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Tenofovir DF 150 mg once daily in HIV-infected adults with moderate renal impairment

Tim R. Cressey
Program for HIV Prevention and Treatment
Faculty of Associated Medical Sciences
Chiang Mai University
Chiang Mai, 50200, Thailand
tim.cressey@phpt.org
t.cressey@hsph.harvard.edu

Tim R. Cressey[1,2,3], Anchalee Avihingsanon[4,5], Guttiga Halue[6], Prattana Leenasirimakul[7], Pra-ornsuda Sukrakanchana[1], Yardpiroon Tawon[1], Nirattiya Jaisieng[1], Gonzague Jourdain[1,2,3], Virat Klinbuayaem[8] and Chureeratana Bowonwatanuwong[9]

[1]Program for HIV Prevention and Treatment (PHPT-IRD URI 174), Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand; [2]Harvard School of Public Health, Boston, MA, [3]Institut de Recherche pour le Développement (IRD) UMI 174-Program for HIV Prevention and Treatment (PHPT), Marseille, France; [4]HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [5]Division of Allergy and Immunology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [6]Phayao Hospital, Phayao, Thailand, [7]Nakornping Hospital, Chiang Mai, Thailand, [8]Thai Government Pharmaceutical Organization, Bangkok, Thailand, [9]Sanpatong hospital, Chiang Mai, Thailand, [10]Chonburi Hospital, Chonburi, Thailand

Original Abstract

Background: Renal impairment significantly alters tenofovir pharmacokinetics. The recommended tenofovir disoproxil fumarate (TDF) dose is 300 mg every 48 hours for adults with moderate renal function impairment (creatinine clearance 30-49 mL/min). New dosage strengths and formations of TDF may permit once daily dosing for these patients. We compared the pharmacokinetics of TDF 300 mg every 48 hours with 150 mg once daily in HIV-infected adults with moderate renal function impairment receiving lopinavir/ritonavir (LPV/r)-based antiretroviral therapy.

Methodology: Phase I, non-randomized, open-label pharmacokinetic study (ClinicalTrials.gov Identifier: NCT01671982). Consenting HIV-positive adults with a confirmed creatinine clearance 30 to <50 mL/min receiving TDF 300 mg every 48 hours as part of LPV/r-based HAART and an HIV-1 RNA viral load (VL) <50 copies/mL were enrolled. HBs-antigen positive adults were excluded. Intensive steady-state 48-hour blood sampling for PK assessment was performed at enrolment; blood samples were collected (pre-dose) and then at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12, 24, 36, 48 hours post-dose. Immediately afterwards, the tenofovir dose was changed to 150 mg once daily. Intensive 24-hour blood sampling was repeated 2 weeks later; blood samples were drawn pre-dose, and at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12, 24 hours post-dose. Subjects returned to the standard TDF dose after the PK sampling. Tenofovir plasma concentrations were determined using a HPLC assay and tenofovir pharmacokinetic parameters were calculated using noncompartmental analysis.

Results: Twenty HIV-infected adults (40% female) were enrolled. Median (range) age was 53 years (39-82), weight 49.5 kg (37.8-75.1), serum creatinine (SCr) 1.3 mg/dL (0.9-2.1), creatinine clearance (CrCL) 42.0 mL/min (31.7-49.7) and CD4 count 596 cell/mm³ (113-1063). Eighteen subjects had evaluable PK data available. With TDF 300 mg every 48 hours, the TDF AUC_{0-48h}, C_{max} and C_{48h} were 9.61 (6.06-18.92) µg.hr/mL, 0.68 (0.44-1.31) µg/L and 0.07 (0.03-0.11), respectively. With TDF 150 mg every 24 hours, the TDF AUC_{0-24h}, C_{max} and C_{24h} were 4.80 (2.61-9.29) µg.hr/mL, 0.42 (0.24-0.73) µg/L and 0.10 (0.05-0.20), respectively. The TDF geometric mean ratio (GMR) of AUC_{0-48h} for every 24- versus every 48 hours dosing was 1.00 (90% CI 0.92-1.09). Tenofovir C_{max} was significant lower (p<0.01) and C_{last} (i.e. C_{48h} vs. C_{24h}) significantly higher (p<0.01) with daily TDF dosing. All subjects remained virologically suppressed and no drug-related adverse events were reported.

