Recommendations for Therapeutic Drug Monitoring of CABOTEGRAVIR and RILPIVIRINE during long-acting injectable administration of Vocabria®/Rekambys® every 2 months in HIV-infected patients

ANRS-MIE - AC43 Pharmacologic and Resistance groups

This document will be updated regularly according to available data from the literature and the evolution of therapeutic management.

Discussion concerning the follow-up and pharmacological management of HIV-infected patients treated with the combination Cabotegravir/Rilpivirine administered intramuscularly every 2 months (long-acting) outside the clinical research protocol.

Therapeutic Drug Monitoring (TDM) of antiretroviral drugs (ARV) is officially recommended in France in a certain number of indications, because of a significant inter-individual pharmacokinetic variability and pharmacokinetic-pharmacodynamic relationships (virological efficacy and/or toxicity) established for most ARVs (1).

In the context of the upcoming availability of the long-acting injectable combination of cabotegravir and rilpivirine, we propose the following modalities for the implementation of TDM for these two compounds.

1. **Level of evidence**

These recommendations are based on:

- **pharmacokinetic data from phase 3 trials** (Flair and Atlas pooled data) at week 48 reporting significant inter-individual variability in trough plasma concentrations (Cmin) of cabotegravir and rilpivirine with values below the respective geometric mean for patients with virologic failure (2).

- **results of the multivariate analysis of virologic failures in the phase 3 Flair and Atlas trials** (3) identifying trough plasma rilpivirine concentration at S8 (i.e., 4 weeks after the initiation injection) as a risk factor for virologic failure. The analysis reported that the presence of at least two of the risk factors at initiation among the A1/A6 viral subtype, the presence of archived rilpivirine resistance mutations, or a BMI \( \geq 30 \text{ kg/m}^2 \) was associated with a higher risk of failure (25.7%). A lower trough cabotegravir plasma concentration at S8 (i.e., 4 weeks after the initiation injection) was also associated with a higher BMI (4). However, although related to virological failure, trough cabotegravir concentration was no longer predictive in the multivariate analysis but should remain a point of vigilance in the real-life setting. Indeed, recent data from the Flair trial at week 124 reported a new virologic failure between S96 and S124 in a patient presenting two of the identified risk factors: viral subtype A6 and a rilpivirine Cmin below 32 ng/mL (i.e 24.6 ng/mL) and a cabotegravir Cmin below 1,120 ng/mL (i.e 1005 ng/mL).

For information, a recent French study conducted in 3 university hospitals in Paris reported a prevalence of 10.1% of A6/A1 viral subtype OR resistant to rilpivirine (i.e with 1 of the 2 virological risk factors for failure) and a prevalence < 0.5% of A6/A1 viral subtype AND resistant to rilpivirine (i.e with the 2 virological risk factors for failure) (5).

- **the French transparency commission, recommending pharmacological monitoring, particularly in obese subjects** (6) :

"Caution is further recommended in the presence of archived resistance to rilpivirine, BMI \( \geq 30 \text{ kg/m}^2 \), or HIV-1 subtype A6/A1, factors associated with the risk of virological failure in studies. In addition, the
trough plasma concentration of rilpivirine at 4 weeks after the initiation injection was associated with the risk of failure, so performing therapeutic drug monitoring of the 2 molecules is worth discussing especially in obese patients."

2. **Indications and modalities of TDM**

The sample is collected on a gel-free lithium heparinate tube (or EDTA, which is compatible with samples collected for plasma HIV-1 RNA), as currently recommended for the TDM of ARV:

- **At week 4 (W4) after initiation of oral treatment**, corresponding to the end of the lead-in phase, after the last oral dose, in the residual period (T>20h).
- **At week 8 (W8), i.e. 4 weeks after the first intra-muscular (IM) injection**, before the new administration
- in the following indications:
  - in case of **missed or delayed injection(s)**, and before resuming the treatment as defined in the Summary of Products Characteristics (SPCs)
  - in case of **occurrence of adverse events**
  - in case of **virological failure**
  - in case of **pregnancy** occurring during treatment*
  - in case of **drug-drug interaction** that may significantly alter the exposure of cabotegravir and/or rilpivirine (**see list below**)
  - along with viral load monitoring in patients with a **BMI > 30 kg/m2 and/or A1/A6 viral subtype**.

