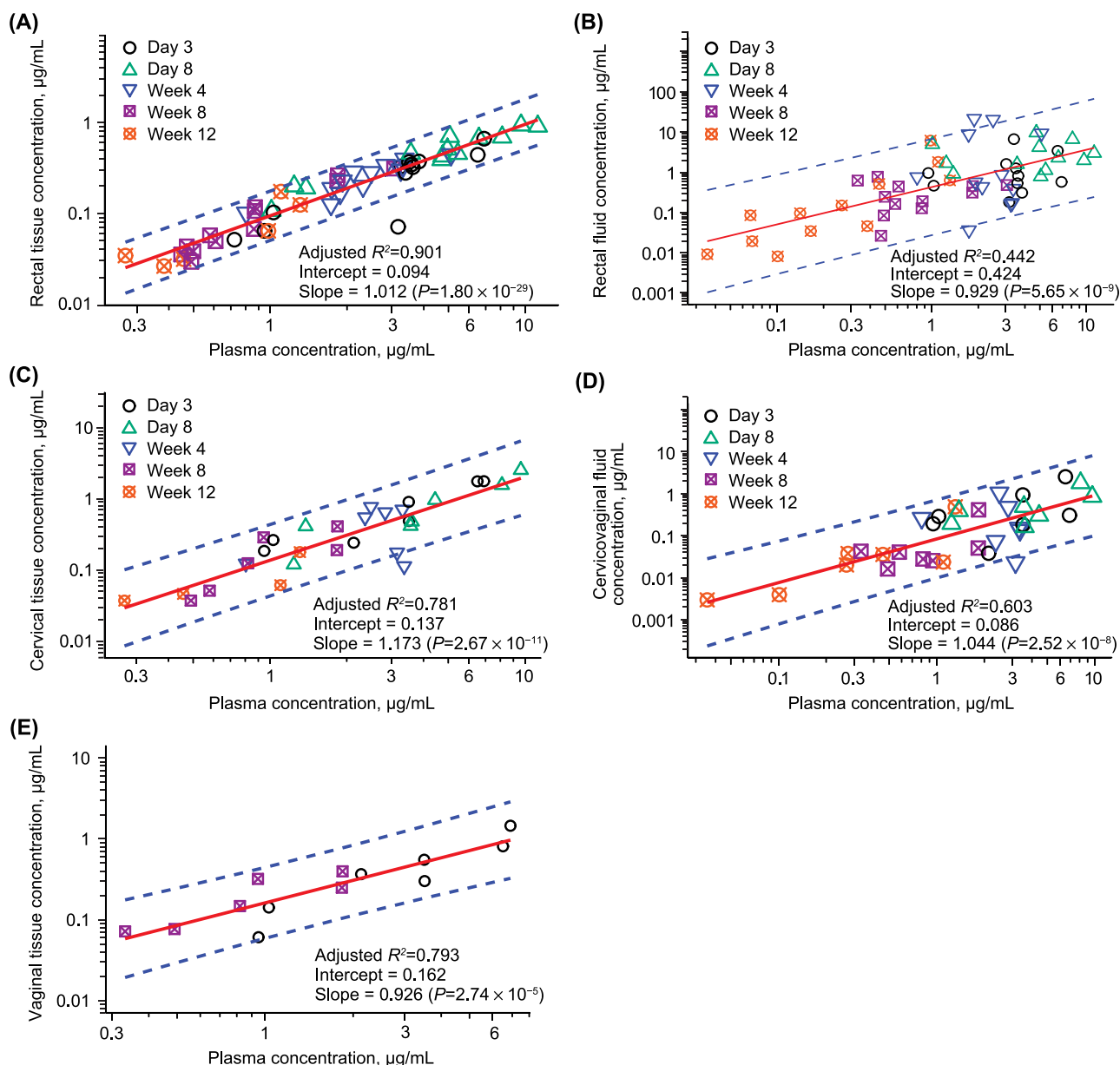


FIGURE 2 Cabotegravir concentration following cabotegravir 600 mg IM injection in plasma vs. time matched samples from (A) rectal tissue, (B) rectal fluid, (C) cervical tissue, (D) cervicovaginal fluid, and (E) vaginal tissue. Log-log linear regression assessed the relationship between plasma and time-matched tissue and fluid concentrations. IM, intramuscular

