Model-Based Comparison of Cabotegravir Pharmacokinetics Following Thigh and Gluteal Injections

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Introduction

- Cabotegravir (CAB) long-acting (LA) intramuscular (IM) gluteal injections dosed once every 2 months (Q2M) are approved for HIV-1 pre-exposure prophylaxis.[1]
- CAB LA plus rilpivirine (RPV) LA IM gluteal injections dosed monthly (QM) or Q2M is approved for HIV-1 treatment.[2]
- The *vastus lateralis* (lateral thigh) muscle is a potential alternative site of administration for injection in cases of fatigue or intolerability of the gluteal injection site, inaccessibility of the gluteal muscle (e.g. buttock implants or insufficient gluteal mass), or physical inconvenience (e.g. prior to prolonged sitting).
- Previous data in 14 healthy volunteers receiving single CAB + RPV LA IM thigh injections in the Phase 1 study 208832 (NCT04371380) suggested faster CAB absorption with thigh vs. gluteal injections.[3]
- Further investigation of short-term repeat IM thigh administration of CAB + RPV LA in 118 participants with ≥3 years' experience of gluteal injections during the ongoing Phase 3b ATLAS-2M study (NCT03299049) supported the potential of rotational/short-term CAB + RPV LA IM lateral thigh administration within an established gluteal regimen.[4]
- This analysis aimed to characterize CAB pharmacokinetics (PK) and its association with demographics following thigh administration in comparison with gluteal administration using population PK (PPK) analysis.

Methods

- Fourteen participants who were HIV-negative and received a 600 mg single thigh injection in the Phase 1 study 208832 and 118 participants who were HIV-positive and received thigh injections (400 mg QM × 4 or 600 mg Q2M × 2) after ≥3 years of gluteal injections in the Phase 3b ATLAS-2M study provided CAB concentrations for the analysis.

PPK Model

- An established oral + gluteal PPK model[5] was modified (**Figure 1**) by adding the thigh injection depot compartment with the absorption rate constant of thigh injection (KA_{thigh}) and relative bioavailability of thigh injection relative to gluteal injection (F_{thigh}), with their respective interindividual variability.
- The PPK model was fit to PK data following both gluteal and thigh injections, enabling within-person comparison in ATLAS-2M participants.
- All parameters were fixed except for KA_{thigh} and F_{thigh}.
- If (1) a strong correlation was observed between the absorption rate constant of gluteal injection ($KA_{gluteal}$) and KA_{thigh}, and (2) the covariate relationships on $KA_{gluteal}$ and KA_{thigh} were deemed similar, it would be considered preferable to model KA_{thigh} as a function of $KA_{gluteal}$ using various linear functions and power functions. Otherwise, covariate relationships would be evaluated through a forward addition and backward elimination approach.
- The adequacy and predictive performance of the final model was assessed using prediction-corrected visual predictive checks (pcVPCs) of 500 replications in addition to standard goodness-of-fit plots.

Simulation

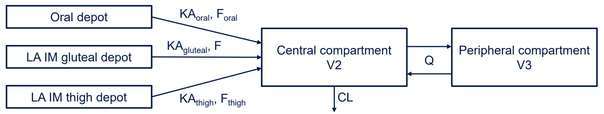
- CAB PK profiles following chronic or intermittent thigh injections administered QM and Q2M were simulated in 5000 virtual participants with 25% females, representing the treatment population observed in Phase 3 treatment studies, and compared with gluteal injections.
- Dosing:
  - QM regimen: 600 mg (3 mL) CAB LA IM (initiation injection) followed by 400 mg (2 mL) CAB LA IM (maintenance dose) QM starting 1 month after the initiation injection. A total of 12 injections per year.
  - Q2M regimen: 600 mg (3 mL) CAB LA IM (initiation injection) followed by 600 mg (3 mL) CAB LA IM (maintenance dose) Q2M starting 1 month after the initiation injection. A total of seven injections for the first year and six injections for subsequent years.
- Intermittent schedules were one-thigh-one-gluteal (one thigh injection followed by one gluteal injection, with this pattern continuing thereafter), with equivalent schedules simulated for two-thigh-two-gluteal and three-thigh-three-gluteal.
  - One-thigh-N-gluteal (N>1) is assumed to be covered by one-thigh-one-gluteal. Two-thigh-N-gluteal (N>2) is assumed to be covered by two-thigh-two-gluteal.

