Plasma and Intracellular Pharmacokinetics of Tenofovir Disoproxil Fumarate 300 mg Every 48 Hours vs 150 mg Once Daily in HIV-Infected Adults With Moderate Renal Function Impairment

Tim R. Cressey, Anchalee Avihingsanon, Guttiga Halue, Prattana Leenasirimakul, Pra-ornsuda Sukrakanchana, Yardpirono Tawon, Nirattiya Jaisieng, Gonzague Jourdain, Anthony T. Podany, Courtney V. Fletcher, Virat Klinbuayaem, and Chureeratana Bowonwatanuwong

1Program for HIV Prevention and Treatment, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand; 2Harvard School of Public Health, Boston, Massachusetts; 3Institut de Recherche pour le Développement UMI 174–Program for HIV Prevention and Treatment, Marseille, France; 4HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross AIDS Research Centre, 5Division of Allergy and Immunology, Faculty of Medicine, Chulalongkorn University, Bangkok, 6Phayao Hospital, and 7Nakornping Hospital, Chiang Mai, Thailand; 8Antiviral Pharmacology Laboratory, College of Pharmacy, University of Nebraska Medical Center, Omaha; and 9Sanpatong Hospital, Chiang Mai, and 10Chonburi Hospital, Thailand

Background. The approved tenofovir disoproxil fumarate (TDF) dose of 300 mg every 48 hours for adults with moderate renal impairment is often confusing and inconvenient. Using a new TDF formulation, we compared the pharmacokinetics of the standard dose with a dose of 150 mg once daily in HIV-infected adults.

Methods. This was an open-label pharmacokinetic study. Virologically suppressed HIV-infected adults with a creatinine clearance 30 to <50 mL/minute receiving TDF 300 mg every 48 hours as part of a nonnucleoside reverse transcriptase inhibitor (NNRTI)– or lopinavir/ritonavir (LPV/r)–based regimen were enrolled. Intensive 48-hour blood sampling for pharmacokinetic assessment was performed at enrollment, after which the TDF dose was changed to 150 mg once daily. Two weeks later, 24-hour blood sampling was performed; subjects then returned to the standard dose. Tenofovir (TFV) pharmacokinetic parameters were calculated using a noncompartmental analysis.

Results. Forty adults (55% female) were enrolled: 20 receiving NNRTI-based and 20 receiving LPV/r-based treatment. Median age was 56 years (range, 44–65 years), weight 51 kg (range, 38–80 kg), and creatinine clearance 43.9 mL/minute (range, 30.9–49.7 mL/minute). The TFV geometric mean ratio of the area under the curve (AUC0–48h) for every 24 hours vs every 48 hours was 1.09 (90% confidence interval [CI], .98–1.22) and 1.00 (90% CI, .92–1.09) for patients receiving NNRTI- and LPV/r-based treatment, respectively. Concomitant LPV/r use markedly increased TFV plasma concentrations, and AUC0–48h was 67% higher with the standard dose, whereas no differences in intracellular TFV diphosphate concentrations were observed. All subjects remained virologically suppressed, and no drug-related adverse events were reported.

Conclusions. TDF 150 mg every 24 hours provides comparable systemic exposure to the standard dose of 300 mg every 48 hours in patients with moderate renal impairment.

Clinical Trials Registration. NCT01671982.

Keywords. HIV; tenofovir; kidney dysfunction.
Tenofovir disoproxil fumarate (TDF) is recommended as one of the preferred drugs to be used as part of combination antiretroviral therapy (ART) in treatment-naïve patients [1]. The approved dose of TDF in adults is 300 mg once daily taken orally [2]. TDF is the oral prodrug of tenofovir (TFV). Following oral absorption, TDF is rapidly converted to TFV, a nucleotide (nucleoside monophosphate) analogue. Intracellularly, TFV is phosphorylated by cellular nucleotide kinase to its active abo-
lite TFV diphosphate (TFV-DP), which is a competitive inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. TFV is primarily excreted unchanged by the renal route through a combination of glomerular filtration, and active tubular secretion and renal impairment can significantly alter TFV pharmacokinetics [3]. A pharmacokinetic (PK) study of TDF in HIV-uninfected subjects with varying degrees of renal impairment showed that subjects with a creatinine clearance (CrCl) ≥50 mL/minute (calculated using the Cockcroft-Gault equation) had similar plasma exposure to those with normal renal function, whereas subjects with a CrCl <50 mL/minute had significantly higher exposures [4]. A PK model was developed based on these data, and model predictions showed that TDF 300 mg every 48 hours in patients with CrCl 30–49 mL/minute would provide similar exposure to that of patients with normal renal function receiving the standard dose. TDF 300 mg twice weekly (every 72–96 hours) was predicted to be adequate for patients with a CrCl 10–29 mL/minute. These TDF dosing interval adjustments for subjects with renal impairment are US Food and Drug Administration (FDA) approved [2], but have not been clinically evaluated in HIV-infected adults.