concentrations in cervical tissue were lower than those observed in cervicovaginal fluid at Week 12. Cabotegravir concentrations were also lower in rectal tissue than rectal fluid after oral dosing and all time points after IM injection. Adjusted R^2 coefficients from log-log linear regression of plasma and time-matched tissue and fluid cabotegravir concentrations following a single IM injection were 0.78, 0.79 and 0.90 for cervical, vaginal and rectal tissues, respectively, and 0.60 and 0.44 for cervicovaginal and rectal fluids, respectively (Figure 2).

Peak cabotegravir concentrations were observed at a median time of maximum observed concentration (t_{\max}) of 7 days following injection in all matrices (Tables 5 and 6). Compared with participants receiving IM injection into the gluteal muscle, the participant with

injection maladministration into the retroperitoneal cavity had decreased plasma PK values for C_{\max} , AUC_{0-Wk4} , AUC_{0-Wk8} and AUC_{0-Wk12} (1.26 $\mu\text{g/mL}$, 736 $\mu\text{g}^*\text{h/mL}$, 1513 $\mu\text{g}^*\text{h/mL}$ and 2130 $\mu\text{g}^*\text{h/mL}$, respectively); this participant had longer overall exposure to plasma cabotegravir, demonstrating increased values for t_{\max} (21 days), $t_{1/2}$ (124 days), AUC_{0-t} (4697 $\mu\text{g}^*\text{h/mL}$) and $AUC_{0-\infty}$ (5502 $\mu\text{g}^*\text{h/mL}$). Rectal fluid had higher exposures (C_{\max} and AUC_{0-Wk12}) and a shorter $t_{1/2}$ vs. cervical tissue, rectal tissue and cervicovaginal fluid.

Sex-based comparison of evaluable cabotegravir plasma PK parameters was performed using a mixed-effect linear model, with sex as a fixed effect and BMI as a continuous covariate. Differences in

TABLE 5 Summary of plasma PK parameters by sex after IM cabotegravir injection

PK parameter	Geometric mean (%CVb), range ^a	Geometric LS mean		Geometric LS mean (90% CI)
	Overall (n = 15)	Men (n = 8)	Women (n = 7)	Women vs. men
C _{max} , µg/mL ^b	5.04 (62), 1.2–11.2	6.26	3.94	0.63 (0.34–1.15)
t _{max} , median (range), d	6.9 (3.9–52.2)	–	–	–
AUC _{0–Wk4} , µg*h/mL	2141 (59), 650–5063	2285	1990	0.87 (0.47–1.62)
AUC _{0–Wk8} , µg*h/mL	3214 (40), 1106–6372	3342	3073	0.92 (0.60–1.42)
AUC _{0–Wk12} , µg*h/mL	3639 (36), 1442–6555	3710	3570	0.96 (0.64–1.44)
AUC _{0–t} , µg*h/mL	3992 (25), 2811–6547	–	–	–
AUC _{0–∞} , µg*h/mL	4172 (24), 2839–6597 ^c	3829	4547	1.19 (0.91–1.54)
t _{1/2} , d	19.1 (81), 9.1–148.6 ^c	14.6	25.1	1.72 (0.78–3.79)
KA _{LA} , h	0.0014 (97) ^c	–	–	–
Time > PA-IC ₉₀ , d ^d	78.3 (46)	66.5	94.3	–

AUC_{0–Wk4}, area under the concentration–time curve from time 0 to Week 4; AUC_{0–Wk8}, area under the concentration–time curve from time 0 to Week 8; AUC_{0–Wk12}, area under the concentration–time curve from time 0 to Week 12; AUC_{0–t}, area under the concentration–time curve from time 0 to the last quantifiable time point; AUC_{0–∞}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed concentration; %CVb, geometric coefficient of variation; IM, intramuscular; KA, absorption rate constant; LA, long acting; LS, least squares; PA-IC₉₀, in vitro protein-adjusted 90% maximal inhibitory concentration; PK, pharmacokinetics; t_{1/2}, apparent terminal phase half-life; t_{max}, time to first occurrence of maximum observed concentration.