CAB Plasma Concentration Benchmark

- The PK benchmark was that 95% of participants maintain concentrations >0.45 µg/mL, corresponding to the 5th percentile of observed CAB trough concentrations following the gluteal initiation injection in Phase 3 studies.

Population PK simulations demonstrate the potential for chronic thigh injections QM and intermittent thigh injections both QM and Q2M of up to 2 consecutive thigh injections but not for chronic Q2M thigh injections

Figure 1. PPK Model



CL, systemic clearance; F, absolute bioavailability of LA IM gluteal injection; F_{oral}, absolute oral bioavailability; F_{thigh}, absolute bioavailability of LA IM thigh injection; IM, intramuscular; $KA_{gluteal}$, absorption rate constant of LA IM gluteal injection; KA_{oral}, absorption rate constant of oral tablet; KA_{thigh}, absorption rate constant of LA IM thigh injection; LA, long-acting; PPK, population pharmacokinetics; Q, intercompartmental clearance; V2, volume of distribution of central compartment; V3, volume of distribution of peripheral compartment.

Results

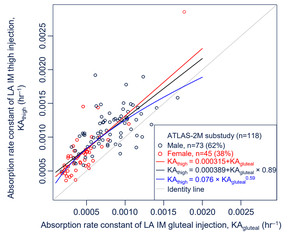
Table 1. Summary of Demographics and Key Clinical Variables

	Study 208832 and thigh PK substudy of ATLAS-2M	Model-building data set of oral + gluteal model
Number of participants, n	132	2694
Number of concentrations, n	3481	34,850
Age (years), median (range)	43 (20–67)	36 (18–83)
Body weight (kg), median (range)	75.8 (50.1–129.7)	76.0 (41.0–168.3)
BMI (kg/m^2), median (range)	25.4 (17.9–50.9)	25.4 (15.3–69.5)
Female (sex at birth), n (%)	50 (38)	742 (28)
PWH	118 (89)	1958 (73)
Smoking status		
Never smoked	75 (57)	983 (36)
Former smoker	21 (16)	329 (12)
Current smoker	36 (27)	703 (26)
Not current smoker*	0 (0)	120 (4)
Unknown	0 (0)	559 (21)

*"Not current smoker" could be "never smoked" or "former smoker."
BMI, body mass index; PK, pharmacokinetics; PWH, people with HIV-1.

- In total, 1249 concentrations from 366 thigh injections, 1998 concentrations from 1618 gluteal injections, and 234 concentrations from oral administration were included from study 208832 and the thigh PK substudy of ATLAS-2M (**Table 1**).
  - All but three thigh injections (0.8%) were administered using a needle length of 1.5 inches, and therefore the needle length data were deemed insufficient for evaluating needle length as a covariate on thigh PK parameters.

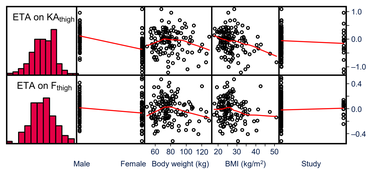
Figure 2. Intraindividual Correlation of *Post Hoc* Estimates of KA_{thigh} and $KA_{gluteal}$



Red, black and blue solid lines represent regression fitting of combined male and female data (separate regression fitting of male or female data alone is not shown).
IM, intramuscular; $KA_{gluteal}$, absorption rate constant of LA IM gluteal injection; KA_{thigh}, absorption rate constant of LA IM thigh injection; LA, long-acting.

- *Post hoc* estimates for KA_{thigh} were correlated with, albeit faster than, matched $KA_{gluteal}$, with a Pearson correlation coefficient (r) of 0.766 in the 118 participants who received both gluteal and thigh injections (**Figure 2**).
- This intraindividual correlation between $KA_{gluteal}$ and KA_{thigh} was strong in both males (r=0.598) and females (r=0.858) (sex at birth) and could be described similarly well by linear functions and power functions.