Conclusions: Switching TDF 300 mg every 48 hours to 150 mg every 24 hours provided equivalent tenofovir exposure in patients with moderate renal function impairment receiving LPV/r-based antiretroviral therapy.

Background

Kidney Dysfunction in HIV-infected Patients

- Chronic kidney disease (CKD) develops as a result of both viral-related risk factors and the more traditional risk factors (diabetes, hypertension, older age, hepatitis B and C infection). Long-term ARV exposure is now a major risk factor of kidney dysfunction.

Tenofovir disoproxil fumarate (TDF, Viread®)

- Approved for the treatment of HIV infection in adults and children (>2 yrs)

Pharmacokinetics
- Oral Bioavailability -25% (fasted state); no hepatic metabolism;
- **Excretion by the kidney**: Glomerular filtration and tubular secretion

Tenofovir DF Kidney Toxicity
- Large prospective clinical trials have shown that TDF is relatively safe for the kidney; however, its use has been associated with a greater decline in creatinine clearance compared to other NRTIs1.
- Greater TDF associated renal decline higher with PIs vs. NNRTIs regimens2.
- Reports of Fanconi syndrome described (kidney tubular dysfunction)3

- Recommended TDF dose is 300 mg every 48 hours for adults with moderate renal function impairment (creatinine clearance 30-49 mL/min).
- New dosage strengths and formations of TDF may permit once daily dosing for these patients.

Hypothesis

- **Providing TDF 150 mg every 24 hours instead of every 300 mg every 48 hours will provide equivalent drug exposure in patients with moderate renal function impairment.**

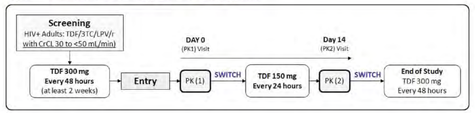
Objective

- To evaluate the pharmacokinetics of TDF in HIV-infected Thai adults with a creatinine clearance between 30 to <50 mL/min when administered at the recommended dose of 300 mg every 48 hours, and at an alternative dose of 150 mg every 24 hours, as part of a lopinavir/ritonavir-based HAART regimen.

Study Design

- Phase I, non-randomized, open-label, pharmacokinetic study in HIV-infected adults [ClinicalTrials.gov: NCT01671982]

Figure 1: Schema of Study Design and PK sampling visits



Study Methods

Study Population

- Screening performed within 30 days of enrollment

Inclusion criteria:

- age >18 years old; written informed consent, confirmed HIV-1 infection
- Confirmed Creatinine clearance (CLcr) result between 30 to <50 mL/min [confirmed defined as two CLcr determinations calculated using the Cockcroft-Gault equation with two weeks of each other within 1 month prior to entry]
- received TDF 300 mg, every 48 hours for at least 2 weeks prior to entry
- HIV-1 RNA viral load < 50 copies/mL within 6 months prior to entry

Exclusion criteria:

- Concomitant use of a ritonavir boosted protease inhibitor, atazanavir, didanosine
- Pregnant
- Grade 3 ≥ : neutrophil, hemoglobin, platelets, AST, or ALT within 30 days prior to entry
- HBs-antigen positive

Tenofovir DF formulation

- All subjects were receiving TDF 300 mg scored tablets manufactured by the Thai Government Pharmaceutical Organization (150 mg administered as 'half' tablet)

PK Sampling

- PK evaluations were scheduled at Day 0 and Day 14 (see Figure 1)
  - TDF was administered with breakfast. Blood samples collected at predose, and at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12, 24 36 (Day 0 only), and 48 (Day 0 only) hours post-dose

Drug Level Measurement and PK analysis

- Measurement of TDF plasma drug levels were performed by a validated HPLC method (lower limit of quantitation of 0. 015 mcg/mL)
- PK data were analyzed using non-compartment methods.

Study approved by the Ethics Committees (EC) at the Ministry of Public Health, Thailand; Faculty of Associated Medical Sciences, Chiang Mai University, and local hospital ECs.

