TDM monograph Darunavir

Synonyms: Prezista, Rezolsta, Symtuza, TMC144

Summary

Indication:	**HIV infection** Indication TDM: Prevention of virological failure
Sample material:	EDTA plasma (without gek)
Time of sampling:	Trough sample, i.e. prior to next dose
Storage conditions:	2-8 ºC (during transport) / -40 ºC (storage until analysis)
Interpretation:	Target trough concentration: 0.50 mg/L
Evidence level:	4

Contents

Introduction

Darunavir (DRV) as an HIV-protease inhibitor cannot be given as a single agent because of its low absorption and rapid elimination. It needs always to be boosted by a CYP3A inhibitor such as ritonavir (RTV) or cobicistat (COBI). Boosters do not have antiviral activity.

Darunavir+ritonavir is often abbreviated as DRV/r.
Darunavir+cobicistat is often abbreviated as DRV/c.

There is a number of different formulations containing DRV available: as a single agent (Prezista® or generic), as a fixed-dose combination with COBI (Rezolsta®) or as a fixed-dose combination with COBI, TAF/FTC (Symtuza®). There is also an oral solution available containing DRV 100 mg/mL (Prezista®)(1-3)

Dosing guidelines

HIV infection (1-3)

DRV, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight

DRV, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults and adolescents (aged 12 years and older, weighing at least 40 kg)

Dosing of boosted-DRV is dependent on the treatment experience of a patient:

ART-naïve adult patients
The recommended dose regimen is DRV 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food.

ART-experienced adult patients
The recommended dose regimen is DRV 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food.

A dose regimen of DRV 800 mg QD with COBI 150 mg QD or RTV 100 mg QD taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without DRV resistance

associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6 /L

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* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Dosing guidelines in children and adolescents (4)

ART-naïve children

Body weight (kg)	DRV Dose (mg)
15-30	600 + 100mg of RTV
30-40	675 + 100mg of RTV
>40	800 + either 100mg of RTV or 150mg of COBI

ART-experienced children

Body weight (kg)	DRV Dose (mg) once-daily
15-30	600 + 100mg of RTV
30-40	675 + 100mg of RTV
>40	800 + either 100mg of RTV or 150mg of COBI

Body weight (kg)	DRV Dose (mg) twice-daily
15-30	380 + 50mg of RTV
30-40	460 + 60mg of RTV
>40	600 + 100mg of RTV

Dosing guidelines in patients with altered pharmacokinetics

Hepatic impairment

DRV is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, DRV should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of DRV exposure and a worsening of its safety profile. Therefore, DRV must not be used in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment

No dose adjustment is required for DRV/r in patients with renal impairment. Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading.

See (5)
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 DRV is the prevention of virological failure. Other potential indications for TDM can be:

- Potential drug concentration-related toxicity
- Special patient populations (pregnancy, children)
- Drug-drug interactions
- Suspicion of nonadherence
- Etc.

Reference values

Treatment-naïve patients & treatment-experienced patients without DRV-associated PI mutations: the target DRV trough is 0.50 mg/L (50% of mean population value). In case DRV trough < 0.50 mg/L: discuss with patient adequate intake of DRV with food, check for interactions, etc.

Treatment-experienced patients with DRV-associated PI mutations: calculate GIQ and consult a virologist

For more information, see below.

Efficacy

The EC_{50} value for in vitro activity of DRV ranges from 1.2 to 8.5 nM, corresponding to 0.7 to 5.0 ng/ml. In the presence of human serum, the EC_{50} thus rises with a median value of 5.4 to 3.9 – 27 ng/ml. It is not known how much higher DRV trough levels must be relative to protein-adjusted EC_{50} to achieve optimal activity in naive patients.

In PI-experienced patients, a change in susceptibility to darunavir of up to 10-fold is not yet considered resistant.

A PK/PD analysis in 468 treatment-experienced patients from the Power 1 and 2 studies, available only in abstract form (6), shows only a weak relationship between pharmacokinetic parameters of DRV and antiviral response. The variation in susceptibility to DRV at baseline, the level of the baseline viral load, and the use of other active agents in the new regimen are much more important.

A strong relationship is found between IQ (inhibitory quotient = trough level divided by EC_{50}), but no cut-off point is mentioned for optimal antiviral response.