Figure 3. Random Effects (ETA) of Thigh PK Parameters vs. Covariates



Red histogram shows the distribution of ETA. Red solid line represents loess smoother. "Study" refers to the thigh PK substudy of ATLAS-2M (left) or Phase 1 study 208832 (right).
BMI, body mass index; ETA, random effects; F_{thigh}, relative bioavailability of thigh injection relative to gluteal injection; IM, intramuscular; KA_{thigh}, absorption rate constant of LA IM thigh injection; LA, long-acting; PK, pharmacokinetics.

- Similar to gluteal administration, KA_{thigh} was associated with sex at birth and body mass index (BMI), being lower in females vs. males and decreasing with higher BMI values (**Figure 3**).
- KA_{thigh} was not associated with study; F_{thigh} was not associated with any covariate evaluated.

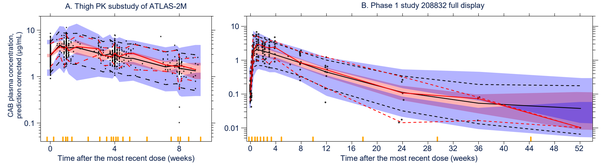
Table 2. Parameter Estimates of the Final Model

	Parameter	Estimate	RSE (%)	IIV (%)	RSE of IIV (%)	Shrinkage (%)
Final model	KA_{thigh} – $KA_{gluteal}$ (hr^{-1})	0.0002527	20.7			
	KA_{thigh} (hr^{-1})			41.6	9.2	24.6
	F_{thigh}	0.899	2.9	22.9	10.8	27.5
oral + gluteal model for comparison	KA_{oral} (hr^{-1})	1.41	3.6	92.0	4.4	76.3
	$KA_{gluteal}$ (hr^{-1})	0.000728	1.7	54.1	2.3	12.7
	F_{oral}	0.783	0.8	17.5	5.5	46.2

F_{oral}, relative bioavailability of oral tablet relative to LA IM gluteal injection; F_{thigh}, relative bioavailability of thigh injection relative to gluteal injection; IIV, interindividual variability; IM, intramuscular; KA_{oral}, absorption rate constant of oral tablet; $KA_{gluteal}$, absorption rate constant for LA IM gluteal injection; KA_{thigh}, absorption rate constant for LA IM thigh injection; LA, long-acting; RSE, relative standard error.

- KA_{thigh} was correlated with and was generally faster than $KA_{gluteal}$, as described by the additive linear relationship: $KA_{thigh} = KA_{gluteal} + 0.000253$ hr^{-1} (**Table 2**).
- The terminal half-life of thigh administration was 26% (male) and 39% (female) shorter than for gluteal administration, an observation driven by the faster KA_{thigh} vs. $KA_{gluteal}$.
- The bioavailability of thigh injection was estimated to be 89.9% of gluteal injection.
- The goodness-of-fit plots from the final model demonstrated good agreement between predicted and observed concentrations, with no apparent bias in residual.

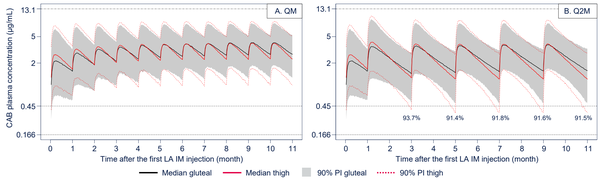
Figure 4. pcVPC of the Final Model for Predicting PK Data Following Thigh Injections



Prediction-corrected observations: Black circles = prediction-corrected observed data, red solid lines = medians, and red dashed lines = 5th and 95th percentiles. Simulated percentiles: Shaded regions represent the 95% CIs of the simulated values of the predicted medians (pink), and 5th and 95th percentiles (blue). Black lines represent medians of the simulated values of the predicted medians (black solid lines), and 5th and 95th percentiles (black dashed lines). Yellow bars on the x axes represent boundaries between bins.
CAB, cabotegravir; CI, confidence interval; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetics.

- Overall, the model predictions adequately captured the observed concentration vs. time points and trends within the 90% prediction interval of the simulated values, including for the thigh PK substudy of ATLAS-2M (**Figure 4A**) and for the terminal phase of the Phase 1 study 208832 (**Figure 4B**).
- The prediction-corrected observed concentrations within 4 weeks post injection in study 208832 appeared to be underpredicted, although the prediction-corrected observed 5th and 95th percentiles both fell within the 95% confidence intervals.