Administering TDF every 48 hours can be confusing and inconvenient for patients, especially if other coadministered antiretrovirals are dosed once and/or twice daily. Lower dosage strengths (150, 200, and 250 mg) and formulations (scored tablets) of TDF have recently become available that may facilitate once-daily dosing for patients with moderate renal impairment. We hypothesized that administration of TDF 150 mg once daily to HIV-infected adults with moderate renal function impairment (CrCl 30 to <50 mL/minute) will provide drug exposure comparable to that of the current recommended dose of TDF 300 mg every 48 hours.

It is also important to assess the pharmacokinetics of TFV in the presence of commonly coadministered drugs. For example, lopinavir/ritonavir (LPV/r) is often prescribed with TDF, particularly as part of second-line regimens in resource-limited settings, and concomitant administration can result in a 32% increase of TFV drug exposure [2, 5].

Our aim was to investigate the plasma and intracellular pharmaco-
kinetics of TFV following a reduced daily dose (TDF 150 mg once daily) vs the current interval adjustment dosing schedule (TDF 300 mg every 48 hours) in HIV-infected adults with moderate renal function impairment receiving either nonnu-
cleoside reverse transcriptase inhibitor (NNRTI)-based or LPV/r-based ART.

**MATERIALS AND METHODS**

**Study Design and Population**

This was a phase 1, nonrandomized, open-label, PK study in HIV-infected adults in Thailand (ClinicalTrials.gov identifier NCT01671982). HIV-infected subjects attending routine outpatient clinic visits with moderate renal impairment and already receiving TDF 300 mg every 48 hours as part of NNRTI- or LPV/r-based ART per standard of care were proposed to participate. The required sample size was 40 adults: 20 subjects receiving TDF plus NNRTI-based highly active antiretroviral therapy (HAART) (group 1) and 20 subjects receiving TDF plus LPV/r-based HAART (group 2) (see “Statistical Considerations and Sample Size” section). All subjects were receiving TDF 300-mg scored tablets manufactured by the Thai Government Pharmaceutical Organization (GPO). The GPO TDF tablet was demonstrated to be bioequivalent to the original Viread formulation (Gilead Sciences, Inc) and has been approved by the Thai FDA. This study was approved by the Ethics Committees at the Ministry of Public Health, Thailand; Faculty of Associated Medical Sciences, Chiang Mai University; and the local hospital ethics committees.

Screening was performed within 30 days of enrollment. ConSENTING subjects were screened for eligibility: age >18 years; confirmed HIV-1 infection; receiving TDF 300 mg every 48 hours for at least 2 weeks as part of an NNRTI-based regimen (group 1) or an LPV/r-based regimen (group 2); CrCl between 30 to <50 mL/minute (defined as 2 CrCl determinations calculated using the Cockcroft-Gault equation within 2 weeks of each other, within 1 month prior to entry); and HIV-1 RNA load <50 copies/mL within 6 months prior to entry. Exclusion criteria were concomitant use of atazanavir or didanosine; pregnan-
cy; any of the following laboratory tests within 30 days prior to entry: neutrophil count, hemoglobin, platelets, aspartate ami-
notransferase, alanine aminotransferase; hepatitis B surface an-
tigen positive; and any clinically significant diseases (other than HIV-1 infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator’s opinion, would compromise participation in this study.

