TDM monograph Dolutegravir

Synonyms: Tivicay, Triumeq, Juluca, GSK1349572,

Summary

Indication:	**HIV infection** Indication TDM: Prevention of virological failure
Sample material:	EDTA plasma (without gel)
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: > 0.30 mg/L
Evidence level:	2

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Introduction

Dolutegravir (DTG) is currently globally the most widely used Integrase strand transfer inhibitor (InSTI).

For the treatment in adults the 50mg dose is available in a number of different formulations: as a single agent (Tivicay®), as part of dual therapy (Dovato®, with lamivudine; Juluca®, with rilpivirine), or as part of triple therapy (Triumeq®, with abacavir/lamivudine, or TLD = tenofovir DF/lamivudine/dolutegravir).

Film-coated tablets of 10mg and 25mg were initially developed as pediatric formulations but these are now being replaced by 5mg/10mg dispersible tablets.

Dosing guidelines

HIV infection (1)

DTG is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV) infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

DTG is dosed as 50mg QD; in case of previous failure on an InSTI-based regimen DTG is dosed 50mg BID.

Dosing guidelines in children and adolescents (2)

Body weight (kg)	Dose
3 to less than 6	5 mg once daily
6 to less than 10	
< 6 months	10 mg once daily
≥ 6 months	15 mg once daily
10 to less than 14	20 mg once daily
14 to less than 20	25 mg once daily
20 or greater	30 mg once daily

Children weighing 20kg or more can also take the adult 50mg film-coated tablets

Dosing guidelines in patients with altered pharmacokinetics

No dosage adjustment is required in patients with mild, moderate or severe (CrCl <30 mL/min, not on

dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population.

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C); therefore dolutegravir should be used with caution in these patients.

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 DTG 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:
> 0.30 mg/L (total DTG)

> 0.003 mg/L (= 3 ug/L)(unbound DTG, see below)

See below for more information.

Efficacy

In a phase IIa study in treatment-naïve patients, 3 doses of DTG were tested for 10 days as monotherapy: 2, 10 and 50mg, all given QD (4)). There appeared to be a clear relationship between DTG trough levels and virological response. An extrapolation of the EC_{50} to an EC_{90} yields a value of 0.32 mg/L (ViiV, internal analysis) (note: the original publication from 2011 has an incorrect x-axis of DTG trough levels, this is later corrected as also stated in a review (5)).

The IC_{90} for DTG determined in vitro and corrected for protein binding is somewhat lower: 0.06 mg/L.

In the SPRING-1 study, DTG doses of 10mg once daily, 25mg once daily and 50mg QD were compared to efavirenz 600mg once daily, all with an NRTI backbone (6, 7). After 96 weeks of treatment, there was no difference in effectiveness between the three DTG arms. The mean trough level in the 10mg group was 0.30 mg/L, in the 25mg 0.54 mg/L, and in the 50mg group 1.2 mg/L. Because 50mg was as well tolerated as 10 and 25mg, the 50mg QD has become the registered dose, but this study shows that lower doses were also effective.

A PK analysis of DTG levels from the Sailing study in treatment-experienced but integrase inhibitor naive patients showed that patients with levels in the lowest quartile (median: 0.30 mg/L; range: < LLOQ – 0.55 mg/L) had a lower virological response than in the other quartiles: 63.5% vs 73-82%. That study also included 16 patients who, in addition to 50mg dolutegravir once daily, were also treated with efavirenz, fosamprenavir and/or tipranavir, which were later known to strongly decrease DTG levels. For these combinations it is now recommended to give dolutegravir 50mg BID.
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Based on the above, the conclusion is currently that the minimum target value for the trough level should be 0.30 mg/L, but that we cannot exclude that levels between 0.06 – 0.30 mg/L are also effective. To be on the safe side, we are currently maintaining a lower limit of 0.30 mg/L.

Relationship with occurrence of side effects

DTG is known to cause neuropsychiatric side effects. It is currently unclear whether these are concentration-related.

For example, in a study of 107 Japanese HIV patients on DTG (8) it was found that patients with neuropsychiatric side effects (dizziness, insomnia, headache, anxiety, agitation) had on average higher DTG trough levels than patients without such side effect: 1.31 vs 1.01 mg/l, p=0.0013). In a multivariate analysis, having a dolutegravir trough level > 1.06 mg/l was an independent risk factor for developing a neuropsychiatric adverse reaction.

In contrast, in a study of 40 HIV patients who started dolutegravir (9), Elliot et al. found no association between the height of the dolutegravir level (Cmax, AUC or Cmin) and a decrease in sleep quality and cognition.

Parant et al. describe a case (10) of a 29-year-old woman with a relatively low body weight (51 kg) who developed serious neurological side effects (dizziness, insomnia, agitation, fatigue) 3 weeks after starting 50 mg DTG QD. Her DTG level 15 hours after dosing was 6.1 mg/l, more than three times higher than the population mean (see below). After the patient was advised to take DTG on an empty stomach, the level dropped to 5.6 mg/L and her symptoms persisted. After she switched to a schedule of 50 mg every 48 hours, her complaints disappeared completely and trough levels were 1.1 - 1.2 mg/L.

