TDM-Monografie.org

TDM monograph Rilpivirine

Synonyms: Edurant, Rekambys, Eviplera, Juluca, TMC275

Summary

Indication:	**HIV infection** • **Oral administration: treatment-naïve patients 12 years and older with a viral load <100.000 copies/mL** • **Intramuscular injection: maintenance therapy, in combination with cabotegravir, in virologically-suppressed patients** Indication TDM: Prevention of virological failure
Sample material:	EDTA plasma (without gel)
Time of sampling:	Trough sample, i.e. prior to next dose (either oral or i.m.)
Storage conditions:	2-8 ºC (during transport) / -40 ºC (storage until analysis)
Interpretation:	Target trough concentration: > 0.040 mg/L (oral administration) > 0.032 mg/L (i.m. administration)
Evidence level:	2

Contents

Introduction

Rilpivirine (RPV) has initially been developed as an orally administered antiretroviral agent to be combined with other active antiretroviral agent(s) as part of combination antiretroviral therapy (cART) (1). RPV is available both as a single agent (Edurant®) and as part of fixed-dose combinations (Eviplera®, Odefsey®, Juluca®). Although it is licensed for use in treatment-naïve HIV-infected patients with viral load < 100.000 c/mL, the primary use of RPV is as a switch option for maintenance therapy in already virologically suppressed patients.

More recently, RPV has been developed in combination with cabotegravir (CAB) as a long-acting intramuscular injection (2), to be administered every 8 weeks. An oral lead in period for 4 weeks is optional. CAB/RPV is indicated as a maintenance treatment of already suppressed HIV-infected patients. Off-label it can also be given to HIV-infected patients with detectable viral load who are not able to take oral medications.

Dosing guidelines

HIV infection

Oral administration: RPV, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/ml (1).

RPV is dosed as 25mg tablet QD to be taken with a meal.

Intramuscular injection: HIV infection, together with CAB, in patients who are already virologically suppressed (viral load < 50 copies/mL) on oral therapy, without evidence of viral resistance or previous history of virological failure on NNRTIs or InSTIs (2)

An oral lead in period of one month containing RPV 25mg QD (plus CAB 30mg QD) is optional.

Maintenance treatment with intramuscular injections every 1 or 2 months is licensed, but in Europe only treatment every 2 months is applied.

A 900mg i.m. loading dose is administered on the last day of oral (lead in) therapy, then a next 900mg i.m. loading dose one month later, and then 900mg i.m. maintenance dose every 2 months

Dosing guidelines in children and adolescents

Oral administration of RPV is currently licensed in patients of 12 years and older, at the same dose as in adults (1)

Intramuscular injection of RPV is currently only licensed in adults 18 years and older (2)

Dosing guidelines in patients with altered pharmacokinetics

RPV dose adjustment (either after oral or i.m. administration) is not needed in patients with mild to moderate renal impairment.

RPV increases serum creatinine through inhibition of OCT2; this is not considered clinically relevant.

No dosage adjustment is needed for RPV in patients with mild to moderate hepatic impairment (CP-score A or B).

See (3)
Page 84: Dose adjustment of ARVs for impaired renal function
Page 93: Dose adjustment of ARVs for impaired hepatic function

Indications/Criteria for TDM

The primary indication for TDM of RPV is the prevention of virological failure. Other potential indications for TDM can be:

- Evaluation of incorrect administration (subcutaneous, missed injections, etc.)
- Potential drug concentration-related toxicity
- Special patient populations (pregnancy, children)
- Drug-drug interactions
- Suspicion of nonadherence after oral administration
- Etc.

Reference values

Target trough concentration:
> 0.040 mg/L (oral administration)
> 0.032 mg/L (i.m. administration)(week 12 or every 8 weeks later)

Efficacy

Oral administration
The EC_{50} value for in vitro activity of RPV is 0.3 ng/ml (0.0003 mg/L) but it has yet to be corrected for protein binding (99.7%) and cannot be used for Therapeutic Drug Monitoring as it is not the EC_{50} is important but the EC_{90} or EC_{95}. However, these are less reliably determined in vitro.