**Plasma and Intracellular PK Assessments**

At study entry (day 0), a 48-hour PK evaluation was performed to evaluate the TDF dose of 300 mg every 48 hours. Following the subject’s normal morning schedule of drug intake, a predose
blood sample was drawn, after which TDF was administered with breakfast by the study nurse using directly observed therapy, and blood samples were drawn at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12, 24, 36, and 48 hours postdose. Peripheral blood mononuclear cells (PBMCs) were also collected at 48 hours postdose for the determination of intracellular TFV-DP concentrations. Immediately after completing the PK sampling, the TDF dose and administration schedule were changed to 150 mg once daily. The TDF 300-mg scored tablet was cut in half to provide the appropriate 150-mg dose. Two weeks later (day 14), subjects had a second series of blood samples drawn identically to those at day 0 over the first 24 hours. A single PBMC sample was also collected 24 hours postdose for determination of intracellular TFV-DP. Once the 24-hour PK sampling was complete, the subjects returned to use the standard TDF dose of 300 mg every 48 hours and were off-study.

**Measurement of TFV Plasma and Intracellular TFV-DP Concentrations**

Blood samples collected for plasma TFV measurements were centrifuged and the plasma was frozen at −20°C. TFV plasma drug concentrations were measured using a high-performance liquid chromatography assay with fluorescent detection [6]. This method was internally validated; the average accuracy was 99%–102%, and precision (inter- and intra-assay) was <6% of the coefficient of variation. The lower limit of assay quantification is 0.015 mg/L. Plasma samples were assayed at the Program for HIV Prevention and Treatment laboratory at Chiang Mai University. PBMCs collected at the specified time points were isolated, extracted, and stored at −70°C. PBMC extracts were assayed for TFV-DP concentration at the Antiviral Pharmacology Laboratory, University of Nebraska Medical Center, using a previously validated liquid chromatography–tandem mass spectrometry assay [7]. Both laboratories participate in the international external quality control program of the AIDS Clinical Trial Group Pharmacology Quality Control (Precision Testing) program [8].

**Pharmacokinetic Analyses**

Steady-state TFV plasma concentration data were analyzed using noncompartmental methods (Phoenix, WinNonLin version 6.3, Pharsight, Missouri). Calculated PK parameters included area under the curve of the plasma concentration vs time profile (AUC0–t), maximum plasma concentration (Cmax), time to Cmax (Tmax), apparent oral clearance (CL/F), minimum plasma concentration during the dosing interval (Cmin), and last concentration measured postdose (Clast). AUC0–t is the exposure during a single dosing interval (ie, AUC0–48 or AUC0–24) and was determined using the linear trapezoidal method. Cmax, Cmin, and Tmax (eg, T24h or T24d, depending on the TDF dosing schedule), and Tlast were taken directly from the observed concentration-time data. The terminal slope λz was determined from the log-linear portion of the curve. Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) were calculated for within-patient comparisons of PK parameters for every-24-hour vs every-48-hour TDF dosing. Nonpharmacokinetic statistical analyses were performed using Stata software (version 10.1, StataCorp LP, College Station, Texas). Wilcoxon rank-sum tests were used to compare TFV PK parameters between groups. A 2-sided P value of ≤0.05 was considered statistically significant.

**Statistical Considerations and Sample Size**

The sample size was based on ensuring precision in PK parameter estimates. The mean (±standard deviation [SD]) TFV AUC reported in HIV-infected adults is 3.32 ± 1.37 mg × hour/L (coefficient of variation 41.2%) following multiple doses of 300 mg once daily in the fed state [2]. Based on this variability at the standard dose and assuming that average AUC results are approximately normally distributed, to be 95% confident that the TFV AUC sample mean is within 0.66 µg hour/mL (equivalent to 20% precision) of the true mean, a sample size of 17 subjects was required per group. Also, for the within-subjects comparison, 17 patients would provide at least 80% power for the width of the 90% CI for the mean log10 AUC difference between 48-hour and 24-hour dosing to be <0.2 on the log10 scale (ie, 90% CI GMR falls between 0.8 and 1.25; assuming a within-subject variance of 0.05). To allow for nonevaluable subjects, 20 subjects were enrolled per group, for a total sample size of 40 subjects.

