TDM monograph Elvitegravir

Genvoya®, Stribild®

Summary

Indication:	HIV infection Off-label indications: none Indications 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: > 0.13 mg/L to prevent virological failure
Evidence level:	3

Contents

Introduction

Elvitegravir (EVG) is an HIV-integrase strand transfer inhibitor (InSTI) that is always combined with cobicistat as a CYP3A booster (EVG/c). EVG when administered alone has low absorption and rapid elimination. EVG/c is only available as part of a single-tablet regimen (STR) with 2 NRTIs.

There are 2 STRs containing EVG/c: Stribild® and Genvoya®. The only difference is the type of prodrug of tenofovir. Stribild contains tenofovir disoproxil fumarate (TDF); Genvoya contains tenofovir alafenamide fumarate (TAF). Genvoya is more widely used.

Dosing guidelines

Indication (1)

Elvitegravir + cobicistat is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in adults and paediatric patients aged from 2 years and with body weight at least 14 kg.

The adult dose is elvitegravir 150mg + 150mg of cobicistat with food.

Dosing guidelines in children and adolescents (1)(2)

Children 2 years of age and older, weighing 14-25kg: 1 tablet of elvitegravir 90mg + 90mg of cobicistat (plus 120mg of emtricitabine and 6mg of tenofovir alafenamide fumarate) with food.
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Children 2 years of age and older, weighing >25kg can take the adult dose with food.

Dosing guidelines in patients with altered pharmacokinetics (1)

No dose adjustment of EVG/c is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 30 mL/min. EVG/c should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment. This is mainly caused by the inclusion of emtricitabine for which dose adjustments are recommended when eGFR declines below 30 mL/min.

No dose adjustment of EVG/c is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis. On days of haemodialysis, EVG/c should be administered after completion of haemodialysis treatment.

EVG/c should be avoided in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min, or < 15 mL/min who are not on chronic haemodialysis, as the safety of EVG/c has not been established in these populations.

No data are available to make dose recommendations in children aged less than 12 years with renal impairment or in children less than 18 years with end stage renal disease.

No dose adjustment of EVG/c is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. EVG/c has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, EVG/c is not recommended for use in patients with severe hepatic impairment.

See also (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 EVG 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:
> 0.13 mg/L to prevent virological failure

Efficacy

Early in the development of EVG it became clear that the trough level was related to the virological response (4). An Emax model showed an almost maximal response at trough levels: the EC_{90} was > 0.13 mg/L. Based on this the dosage of elvitegravir (150mg) was also chosen as well as the required dose of the booster (initially ritonavir (100mg), later cobicistat (150mg).

Relationship with occurrence of side effects

No relationship has been described between EVG plasma concentrations and adverse events.

Toxicity (1)

The most frequently reported adverse reactions in clinical studies through 144 weeks were nausea (11%), diarrhoea (7%), and headache (6%).

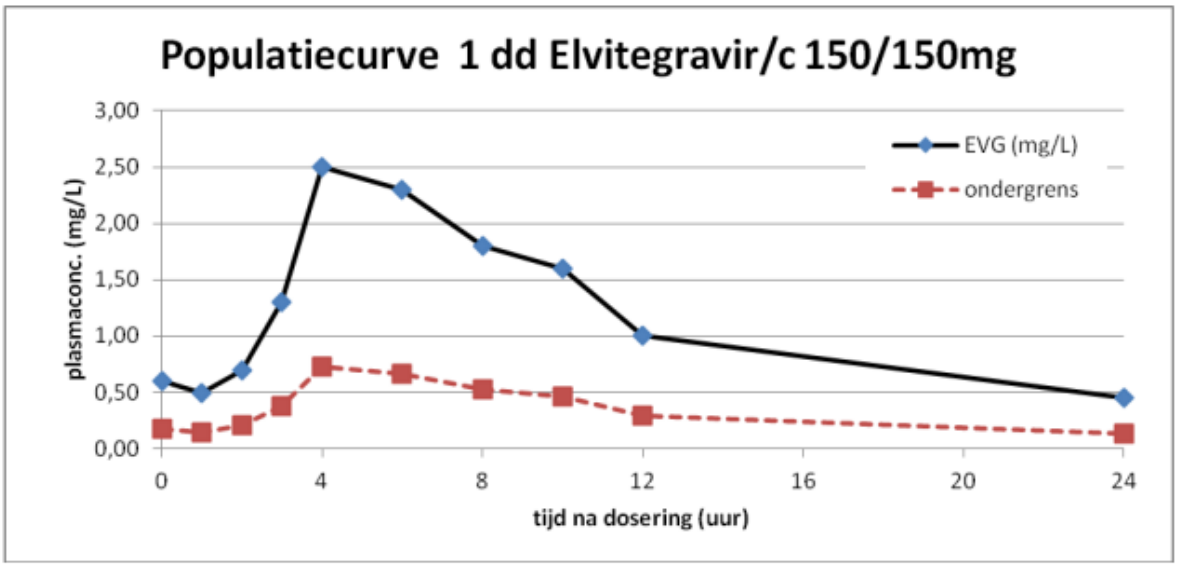
Sampling conditions

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

tijd (h)	EVG (mg/L)	ondergrens
0	0,60	0,17
1	0,49	0,14
2	0,70	0,20
3	1,30	0,38
4	2,50	0,73
6	2,30	0,67
8	1,80	0,52
10	1,60	0,46
12	1,00	0,29
24	0,45	0,13

The population curve has been derived from the paper of Ramanathan et al. (5)



Background information [extended]

Pharmacodynamics (1)

Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 deoxyribonucleic acid (DNA) into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection.

Cobicistat is a selective, mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism

Pharmacokinetics (1)

Following oral administration with food in HIV-1 infected patients, peak plasma concentrations were observed approximately 4 hours post-dose for EVG and 3 hours post-dose for cobicistat. The steady-state mean Cmax, AUCtau, and Ctrough (mean ± SD) in HIV-1 infected patients, respectively, were 1.7 ± 0.39 µg/mL, 23 ± 7.5 µg•h/mL, and 0.45 ± 0.26 µg/mL for EVG, which provides inhibitory quotient of ~10 (ratio of Ctrough: protein binding-adjusted IC95 for wild-type HIV-1 virus).

For EVG, Cmax and AUC increased 22% and 36% with a light meal, and 56% and 91% with a high-fat meal, relative to fasting conditions.

EVG is 98-99% bound to human plasma proteins and binding is independent of drug concentration over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio was 1.37.

Cobicistat is 97-98% bound to human plasma proteins and the mean plasma to blood drug concentration ratio was 2.

EVG undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of boosted [14C]-elvitegravir, elvitegravir was the predominant species in plasma, representing ~94% of the circulating radioactivity. Aromatic and 32 aliphatic hydroxylation or glucuronidation metabolites are present in very low levels, displaying considerably lower antiviral activity against HIV-1 and do not contribute to the overall antiviral activity of EVG.

Cobicistat is metabolised via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [14C]-cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat

Pharmacogenetics

In a small study with 15 patients, no association between EVG trough levels and a series of SNPs was found (6)

Interactions

See (7)

www.hiv-druginteractions.org

PK parameters

	F (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	$\mathbf{t_{1/2}}$ (h^{-1})	Protein binding	Tmax (h)	Ref.
HIV-infected patients	Not assessed			13	98-99%	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		0.134	12.9		6.55	(8)

Literatuur

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Colophon

This guideline has been constituted by David Burger, PharmD, PhD
Date: January 13, 2025

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 [Jan 13, 2025]