Relevant information can be found in the Clinical Pharmacology and Biopharmaceutics Review of oral RPV from the FDA's Center for Drug Evaluation and Research (4). Shown there is an analysis of 645 patients

from the TMC278-C209 and -215 studies in which the RPV trough level (or AUC) is divided into 8 octiles (1/12th of the whole group). Patients who self-reported less than 90% compliance were excluded from the analysis. Only the patients in the lower octile with a median trough level of 0.040 mg/L were found to have a lower virologic response: 70% vs. >80% for all other patients.

The same paper also shows a sub-analysis of concentration-effect relationships of oral RPV in patients with baseline viral load greater or less than 100,000 copies/mL. The phase III studies showed that RPV is less effective than efavirenz when the viral load is > 100,000 copies/mL. In this analysis, RPV trough levels after oral RPV administration were divided into quartiles and showed a lower virological response only in patients with viral load > 100,000 copies/mL and the lowest quartile of RPV trough levels: 68% had viral load < 50 copies /mL at 48 weeks vs >80% in all other subgroups. The median trough level in the lower response quartile was 0.042 mg/L.

Néant and colleagues (5) investigated the concentration-effect relationship after oral administration of RPV in a cohort of 60 treatment-naïve and 39 treatment-experienced patients. The pharmacodynamic model they developed gave an EC_{50} of 0.065 mg/L, which suggested a C_{min} of at least 0.10 mg/L to produce an optimal virological response in more than 80% in both populations. However, it seems unlikely that this is the appropriate target value for RPV trough levels in TDM as this value corresponds to the mean value in the population at 25mg once daily, which would mean that 50% of the population is undertreated and would require a dose increase. This is not congruent with the reported efficacy of RPV at the standard dose of 25mg QD.

In a follow-up study, the same researchers (6) examined a much larger cohort of 379 patients on oral RPV and found a cut-off value of 0.070 mg/L for RPV trough levels via an ROC analysis.

Intramuscular injection

The association between RPV plasma concentrations and virologic failure was assessed in a post hoc analysis of phase III clinical trial participants (7). In the univariate analysis, the week 8 (steady-state) RPV plasma concentration was associated with virological failure, as was the case for the week 8 CAB plasma concentration and BMI. In the multivariate analysis, the week 8 RPV concentration remained significantly related to virological failure.

Seven out of 13 patients with confirmed virological failure had both CAB and RPV week 8 plasma concentrations below the 25% percentile (Q1) of exposure, which is 0.032 mg/L for RPV. The presence of an RPV trough levels below 0.032 mg/L with at least one other risk factor (either BMI > 30 kg/m^2, RPV mutation or A1/A6 HIV subtype) was predictive of virological failure.

An updated analysis of phase III trial participants was published 2 years later (8). That analysis included more patients with a longer follow-up. There were 22 patients who had confirmed virological failure and CAB and/or RPV plasma concentrations available. 10 of these 22 patients had both CAB and RPV plasma concentration below Q1 (1.12 mg/L for CAB; 0.032 mg/L for RPV). Another 8 of the 22 patients had either CAB or RPV plasma concentration below Q1.