A PK/PD analysis in 292 patients from the Power 3 study, also available only as an abstract (7), shows that PK parameters (AUC, Cmax, Cmin) are not related to the decrease in HIV-1 RNA at week 24 after starting therapy. However, IQ was strongly related to HIV-1 RNA decline. This relationship appeared to be mainly determined by the variation in the EC_{50} change at baseline, which was many times greater than the variation in Cmin. Unfortunately, a target value for this IQ is also not mentioned in this study.

Pellegrin et al. describe a study (8) in 65 treatment-experienced patients treated with a DRV-containing regimen in France and evaluated the effect of baseline mutations, phenotypic susceptibility and

pharmacokinetic parameters on antiviral response after 12 weeks of treatment. The median Cmin of DRV was 3.5 mg/L which was not related to antiviral response. The median GIQ (genotypic inhibitory quotient = trough level divided by number of mutations) was 0.87 mg/l per mutation, which was strongly related to antiviral response at week 12 (p=0.006). According to the authors, the breakpoint for GIQ was found to be 1.8: if the GIQ was < 1.8, the patient had a 55% chance of virologic failure (defined as a viral load >500 copies/ml) vs. 0% probability of virologic failure if the GIQ was > 1.8 (p < 0.001). Also in a multivariate analysis, GIQ remained an independent predictor of virologic failure.

Molto et al. (9) studied 37 patients who had been pre-treated with other protease inhibitors and started on a DRV-containing regimen. The decline in viral load at week 48 was not correlated with DRV trough level but was correlated with virtual IQ (vIQ = trough level darunavir (in ng/ml) / change in darunavir IC_{50} relative to wild-type virus). A more hands-on approach was also used by calculating the GIQ as above, using as mutation list: 11I, 32I, 33F, 47V, 50V, 54M/L, 73S, 76V, 84V and 89V. The cut-off value of the GIQ was 2.4 (expressed as mg/L/mutation) In virological responders, 71.4% of patients had a gIQ above 2.4 and only 43.8% in virological failures. In other words, patients with a GIQ > 2.4 had 4x greater chance of response than patients with a GIQ < 2.4, but this was just not significant (p=0.089) .

It is not clear which calculation of the darunavir GIQ is better: that of Pellegrin or that of Molto. Nowadays, DRV treatment in patients with previously-developed PI mutations is hardly needed, but the general principle that higher DRV troughs are needed when there are more DRV-associated mutations remains valid.

As mentioned above DRV/r and DRV/c are also registered in treatment-naive patients in a QD dose of 800/100mg and 800/150mg, respectively. Logically, the mean trough level at 800mg QD is lower than at 600 BID. In a patient without PI mutations, this is not a problem and DRV QD can be given. No relationship could be found between DRV levels and virologic failure in treatment-naïve patients (10).

The observed lack of a correlation between DRV exposure and virological response was later repeated in a number of treatment-naïve trials:

- COBI-boosted DRV + TAF/FTC (11)
- DRV + either raltegravir or TDF/FTC (12)

The target of 0.50 mg/L that we propose for patients without PI mutations is selected to define patients who have a large reduction in DRV exposure (>50%), and the reason for this should be investigated. There is no evidence for increased risk of virological failure in patients with DRV troughs < 0.50 mg/L.

Relationship with occurrence of side effects

The same studies as described above also looked at possible relationships between darunavir pharmacokinetic parameters and the occurrence of adverse events, but no relationship was found.

Toxicity

The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting (1-3).

