TDM monograph Tenofovir

Synonyms: Viread, Vemlidy, Truvada, Descovy

Summary

Indication:	Treatment of HIV infection Treatment of HBV infection Prevention of HIV infection (pre-exposure prophylaxis (PrEP) TDF only) Indication TDM: Prevention of virological failure
Sample material:	EDTA (without gel)
Time of sampling:	Trough sample
Storage conditions:	-40º C
Interpretation:	Mean TFV plasma trough levels after intake of TDF 245mg QD or TAF 25mg QD are 0.070 mg/L and 0.009 mg/L, respectively
Evidence level:	4

Contents

Introduction

Tenofovir (TFV) is a nucleotide reverse transcriptase inhibitor. Because absorption of tenofovir alone is minimal, it is formulated as a prodrug, either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF). TFV plasma concentrations in plasma after intake of TAF are much lower than for TDF; in contrast, intracellular levels of the active component, TFV-diphosphate (TFV-DP), are much higher after intake of TAF vs for TDF. Measurement of intracellular levels of TFV-DP is not possible as part of TDM, measurement of TFV in plasma can be seen as a surrogate marker of TFV-DP concentrations intracellularly.

Dosing guidelines

Treatment of HIV infection & & Treatment of HBV infection

HIV infection: TDF: 245mg QD (NB in the US this is 300mg QD because there the dose is calculated as TDF; in Europe the dose is calculated as TD. In both circumstances, the dose of active TFV is similar (1))

HIV infection: TAF 25mg QD. When co-formulated with a booster such as cobicistat or ritonavir: 10mg QD (2)

Prevention of HIV infection (pre-exposure prophylaxis (PrEP) TDF only)

Pre-exposure prophylaxis of HIV infection (TDF only): 245mg QD or on demand TDF: 2-1-1 schedule (1)

Dosing guidelines in children and adolescents

Although TDF is licensed in children 6 years and older, the potential side effect on bone growth will limit its use in children. TAF is also licensed in children >6 years and has a better safety profile (3).

Dosing guidelines in patients with altered pharmacokinetics

See (4)
Page 84: Dose adjustment of ARVs for impaired renal function
Page 93: Dose adjustment of ARVs for impaired hepatic function

Indications/Criteria for TDM

Because TFV in plasma is not the active component, there is no therapeutic range defined for TFV plasma concentrations. Measurement of TFV in plasma can be seen as a surrogate of TFV-DP levels intracellularly.

The main indication of TDM of tenofovir in plasma is to check for nonadherence. When tenofovir plasma concentrations are below the LLOQ, a suspicion of nonadherence can be confirmed.

When TDF is used as daily PrEP (245mg QD), a target of 0.016 mg/L has been defined as being protective (5)

Reference values

HIV and HBV treatment: Mean TFV plasma trough levels after intake of TDF 245mg QD or TAF 25mg QD are 0.070 mg/L and 0.009 mg/L, respectively (1, 2).

PrEP (daily TDF only): TFV trough level > 0.016 mg/L (5)

Efficacy

For treatment of HIV or HBV infection, no relationship between plasma concentrations of TFV and virological response has been determined.

TDF (in combination with emtricitabine) is also being used as pre-exposure prophylaxis (PREP) to prevent HIV infection. Extensive research on TFV PK/PD has shown that TFV trough levels of at least 0.016 mg/L in men are protective. This trough level corresponds to TFV-DP levels that have been observed with adherence levels of approx. 4/7 days that were still protective.

Relationship with occurrence of side effects

The major toxicity of TFV is impairment of renal function (1). When using TDF, approximately 15% of chronic HIV-infected patients have TDF-induced nephrotoxicity after 2-9 years of use. These include renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome). Remarkably, renal toxicity of TDF in HBV-infected patients is less prominent than in HIV-infected patients, suggesting an influence of HIV (or co-medication) itself.

TFV plasma concentrations after ingestion of TDF were linked to renal tubular dysfunction (6). With the use of TAF, the occurrence of renal dysfunction is rare.