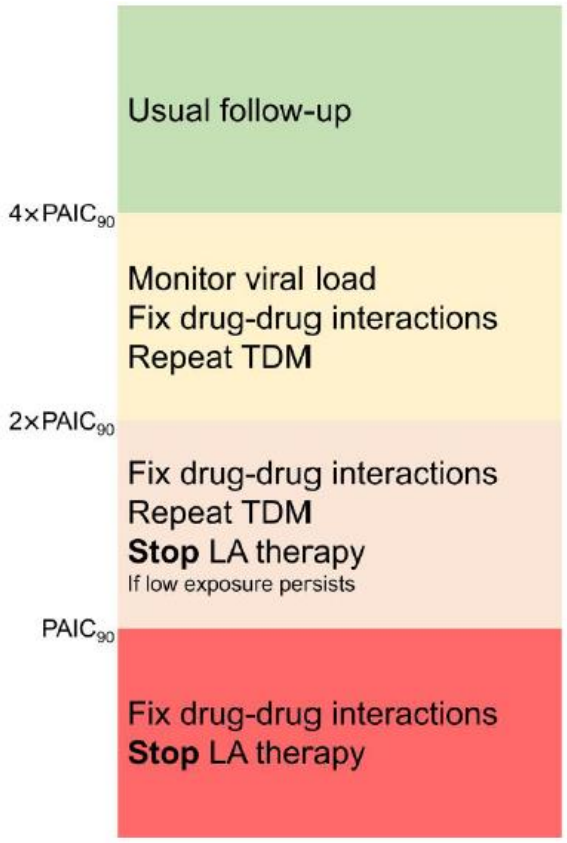
Besides the effect of drug concentration, other baseline factors associated with the risk of virological failure were: HIV-1 subtype A6/A1; RPV resistance associated mutations; or BMI > 30 kg/m^2 (8). Patients need to have at least 2 of these risks factor to become at risk for virological failure

Please note that the large majority (>95%) of patients with an RPV (or CAB) plasma concentration below Q1 and no other risk factors for virological failure will have virological response. And this percentage is almost 100% when an RPV (or CAB) concentration is above Q1.

Although the pharmacokinetic profile of RPV after oral administration is completely different from the profile after i.m. administration, the target for RPV trough concentration is more or less in the same range: 0.032 – 0.040 mg/L).

Recently, in the Netherlands, five patients have been described who had unexpected virological failure with development of resistance (9). All five patient had at least CAB or RPV below the Q1 target, confirming the above-mentioned multivariable analysis by Orkin et al.

Others have argued that Q1 may not be the appropriate target for CAB and/or RPV as this concentration does not have a direct relation with the protein-binding adjusted IC_{90} (PA-IC_{90})(10). They propose the following flowchart using targets equivalent to 1, 2, or 4 times the PA-IC_{90}:



This table gives an overview of the proposed targets. Please note that for CAB Q1 is > 4x PA-IC_{90} but that for RPV 4x PA-IC_{90} is > Q1.

	Proposed targets

	Cabotegravir (mg/L)	Rilpivirine (mg/L)
PA-IC_{90}	0.166	0.012
2x PA-IC_{90}	0.32	0.024
4x PA-IC_{90}	0.66	0.050
Q1	1.12	0.032

Although a target related to PA-IC_{90} makes sense from a pharmacological point of view, there is currently no evidence that this target differentiates failures from responders better than the Q1 target. Therefore, we keep Q1 as the best-studied target for both CAB and RPV.

Relationship with occurrence of side effects

The main side effect of RPV when administered orally is ECG changes. In phase II, higher doses than 25mg were investigated (75mg and 150mg), but these showed too many ECG abnormalities, so 25mg was chosen. There appears to be a relationship between the C_{max} of RPV and the occurrence of QTc prolongation (4). At 25mg, 75mg and 300mg once daily, C_{max} were resp. 200 ng/mL (0.20 mg/L), 600 ng/mL (0.60 mg/L), and 1600 ng/mL (1.6 mg/L). The corresponding QTc prolongations were 4, 9 and 23 ms, respectively. Prolongations <10 ms are considered clinically irrelevant. A maximum RPV concentration of 0.60 mg/L can therefore be regarded as an upper limit. The T_{max} is approximately 4 hours after oral administration.

All other adverse events reported in phase III studies were found to be unrelated to RPV levels..

Toxicity

After oral administration the most frequently reported adverse events of at least moderate severity were depression (4.1%), headache (3.5%), insomnia (3.5%), rash (2.3%) and abdominal pain (2.0%)(1)

The most frequent adverse events of RPV after i.m. administration are injection-site reactions (76-84%), headache (7-12%) and pyrexia (7-10%)(2)

Sampling & Storage conditions

A TDM sample should be taken in an EDTA tube without gel. RPV is sensitive to light. TDM blood samples should be processed within 30 minutes, or protected from light. Transport to an external laboratory should be at 2-8 ºC. Samples should be stored at -40 ºC pending analysis.

