



## 12.3 Pharmacokinetics

The effect of food on evelring, lamivudine and tenofovir disoproxil fumarate has not been evaluated.

**Evelring:** In HIV-infected subjects, time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached at 8 to 10 days. ETV is highly bound (approximately 99.3 to 99.7%) to human plasma proteins, predominantly albumin. Following administration of <sup>14</sup>C-labeled ETV, 14 to 34% of the dose was recovered in the urine (mostly as metabolites) and 16 to 61% was recovered in feces (mostly as parent drug). In vitro studies confirmed CYP3A4 and CYP2C8 as the major isoenzymes responsible for ETV clearance. ETV has been shown to induce CYP3A4, resulting in induction of its own metabolism. ETV has terminal half-life of 52 to 70 hours after single doses and 40 to 50 hours after multiple doses.

**Lamivudine:** After oral administration of a single 150 mg tablet of ETV twice a day to adults with HIV-1, the peak serum C<sub>max</sub> concentration (C<sub>max</sub>) was 1.5 to 0.5 mg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C<sub>min</sub> increased in proportion to the dose over the range from 0.25 to 10 mg/kg and absolute bioavailability was 86% ± 14% (mean ± SD) for the 150 mg tablet and 87% ± 13% for the oral solution. Binding of ETV to human plasma proteins is low (< 30%). Within 12 hours after a single oral dose of 150 mg, ETV is eliminated almost entirely as active organic conjugates and the observed mean elimination half-life (t<sub>1/2</sub>) ranged from 1.5 to 1.9 hours in most study subjects with serum sampling for 24 hours after dosing.

**Tenofovir Disoproxil Fumarate:** Following oral administration of a single 300 mg dose of TDF to HIV-1 infected subjects in the latest study, maximum serum concentrations (C<sub>max</sub>) were achieved at 1.0 to 4.4 hours (mean ± SD) and C<sub>min</sub> values were 296.0 ng/mL and 0.287 to 0.852 ng/mL, respectively. The oral bioavailability of tenofovir from TDF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.1 to 250 mg/mL. Approximately 70% of the total intracellular dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated as a combination of general filtration and active tubular secretion with a renal clearance in adults with normal renal function of 42 to 23 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

### Special Populations

**Evelring and Lamivudine:** There are no significant or clinically relevant racial differences in ETV and 3TC pharmacokinetics.

**Tenofovir Disoproxil Fumarate:** There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

**Gender:** There are no significant or clinically relevant gender differences in the pharmacokinetics of ETV, 3TC, and TDF.

**Geriatric Patients:** The pharmacokinetics of 3TC and TDF were not studied in patients over the age of 65 years.

**Patients with Renal Impairment (See Use in Specific Populations (6.2))**

**Patients with Hepatic Impairment (See Use in Specific Populations (6.3))**

**Lamivudine:** The pharmacokinetics of 3TC were not studied in subjects with renal impairment (See Use in Specific Populations (6.2)).

### Table 7. Pharmacokinetic Parameters (Mean ± SD) of Tenofovir After a Single 300-mg Oral Dose of TDF in Subjects with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Category (Subjects of Total Population)			
	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)	60 to 80 mL/min (N = 4)	30 to 60 mL/min (N = 11)	< 10 mL/min (N = 6)
-----------	---------------------	-------------------------	--------------------------	---------------------

Parameter	> 80 mL/min (N = 6)
-----------	---------------------