Time to Onset of Protection with *Apretude* When Used as Pre-Exposure Prophylaxis

Summary

- The time to onset of protection after administration of *Apretude* (long-acting cabotegravir [CAB LA]) is unknown.
- When administered with or without the oral lead-in (OLI), the median plasma concentration of cabotegravir was predicted to be >4x the protein-adjusted (PA)-IC_{90} (>0.664 µg/mL) within 1 day.[1]
    - Plasma concentrations of cabotegravir (without the administration of the OLI) are predicted to be >4x the PA-IC_{90} in 90% of patients by approximately 3 days after injection and in 95% of patients by approximately 1 week (regardless of sex assigned at birth).[1]
- The correlate of protection for CAB LA is not known. Partitioning of cabotegravir into potential target tissues results in concentrations that range from 8 to 32% of plasma.[2,3]
- Important Safety Information and Boxed Warning can be found in the Prescribing Information and can also be accessed from the Our HIV Medicines section of viivhealthcare.com/us.

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The time to onset of protection after administration of CAB (oral and LA) is unknown. The oral CAB lead-in was used to evaluate for tolerability prior to initiation injections. No data are available currently from HPTN 083 and 084 to estimate time from initiation of CAB LA injections to maximal protection against HIV infection.

Data from pre-clinical studies in male and female macaques suggested that CAB LA administered prior to viral challenge could prevent a high percentage of transmissions of simian HIV (SHIV) administered by the penile, intrarectal, intravaginal, or intravenous routes.[4-8] In these studies, plasma cabotegravir trough concentrations >1x the PA-IC_{90} (>0.166 µg/mL), and particularly >4x the PA-IC_{90}, were associated with protection from infection.

The dose used in HPTN 083 and 084 was established in HPTN 077.[9-11] In this trial, all participants had plasma cabotegravir trough concentrations >1x the PA-IC_{90} and a high percentage of participants were >4x the PA-IC_{90}, particularly with repeat dosing. After the 5th injection, 97% of women and 89% of men had plasma trough concentrations >4x the PA-IC_{90}.

Population pharmacokinetic modelling was undertaken to predict the plasma concentrations of cabotegravir following administration of 4 weeks of oral cabotegravir 30 mg once-daily followed by a single dose of CAB LA 600 mg versus administration of a single dose of CAB LA 600 mg alone.[1]

As can be seen in Table 1, the median plasma concentration of cabotegravir is predicted to exceed 4x the PA-IC_{90} (0.664 µg/mL) within 1 day of administration of a single dose of CAB LA 600 mg (see red text in table).[1]

Plasma concentrations of cabotegravir (without the administration of the OLI) are predicted to be above 0.664 µg/mL in 90% of patients by approximately 3 days, and in 95% of patients by approximately 1 week, after injection.[1]

Table 1. Predicted Median (5th, 95th percentile) Cabotegravir Plasma Concentrations Following IM Injection[1]

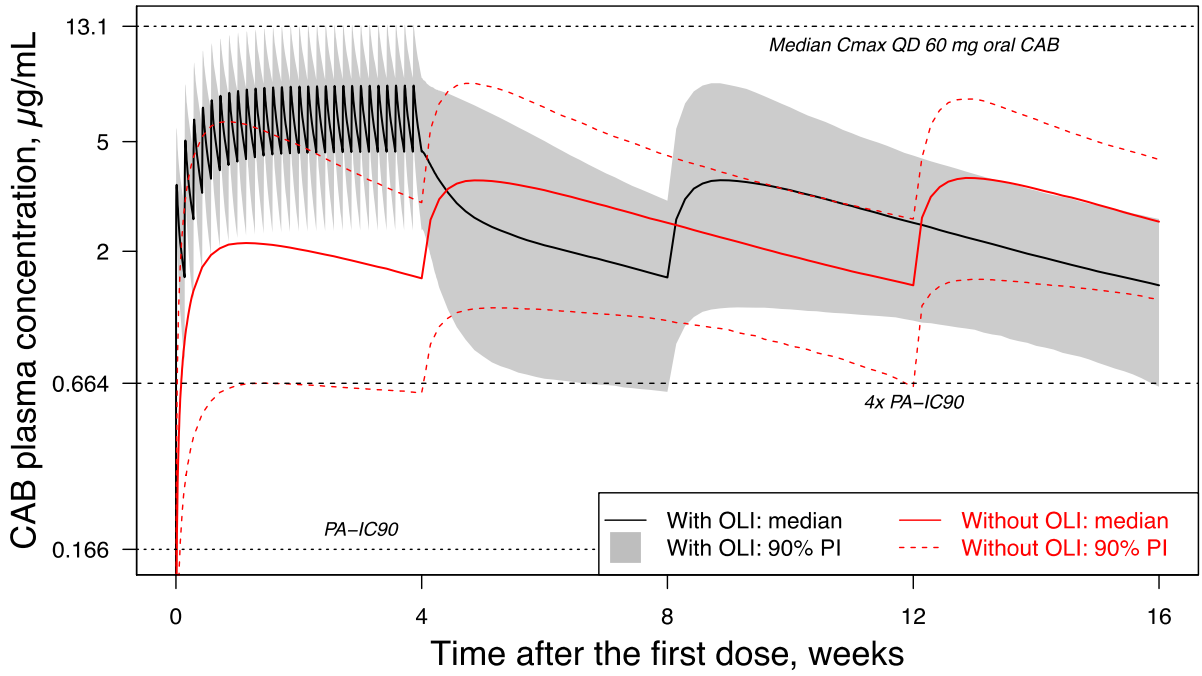
Time Since Injection	CAB LA with OLI (µg/mL)	CAB LA without OLI (µg/mL)
0.5 hours	2.08 (1.24, 3.42)	-
1 hours	2.99 (1.79, 4.86)	-
2 hours	3.43 (2.08, 5.48)	-
1 day	1.59 (0.82, 2.74)	0.921 (0.28, 2.78)
2 days	2.57 (1.37, 4.41)	1.40 (0.42, 4.20)
1 week	4.20 (2.26, 7.39)	2.08 (0.66, 5.62)
4 weeks	4.58 (2.40, 8.39)	1.56 (0.63, 2.96)*
8 weeks	1.57 (0.63, 2.98)*	-

Red text indicates the median plasma concentration of cabotegravir is predicted to exceed 4x the PA-IC_{90} (0.664 µg/mL) within 1 day of administration of a single dose of CAB LA 600 mg

*4 weeks after first initiation injection

IM = intramuscular; CAB LA = long-acting cabotegravir; OLI = oral lead-in

Figure 1. Predicted Plasma Concentration Versus Time Profile of Cabotegravir After Administration of CAB LA, With or Without the Oral Lead-In[1]



It is important to note that the correlate of protection is not known. Median concentrations in potential target tissues (e.g., cervical tissue, rectal tissue, etc.) range from 8 to 32% of plasma depending on the tissue.[2,3]

This information is scientific and non-promotional in nature and is not intended for further distribution.

This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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