# Intramuscular cabotegravir/ rilpivirine concentrations after switching from efavirenz

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## BACKGROUND

Intramuscular cabotegravir and rilpivirine (IM CAB/RPV) are used once viral load suppression is achieved.

While CAB/RPV are substrates of UGT1A1/CYP3A4, efavirenz induces these enzymes therefore switching from an efavirenz containing regimen to IM CAB/RPV could possibly result in a time window with suboptimal drug levels.

## AIM

To simulate the initial IM CAB/RPV concentrations after stopping efavirenz using physiologically based pharmacokinetic (PBPK) modelling.

## METHODS

The *in-house* PBPK model implemented with a mechanistic intramuscular framework was validated against clinically observed data [1]. The model was considered validated if the predictions were within 2-fold of observed clinical data.

**VALIDATION STEP#1**

The model was verified for cabotegravir, rilpivirine, and efavirenz separately

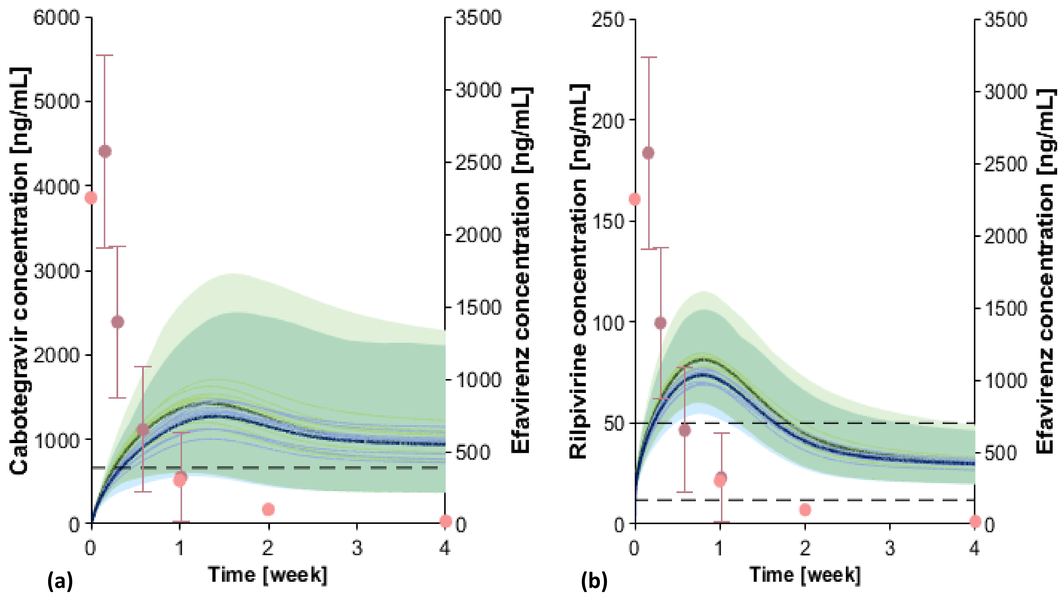
**VALIDATION STEP#2**

Switch scenario from efavirenz to oral rilpivirine and dolutegravir

A cohort of 100 virtual individuals (20-50 years old, 50% female, 18.5-30 kg/m$^2$) was generated to simulate IM CAB/RPV concentrations over the dosing interval when administering IM CAB/RPV loading dose (600/900 mg) 12 hours after the last oral dose of efavirenz (600 mg). IM CAB/RPV concentrations during the switch period were compared to those in absence of residual efavirenz concentrations.

**No risk of suboptimal drug levels during the switch from an efavirenz containing regimen to long-acting intramuscular cabotegravir/ rilpivirine.**

**Figure 1. Concentration-time profiles for (a) cabotegravir 600 mg intramuscular loading dose, (b) rilpivirine 900 mg intramuscular loading dose in absence (green) and presence (blue) of efavirenz residual induction**




Legend: the solid lines, the solid bold line, and the shaded area represent the geometric mean of each virtual trial, the geometric mean of all trials, and the 90% normal range of all virtual individuals. In figure (a) the dashed line represents the 4-fold PA-IC$_{90}$ for cabotegravir (664 ng/mL). In figure (b) the dashed lines represent the PA-IC$_{90}$ for rilpivirine (12 ng/mL) and the minimal concentration for therapeutic response (50 ng/mL). The lilac and the pink markers represent the mean measured efavirenz plasma decay concentration as reported by Crauwels et al. [2] and by Mills et al., [3] respectively.

## RESULTS

- The model was successfully verified as all predictions were within 2-fold of observed clinical data.
- Initiating IM CAB/RPV 12 hours after the last dose of efavirenz was predicted to have a minimal effect on CAB and RPV concentrations (Table 1).
- Efavirenz was predicted to have a modest effect on IM RPV concentrations with the lowest reduction being 10% after 7 days from the last dose of efavirenz (Table 1). Residual efavirenz concentrations were predicted to have a less pronounced effect on IM RPV compared to the observed switch data with oral RPV as RPV has a high first-pass metabolism [2].

**Table 1. Predictions of IM cabotegravir and rilpivirine concentrations at days 1, 7, 14, and 28 after stopping efavirenz. The results are expressed as geometric mean (CV).**

| | $C_\tau$ [ng/mL] absence of efavirenz | $C_\tau$ [ng/mL] after stopping efavirenz | $C_\tau$ ratio |
|---|---|---|---|
| **Intramuscular cabotegravir** | | | |
| **Day 1** | 421 (20) | 373 (22) | 0.89 |
| **Day 7** | 1362 (41) | 1180 (40) | 0.87 |
| **Day 14** | 1251 (55) | 1153 (50) | 0.92 |
| **Day 28** | 962 (59) | 939 (54) | 0.98 |
| **Intramuscular rilpivirine** | | | |
| **Day 1** | 45 (17) | 42 (16) | 0.94 |
| **Day 7** | 79 (24) | 71 (21) | 0.90 |
| **Day 14** | 45 (35) | 41 (29) | 0.92 |
| **Day 28** | 31 (35) | 30 (30) | 0.98 |

## CONCLUSIONS

The PBPK model predicts that switching from an efavirenz-containing regimen to IM CAB/RPV does not put at risk of having a time window with suboptimal drug levels.

**REFERENCES:**

[1]. Bettonte et al., Clinical Infectious Diseases 2022
[2]. Crauwels et al., Antiviral Therapy 2012
[3]. Mills et al., HIV Clin Trials 2013

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