For oral administration of RPV: a trough sample is taken just prior to the next oral administration.
For i.m. administration: the first sample can be taken 8 weeks after the 2nd loading dose, or 8 weeks after the last maintenance dose.

Additional information concerning the interpretation of results

Oral administration

The desired trough level of RPV after oral administration is at least 0.040 mg/L; this corresponds to a concentration ratio to population mean (0.090 mg/L) of 0.44. According to the French publication, a trough level between 0.040 and 0.070 mg/L also increases the risk of virological failure, but we would like to see this confirmed before we adopt that. It can do no harm to find out why a level in that area is lower than the population average of 0.090 mg/L, e.g. use of antacids or insufficient food intake.

The maximum allowable peak level is 0.60 mg/L; at a population mean of 0.20 mg/L, this corresponds to a concentration ratio of 3.0.

If 1st trough level < 0.040 mg/L or CR < 0.44: discuss intake with food, change if necessary time of intake with more food, check co-medication, incl. herbs, and repeat TDM request.

If 2nd trough level < 0.040 mg/L and/or CR < 0.44: increase dose to 50 mg once a day with the most fat-rich meal of the day.

If C_{max} > 0.60 mg/L or CR > 3.0: record ECG. If ECG abnormal: discontinue RPV

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Intramuscular injection
Advice in case RPV plasma concentration < Q1 (0.032 mg/L) and at least one other risk factor for virological failure (i.e. HIV-1 subtype A6/A1; RPV resistance associated mutations; or BMI > 30 kg/m^2): discuss one of the following options:

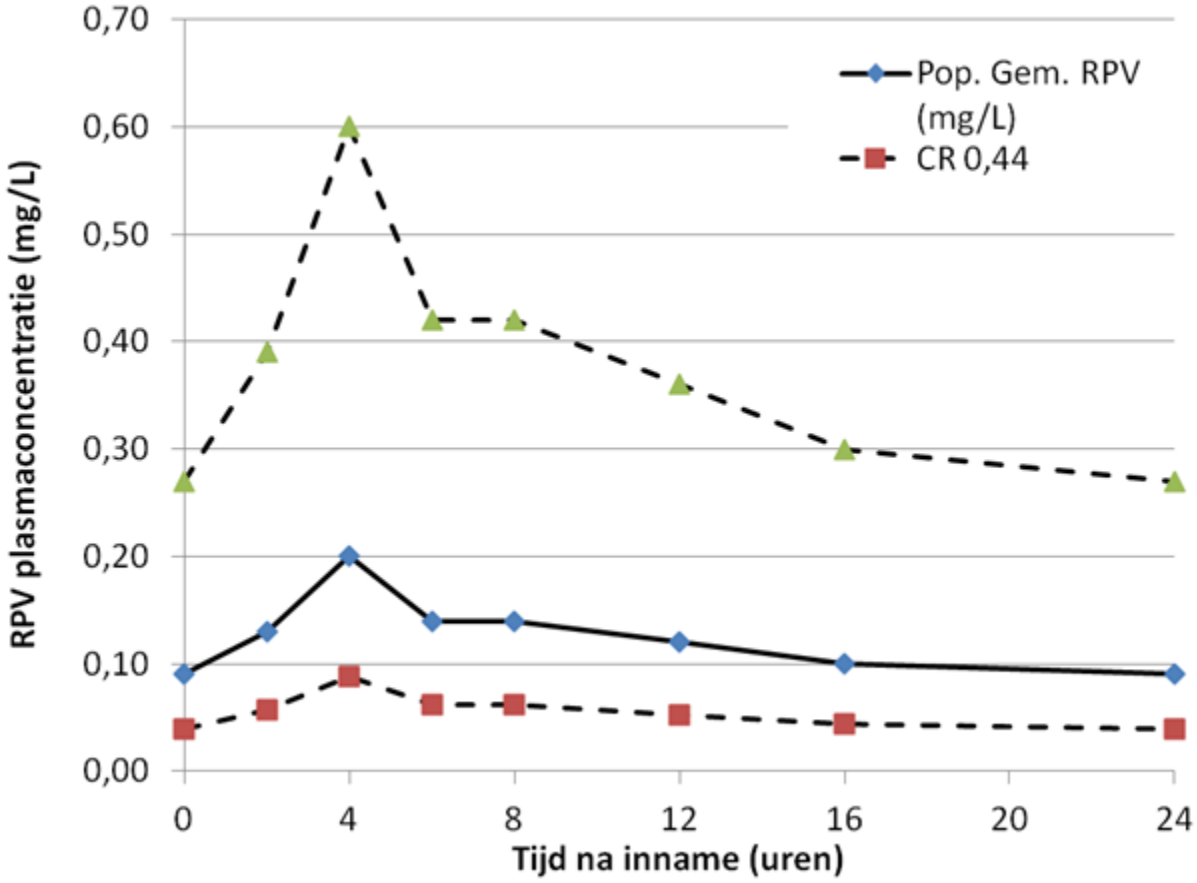
- Increase frequency of viral load monitoring
- Shorten dose interval to 6 weeks
- Increase RPV dose to 1200mg i.m. every 8 weeks