^aExcept where noted for t_{max}.

^bThe lower limit of quantification was 0.025 µg/mL.

^cn = 14. ^dPA-IC₉₀ = 0.166 µg/mL.

TABLE 6 Tissue and fluid PK parameters after IM cabotegravir injection

Geometric mean, %CVb ^a	Cervical tissue (n = 7)	Cervicovaginal fluid (n = 7)	Rectal tissue (n = 13)	Rectal fluid (n = 12)
C _{max} , µg/mL ^b	0.81 (105)	0.55 (118)	0.50 (47)	3.27 (172)
Ratio to plasma C _{max} (95% CI)	0.20 (0.16–0.25)	0.13 (0.07–0.26)	0.10 (0.08–0.11)	0.62 (0.31–1.25)
t _{max} , median (range), d	7.0 (1.9–30.0)	7.0 (1.9–84.0)	7.0 (6.9–52.2)	7.0 (6.9–80.0)
AUC _{0–Wk4} , µg*h/mL	277 (104)	203 (126)	206 (57)	1170 (192)
Ratio to plasma AUC _{0–Wk4} (95% CI)	0.16 (0.09–0.26)	0.10 (0.04–0.25)	0.10 (0.09–0.11)	0.55 (0.23–1.28)
AUC _{0–Wk8} , µg*h/mL	365 (85)	282 (125)	287 (39)	1576 (203)
Ratio to plasma AUC _{0–Wk8} (95% CI)	0.15 (0.07–0.33)	0.09 (0.04–0.23)	0.11 (0.09–0.13)	0.49 (0.21–1.11)
AUC _{0–Wk12} , µg*h/mL	350 (79)	381 (108)	324 (55)	1345 (138)
Ratio to plasma AUC _{0–Wk12} (95% CI)	0.12 (0.04–0.38)	0.09 (0.02–0.33)	0.11 (0.09–0.14)	0.39 (0.14–1.07)
AUC _{0–t} , µg*h/mL	523 (77)	324 (121)	348 (36)	1841 (194)
AUC _{0–∞} , µg*h/mL ^c	696 (NA)	399 (100)	292 (35)	850 (43)
t _{1/2} , d ^c	15.14 (NA)	14.83 (79)	23.65 (23)	12.77 (4)
Time > PA-IC ₉₀ , d ^d	18.7 (190)	10.8 (203)	24.9 (75) ^e	33.1 (140) ^f

AUC_{0–Wk4}, area under the concentration–time curve from time 0 to Week 4; AUC_{0–Wk8}, area under the concentration–time curve from time 0 to Week 8; AUC_{0–Wk12}, area under the concentration–time curve from time 0 to Week 12; AUC_{0–t}, area under the concentration–time curve from time 0 to the last quantifiable time point; AUC_{0–∞}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed concentration; %CVb, geometric coefficient of variation; IM, intramuscular; KA, absorption rate constant; LA, long acting; NA, not available; PA-IC₉₀, in vitro protein-adjusted 90% maximal inhibitory concentration; PK, pharmacokinetics; t_{1/2}, apparent terminal phase half-life; t_{max}, time to first occurrence of maximum observed concentration.

^aExcept where noted for t_{max} and ratios to plasma parameters.

^bLower limits of quantification were 0.025, 0.0000625 and 0.000050 µg/mL for plasma, fluids and tissues, respectively.

^cn = 14.

^dPA-IC₉₀ = 0.166 µg/mL.

^en = 11.

^fn = 10.

TABLE 7 Summary of AEs

Preferred term, n (%)	Oral lead-in cabotegravir 30 mg once daily (n = 19)	Cabotegravir long-acting intramuscular injection 600 mg (n = 17)
Total AE ^a	10 (53)	17 (100)
Injection-site pain	—	15 (88)
Viral gastroenteritis	3 (16)	0
Increased blood glucose	2 (11)	0
Depression	0	2 (12)
Headache	0	2 (12)
Injection-site erythema	—	2 (12)
Insomnia	0	2 (12)
Palpitations	0	2 (12)
Pyrexia	0	2 (12)
Fatigue	1 (5)	1 (6)
Drug-related AE	0	15 (88)
Injection-site pain	—	14 (82)
Injection-site erythema	—	2 (12)
Gait disturbance	0	1 (6)
Injection-site induration	—	1 (6)
Injection-site pruritus	—	1 (6)
Injection-site reaction	—	1 (6)
Injection-site swelling	—	1 (6)
Insomnia	0	1 (6)
Myalgia	0	1 (6)

AE, adverse event.