**RESULTS**

**Subject Characteristics**

A total of 40 adults (55% female) were enrolled: 20 subjects in group 1 receiving TDF with an NNRTI and 20 subjects in group 2 receiving TDF with LPV/r. All 40 subjects completed both PK sampling visits. The clinical characteristics of the study population by group at study entry are presented in Table 1. The overall median age was 56 years (range, 44–65 years), weight 51 kg (range, 38–80 kg), serum creatinine 1.3 mg/dL (range, 0.8–2.1 mg/dL), CrCl 43.9 mL/minute (range, 30.9–49.7 mL/minute) and CD4 count 502 cells/µL (range, 113–1063 cells/µL). Within group 1, 10 subjects were receiving efavirenz and 10 were receiving nevirapine. One subject in group 1 and 2 subjects in group 2 were excluded from the PK analysis due to blood sampling errors.

**TFV Plasma Pharmacokinetics: 300 mg Every 48 Hours Versus 150 mg Every 24 Hours**

The plasma TFV PK parameters with 300 mg every 48 hours (day 0) and 150 mg once daily (day 14) for group 1 and group 2 are presented in Table 2. The mean TFV concentration versus time curves following TDF 300 mg every 48 hours and TDF 150 mg once daily for both groups are shown in Figure 1.
Group 1 (TDF/lamivudine/NNRTI): The geometric mean AUC$_{0-48h}$ ratio (GMR) of TDF 150 mg every 24 hours/300 mg every 48 hours was 1.09 (90% CI, .98–1.22). The mean TFV C$_{max}$ was reduced by 29% with the lower 150-mg dose (GMR, 0.71 [90% CI, .62–.80]), but the Cl$_{ast}$ was 63% higher (GMR, 1.63 [90% CI, 1.34–1.99]). Group 2 (TDF/lamivudine/LPV/r):

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1: TDF-NNRTI (n = 20)</th>
<th>Group 2: TDF-LPV/r (n = 20)</th>
<th>Total (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (30%)</td>
<td>12 (60%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (70%)</td>
<td>8 (40%)</td>
<td>22 (55%)</td>
</tr>
<tr>
<td><strong>Race/ethnicity: Asian</strong></td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td>40 (100%)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>59 (44–65)</td>
<td>53 (39–82)</td>
<td>56 (39–82)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>54.0 (40.0–80.0)</td>
<td>49.5 (37.8–75.1)</td>
<td>50.6 (37.8–80)</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m$^2$</strong></td>
<td>21.8 (17.9–32.9)</td>
<td>19.2 (16.3–29)</td>
<td>20.8 (16.3–32.9)</td>
</tr>
<tr>
<td><strong>Creatinine, mg/dL</strong></td>
<td>1.2 (0.8–1.9)</td>
<td>1.3 (0.9–2.1)</td>
<td>1.3 (0.8–2.1)</td>
</tr>
<tr>
<td><strong>Creatinine clearance, mL/min</strong></td>
<td>45.7 (30.9–49.6)</td>
<td>42.0 (31.7–49.7)</td>
<td>43.9 (30.9–49.7)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA load, copies/mL</strong></td>
<td>&lt;50 (&lt;50 to &lt;50)</td>
<td>&lt;50 (&lt;50 to &lt;50)</td>
<td>&lt;50 (&lt;50 to &lt;50)</td>
</tr>
<tr>
<td><strong>CD4 count, cells/µL</strong></td>
<td>465 (170–773)</td>
<td>596 (113–1063)</td>
<td>502 (113–1063)</td>
</tr>
<tr>
<td><strong>HAART regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF + 3TC + EFV</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF + 3TC + NVP</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF + 3TC + LPV/r</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF + 3TC + ZDV + LPV/r</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as No. (%) or median (range).

Abbreviations: 3TC, lamivudine; EFV, efavirenz; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