This is also dependent on the result of CAB TDM.

When patients do not have another risk factor virological failure, the contribution of a low drug level may be minimal, if not absent. Also, when patients already have 2 or more risk factors for virological failure, the drug level might be less important as the risk on failure is already increased.

Population data after oral administration

Tijd (h)	Pop. Gem. RPV (mg/L)	CR 0,44	CR 3,0
0	0,090	0,040	0,270
2	0,130	0,057	0,390
4	0,200	0,088	0,600
6	0,140	0,062	0,420
8	0,140	0,062	0,420
12	0,120	0,053	0,360
16	0,100	0,044	0,300
24	0,090	0,040	0,270



Background information [extended]

Pharmacodynamics

RPV is a diarylpyrimidine NNRTI of HIV-1. RPV activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). RPV does not inhibit the human cellular DNA polymerases α, β and γ (1).

Pharmacokinetics

Oral administration
T_{max} of RPV after oral administration is achieved in 4-5 hours. Exposure to RPV is 40% lower when taken on an empty stomach. It is recommended that RPV is taken with the largest meal of the day.

RPV is 99.7% bound to plasma proteins, primarily albumin.

RPV undergoes oxidative metabolism through CYP3A. the terminal elimination half-life is 45 hours. Unchanged RPV can be found in feces for 25% of the administered dose; in urine this is <1%.

Intramuscular administration
After injection RPV exhibits absorption-limited (flip-flop) pharmacokinetics. The slow absorption from the injection site in the muscle determines the plasma concentration and its elimination half-life.

T_{max} is reached after 3-4 days.

RPV elimination half-life varies between 13-28 weeks.

The average steady-state RPV trough concentration is 0.066 mg/L.

Inter-patient variability in RPV plasma concentrations is almost 4 times higher than intra-patient variability (94% vs 27%)(11)

Pharmacogenetics

No information

Interactions

See (12)

www.hiv-druginteractions.org

PK parameters

	F (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	**$t_{1/2}$** (h^{-1})	Protein binding	Tmax (h)	Ref.
Oral administration				45	99.7%	4-5	(1)
Intramuscular administration		5.1	1.9	13-28 weeks	99.7%	3-4 days	(2)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/ h^{-1}) **/ F**	Ref.
HIV-infected patients	Oral administration	1.49	912		11.8	(4)
HIV-infected patients	Intramuscular injection	0.00346 (d^{-1})	132			(13)

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Colophon

This guideline has been constituted by David Burger, PharmD, PhD
Date: [May 14, 2024]

Appendices

Not applicable

Revision

This guideline has been revised by David Burger, PharmD, PhD under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)The guidelines was updated based on most recent literature and translated to English. Date: [May 14, 2024]