^aAEs reported in >1 participant.

plasma cabotegravir exposures varied between men and women, with an increased C_{max} (6.26 vs. 3.94 $\mu\text{g}/\text{mL}$) and decreased $t_{1/2}$ (14.6 vs. 25.1 days) in men vs. women, respectively (Table 5).

3.3 | Safety

Eighty-six AEs were reported; all participants experienced at least 1 AE. Ten participants reported AEs during the oral lead-in phase; none were considered drug-related (Table 7). Seventeen participants reported AEs following IM injection. Excluding injection-site reactions (ISRs), the most frequently reported AEs were depression, headache, insomnia, palpitations and pyrexia (two participants for each event [12%]). Most AEs were grade 1 (60%) or 2 (33%) in intensity, and none led to study withdrawal. Drug-related AEs determined by the

investigator were reported by 15 participants following IM injection, including ISRs of pain (14 participants [82%]), erythema (two participants [12%]), and induration, pruritus, muscle cramp and swelling (one participant for each event [6%]). Most drug-related ISR AEs were of grade 1 intensity; all resolved (median duration, 6 d) and none led to study withdrawal. Two participants withdrew early prior to receiving IM injection based on investigator discretion due to missed study visits and loss to follow-up. No obvious trends in clinical laboratory abnormalities were noted.

Two participants reported a total of 11 serious AEs (SAEs) during the study. No deaths occurred during the study. One participant with a personal history of recurrent pregnancy loss reported pregnancy at her Week 52 visit and experienced a suspected spontaneous abortion no more than 2 days later. The second participant developed serotonin syndrome 9 weeks following injection that was related to 4 serotonergic drugs that the participant concomitantly received during the study. Due to subsequent prolonged hospitalization and consequent complications resulting in additional hospital-related SAEs, including upper extremity deep venous thrombosis, extensive intraparenchymal haemorrhage after anticoagulation for deep venous thrombosis, aphasia, dysphagia and urinary tract infection with leucocytosis, the participant was withdrawn from the study but monitored in long-term follow-up up to Week 52. Two additional SAEs reported by this participant were related to 2 subsequent hospitalizations, including a brief hospitalization for dyspnoea and subsequent hospitalization for post-traumatic stress disorder. After discharge, adjustments were made to the participant's anti-anxiety medications; the participant subsequently returned to the approximate baseline level of psychological functioning that existed prior to the first SAE being reported. All SAEs resolved except for intracerebral haemorrhage, which was still resolving at the last clinical follow-up visit. No SAEs reported in any study participant were considered to be study drug related.

4 | DISCUSSION

After a single ultrasound-guided IM injection of cabotegravir 600 mg, drug concentrations were quantifiable in plasma and in most tissue and fluid samples over 12 weeks postinjection from anatomical sites associated with sexual HIV-1 acquisition. Median plasma cabotegravir concentrations remained $\geq 4\times$ PA-IC₉₀ through Week 8, a clinical threshold associated with efficacy in study participants with HIV infection in phase II and III treatment trials and expected to be associated with efficacy when using the identical regimen for HIV-1 PrEP, and above PA-IC₉₀ through Week 12. All participants had plasma cabotegravir concentrations that were $\geq 4\times$ PA-IC₉₀ beginning as early as Day 3 through Week 4 and above PA-IC₉₀ through Week 8. Plasma cabotegravir concentrations were detectable in 12% of participants 52 weeks after the last injection, a finding similar to those observed in men following the final injection in ECLAIR (17%) and 52–60 weeks following the final injection in men in HPTN 077 (23%).^{22,29} However, most participants in this study had no measurable plasma cabotegravir concentrations 24 weeks after injection