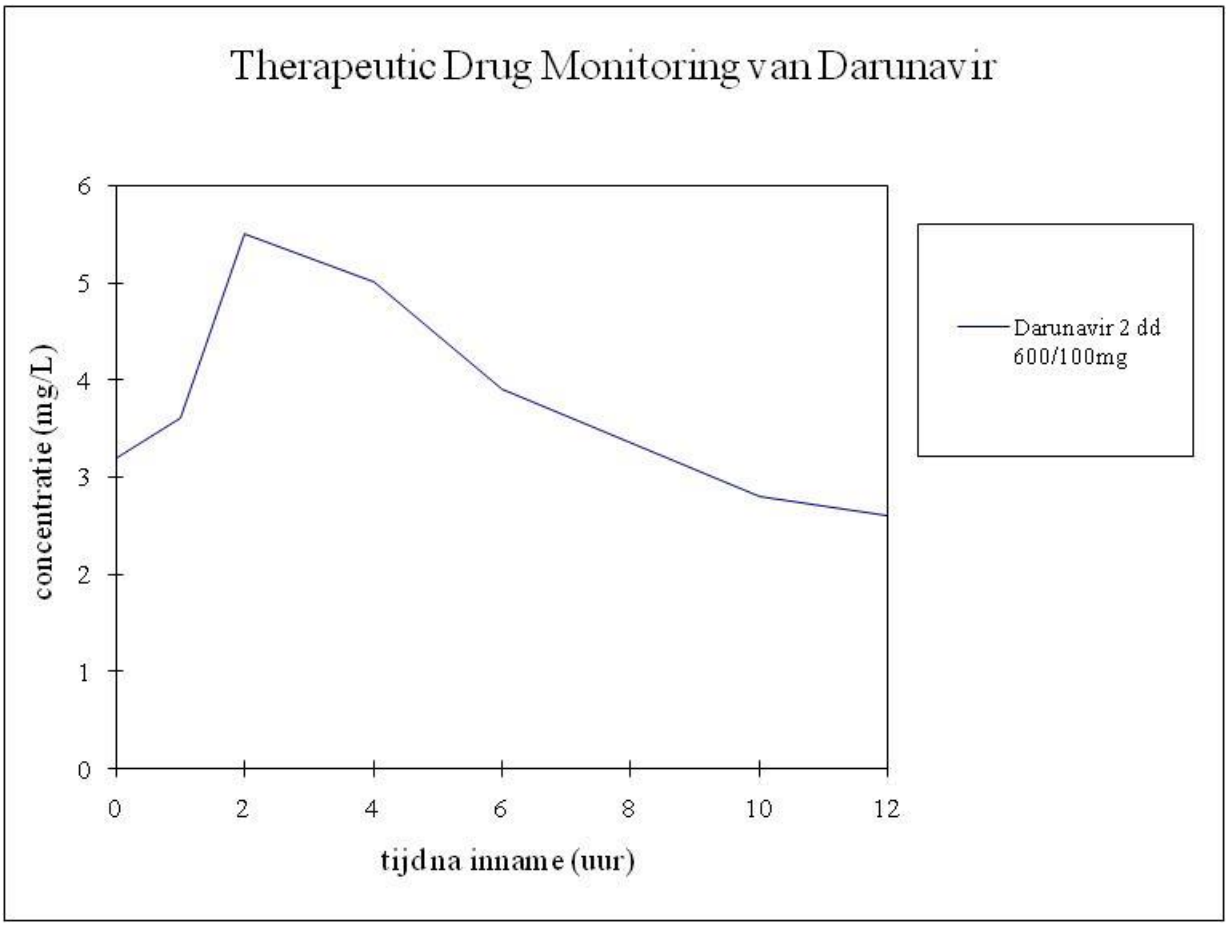
Sampling & storage conditions

A TDM sample should be taken in an EDTA tube without gel. Samples should be stored at -40 ºC pending analysis.