**Table 2. Steady-State Tenofovir Pharmacokinetic Parameters With Tenofovir Disoproxil Fumarate 300 mg Every 48 Hours or 150 mg Once Daily as Part of Nonnucleoside Reverse Transcriptase Inhibitor– and Lopinavir/Ritonavir–Based Treatment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TDF 300 mg, Every 48 h</th>
<th>TDF 150 mg, Every 24 h</th>
<th>GMR (90% CI) 24 h/48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: TDF/3TC/NNRTI (n = 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-τ}$, mg × h/L</td>
<td>5.76 (3.34–11.08)</td>
<td>3.15 (1.73–6.49)</td>
<td>NA</td>
</tr>
<tr>
<td>AUC$_{0-48h}$, mg × h/L</td>
<td>5.76 (3.34–11.08)</td>
<td>6.29 (3.45–12.99)$^a$</td>
<td>1.09 (.98–1.22)</td>
</tr>
<tr>
<td>C$_{max}$, mg/L</td>
<td>0.44 (0.23–0.67)</td>
<td>0.31 (0.16–0.55)</td>
<td>0.71 (.62–.80)</td>
</tr>
<tr>
<td>C$_{ast}$, mg/L</td>
<td>0.04 (0.02–0.10)</td>
<td>0.07 (0.03–0.14)</td>
<td>1.63 (1.34–1.99)</td>
</tr>
<tr>
<td>C$_{min}$, mg/L</td>
<td>0.04 (&lt;0.008–0.10)$^b$</td>
<td>0.07 (0.03–0.14)</td>
<td>1.90 (1.57–2.30)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>23.60 (12.26–40.73)</td>
<td>21.61 (10.47–39.37)</td>
<td>0.91 (.82–1.02)</td>
</tr>
<tr>
<td>T$_{max}$, h</td>
<td>1.50 (0.50–8.00)</td>
<td>1.00 (0.50–4.00)</td>
<td>0.57 (0.40–8.1)</td>
</tr>
</tbody>
</table>

Group 2: TDF/3TC/LPV/r (n = 18)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TDF 300 mg, Every 48 h</th>
<th>TDF 150 mg, Every 24 h</th>
<th>GMR (90% CI) 24 h/48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-τ}$, mg × h/L</td>
<td>9.61 (6.06–18.92)</td>
<td>4.80 (2.61–9.29)</td>
<td>NA</td>
</tr>
<tr>
<td>AUC$_{0-48h}$, mg × h/L</td>
<td>9.61 (6.06–18.92)</td>
<td>9.61 (5.21–18.59)$^a$</td>
<td>1.00 (.92–1.09)</td>
</tr>
<tr>
<td>C$_{max}$, mg/L</td>
<td>0.68 (0.44–1.31)</td>
<td>0.42 (0.24–0.73)</td>
<td>0.55 (.49–.63)</td>
</tr>
<tr>
<td>C$_{ast}$, mg/L</td>
<td>0.07 (0.03–0.11)</td>
<td>0.10 (0.05–0.20)</td>
<td>1.59 (1.35–1.87)</td>
</tr>
<tr>
<td>C$_{min}$, mg/L</td>
<td>0.06 (0.03–0.09)</td>
<td>0.09 (0.04–0.18)</td>
<td>1.42 (1.18–1.72)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>14.15 (7.19–22.44)</td>
<td>14.17 (7.32–26.08)</td>
<td>1.00 (.92–1.08)</td>
</tr>
<tr>
<td>T$_{max}$, h</td>
<td>1.01 (0.48–4.00)</td>
<td>1.25 (0.50–4.00)</td>
<td>1.18 (.83–1.68)</td>
</tr>
</tbody>
</table>

Data are presented as median (range) unless otherwise specified.

Abbreviations: 3TC, lamivudine; AUC$_{0-τ}$, area under the curve of the plasma concentration vs time profile within a single dosing interval; AUC$_{0-48h}$, area under the curve of the plasma concentration vs time profile over 48 hours; CI, confidence interval; CL/F, apparent oral clearance; C$_{max}$, maximum plasma concentration; C$_{min}$, minimum plasma concentration during the dosing interval; GMR, geometric mean ratio; LPV/r, lopinavir/ritonavir; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; T$_{max}$, time to maximum plasma concentration.

$^a$ Calculated as $2 \times$ AUC$_{0-24}$.

$^b$ Assay lower limit of quantification (LLOQ) was 0.008 mg/L (4 samples below the LLOQ from 2 patients).
The geometric mean AUC_{0–48h} ratio (GMR) of TFV was 1.00 (90% CI, 0.92–1.09). The mean TFV C_{\text{max}} was reduced by 45% with the lower 150-mg dose (GMR, 0.55 [90% CI, 0.49–0.63]), but the C_{\text{last}} was 59% higher (GMR, 1.59 [90% CI, 1.35–1.87]).

