Time to Onset of Protection with Long-Acting Cabotegravir When Used as Pre-Exposure Prophylaxis

Summary

- The time to onset of protection after administration of long-acting cabotegravir (CAB LA) is unknown.
- The dose used in HPTN 083 and 084 was predicted to achieve plasma cabotegravir trough concentrations of >4x the protein-adjusted (PA)-IC_{90} (0.664 µg/mL) of wild-type HIV-1 in 80% of subjects and >1x PA-IC_{90} (0.166 µg/mL) in 95% of subjects.
- When CAB LA is administered without the oral lead-in (OLI), the median plasma concentrations of cabotegravir are predicted to be above 0.664 µg/mL within 1 day.
    - Plasma concentrations of cabotegravir are predicted to be above 0.664 µg/mL in 90% of subjects by approximately 3 days after injection and in 95% of subjects by approximately 1 week.
- It is important to note that the correlate of protection is not known. Median concentrations of cabotegravir in potential target tissues (e.g., cervical tissue, rectal tissue, etc.) range from 8 to 32% of plasma depending on the tissue.
- 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 LA is unknown. 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.

The dose used in HPTN 083 and 084 was predicted to achieve plasma cabotegravir trough concentrations of >4x the PA-IC_{90} (0.664 µg/mL) of wild-type HIV-1] in 80% of subjects and >1x PA-IC_{90} (0.166 µg/mL) in 95% of subjects.[1-3] These targets were based on data from studies in male and female macaques that suggested that CAB LA administered prior to viral challenge can prevent a high percentage of transmissions of simian HIV (SHIV) administered by the penile, intrarectal, intravaginal, or intravenous routes.[4-8]

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

Plasma concentrations of cabotegravir (without the administration of the OLI) are predicted to be above 0.664 µg/mL in 90% of subjects by approximately 3 days, and in 95% of subjects by approximately 1 week, after injection.[9]

The plasma concentration versus time profiles of cabotegravir after repeated dose of CAB LA, with and without the OLI, are visually represented in Figure 1 below.[9]

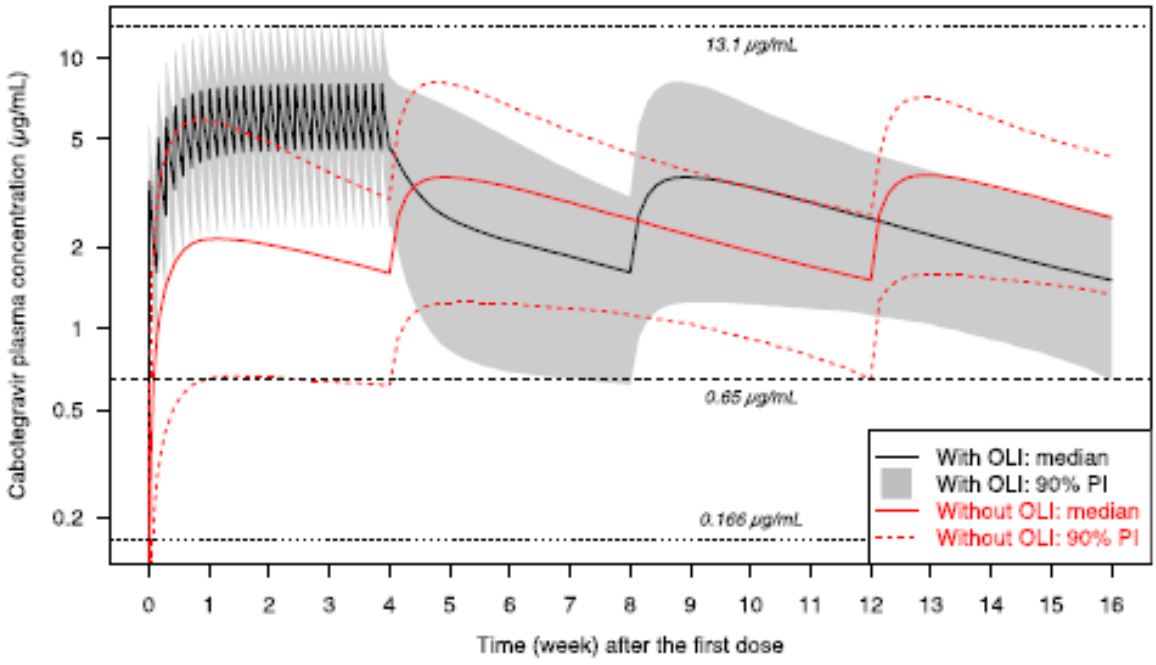
Table 1. Predicted Median (5th, 95th percentile) Cabotegravir Plasma Concentrations Following IM Injection[9]

Time Since First Dose of Oral or Long-Acting CAB	CAB Concentrations After 4 Weeks of Oral CAB Followed by a Single Dose of CAB LA (µg/mL)	CAB Concentrations Following a Single Dose of CAB LA Only (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)*	-

Shaded areas above indicate predicted median cabotegravir concentrations following administration of a single dose of CAB LA 600 mg. The * indicates the plasma concentration 4 weeks after the administration of CAB LA.

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[9]



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.[10,11] For more information on the distribution of cabotegravir into tissues click here.

Some information contained in this response is outside the approved Prescribing Information. This product is not approved for the use described. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order 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. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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