Other factors associated with higher plasma TFV levels are older age and low BMI (7)

Toxicity

TDF: In patients receiving tenofovir disoproxil, rare events of renal impairment,
renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (1)

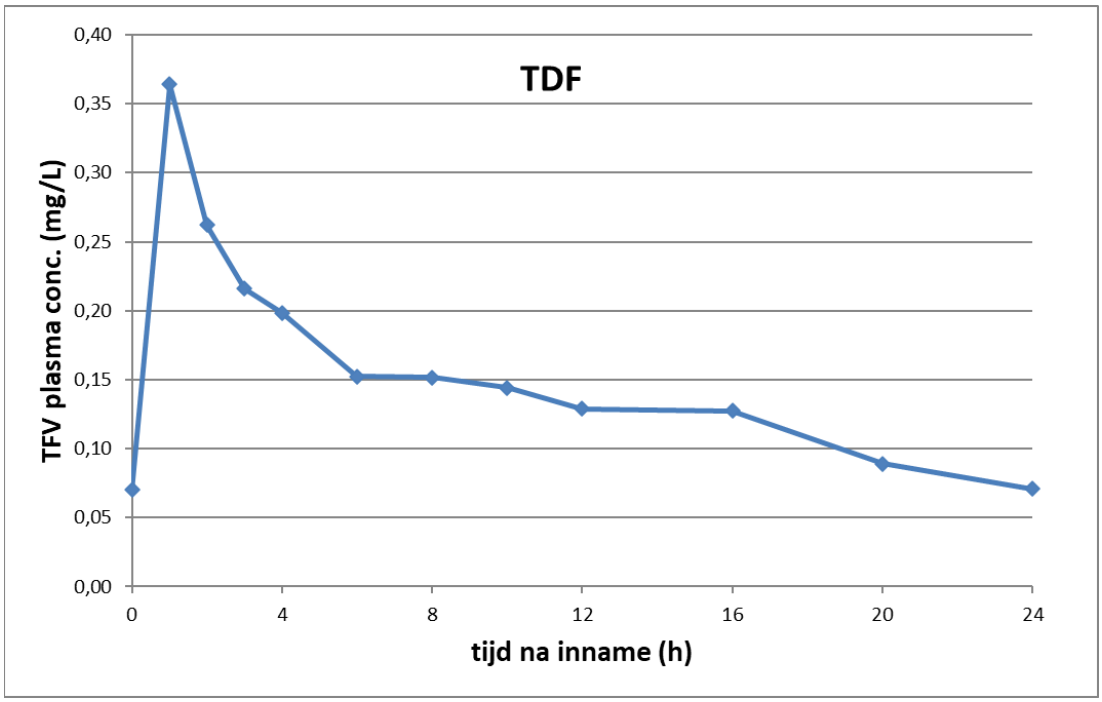
TAF: Assessment of adverse reactions is based on clinical study data and postmarketing data. In pooled safety data from 2 controlled Phase 3 studies (GS-US-320-0108 and GS-US-320-0110; “Study 108” and “Study 110”, respectively), the most frequently reported adverse reactions at Week 96 analysis were headache (12%), nausea (6%), and fatigue (6%). After Week 96, patients either remained on their original blinded treatment up to Week 144 or received open-label tenofovir alafenamide (2)