No differences in PK parameters between sexes within each group were observed. All subjects in group 1 and group 2 remained virologically suppressed, and no adverse events or serious adverse events were reported during the study.

**Comparison of TFV Plasma Pharmacokinetics With NNRTI Versus LPV/r**

With the standard TDF dose of 300 mg every 48 hours, TFV exposure was significantly higher with the concomitant use of LPV/r compared with NNRTIs (Figure 1) (AUC_{0–48h}, 9.61 vs 5.76 mg x hour/L; P < .001). The TFV AUC_{0–48h}, C_{\text{max}}, and C_{\text{last}} were 67%, 55%, and 75% higher, respectively, with LPV/r. Similar increases were also observed after subjects switched to 150 mg every 24 hours; the TFV AUC_{0–48h}, C_{\text{max}}, and C_{\text{last}} were 52%, 35%, and 42% higher, respectively, with LPV/r compared to NNRTIs. The TFV oral clearance (CL/F) was approximately 40% slower in the presence of LPV/r.

**Intracellular TFV-DP Concentrations in Patients With Moderate Renal Dysfunction**

The TFV-DP C_{\text{last}} with 300 mg every 48 hours and 150 mg once daily for group 1 and group 2 are presented in Figure 2. The median duration of TDF 300 mg every 48 hours prior to enrollment was 41 weeks (2–280 weeks). No statistically significant difference was found between TFV-DP C_{\text{last}} with 300 mg every 48 hours vs 150 mg every 24 hours for either group. Four patients (2 per group) received between 2 and 4 weeks of TDF 300 mg every 48 hours prior to enrollment and therefore may not have achieved steady-state intracellular levels (based on an intracellular half-life of 87 hours [9]). TFV-DP levels were reexamined without these patients, but the results did not change. Also, no significant difference was observed between TFV-DP C_{\text{last}} with NNRTIs compared to LPV/r. With TDF 300 mg every 48 hours, the median TFV-DP C_{\text{last}} was 129 (range, 27–945) fmol/10^6 cells with NNRTIs vs 188 (range, 25–497) fmol/10^6 cells with LPV/r (P = .50); whereas for 150 mg every 24 hours, TFV-DP C_{\text{last}} was 158 (range, 47–715) fmol/10^6 cells with NNRTIs vs 182 (range, 33–1030) fmol/10^6 cells with LPV/r (P = .88).

**DISCUSSION**

This is the first report assessing alternative dosing of TDF in HIV-infected adults with moderate renal dysfunction. Our data demonstrate that reducing the approved TDF dose of 300 mg every 48 hours in adults with a CrCl between 30 and <50 mL/minute to 150 mg once daily provides comparable exposure over a 48-hour period when receiving an NNRTI- or LPV/r-based regimen. Additionally, as observed in adults with normal renal function, TFV plasma exposure was significantly higher with concomitant LPV/r use.

In the package insert of TDF (VIREAD), the mean (±SD) TFV AUC_{0–\text{infty}} and C_{\text{max}} following a single 300-mg dose was 6.01 ± 2.05 mg x hour/L and 0.37 ± 0.16 mg/L in subjects with a CrCl between 30 and 49 mL/minute (n = 8) [2]. These values are similar to those observed in the patients enrolled in group 1 receiving TDF with an NNRTI and a CrCl between 30 and 49 mL/minute following multiple doses of TDF 300 mg
every 48 hours (AUC$_{0\text{-}48}$ 5.76 mg × hour/L and C$_{\text{max}}$ 0.44 mg/L). The total apparent CL/F of TFV in group 1 was 23.60 L/hour, which is consistent with the 26.7 L/hour reported in the package insert for patients with a similar degree of renal function impairment. Furthermore, the TFV AUC$_{0\text{-}48}$ in the present study for Thai HIV-infected adults receiving an NNRTI-based regimen was similar to that for adults in the United States with normal renal function receiving the standard 300-mg once-daily dose (5.74 mg × hour/L [2 × AUC$_{0\text{-}24}$] [10]). Although several formulas are now available to estimate CrCl, we used the Cockcroft-Gault equation to be consistent with the package insert and have recently shown in a population PK analysis that CrCl estimated using the Cockcroft-Gault equation significantly influenced TFV oral clearance [11]. Based on our results, we can also speculate that further reduced daily doses of TDF may also be an alternative for patients with severe renal impairment (CrCl of 10–29 mL/minute)—that is, 75 mg once daily—but formal PK studies are needed in this patient group.