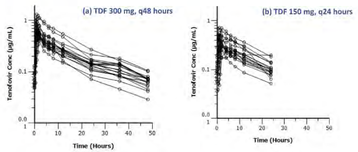
Clinical Characteristics

Table 1: Patient Characteristics at the Screening Visit

Characteristics	Median (range), N=20
Gender	
Male	12 (60%)
Female	8 (40%)
Race/Ethnicity: Asian	20 (100%)
Age (yrs)	53 (39-82)
Weight (kg)	49.5 (37.8-75.1)
Body Mass Index (cells/mm³)	19.2 (16.3-29)
Creatinine (mg/dL)	1.3 (0.9-2.1)
Creatinine Clearance (mL/min)	42.0 (31.7-49.7)
HIV-1 RNA Viral Load (copies/mL)	<50 (<50-<50)
CD4 Cell Count (cell/mm3)	596 (113-1063)

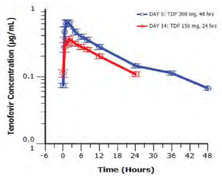
Tenofovir Concentration Vs Time Curves

Figure 2: Individual tenofovir concentration vs. time curves for subjects following (i) 300 mg, q48 hours and (ii) 150 mg, every 24 hours, (N=18) as part of a LPV/r based HARRT regimen.



Tenofovir Concentration Vs Time Curves

Figure 3: Mean (+/-SE) tenofovir concentration vs. time curves for subjects following (i) 300 mg, q48 hours and (ii) 150 mg, every 24 hours, (N=18) as part of a LPV/r based HARRT regimen.



Tenofovir PK Parameters

Table 2: Tenofovir pharmacokinetic parameters at Day 0 (300 mg every 48 hours) and Day 14 (150 mg once daily) as part of LPV/r-based HAART, N=18

	Tenofovir 300 mg, every 48 hrs	Tenofovir 150 mg, every 24 hrs	P value[b]	GM Ratio (90% CI) 24 hr / 48 hr
AUC_{0-t} (mg.hr/L)	9.61 (6.06 - 18.92)	4.80 (2.61 - 9.29)	NA	NA
AUC_{0-48h} (mg.hr/L)	9.61 (6.06 - 18.92)	9.61 (5.21 - 18.59)[a]	0.45	1.00 (0.92 to 1.09)
Cmax (mg/L)	0.68 (0.44 - 1.31)	0.42 (0.24 - 0.73)	<0.01	0.55 (0.49 to 0.63)
Clast (mg/L)	0.07 (0.03 - 0.11)	0.10 (0.05 - 0.20)	<0.01	1.59 (1.35 to 1.87)
Cmin (mg/L)	0.06 (0.03 - 0.09)	0.09 (0.04 - 0.18)	<0.01	1.42 (1.18 to 1.72)
CL/F (L/hr)	31.20 (15.86 - 49.49)	31.26 (16.14 -57.52)	0.62	1.00 (0.92 to 1.08)
Tmax (hr)	1.01 (0.48 - 4.00)	1.25 (0.50 - 4.00)	0.48	1.18 (0.83 to 1.68)
$T_{1/2}$ (hr)	18.91 (12.51 - 23.31)	13.30 (6.09 -42.05)	0.04	0.76 (0.64 to 0.91)

Values: median (range) unless otherwise stated. GM, geometric mean; NA, not applicable
[a]Calculated as 2×AUC0-24
[b]TDF 300 mg every 48 hours compared with TDF 300 mg every 24 hours Wilcoxon signed rank test. P values < 0.05 are bolded

- The TDF geometric mean ratio (GMR) of AUC0-48h for every 24- versus every 48 hours dosing was 1.00 (90% CI 0.92-1.09).
- Tenofovir Cmax was significant lower (p<0.01) and Clast (i.e. C48h vs. C24h) significantly higher (p<0.01) with daily TDF dosing.
- All subjects remained virologically suppressed and no drug-related adverse events were reported.

Conclusion

- Switching TDF 300 mg every 48 hours to 150 mg every 24 hours provided equivalent tenofovir exposure in patients with moderate renal function impairment receiving LPV/r-based antiretroviral therapy.
- Assessment of a second group of subjects receiving TDF+3TC+NNRTI (nevirapine or efavirenz) is ongoing and results expected March 2014

References

Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis 2005;40:1194-1198
Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. J Infect Dis 2008;197:102-108
Verhelst D, Monge M, Meynard JL, Fouqueray B, Mougenot B, Girard PM, Ronco P, Rossert J. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis. 2002 Dec;40(6):1331-3.

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