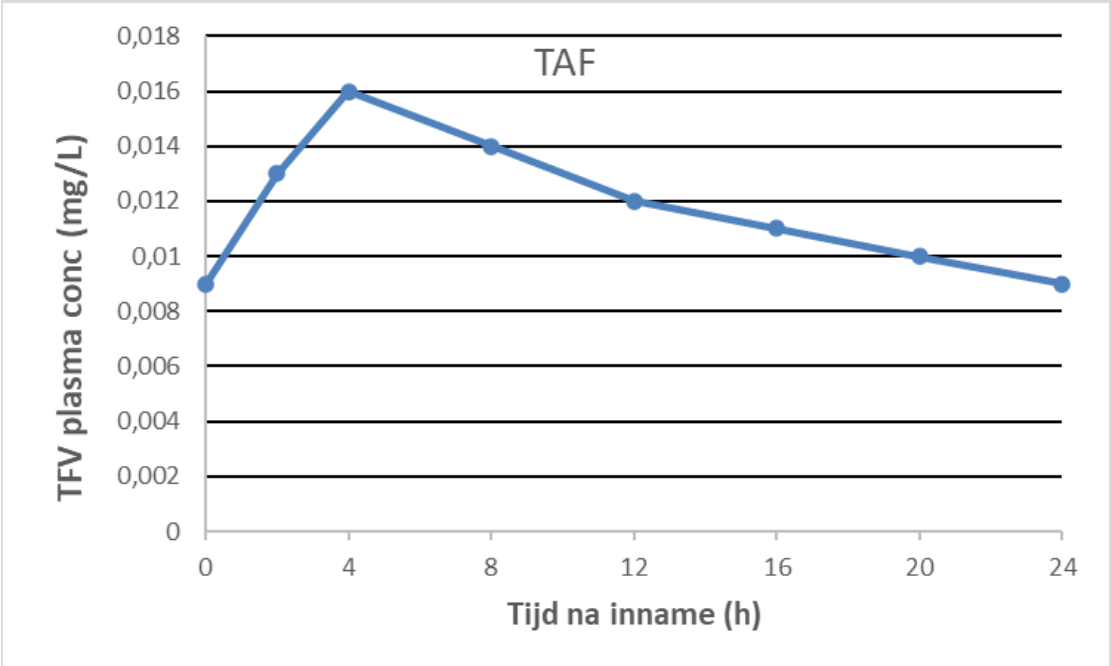
Sampling conditions

N.A.

Additional information concerning the interpretation of results

Population curves:





Background information [extended]

Pharmacodynamics

TDF: Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in in vitro assays (1).

TAF: Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is primarily hydrolysed to form tenofovir by carboxylesterase 1 in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination.
Tenofovir has activity that is specific to HBV and HIV (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses (2).

Pharmacokinetics

TDF: TDF is a water soluble ester prodrug of tenofovir. After absorption TDF is rapidly converted by plasma esterases to tenofovir which is then available for cellular uptake and conversion to its active metabolite TFV-DP. A high fat meal increases the bioavailability of TFV.

Protein binding of TFV is <10%. TFV is not subject of hepatic metabolism but primary excreted unchanged by the kidneys. Elimination half-life is 12-18h (1)

TAF: TAF is a water soluble ester of tenofovir which is more stable in plasma than TDF. A high fat meal increases the bioavailability of TAF.

TAF is converted to tenofovir by intracellular enzymes. TAF is minimally metabolized by CYP3A. The elimination half-life of TAF and TFV (from TAF) are 0.5 and 32h, respectively. (2)

Pharmacogenetics

Not applicable

Interactions

See (8)

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.
TFV (from TDF)			0,8	12-18	<10%	1	(1)
TFV (from TAF)				32	<10%	4	(2)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/h^{-1}) **/ F**	Ref.
HIV-infected patients	TDF	3.04	356		44.7	(9)
HIV-infected patients	TAF	1.45	356		44.7	(9)

Literature

1. EMA. Viread; Summary of Product Characteristics 2014 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000419/WC500051737.pdf.
2. EMA. Vemlidy. Summary of Product Characteristics (SmPC). 2021.
3. Kinderformularium. Tenofovir. https://www.kinderformularium.nl/geneesmiddel/3407/tenofovir-disoproxil-als-fumaraat
4. EACS. the European Guidelines for the treatment of HIV-positive adults in Europe: version 12.0 2023 [Available from: https://www.eacsociety.org/media/guidelines-12.0.pdf.
5. Garcia-Cremades M, Vucicevic K, Hendrix CW, Jayachandran P, Jarlsberg L, Grant R, et al. Characterizing HIV-Preventive, Plasma Tenofovir Concentrations-A Pooled Participant-level Data Analysis From Human Immunodeficiency Virus Preexposure Prophylaxis Clinical Trials. Clinical Infectious Diseases. 2022;75(11):1873-82.
6. Ezinga M, Wetzels JF, Bosch ME, van der Ven AJ, Burger DM. Long-term treatment with tenofovir: prevalence of kidney tubular dysfunction and its association with tenofovir plasma concentration. Antivir Ther. 2014;19(8):765-71.
7. Baxi SM, Greenblatt RM, Bacchetti P, Scherzer R, Minkoff H, Huang Y, et al. Common clinical conditions - age, low BMI, ritonavir use, mild renal impairment - affect tenofovir pharmacokinetics in a large cohort of HIV-infected women. AIDS. 2014;28(1):59-66.
8. University of Liverpool. HIV drug interactions [Available from: https://www.hiv-druginteractions.org/.
9. Kawuma AN, Wasmann RE, Sinxadi P, Sokhela SM, Chandiwana N, Venter WDF, et al. Population pharmacokinetics of tenofovir given as either tenofovir disoproxil fumarate or tenofovir alafenamide in an African population. CPT: pharmacometrics & systems pharmacology. 2023;12(6):821-30.

Colophon

This guideline has been constituted by DM Burger, PharmD, PhD
Date: May 14, 2024 (version 1.0)
Date: January 2025 (version 2.0)

Appendices

Not applicable

Revision

This guideline has been revised by DM 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)
Date: 22-01-2025

The guidelines was updated based on most recent literature and translated to English