TDM monograph Doravirine

Synonyms: Pifeltro, Delstrigo

Summary

Indication:	**HIV infection** Indication TDM: Prevention of virological failure
Sample material:	EDTA plasma
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: > 0.23 mg/L
Evidence level:	4

Contents

Introduction

Doravirine (DOR) is the most recently developed non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment in HIV-infected patients.

For the treatment in adults the 100mg dose is available in two different formulations: as a single agent (Pifeltro®), or as part of fixed-dose triple combination (Delstrigo®, with TDF/3TC). Most patients on DOR are treated with Delstrigo®.

Dosing guidelines

HIV infection

DOR is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults, and adolescents aged 12 years and older weighing at least 35 kg infected with HIV-1 without past or present evidence of resistance to the NNRTI class (1)

Dosing guidelines in children and adolescents

Adolescents aged 12 years and older weighing at least 35kg can take the adult dose of DOR = 100mg QD (1)

Dosing guidelines in patients with altered pharmacokinetics

No dose adjustment of DOR is required in patients with mild, moderate, or severe renal impairment. The pharmacokinetics of DOR has been studied in four patients with end-stage renal disease undergoing hemodialysis (2). DOR was administered after dialysis. The elimination half-life of DOR was reduced. TDM of DOR was recommended by these authors for patients on hemodialysis.

No dose adjustment of DOR is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DOR has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

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 DOR 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

Target trough concentration:
> 0.23 mg/L

See below for more information.

Efficacy

In a phase IIb study (4), treatment-naïve HIV-positive participants were treated with DOR 25mg, 50mg, 100mg, or 200mg QD, all combined with tenofovir DF/emtricitabine (TDF/FTC) for 24 weeks. There was no clear relationship between DOR exposure (AUC0–24, Cmin , or Cmax) and virological response. In a phase III study (5)), treatment-naïve HIV-positive subjects treated with 100mg DOR once daily with tenofovir DF/lamivudine (TDF/3TC) were found to be “non-inferior” to efavirenz + TDF/3TC at 48 weeks. The 100mg DOR QD dose has become the registered dose.

A population PK analysis (6) found a weak but statistically significant relationship between Cmin levels in the lowest 10% percentile and failure to achieve a viral load <50 copies/mL at week 48. The value of the 10% percentile was 0.23 mg/L (540 nM) and is approximately 40% lower than the geometric mean of the DOR trough level at 100 mg QD in the population (0.39 mg/L = 930 nM). There was evidence that patients in this lowest 10% percentile were more likely to be non-compliant and therefore have these low levels. Based on these data, it is assumed that levels that are at least 60% of the mean trough level can be regarded as virologically effective (7).

In vitro EC50s of DOR was 0.005 mg/L (12 nM) for wild-type virus, and 0.009, 0.013, 0.014, and 0.023 mg/L (21, 31, 33, and 55 nM) for strains with the K103N, Y181C, G190A, or K103N/Y181C mutations, respectively (in 100% human serum)(Feng et al 2016). Merck has set target values for DOR at trough levels of at least 6x the EC50 (0.030 mg/L = 78nM), but this value has not been clinically validated. The true minimum effective concentration for DOR may be somewhere in the range 0.030 – 0.23 mg/L.

Relationship with occurrence of side effects

No relationship has been found between DOR levels and the occurrence of side effects or laboratory abnormalities (8). Safety and tolerability was similar for all DOR doses (25 mg to 200 mg QD) tested in Phase IIb studies (4).

In a phase 1 study, a single supratherapeutic dose of 1200mg DOR was well tolerated and did not lead to significant changes in QTc interval (9); the same applied to multiple doses up to 750mg QD (8)

Toxicity

The most frequently reported adverse reactions considered possibly or probably related to DOR were nausea (4 %) and headache (3 %) (1).

