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# Therapeutic Drug Monitoring in HIV treatment: time for a comeback?

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## The promise of TDM in HIV treatment

**Therapeutic Drug Monitoring, or TDM, found its way into HIV management shortly after the introduction of combination antiretroviral therapy (cART) in the late 90s of the last century. In these days, unboosted HIV protease inhibitors such as indinavir, saquinavir and nelfinavir were introduced as part of life-saving cART, but also appeared to have a narrow therapeutic range. [1-3] In addition, given the large intersubject variability in plasma concentrations of these agents, HIV physicians were insecure whether every patient they treated with cART would optimally benefit from these new agents. The same was true when the first NNRTIs, nevirapine and efavirenz, were introduced to the market. [4,5]**

**The idea started to rise that by routinely measuring drug levels of these agents, those patients at risk for virological failure could be detected, and a proper intervention could be applied. [6] Similarly, if patients were suffering from adverse events, and a relationship between drug levels and toxicity was known, TDM could be a helpful instrument in managing the toxicity by dose reductions. Evidence for such intervention was demonstrated for renal stones in patients on indinavir, [7] or CNS toxicity in patients on efavirenz. [5]**

**Finally, randomized clinical studies comparing TDM vs no TDM demonstrated a clinical benefit for TDM, esp. for unboosted PIs. [8,9]**

## Novel ART agents, less TDM?

With the introduction of boosted PIs, and later the group of InSTIs, the need for TDM became much smaller. These agents have much more predictable pharmacokinetics, a wider therapeutic range, and very few patients with plasma concentrations below a minimum effective concentration. Not surprisingly, current cART regimens – as long as adherence is sufficient – have such a good virological efficacy. And if toxicity occurs, it is difficult to correlate this to higher drug exposure.

Since then, TDM in HIV infection was no longer indicated as a routine measurement. Still, TDM requests continued to be received by TDM labs in case of suspicion of non-adherence, unsuspected virological failure or toxicity, or for special patient populations such as pregnant women, children, patients with liver or kidney impairment, etc. But the number of TDM requests was only a fraction when compared to the early days of cART.

## Long-acting cabotegravir/rilpivirine: a new candidate for TDM?

Before we answer this question, it is good to discuss more in general when a drug is a candidate for TDM, independent of the therapeutic area. This has nicely been summarized in a landmark article by Ensom et al. in 1998. [10]

Only when all these questions can be positively answered, physicians should start thinking of implementing TDM in their clinical practice for a specific drug.

In the last 1-2 years, some evidence has been collected that the novel long-acting cART regimen consisting of cabotegravir + rilpivirine could be a candidate for TDM.

| Table 1: Criteria for applying TDM (modified from Ensom et al. 1998 [10]) |
|---|
| Is the patient on the best drug for his/her disease/indication? |
| Can the drug be measured in the desired biological sample? |
| Is there a good drug concentration-effect relationship? |
| Is the drug's pharmacological response not easily assessed otherwise? |
| Does the drug has a narrow therapeutic range? |
| Is there a large interpatient (or intrapatient) variability in drug levels? |
| Is the duration of therapy long enough for the patient to benefit from TDM? |
| Will the results of TDM be used in the clinical decision-making process? |

**So let us review what we currently (April 2024) know about the TDM criteria for cabotegravir + rilpivirine:**

*Is the patient on the best drug for his/her disease/indication?*

Yes, long-acting cabotegravir+rilpivirine has been demonstrated to be non-inferior as a maintenance strategy to daily oral cART. [11] So patients do not have two or more risk factors for virological failure (i.e. A6/A1 subtype, RPV major mutations, BMI > 30 kg/m$^2$) and they switch from suppressive daily oral cART, they're on a potent drug combination. Other risk factors such as INSTI mutations are also not in label. Of note, A1 does not seem to be associated with an increased risk. [16]

*Can the drug be measured in the desired biological sample?*

Yes, plasma drug concentrations of cabotegravir and rilpivirine have been associated with virological response, and bio-analytical assays have been reported in the literature. [12]

*Is there a good drug concentration-effect relationship?*

To some extent, based on what we have learnt so far. Extensive multivariable analyses reported by Orkin et al. [13] showed that having a low (defined as within the lowest quartile = 25 % of the patient population drug levels) cabotegravir and/or rilpivirine measurement alone is not sufficient for predicting virological failure, but in case one or more other risk factors are present, the risk on confirmed virological failure increases rapidly and becomes significantly higher than the average risk in the whole population (1-2 %).

*Is the drug's pharmacological response not easily assessed otherwise?*

Yes. Of course one can monitor viral load but in case of virological breakthrough and possible development of drug resistance, one is too late, and this should be prevented, possibly by performing TDM.