TDM should be performed preferentially either prior to the next injection or before re-starting treatment as recommended in the SPCs for missed injections (specify the estimated time of interruption) (7,8).

*In case of pregnancy occurring during treatment, monitoring plasma of concentrations is recommended whether the treatment is maintained (documentation and follow-up with bodyweight changes) or stopped (monitoring of the decrease in plasma concentrations, given the long elimination half-life of the two compounds). The frequency of the pharmacological follow-up will be determined on a case-by-case basis according to the context and discussed in a multidisciplinary staff.

3. **TDM interprétation**

To date, no specific target value are officially validated for maintenance treatment and IM administration.

To date, TDM is therefore proposed in accordance with the expected values published in the respective SPCs, with **an alert threshold corresponding to the 1st quartile of trough plasma concentrations** presented in the multivariate analysis of failures (3,7-8).

In case of a Cmin below this threshold, close virological monitoring is recommended along with a new pharmacological control after checking the absence of other factors associated with virological failure (viral sub-type, resistance profile, BMI).
Cabotegravir and Rilpivirine trough plasma concentrations after oral administration and long-acting IM administration every two months

Geometric mean [5th; 95th percentiles]\(\dagger\)

<table>
<thead>
<tr>
<th></th>
<th>W4* End of oral lead-in period</th>
<th>W8** 4 weeks after the 1st IM injection</th>
<th>W48 At steady-state</th>
<th>Alert threshold‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabotegravir, (ng/mL)</td>
<td>4,600 [2,800 ; 7,500]</td>
<td>1,500 [650 ; 2,900]</td>
<td>1,600 [800 ; 3,000]</td>
<td>&lt; 1,120</td>
</tr>
<tr>
<td>Rilpivirine (ng/mL)</td>
<td>79.4 [31.8 ; 177]</td>
<td>42.0 [21.8 ; 78.9]</td>
<td>65.6 [36.9 ; 113]</td>
<td>&lt; 32</td>
</tr>
</tbody>
</table>

*W4 : End of oral lead-in period, i.e after the last oral dose; **W8 : 4 weeks after the 1st IM injection; †individual post-hoc estimates from the population pharmacokinetic model of pooled data from the Flair/Atlas/Atlas-2M phase 3 trials (7,8); ‡value corresponding to the 1st quartile of Cmin at W8 of the pooled data analysis of the phase 3 trials (3).

For information, the protein binding adjusted inhibitory concentration 90% or IC90-ap is 166 ng/mL for cabotegravir and 12 ng/mL for rilpivirine, respectively.

** List of contraindicated and not recommended drug-drug interactions with cabotegravir and/or rilpivirine for intramuscular administration :

- **contraindicated** because of significant decrease in cabotegravir and rilpivirine plasma exposure: dexamethasone (except in single dose), carbamazepine, St. John's wort, phenytoin, phenobarbital, oxcarbazepine, rifabutin, rifampicin, rifapentin.

- **not recommended** as expected increase in rilpivirine plasma exposure: clarithromycin, erythromycin

- rilpivirine should be used with caution if co-administered with drugs with a known risk of torsade de pointes

- other drugs to be used with caution due to moderate inductive and/or inhibitory effect which may significantly modulate cabotegravir and/or rilpivirine plasma exposures (non-exhaustive list) (9) : artemisinin, betamethasone, bexarotene, bosantan, clobazam, enzalutamide, fluconazole, ginkgo biloba, griseofulvin, ifosfamide, modafinil, paclitaxel, primidone, vinblastine.

* List of additional drug-drug interactions only contraindicated or not recommended with cabotegravir and/or rilpivirine during the oral "lead-in" phase or when oral therapy is resumed: proton pump inhibitors (omeprazole/esomeprazole, lansoprazole, pantoprazole, rabeprazole)

Respect the staggered dosing as recommended in SPCs with antacids and all specialties containing divalent (Al, Ca, Mg, Iron ...), anti-H2 (famotidine, ranitidine) et le liraglutide.
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References


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