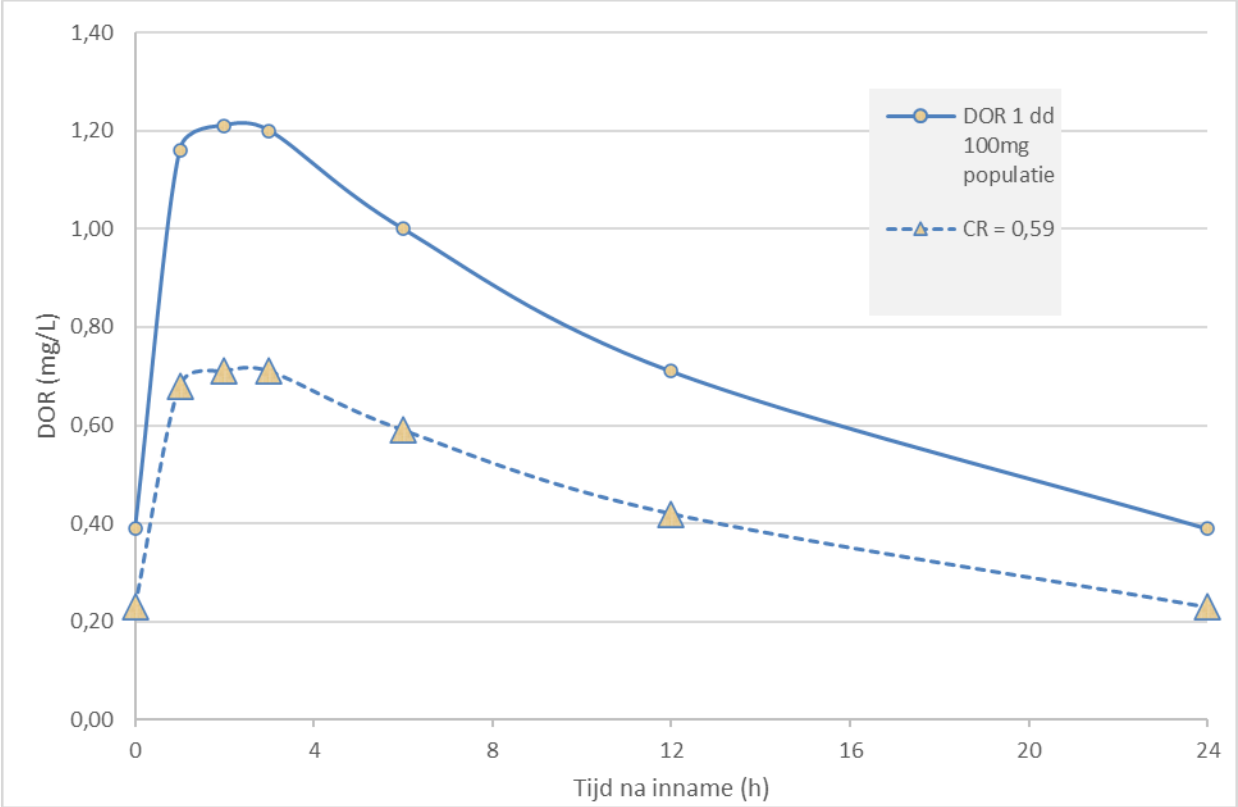
Sampling conditions

A TDM sample should be taken in an EDTA tube without gel. Transport to an external laboratory should be at 2-8 ºC. Samples should be stored at -40 ºC pending analysis.

Additional information concerning the interpretation of results

The target value for DOR trough level is set at 0.23 mg/L, which corresponds to a concentration ratio (CR) of 0.59 (= 0.23 / 0.39). 0.39 mg/L is the population mean.

If DOR trough level is <0.23 mg/L: discuss the importance of compliance, check co-medication for interactions, and if necessary increase the dose to 100 mg BID. Taking with food only causes a limited increase in DOR level (26-36%) but can be a 1st intervention before increasing the dose.



DOR 100 mg QD steady state*		
time (h)	DOR (mg/l) population	DOR (mg/L) CR = 0,59
0	0,39	0,23
1	1,16	0,68
2	1,21	0,71
3	1,20	0,71
6	1,0	0,59
12	0,71	0,42
24	0,39	0,23

Background information [extended]

Pharmacodynamics

DOR is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). DOR does not inhibit the human cellular DNA polymerases α, ß, and mitochondrial DNA polymerase γ.

Pharmacokinetics

T_{max} after oral administration is 2 post-dose.

The administration of a single DOR tablet with a high-fat meal to healthy subjects resulted in a 16 % and 36 % increase in DOR AUC and C24, respectively, while C_{max} was not significantly affected. DOR can be taken without regard to food.

DOR is approx.. 76% bound to plasma proteins.

DOR is metabolized through CYP3A. Biliary excretion of unchanged medicinal product may contribute to the elimination of DOR, but this elimination route is not expected to be significant. Excretion of unchanged medicinal product via urinary excretion is minor.

The elimination half-life of DOR is 15h (1).

Pharmacogenetics

No clinically relevant racial differences in the pharmacokinetics of DOR have been identified based on a population pharmacokinetic analysis of DOR in healthy and HIV-1 infected subjects.

Interactions

See (10)

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 patient	64		0.86	15	76%	2	(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		1.4	162		6.34	(6)

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 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]