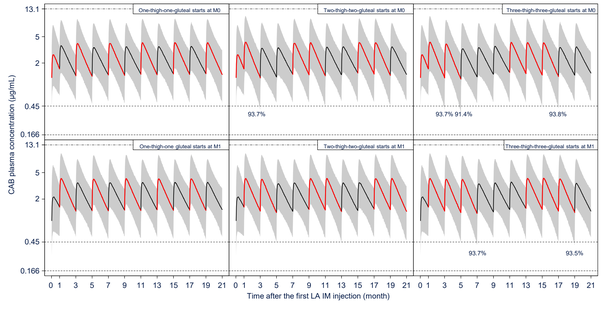
Figure 5. Simulated Chronic CAB QM (A) and Q2M (B) Administration to the Lateral Thigh and Gluteal Muscles



Simulations were performed in a population of 25% females. Percentages represent the proportions of simulated participants with C_{trough} >0.45 µg/mL at the time points for which the percentage was predicted to be <95%. Reference lines: 0.166 µg/mL = PA-IC_{90}; 0.45 µg/mL = 5th percentile of observed C_{trough} following the gluteal initiation injection in Phase 3 treatment studies; 13.1 µg/mL = median C_{max} following daily administration of oral CAB 60 mg observed in study LAI116482 (LATTE) without dose-limiting toxicity.
CAB, cabotegravir; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration at the end of the dosing interval; gluteal, gluteal injection; IM, intramuscular; LA, long-acting; PA-IC_{90}, protein-adjusted 90% maximal inhibitory concentration; PI, prediction interval; Q2M, every 2 months; QM, monthly; thigh, thigh injection.

- The PK benchmark was maintained following chronic thigh and gluteal QM injections (**Figure 5A**) but not following chronic Q2M thigh injections (**Figure 5B**).

Figure 6. Simulated Intermittent CAB Q2M Administration to the Lateral Thigh and Gluteal Muscles



Simulations were performed in a population of 25% females. Percentages represent the proportions of simulated participants with C_{trough} >0.45 µg/mL at the time points for which the percentage was predicted to be <95%. Reference lines: 0.166 µg/mL = PA-IC_{90}; 0.45 µg/mL = 5th percentile of observed C_{trough} following the gluteal initiation injection in Phase 3 treatment studies; 13.1 µg/mL = median C_{max} following daily administration of oral CAB 60 mg observed in study LAI116482 (LATTE) without dose-limiting toxicity.
CAB, cabotegravir; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration at the end of the dosing interval; gluteal, following gluteal injection; IM, intramuscular; LA, long-acting; M, month; PA-IC_{90}, protein-adjusted 90% maximal inhibitory concentration; PI, prediction interval; Q2M, every 2 months; QM, monthly; thigh, thigh injection.

- The PK benchmark was maintained following alternating thigh and gluteal injections for both QM and Q2M regimens (**Figure 6**; QM not shown).

Conclusions

- The absorption rate of thigh injection was lower in females than males and decreased with increasing BMI.
- Absorption following thigh injection was correlated with, and generally faster than, gluteal injection and is best described by the additive linear relationship: $KA_{thigh} = KA_{gluteal} + 0.0002527$ hr^{-1}.
- The terminal half-life of thigh injection was 26% and 39% shorter than that of gluteal injection for males and females, respectively.
- The bioavailability of thigh injection was estimated to be 89.9% of gluteal injection.
- Simulations demonstrate the potential for chronic thigh injections QM and intermittent thigh injections both QM and Q2M of up to two consecutive thigh injections, but not for chronic Q2M thigh injections.
- CAB + RPV LA thigh administration has not been approved by regulatory agencies, as long-term safety and efficacy are unknown.

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References: 1. ViiV Healthcare. Cabotegravir (Apretude) PI. USA, 2021. **2.** ViiV Healthcare. Cabotegravir (Cabenuva) PI. USA, 2021. **3.** Han K, et al. *Antimicrob Agents Chemother.* 2024;68(1):e0078123. **4.** Felizarta F, et al. CROI 2023 (Poster 519); **5.** Han K,et al. *Br J Clin Pharmacol.*2022;88(10):4607–4622.

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