Additional information concerning the interpretation of results

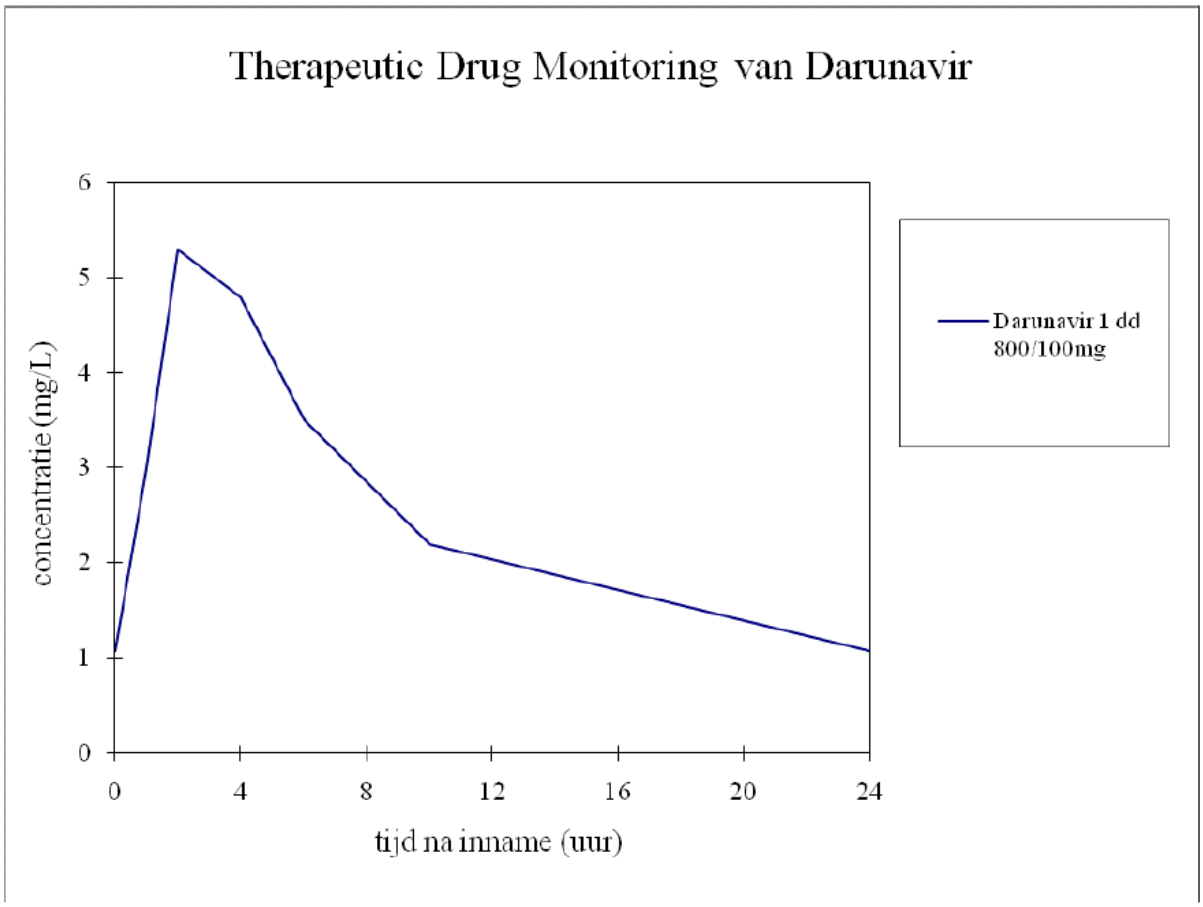
2 dd 600/100mg DRV/rtv

time (hr)	conc. (mg/l)
0	3.20
1	3.60
2	5.50
4	5.00
6	3.90
10	2.80
16	1.80
12	2.60



800/100mg DRV/rtv QD

time (hr)	conc. (mg/L)
0	1.07
1	3.00
2	5.30
4	4.80
6	3.50
10	2.20
24	1.07



Background information [extended]

Pharmacodynamics

DRV is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (KD of 4.5 x 10-12M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles (1-3).

Pharmacokinetics

Tmax after oral administration is 2.5-4 hours.

When administered without food, the relative bioavailability of DRV in the presence of cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, DRV tablets should be taken with cobicistat or ritonavir and with food. The type of food does not affect exposure to DRV. DRV is approximately 95% bound to plasma proteins, primarily alpha1-acid glycoprotein (AAG).

DRV is metabolized through CYP3A. 41.2% of a DRV dose boosted by RTV is excreted unhanged by the feces. Elimination of unchanged DRV in the urine is 7.7%

The elimination half-life of DRV is approx. 15h as long as the booster (RTV or COBI) is present in plasma at concentrations that inhibit CYP3A. Beyond the regular dose interval, the boosting capacity of in particular COBI is rapidly reduced, with a more rapid decline of DRV levels as a result.

Pharmacogenetics

No data

Interactions

See (13)

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. DRV boosted by RTV or COBI	82%	5.9	1.9	15	95%	2.5-4.0	(1-3)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/ h^{-1}) **/ F**	Ref.
HIV-infected patients		0.455	131		51.4	(6)

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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]