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Tenofovir PK in Adults with Renal Dysfunction on LPV/r and NNRTI-based ART

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Original Abstract

Background: 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). Coadministration of TDF with lopinavir/ritonavir (LPV/r) increases plasma tenofovir (TFV) concentrations in adults with normal renal function. We compared the plasma and intracellular pharmacokinetics (PK) of TDF 300 mg every 48 hours in HIV-infected adults with moderate renal function impairment receiving LPV/r and NNRTI-based antiretroviral therapy.

Methodology: Data were collected within a phase I, non-randomized, open-label pharmacokinetic study of TDF in patients with renal dysfunction (ClinicalTrials.gov Identifier: NCT01671982). Consenting HIV-positive adults with a confirmed creatinine clearance (CrCL) 30 to <50 mL/min receiving TDF 300 mg every 48 hours per standard of care as part of a LPV/r- or NNRTI-based ART and an HIV-1 RNA viral load (VL) <50 copies/mL were included. HBs-antigen positive adults were excluded. Intensive steady-state 48-hour blood sampling for PK assessment was performed, 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. Peripheral blood mononuclear cells (PBMCs) were also collected at 48 hours post-dose for assessment on intracellular tenofovir di-phosphate concentrations. PK parameters were calculated using non-compartmental analysis.

Results: 40 HIV-infected adults (55% female) were enrolled. Median (range) age was 56 years (39-82), weight 51 kg (38-80), serum creatinine (SCr) 1.3 mg/dL (0.8-2.1), CrCL 43.9 mL/min (30.9-49.7) and CD4 count 502 cells/mm^3 (113-1063). Tenofovir PK data were evaluable from 19 subjects receiving an NNRTI- (9 nevirapine and 10 efavirenz) and 18 receiving LPV/r-based HAART. Tenofovir plasma and intracellular PK parameters are presented in the table below:

PK Parameters	TDF 300 mg every 48 hours /NNRTI-based HAART (n=19)	TDF 300mg every 48 hours /LPV/r-based HAART (n=18)	P-Value*
TFV Plasma			
AUC_{0-48} (mg.hr/L)	5.76 (3.34 - 11.08)	9.61 (6.06 - 18.92)	<0.001
Cmax (mg/L)	0.44 (0.23 - 0.67)	0.68 (0.44 - 1.31)	<0.001
Ctrough (mg/L)	0.04 (0.02 - 0.10)	0.07 (0.03 - 0.11)	0.004
CL/F (L/hr)	23.60 (12.26 - 40.73)	14.15 (7.19 - 22.44)	<0.001
TFV-DP intracellular			
Ctrough (fmol/10^6 cells)	130 (27-945)	188 (25-497)	0.504

Values: median (range). *signed rank test

Mean tenofovir plasma AUC_{0-48} was 1.7-fold higher with coadministration of LPV/r compared to NNRTIs.

Conclusions: Tenofovir plasma exposure was significantly higher with LPV/r versus NNRTI based ART in patients with moderate renal function impairment. In contrast, trough intracellular TFV-diphosphate concentrations were similar between the two ART regimens.

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 NRTIs[1].
- Greater TDF associated renal decline higher with PIs vs. NNRTIs regimens[2].
- 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).

Objective

- To compared the plasma and intracellular pharmacokinetics (PK) of TDF 300 mg every 48 hours in HIV-infected adults with moderate renal function impairment receiving LPV/r and NNRTI-based antiretroviral therapy

Study Design & Methods

Study Design

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

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 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

PK Sampling

- PK evaluations were scheduled at Day 0 to assess the 300 mg, every 48 hour dose
  - 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 and 48 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.