(82%), similar to what was observed after the final injection in ECLAIR (81%). In the HPTN 077 study, cabotegravir LA 600 mg every 8 weeks yielded plasma cabotegravir trough concentrations at or above $1\times$ and $4\times$ PA-IC₉₀ targets in 95 and 80% of participants, respectively, for 8 weeks after the last injection; therefore, dosing every 8 weeks is likely to be sufficient to provide coverage for most participants regardless of absorption kinetics.²³

Of the anatomical sites sampled, median cabotegravir concentrations were highest in rectal fluid, followed by vaginal tissue, cervical tissue, rectal tissue and, lastly, cervicovaginal fluid. Peak concentrations occurred at approximately 7 days in all tissues and fluids. Median cabotegravir concentrations following a single 600-mg IM injection were greater than PA-IC₉₀ in cervical and rectal tissues through Week 4 and in rectal fluid through Week 8. Median cabotegravir concentrations were less than PA-IC₉₀ in all tissue and fluid samples at Week 12. At Week 4, 71 and 77% of participants had cabotegravir concentrations above PA-IC₉₀ in cervical and rectal tissue, respectively, consistent with a prior study that demonstrated lower absolute tissue concentrations relative to plasma.²⁶ At Week 12, only a small proportion of participants had cabotegravir concentrations above PA-IC₉₀ in cervical and rectal tissue and cervicovaginal fluid. Median concentration–time profiles in plasma, tissues and fluids had comparable slopes. Strong correlations (adjusted $R^2 > 0.75$) were observed between plasma and time-matched cervical, vaginal and rectal tissue cabotegravir concentrations. By contrast, correlations were weaker between plasma and cervicovaginal fluid (adjusted $R^2 = 0.60$) and rectal fluid (adjusted $R^2 = 0.44$), probably due to increased variability in fluid concentration between participants and possibly from variability in active and passive transport of drug from cells into fluid. Rectal fluid cabotegravir concentrations at Week 4 in 2 participants (1 man, 1 woman) were $>30\times$ median concentration ($0.66 \mu\text{g/mL}$), potentially contributing to its lower correlation coefficient. The slope of the log–log linear regression for all tissues and fluids was approximately 1, indicating a direct correlation with plasma concentrations. Overall, cabotegravir concentrations were the most variable in rectal fluid, followed by plasma and cervicovaginal fluid, with tissues demonstrating much lower variability between participants.

Distribution of cabotegravir into tissues and fluids was similar between oral dosing and IM injection. Furthermore, tissue-to-plasma ratios after a single 600-mg IM injection were similar to those observed following cabotegravir 400-mg IM split or nonsplit injections in the 114433 study (Table 4).²⁶ Taken together, these results suggest that distribution of cabotegravir into tissues associated with HIV-1 sexual transmission sites remains consistent and declines in a parallel fashion, regardless of dose, dose splitting or administration. Tissue-to-plasma ratios following a single cabotegravir 600-mg injection were generally low, with values ≤ 0.16 across all tissues. Cabotegravir 600 mg every 8 weeks starting 4 weeks after an initial loading injection demonstrated efficacy for PrEP in HPTN 083 and HPTN 084,^{17,24} suggesting that cabotegravir concentrations in tissues, plasma or both, similar to those observed here sufficiently confer a high rate of protection. Because HPTN 083 and HPTN 084 did not involve compartmentalized collections, direct

comparisons to this study can be made for plasma alone. Understanding cabotegravir PK and pharmacodynamics within genital tract compartments in study participants would assist in interpreting PrEP effectiveness.

