TDM monograph Cabotegravir

Synonyms: Vocabria. Cabenuva, S/GSK1265744

Summary

Indication:	**Maintenance treatment of HIV infection** Off-label indications: Treatment-naive HIV-infected patients; HIV prevention Indication TDM: Prevention of virological failure
Sample material:	EDTA plasma (without gel)
Time of sampling:	Trough sample, i.e. prior to next injection every 8 weeks
Storage conditions:	2-8 ºC (during transport) / -40 ºC (storage until analysis)
Interpretation:	Target concentration: > 1.12 mg/L
Evidence level:	2

Contents

Introduction

Cabotegravir (CAB) is being used in combination with rilpivirine (RPV) as a long-acting intramuscular injection, 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. (1).

Off-label it can also be given to HIV-infected patients with detectable viral load who are not able to take oral medications. CAB monotherapy has also been approved for HIV prevention but not yet available in all countries.

Dosing guidelines

Maintenance treatment of HIV infection

HIV infection, together with RPV, 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 (1).

An oral lead in period of one month containing 30mg CAB QD (plus RPV 25mg 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 600mg i.m. loading dose is administered on the last day of oral (lead in) therapy, then a next 600mg i.m. loading dose one month later, and then 600mg i.m. maintenance dose every 2 months

Dosing guidelines in children and adolescents

CAB is currently only licensed in patients of 18 years and older

Dosing guidelines in patients with altered pharmacokinetics

No dosage adjustment is required in patients with mild to severe renal impairment (CrCl <30 mL/min

and not on dialysis). CAB has not been studied in patients with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir.

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). CAB has not been studied in patients with severe hepatic impairment (Child-Pugh score C.

See (2)
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 CAB 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
- Etc.

Reference values

Target concentration: > 1.12 mg/L (for more information, see below)

Efficacy

The association between CAB plasma concentrations and virologic failure was assessed in a post hoc analysis of phase III clinical trial participants (3). In the univariate analysis, the week 8 (steady-state) CAB plasma concentration was associated with virological failure, as was the case for the week 8 RPV plasma concentration and BMI. In the multivariate analysis, CAB plasma concentrations were no longer independently associated with virological failure; most likely because BMI was retained in the model, and CAB plasma concentrations are dependent on BMI. The week 8 RPV concentration was significantly related to virological failure (see TDM monograph RPV).

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 1.12 mg/ for CAB. In a subset of patients with BMI > 30 kg/m^2 6 out of the 8 patients with confirmed virological failure had a week 8 CAB plasma concentration below Q1.

An updated analysis of phase III trial participants was published 2 years later (4). 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

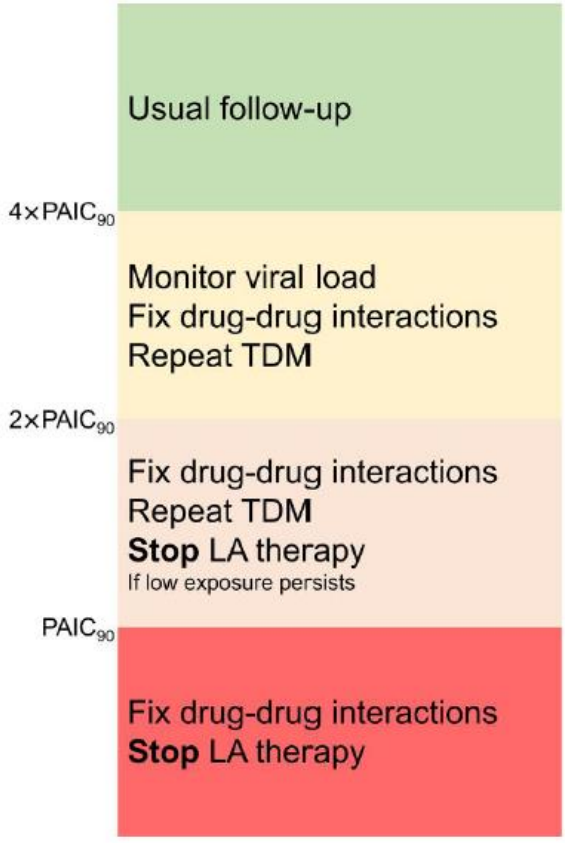
concentration below Q1 (1.12 mg/L for CAB; 0.032 mg/L for RPV). Another 8 of the 22 patients had either CAB or RPV plasma concentration below Q1.

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 (4). 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 a CAB (or RPV) plasma concentration below Q1 will have virological response. And this percentage is almost 100% when a CAB (or RPV) concentration are above Q1.

Recently, in the Netherlands, five patients have been described who had unexpected virological failure with development of resistance (5). All five patients 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})(6). 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.

There is currently no information on targets for CAB in HIV prevention.

Relationship with occurrence of side effects

So far, no concentration-toxicity effect relationships have been found for CAB.

Toxicity

The most frequent adverse events are injection-site reactions (76-84%), headache (7-12%) and pyrexia (7-10%)(1).

Sampling & storage conditions

A TDM sample should be taken in an EDTA tube without gel. CAB 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.

The first sample can be taken 8 weeks after the 2nd loading dose, or 8 weeks after the last maintenance dose of CAB.

Additional information concerning the interpretation of results

Advice in case CAB plasma concentration < Q1 (1.12 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 CAB dose to 900mg i.m. every 8 weeks

This is also dependent on the result of RPV 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.

Background information [extended]

Pharmacodynamics

CAB inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. The protein binding adjusted IC_{90} for CAB is 0.166 mg/L (1).

Pharmacokinetics

After injection CAB 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 7 days.

CAB is highly bound (>99%) to human plasma proteins. It is primarily metabolized by UGT1A1 with a minor UGT1A9 component. Renal elimination of unchanged CAB is low (<1%).47% of CAB is excreted unchanged by the faeces.

CAB elimination half-life varies between 5.6-11.5 weeks.

The average steady-state CAB trough concentration is 1.6 mg/L.

Inter-patient variability in CAB plasma concentrations is about 2 times higher than intra-patient variability (101 vs 50%)(7).

Pharmacogenetics

HIV-infected subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.2-fold mean increase in steady-state cabotegravir AUC, Cmax, and Ctau following long acting injection administration compared with subjects with genotypes associated with normal metabolism via UGT1A1. This is not considered to be clinically relevant (8).

Interactions

See (9)

www.hiv-druginteractions.org

PK parameters

	F (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	**$t_{1/2}$** (h^{-1})	Protein binding	Tmax (h)	Ref.
HIV-infected patients		0.15	0.075	5.6-11.5 weeks	>99%	7 days	(1)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/ h^{-1}) **/ F**	Ref.
HIV infected patients		0.0003-0.0005	7.0-7.8		0.225	(10)

Literature

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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 [May 14, 2024]