*Does the drug has a narrow therapeutic range?*

Formally, we should answer this question with "No". Both cabotegravir and rilpivirine appear to have a wide therapeutic range. But one could argue that this therapeutic range is more narrow than for daily oral cART such as with oral InSTIs. We hardly see virological failure with resistance development in these patients, so any new patient failing on long-acting cabotegravir/rilpivirine comes as a surprise.

*Is there a large interpatient (or intrapatient) variability in drug levels?*

Yes, there is roughly a 5-10 fold variability in cabotegravir and rilpivirine plasma concentrations between patients. Less is known about intrapatient variability. Factors explaining variability are yet to be defined in more detail. Sometimes, difficulties in adequately injecting one or both agents, esp. in patients with a high BMI, may explain some of the variability.

*Is the duration of therapy long enough for the patient to benefit from TDM?*

Yes. cART is lifelong treatment.

*Will the results of TDM be used in the clinical decision-making process?*

This is the last but quite an important question. The physician should have a specific reason to request a drug level measurement, and prepared to act based on the result. This does require a clear and evidence-based advice provided by the lab responsible for TDM. For instance, a low cabotegravir or rilpivirine (below Q1) plasma concentration without any other risk factors has not been associated with virological failure. [13] One could even question whether TDM is indicated in a well-suppressed patient with no relevant risk factors.

## Recommendations for TDM of cabotegravir + rilpivirine

Based on limited data as of April 2024, we can recommend to perform TDM of cabotegravir + rilpivirine in patients with at least one risk factor for virological failure. The timing should always be at the end of a dose interval, prior to the next injection, when steady state is reached (week 12 or every 8 weeks later). In case one or both levels are below the target, an intervention is indicated. This should be patient-tailored, and can be either intensified viral load monitoring, shortening of the dose interval to 6 weeks (although there is no data yet), or even the advice to stop long-acting cabotegravir + rilpivirine and to return to previous suppressive oral cART regimen. A repeat TDM is also defendable, esp. when only one level is subtherapeutic, and close to the target. Retrospective TDM is also recommended in case of unsuspected virological failure, and can be performed in stored left-over samples for viral load measurement. Viral blips may also occur during long-acting cabotegravir + rilpivirine, but appear not to be linked to drug levels, and are therefore currently not an indication for TDM.

The targets to be used in TDM for cabotegravir + rilpivirine are not yet set in stone. Initially, the cut-off for Q1 (i. e. lowest 25 % of patient population levels) has been proposed in French TDM guidelines [14] because almost all virological failures in the registrational studies occurred in that range. It should be noted that, per definition, many patients will have a level below Q1 and will not have virological failure, as this incidence is 1-2 %, and not 25 %. Another argument against using Q1 as target is that it has no relation to $IC_{90}$ values for both cabotegravir and rilpivirine. For that reason, others have used the protein-adjusted $IC_{90}$ (PA-$IC_{90}$), or the 2- or 4-fold the PA-$IC_{90}$ as more clinically meaningful cut-off. However, this does not solve the problem completely because 4-fold PA-$IC_{90}$ for rilpivirine is 50 ng/mL, which is actually higher than the Q1 for rilpivirine (32 ng/mL). Based on drug levels reported so far to be associated with virological failure, investigators from the Swiss HIV Cohort Study [15] propose to use the PA-$IC_{90}$ for cabotegravir and Q1 for rilpivirine. See Table 2. One should realize that currently any cut-off based on PA-$IC_{90}$ has not been derived from multivariable analyses in large cohorts.

Finally, it must be noted that evaluation of target drug levels must be seen in relation to the presence or absence of other risk factors. For instance, when a patient already has two or more risk factors for virological failure, failure may occur even in the presence of adequate drug levels. In our opinion, the most relevant indication for TDM is when a patient only has one risk factor, because then the TDM result may largely influence the risk on virological failure. And most importantly, in contrast to other risk factors, the drug level is the only factor that potentially can be modified.

**Table 2: Proposed target for TDM of cabotegravir and rilpivirine (after Thoueille et al.[15])**

| Plasma trough concentration | % of patients in SHCS below target | % of patients with virological failure |
|---|---|---|
| **Cabotegravir** | | |
| Q1 = 1120 ng/mL | 40.9 % | 46.7 % |
| 4-fold PA-$IC_{90}$ = 664 ng/mL | 15.6 % | 26.7 % |
| PA-$IC_{90}$ = 166 ng/mL | 1.4 % | 0.0 % |
| **Rilpivirine** | | |
| 4-fold PA-IC90 = 50 ng/mL | 47.6 % | 60.0 % |
| Q1 = 32 ng/mL | 17.8 % | 33.3 % |
| PA-IC90 = 12 ng/mL | 0.5 % | 13.3 % |
| **Proposed targets by SHCS** | **Cabotegravir: 664 ng/mL** | **Rilpivirine: 32 ng/mL** |

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