Cabotegravir LA exhibits absorption-limited *flip-flop* kinetics.³¹ Plasma cabotegravir PK parameters were consistent with results from previous studies.^{22,23} Plasma PK exposures (C_{max} and $\text{AUC}_{0-\text{Wk}12}$) were similar to those following cabotegravir 800 mg IM split injection in ECLAIR despite the lower dose and nonsplit injection in the present study.²² Geometric mean of the cabotegravir LA absorption constant observed in participants with higher absorption rate was similar between the current study (0.0014) and ECLAIR (0.0011).³² The higher C_{max} , which is reflective of absorption rate, and lower $t_{1/2}$ observed in men vs. women in the present study was consistent with differing sex-specific PK parameter results observed in HPTN 077.^{23,33} Cabotegravir LA for PrEP demonstrated superior efficacy among men and transgender women in HPTN 083 and cisgender women in HPTN 084 using an every-8-week dosing regimen of the identical dose used in this study, indicating that the observed sex-specific PK differences are unlikely to impact the rate of protection.^{17,24} It is unknown whether ultrasound-guided IM delivery of cabotegravir using a longer needle to ensure deep gluteal IM injection in this study, rather than using standard 3.8- or 5.1-cm needle lengths with typical free-hand IM gluteal injection in clinical studies, might have impacted the rate of drug absorption from the injection site. Achieving true IM injection is challenging, even with direct ultrasound guidance. However, all participants maintained plasma cabotegravir concentrations $\geq 4\times$ PA-IC₉₀ through 4 weeks following a single 600-mg IM injection. A loading dose strategy with every-8-week dosing, in which participants receive initial loading injections at Weeks 0 and 4 before maintenance injections every 8 weeks starting at Week 12, achieved cabotegravir trough concentrations $>4\times$ PA-IC₉₀ in 95% of participants in a phase IIIb HIV-1 treatment study and would be expected when using this identical regimen for HIV-1 PrEP.³⁴ One participant who received an injection into the retroperitoneal cavity exhibited plasma exposures that continued to decrease through Week 12 postinjection but were higher overall, with a prolonged $t_{1/2}$ compared with participants who received injections into the gluteal muscle. However, in routine settings, it is unlikely that using a shorter needle (generally 3.8 cm) to administer an IM injection, which is recommended in clinical practice, would reach the depth required for inadvertent drug deposition into the retroperitoneal cavity. Data are limited regarding cabotegravir LA PK following confirmed injection maladministration.

This study has some limitations. The sample size was small and was further reduced by 3 withdrawals and 2 participants who did not undergo tissue PK sampling. The study population was limited to a small overall range of BMI ($18.5\text{--}35.0 \text{ kg/m}^2$) to reduce PK variability and better permit interpretation of the results. Thus, extrapolation of these results to individuals with higher BMIs may be difficult. Cabotegravir concentrations in tissues and fluids could be overestimated due to possible blood contamination while collecting samples. Tissue cabotegravir concentrations were evaluated

after tissue homogenization and may not be reflective of total tissue concentrations. Because cabotegravir protein binding data are only available for plasma, the tissue and fluid cabotegravir concentration ratios are not adjusted for protein binding. These data reflect cabotegravir PK in plasma, tissues and fluids following an ultrasound-guided injection, which may differ when administered as a free-hand gluteal injection without imaging guidance as intended in the clinic.

Following a single IM LA injection, cabotegravir was detected in tissues and fluids of anatomical sites associated with sexual HIV-1 transmission. Tissue and fluid cabotegravir concentrations were proportional to plasma over time, and time-matched tissue concentrations were strongly correlated with plasma concentrations. Plasma PK parameters and tissue-to-plasma ratios were similar to those observed in previous studies. Given the apparently sufficient distribution of cabotegravir into mucosal tissues and fluids related to sexual HIV-1 transmission, this study provides data to inform the conduct and interpretation of future cabotegravir PrEP studies.

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CONTRIBUTORS

All authors have: made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published; have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions

related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

STUDY PI DECLARATION

The authors confirm that the PI for this paper is Craig Hendrix, MD and that he had direct clinical responsibility for patients.

ETHICS APPROVAL

The study was conducted at Johns Hopkins Hospital (Baltimore, MD, USA) and the University of Pittsburgh Medical Center (Pittsburgh, PA, USA) from 27 February 2017 to 25 July 2019 in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and the principles of the Declaration of Helsinki. Johns Hopkins Medicine Institutional Review Board (Baltimore, MD, USA) and Western Institutional Review Board (Puyallup, WA, USA) approved the study protocol and conduct.

PATIENT CONSENT

All participants provided written informed consent and could withdraw from the study at any time.

CLINICAL TRIAL REGISTRATION

NCT02478463.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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