A drug–drug interaction between TDF and LPV/r is somewhat unexpected, as these drugs are cleared from the body through different pathways (ie, renal extraction for TFV and hepatic extraction for LPV/r). A greater TFV-associated decline in renal function has been reported with protease inhibitors vs NNRTI-based regimens [12]. Indeed, the TFV AUC$_{0\text{-}24}$, C$_{\text{max}}$, and C$_{\text{last}}$ were observed to be 32%, 15%, and 51% higher in the presence of LPV/r [10]. Another study has found that the renal clearance of TFV was 18% slower in patients with concomitant LPV/r use compared to those receiving no protease inhibitor [5]. We observed a significantly higher TFV exposure among patients receiving LPV/r compared with those receiving an NNRTI, and this was independent of TDF dose. Interestingly, this increase of TFV AUC$_{0\text{-}48}$ and C$_{\text{max}}$ in the presence of LPV/r was approximately 2-fold higher than that previously reported in adults with normal renal function [2]. The mean CL/F of TFV in group 1 was reduced by 40% compared with group 2. Overall, the impact of LPV/r on TFV pharmacokinetics in patients with moderate renal function impairment seems to be higher than in patients with no renal dysfunction; therefore, closer monitoring for drug-related toxicities would be advisable for these patients regardless of TDF dosing interval.

Drug influx/efflux transporters play a key role in the disposition of TFV and may help explain the mechanism of the observed drug–drug interaction. TFV is transported into proximal tubular cells by organic anion transporters located on the basolateral membrane [13]. Three ATP-binding cassette (ABC) transporters—ABCC2 (MRP2) [14], ABCC4 (MRP4) [15], and ABCC10 (MRP7) [16]—have been implicated as playing a role in transporting TFV into the urine. A combination of drug transporter interactions between TFV and LPV/r in the kidney tubular cells may contribute to the changes in TFV pharmacokinetics. TDF is also a substrate for the efflux transporter p-glycoprotein, which is highly expressed in the small intestine. Ritonavir is a potent inhibitor of p-glycoprotein [17], and inhibition of p-glycoprotein in the gut could potentially lead to increased absorption.

In contrast to the plasma TFV concentrations, there was no significant difference in TFV-DP C$_{\text{last}}$ between subjects using NNRTI- or LPV/r-based HAART, although the median values with LPV/r were numerically higher. Also, the TFV-DP C$_{\text{last}}$ was noted to be higher than that reported in HIV-infected adults with normal kidney function, but the between-patient

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**Figure 2.** Intracellular tenofovir diphosphate (TFV-DF) last concentration measured postdose (C$_{\text{last}}$) in patients with moderate renal dysfunction, as part of tenofovir disoproxil fumarate (TDF) plus nonnucleoside reverse transcriptase inhibitor (NNRTI)-based (A) or lopinavir/ritonavir (LPV/r)-based (B) treatment every 48 hours (q48), or once daily (OD). Box-plot represents median and interquartile range.
variability we observed was relatively high. The median TFV-DP concentration 24 hours postdose was 87.2 fmol/10^6 cells in adults with normal renal function (n = 7) receiving 300 mg once daily [18]. However, glomerular filtration rate (GFR) has been shown to be predictive of TFV-DP concentrations, with an 8% increase in intracellular TFV-DP concentration for every 10-mL/minute decrease in GFR [19]. Higher TFV-DP is perhaps reassuring in terms of efficacy, but its consequence on renal tubular toxicity need to be determined.

In summary, our data demonstrate that switching TDF to 150 mg once daily in HIV-infected adults with moderate renal function impairment leads to comparable exposure to the current recommended dose of 300 mg every 48 hours. Although the duration of the reduced TDF dose was relatively short, the preservation of virologic suppression and lack of adverse events were reassuring. This daily TDF dose option for this subpopulation of patients may be preferable to simplify their regimen and facilitate drug adherence, but renal function should be continued to be closely monitored in these patients.

**Notes**

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