Toxicity

The most commonly seen treatment emergent adverse reactions in patients on DTG were nausea (13%), diarrhoea (18%) and headache (13%) (1)

Sampling conditions

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

Additional information concerning the interpretation of results

Trough levels should be > 0.30 mg/l in treatment-naive patients; higher levels are required for pre-treated patients, probably depending on the number of integrase mutations, but this is not yet precisely known.

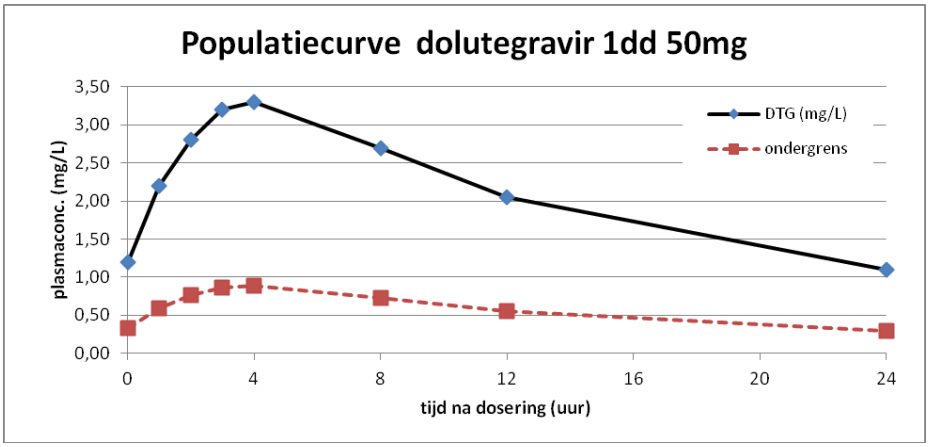
In any case, the advice for integrase-pretreated patients is to take dolutegravir 50 mg BID with food.

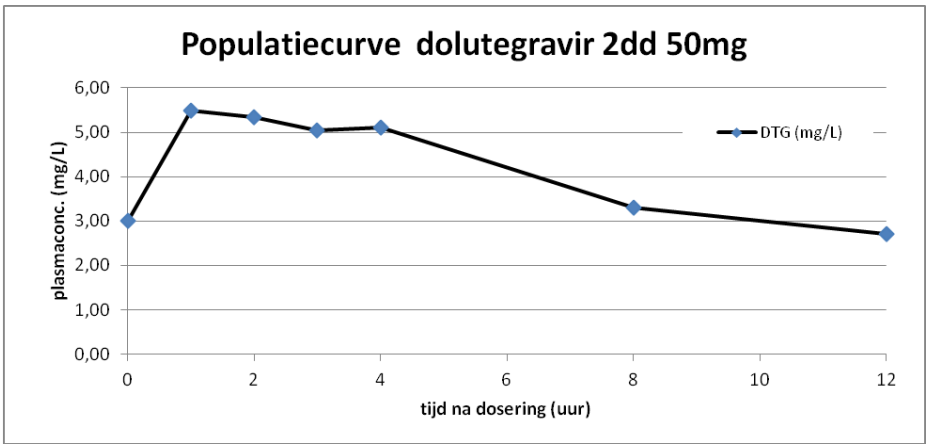
If the level is < 0.30 mg/L: discuss the importance of adherence to therapy, check co-medication for interactions; recommend taking DTG with food and increase the dose if necessary.

In patients with serious neuropsychiatric complaints, a (trough) level can be taken; if this is e.g. more than two times higher than the population value, a dose reduction accompanied by TDM can be considered.

	50mg QD	
tijme (h)	DTG (mg/L)	Lower bound
0	1,20	0,32
1	2,20	0,59
2	2,80	0,76
3	3,20	0,86
4	3,30	0,89
8	2,70	0,73
12	2,05	0,55
24	1,10	0,30

50mg BID	
tijme (h)	DTG (mg/L)
0	3,00
1	5,50
2	5,35
3	5,05
4	5,10
8	3,30
12	2,70





Background information [extended]

Pharmacodynamics

DTG 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 (1).

Pharmacokinetics

T_{max} after oral administration is 2-3h post-dose. Food increases the extent of absorption 33-55% depending on fat content of the meal. However, because absorption on an empty stomach is already adequate, DTG can be taken without regard to intake of food (as long as no InSTI resistance is present).

DTG is highly bound to plasma proteins (>99%). There are a number of situations where interpretation of total DTG levels may be misleading. This is for instance in case the patient is also treated with valproic acid which is known to replace DTG from its protein binding sites (11). Total DTG levels can then decrease,

while free fraction and unbound DTG levels are increased. Not realizing this phenomenon may lead to the incorrect judgement that total DTG levels are subtherapeutic.

A similar mechanism may place in malnourished patients, for instance co-infected with TB. In these case determination of free DTG levels is indicated. Target trough value is then > 0,003 mg/L = 3 ug/L).

DTG is metabolized through UGT1A1 with a minor CYP3A component. 53% of a DTG dose is excreted unhanged by the feces. Elimination of unchanged DTG in the urine is <1%

The elimination half-life of DTG is 14h.

Pharmacogenetics

There is no evidence that common polymorphisms in drug metabolising enzymes alter DTG pharmacokinetics to a clinically meaningful extent. In a meta-analysis (12) using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor DTG metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

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		1.0	0.26	14	>99.0%	2-3	(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		2.24	0.768		0.438	(14)

Literatuur

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Colophon

This guideline has been constituted by David Burger, PharmD,
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