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Vemlidy® (tenofovir alafenamide) Mechanism of Action vs Viread® (tenofovir disoproxil fumarate)

This document is in response to your request for information regarding the molecular pharmacology and mechanism of action (MOA) of Vemlidy® (tenofovir alafenamide [TAF]), compared with that of Vemlidy® (tenofovir disoproxil fumarate [TDF]).

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Product Labeling

Microbiology

TAF MOA[1]

TAF is a phosphonamidate prodrug of TFV (2'-deoxyadenosine MP analog). TAF as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. TAF is then converted to TFV through hydrolysis primarily by CES1 in primary hepatocytes. Intracellular TFV is subsequently phosphorylated by cellular kinases to the pharmacologically active metabolite TFV-DP. TFV-DP inhibits HBV replication through incorporation into viral DNA by the HBV RT, which results in DNA chain-termination.

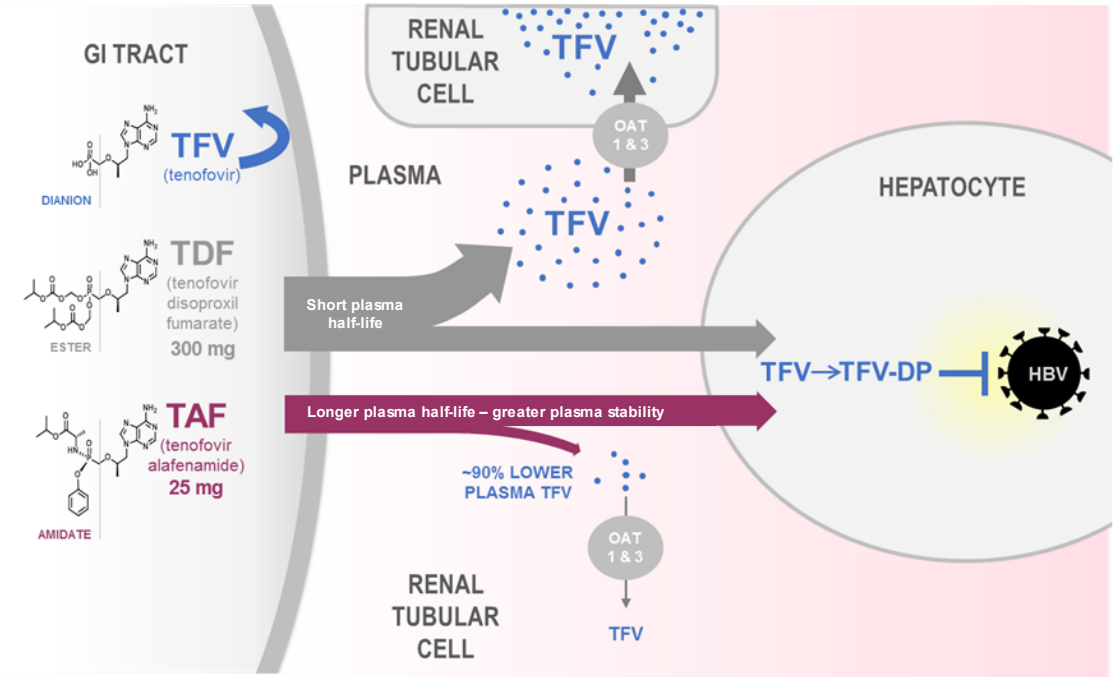
TDF MOA[2]

TDF is an acyclic nucleoside phosphonate diester analog of adenosine MP. TDF requires initial diester hydrolysis for conversion to TFV and subsequent phosphorylations by cellular enzymes to form TFV-DP, an obligate chain terminator. TDF inhibits the activity of HIV-1 RT and HBV RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

MOA and Pharmacology

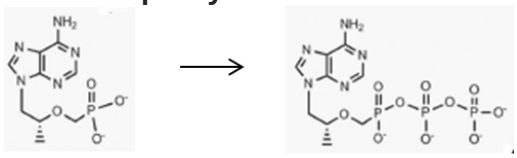
TFV, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-MP, undergoes phosphorylation within hepatocytes to the active metabolite, TFV-DP, which is an effective inhibitor of HBV RT (Figure 1 and Figure 2).[1,2]

Figure 1. MOA and PK of TFV Prodrugs[3,4,9]



Abbreviation: GI=gastrointestinal.

Figure 2. Phosphorylation of TFV to TFV-DP[3,4]



TFV TFV-DP

The presence of two negative charges on TFV (dianion), however, limits its cellular permeability and precludes oral administration. To overcome this limitation, TFV prodrugs have been designed.[5]

TDF is an ester prodrug of TFV that uses two lipophilic groups to improve its permeability. Upon oral administration, TDF is rapidly converted to TFV in plasma by undergoing esterase hydrolysis, which removes two ester groups, and which contributes to its short plasma $t_{1/2}$.[3]

TAF is a novel amidate prodrug of TFV that contains phenol and alanine isopropyl esters as the dianion masking groups, resulting in enhanced stability in plasma compared with TDF. Within the hepatocyte, TAF is broken down to TFV by CES1 and in other cells by Cathepsin A.[4-6]

TAF has an in vitro plasma $t_{1/2}$ of 30 to 90 minutes compared with 0.4 minutes for TDF.[1,7,8] This increased TAF serum stability results in a lower plasma exposure of TFV by 89% compared with TDF (Figure 1).[9]

Renal tubular cells assist in clearing out TFV from the plasma via organic anion transporters, specifically OAT1 and OAT3.[10]

References

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Abbreviations

CES=carboxylesterase
MOA=mechanism of action
MP=monophosphate
OAT=organic anion transporter
PK=pharmacokinetic(s)
RT=reverse transcriptase
$t_{1/2}$=half-life
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy and Viread US prescribing information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/viread/viread_pi.

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