Management of Underdosing During the Administration of Long-Acting Cabotegravir and Rilpivirine Every-2-Months

Summary

- In the setting of administration of 2 mL of long-acting cabotegravir and/or rilpivirine or significant leakage of one or both medicines from the injection site an additional full dose (3 mL) of one or both medicines is recommended.
- Administration of a corrective dose as soon as possible is recommended to minimize the risk of obtaining plasma concentrations of cabotegravir and rilpivirine below those expected if 3 mL of each medicine had been administered.
- The systemic exposure after a corrective dose is expected to remain below the respective safety thresholds for cabotegravir and rilpivirine, even if two 3 mL injections of both drugs are given on the same day.
- The HCP may consider conducting a plasma HIV-1 RNA test at the first and second injection visits after the underdosing if the corrective action is not taken immediately.
- Important Safety Information can be found in the Prescribing Information and can also be accessed from Our HIV Medicines.

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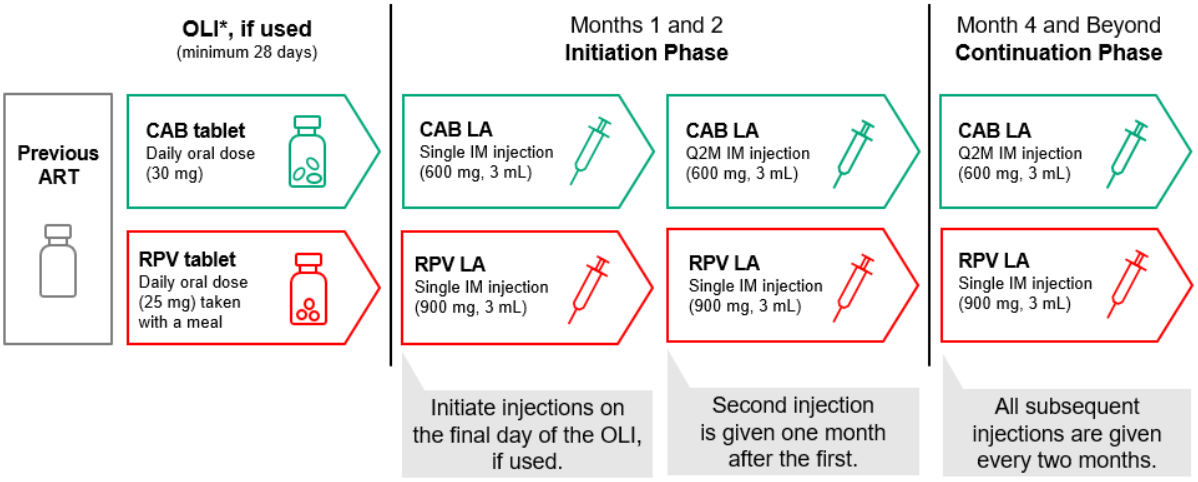
A schematic of how to initiate treatment with long-acting cabotegravir and rilpivirine (CAB + RPV LA) administered every-2-months can be found in Figure 1 below.[1]

After initiation, CAB + RPV LA should be administered every-2-months on the same date (the target date).[1] Injections may be given 7 days before or 7 days after the target date.

Figure 1. Schematic of How to Initiate Every-2-Month CAB + RPV LA[1]



*The optional OLI may be used to assess the tolerability of cabotegravir and rilpivirine prior to initiation of CAB + RPV LA

CAB + RPV LA = long-acting cabotegravir and rilpivirine; OLI = oral lead-in; ART = antiretroviral therapy; IM intramuscular; Q2M = every-2-months

Scenario: Accidental administration of 2 mL of long-acting cabotegravir and/or rilpivirine as initiation injection(s) or a partial dose was delivered due to significant medication leakage from the injection site[2]

Corrective Action

- Administer 3 mL of long-acting cabotegravir and/or rilpivirine as soon as possible.
- If only 1 of the medicines was underdosed and corrected, keep the target treatment date the same
- If both medicines were underdosed and corrected, resetting the target treatment date is an option

The systemic exposure after a corrective dose is expected to remain below the respective safety thresholds for cabotegravir and rilpivirine, even if two 3 mL injections of both drugs are given on the same day.

Cabotegravir

The short-term safety threshold of 22.5 µg/mL was established after administration of a supratherapeutic dose of oral cabotegravir 150 mg (30 mg x5 tablets) administered every 12 hours for 3 doses.[3] At this level of exposure, there were no serious or significant adverse events or deaths reported.

Administration of 1200 mg of CAB LA, twice the dose approved to be administered every 2 months, is predicted to yield an upper bound of the 90% prediction interval of 15.8 µg/mL.[2] This is less than the safety threshold cited above as well as similar to the upper bound of the 95% confidence interval associated with the geometric mean plasma concentration (15 µg/mL) but below the highest maximum concentration (Cmax) achieved (18.5 µg/mL) with oral cabotegravir 60 mg administered once-daily in a phase 2 treatment trial (LATTE).

Rilpivirine

The highest approved dose of RPV LA is 900 mg. A single loading dose of 1200 mg was studied in healthy participants.[4] All adverse events were mild to moderate and injection site reactions were most common.

No simulations of over or underdosing have been conducted.[2] During clinical development, no safety parameters were found to be associated with rilpivirine plasma concentrations except for QT prolongation and only at supratherapeutic doses of oral rilpvirine.

The mean steady-state Cmax of rilpivirine (168 ng/mL) after administration of RPV LA 900 mg every 8 weeks was 3.7- and 9.9-fold lower than the mean steady-state Cmax associated with supratherapeutic doses of oral rilpivirine 75 mg and 300 mg once daily, respectively.[2] The mean steady-state Cmax of oral rilpivirine 25 mg once-daily was 220 ng/mL and was not associated with any clinically relevant effect of the corrected QT interval.

Additional Follow-Up[2]

In a case where the corrective action is delayed, consider conducting a plasma HIV-1 RNA test at the first and second injection visits after the underdosing.

REFERENCES

1. ViiV Healthcare Local Label.
2. Data on File. 2021N478357.
3. Lou Y, Buchanan AM, Chen S, et al. Effect of Cabotegravir on Cardiac Repolarization in Healthy Subjects. *Clin Pharmacol Drug Dev*. 2016;5(6):509-516. doi:http://dx.doi.org/10.1002/cpdd.272.
4. Spreen W, Williams P, Margolis D, et al. Pharmacokinetics, safety, and tolerability with repeat doses of GSK1265744 and rilpivirine (TMC278) long-acting nanosuspensions in healthy adults. *J Acquir Immune Defic Syndr*. 2014;67(5):487-492. doi:http://dx.doi.org/10.1097/QAI.0000000000000365.