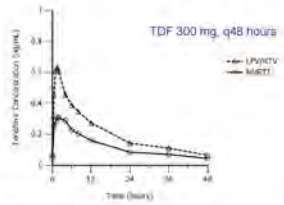
Clinical Characteristics

Table 1: Patient Characteristics

Median (range)	Group 1: TDF-NNRTI (n=20)	Group 2: TDF-LPV/r (N=20)	Total (n=40)
Gender			
Male	6 (30%)	12 (60%)	18 (45%)
Female	14 (70%)	8 (40%)	22 (55%)
Race/Ethnicity: Asian	20 (100%)	20 (100%)	40 (100%)
Age (yrs)	59 (44-65)	53 (39-82)	56 (39-82)
Weight (kg)	54.0 (40.0-80.0)	49.5 (37.8-75.2)	50.6 (37.8-80)
Body Mass Index (cells/mm^3)	23.8 (17.9-32.9)	19.2 (16.3-29)	20.8 (16.3-32.9)
Creatinine (mg/dL)	1.2 (0.8-1.9)	1.3 (0.9-2.1)	1.3 (0.8-2.1)
Creatinine Clearance (mL/min)	45.7 (30.0-49.6)	42.0 (31.7-49.7)	43.9 (30.9-49.7)
HIV-1 RNA Viral Load (copies/mL)	<50 (<50-<50)	<50 (<50-<50)	<50 (<50-<50)
CD4 Cell Count (cell/mm3)	465 (170-779)	598 (113-1063)	502 (113-1063)
HAART Regimen			
TDF+3TC+EFV	10		
TDF+3TC+NVP	10		
TDF+3TC+LPV/r		18	
TDF+3TC+ZDV+LPV/r		1	

Tenofovir Concentration Vs Time Curves

Figure 1: Mean tenofovir concentration vs. time curves for subjects following 300 mg, q48 hours as part of a NNRTI (n=19) or LPV/r- (n=18) based HARRT regimen.



Tenofovir PK Parameters

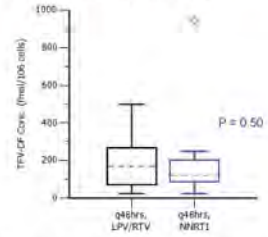
Table 2: Comparison between tenofovir pharmacokinetic parameters after administration of TDF 300 mg every 48 hours when part of NNRTI or LPV/r-based regimen

	Group 1 TDF/3TC/NNRTI 300 mg, every 48 hours (N=19)	Group 2 TDF/3TC/LPV/r 300 mg, every 48 hours (N=18)	P-value*
AUC_{0-48} (mg.hr/L)	5.76 (3.34 - 11.08)	9.61 (6.06 - 18.92)	<0.001
C_{max} (mg/L)	0.44 (0.23 - 0.67)	0.68 (0.44 - 1.31)	<0.001
C_{trough} (mg/L)	0.04 (0.02 - 0.10)	0.07 (0.03 - 0.11)	0.004
C_{trough} (mg/L)	0.04 (<0.008 - 0.10)	0.06 (0.03 - 0.09)	0.002
CL/F (L/hr)	23.60 (12.26 - 40.73)	14.15 (7.19 - 22.44)	<0.001
Vd (L)	1430 (829 - 2792)	842 (344 - 1382)	<0.001
T_{max} (hr)	1.50 (0.50 - 8.00)	1.01 (0.48 - 4.00)	0.15

- With the standard TDF dose of 300 mg every 48 hours, tenofovir exposure was significantly higher with the concomitant use of lopinavir/ritonavir compared to NNRTIs [AUC_{0-48h} 9.61 versus 5.76 mg.hr/L, p<0.001].
- Tenofovir AUC_{0-48h}, C_{max} and C_{last} were 67%, 55% and 75% higher, respectively, with LPV/r.

Intracellular tenofovir-diphosphate Concentrations

Figure 2: Intracellular tenofovir-diphosphate (TVF-DP) C_{last} in patients with moderate renal dysfunction, as part of (a) NNRTI- (b) LPV/r-based treatment. Box-plot represents median and interquartile range.



- With TDF 300 mg, every 48 hour the TFV-DP C_{last} was 130 (27-945) fmol/10^6 cells with NNRTIs versus 188 (25-497) fmol/10^6 cells with LPV/r (p=0.50)
- No significant difference was observed between TFV-DP C_{last} with NNRTIs compared to LPV/r.
- All subjects remained virologically suppressed and no drug-related adverse events were reported.

Conclusion/Discussion

- We observed a significantly higher tenofovir exposure among patients with moderate renal dysfunction receiving lopinavir/ritonavir compared to those receiving an NNRTI.
- Interestingly, this increase of tenofovir AUC_{0-48} and Cmax in the presence of LPV/r was approximately 2-fold higher than those previously reported in adults with normal renal function, but no difference in TVF-DF C_{last} was found

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