**Tenofovir DF Dosing in Renal Impairment**

The pharmacokinetics, safety, and efficacy of tenofovir DF in patients with renal insufficiency or renal failure, including those who are receiving hemodialysis, have not been evaluated. In tenofovir DF clinical trials, patients with renal insufficiency were excluded from enrollment. Because tenofovir is primarily renally eliminated, tenofovir pharmacokinetics will be affected by renal impairment. As stated in the Viread prescribing information, tenofovir DF should not be administered to patients with renal insufficiency (CrCl <60 mL/min) until further data become available describing the disposition of tenofovir DF in these patients.

Currently, a pharmacokinetic study in renally impaired and renal failure patients, including those who are receiving hemodialysis, is in progress.

**Pharmacokinetics of Tenofovir DF in Normals**

**Absorption and Bioavailability**

Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Following oral administration in HIV-infected patients, tenofovir DF is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from the tenofovir DF 300 mg tablet in fasted patients is approximately 25% (Viread Prescribing Information).

**Effects of Food on Oral Absorption**

Administration of a tenofovir DF 300 mg tablet immediately after a standardized high fat meal (approximately 700-1000 kcal, 40-50% fat) enhanced bioavailability, with an increase in tenofovir AUC and Cmax of approximately 40% and 14%, respectively (Kearney et al. 2001a; Viread Prescribing Information). Using the pharmacokinetic data from IV administration of tenofovir, the oral bioavailability of tenofovir DF 300 mg in the fed state was estimated to be 39% (Barditch-Crovo et al. 2001). Food also delayed Tmax by approximately 1 hour.

**Distribution**

After oral administration of tenofovir DF to dogs, tenofovir is distributed into most tissues with the highest concentration occurring in the kidney and liver (data on file, Gilead Sciences, Inc.). In vitro protein binding of tenofovir to human plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range of 0.01 to 25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following IV administration of tenofovir 1.0 mg/kg and 3.0 mg/kg, respectively (Viread Prescribing Information).

**Half-life**

The terminal elimination half-life of tenofovir is approximately 17 hours (Kearney et al. 2001a). In an in vitro study, the half-life of tenofovir diphosphate in resting human peripheral blood mononuclear cells (PBMCs) was found to be approximately 50 hours, whereas the half-life in activated human PBMCs was found to be approximately 10 hours (Robbins et al. 1998).

**Elimination**

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. After multiple oral doses of tenofovir DF 300 mg once daily (under fed conditions), 32% of the administered dose is recovered in urine over 24 hours (Viread Prescribing Information).
Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion as renal clearance is approximately 2 times the glomerular filtration rate. There may be competition for elimination with other compounds that are also renally eliminated (Viread Prescribing Information). The removal of tenofovir by hemodialysis or peritoneal dialysis is unknown at this time.

**Dosing in Renal Impairment**

In situations where drug-specific data or guidelines are not available for dosing in renal impairment, some clinicians may elect to use general dosage equations. In the approach developed by Rowland and Tozer (1989), only basic pharmacokinetic parameters are necessary to construct a dosing estimate. The parameters required include the fraction of drug (assuming complete absorption) excreted unchanged in urine and the ratio of the patient's renal function (as estimated by the Cockcroft and Gault [1976] method) to that of normal. For drugs with minimal protein binding (<25%) and a fraction excreted unchanged in urine of ≥70%, a simplified method for extending the dosage interval while maintaining the standard dose has been developed (See Table 1; Matske et al. 1992, 2002; Rowland et al. 1989).

**Table 1: Practical Dosing Intervals for use of Tenofovir DF 300 mg in Renal Impairment as Estimated by the Matzke Method**

<table>
<thead>
<tr>
<th>Creatinine Clearance ( \text{mL/min} ) (degree of impairment)</th>
<th>Dosing Interval Range Predicted by Method</th>
<th>Practical Dosage Estimate by Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 (none to mild)</td>
<td>42 - 24 hr</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td>30 – 49 (moderate)</td>
<td>55 – 43 hr</td>
<td>300 mg every 48 hr</td>
</tr>
<tr>
<td>10 – 29 (severe)</td>
<td>77 – 56 hr</td>
<td>300 mg every 72 hr</td>
</tr>
<tr>
<td>&lt;10 (end stage)</td>
<td>96 – 78 hr</td>
<td>300 mg every 96 hr</td>
</tr>
<tr>
<td>ESRD(^a) requiring hemodialysis</td>
<td>NA(^b)</td>
<td>NA(^b)</td>
</tr>
</tbody>
</table>

\(^{a}\)Matske et al. 1992, 2002  
\(^{b}\)ESRD = end stage renal disease  
\(^{b}\)NA = not applicable and cannot be derived from the dosing method

It is important to recognize the major assumptions and limitations inherent in using this approach to dose drugs in renal impairment. The method assumes that: 1) drug bioavailability is unchanged in renal impairment; 2) drug metabolites are not therapeutically active or toxic; 3) drug metabolism is not altered by decreased renal function; 4) the drug does not exhibit concentration-dependent pharmacokinetics; 5) patient renal function is constant over time; and 6) renal clearance of the drug is proportional to creatinine clearance.

Tenofovir DF is principally eliminated by the kidney. Tenofovir DF should not be administered to patients with renal insufficiency (creatinine clearance <60 mL/minute) until data become available describing the disposition of tenofovir DF in these patients (Viread Prescribing Information).

Post-approval, renal impairment, which may include hypophosphatemia, has been reported with the use of tenofovir DF. The majority of these cases occurred in patients with underlying systemic or renal disease or in patients taking nephrotoxic agents.

Tenofovir DF should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be periodically monitored for changes in serum creatinine and phosphorus.
Tenofovir DF Dosing in Renal Impairment References:


