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Pharmacokinetic Drug Interaction and Long Term Safety Profile of Tenofovir DF and Lopinavir/Ritonavir

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Background

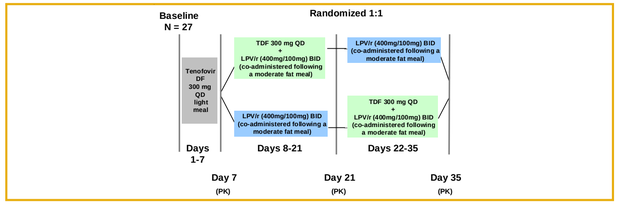
- Tenofovir DF (TDF), a NtRTI approved for once daily treatment of HIV, is frequently used in HAART regimens of treatment naive and treatment experienced patients
- Lopinavir/ritonavir (LPV/r) is a potent, boosted HIV protease inhibitor that is also frequently used in these patient populations
- A previous drug-drug interaction study identified small changes in the PK of tenofovir, lopinavir (LPV), and ritonavir (RTV) during their co-administration that were not considered clinically relevant[1,2]
  - Similar LPV + RTV PK reported in HAART regimens with or without TDF[3, 4]
- A second PK study was conducted to confirm those findings
- A long-term safety analysis was conducted to assess the safety of these agents when used in combination in patients with advanced HIV disease

Objective

- To evaluate the effect of TDF and LPV/r co-administration on the PK and safety of tenofovir, LPV and RTV
- To evaluate the long term safety of concomitant use of TDF and LPV/r in HAART regimens of heavily treatment-experienced patients with advanced HIV disease

Methods

Figure 1. Pharmacokinetic Study Design



Pharmacokinetic and Long Term Safety Evaluations

- Study drugs (LPV/r 400/100 mg; TDF 300 mg) were administered within 5 minutes of completion of a standardized light meal (~373 kcal, 20% fat)
- Blood sampling was performed over 24 hours in EDTA containing collection tubes
- Tenofovir, LPV and RTV concentrations in plasma determined by validated LC/MS/MS assays
- PK parameters estimated by noncompartmental methods using WinNonlin™
- AUC_{ss}, C_{max} and C_τ results reported as 90% confidence intervals about the ratio of geometric means [GMR (90% CI)] for TDF and LPV/r administered together vs. alone
  - No change in PK concluded if 90% CI of GMR lies within 80-125% range
- Patients in a compassionate access study (GS-908) receiving TDF + LPV/r were assessed for evidence of clinically significant nephrotoxicity through analysis of confirmed changes in serum creatinine (> 2.0 mg/dL) and phosphorus (< 1.5 mg/dL) using a centralized laboratory

Results

Pharmacokinetic Study Results

- 27 subjects enrolled; 23 subjects completed study
  - 16 males; 11 females
  - mean age: 34 yr (range: 20 - 58 yr)
  - mean weight: 75 kg (range: 61 - 89 kg)
  - race: 25 Caucasian, 1 African American, 1 Middle Eastern/European
- LPV + RTV PK were similar to historical data (Figure 2)
- Steady state tenofovir PK following administration of TDF alone were similar to historical data (Figure 3)

Figure 2. Steady State LPV and RTV Concentration - Time Profiles

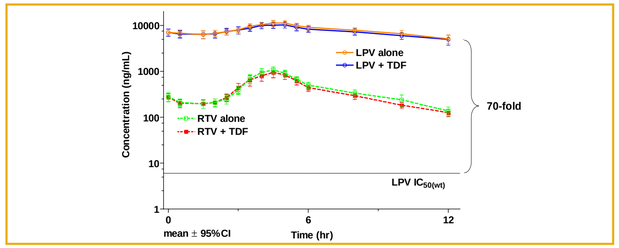


Table 1. Steady State LPV and RTV Pharmacokinetics Alone and with TDF

Pharmacokinetic Parameter	LPV/r Alone	LPV/r + TDF	% Mean Ratio (90% CI)
Lopinavir			
AUC_{ss} (ng•hr/mL)	91600 (33.1)	93100 (31.9)	103 (96.1, 111)
C_{max} (ng/mL)	11900 (27.2)	12200 (28.8)	103 (97.2, 110)
C_τ (ng/mL)	4940 (61.5)	5130 (44.6)	111 (98.4, 125)
$T_{1/2}$ (hr)*	6.04 (3.93 – 8.72)	6.22 (4.42 – 10.7)	NA
Ritonavir			
AUC_{ss} (ng•hr/mL)	4560 (35.2)	4700 (30.9)	104 (97.3, 110)
C_{max} (ng/mL)	1080 (39.1)	1150 (42.3)	104 (93.4, 116)
C_τ (ng/mL)	128 (52.9)	136 (37.1)	110 (99.4, 122)
$T_{1/2}$ (hr)	3.06 (2.65 – 3.36)	3.19 (2.70 – 3.87)	NA

AUC_{ss}= steady state area under the curve over the dosing interval; C_{max} = maximum plasma concentration;
C_τ = minimum (trough) plasma concentration; $T_{1/2}$ = elimination half-life
Data expressed as arithmetic mean (%CV) or *median (IQR)
% Geometric Mean Ratio is the model-based anti-log of the difference of the treatment of LPV/r + TDF vs. LPV/r alone
(90% confidence interval of the ratio)

Figure 3. Steady State Tenofovir Concentration - Time Profiles

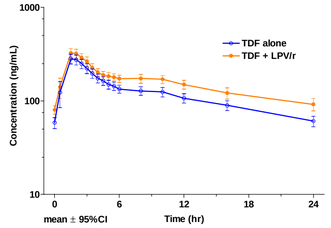


Table 2. Steady State Tenofovir Pharmacokinetic Parameters Alone and with LPV/r

Tenofovir Pharmacokinetic Parameter	TDF Alone	TDF + LPV/r	% Mean Ratio (90% CI)
AUC_{ss} (ng•hr/mL)	2870 (26.3)	3740 (24.3)	132 (125, 138)
C_{max} (ng/mL)	314 (26.3)	360 (26.0)	115 (107, 122)
C_τ (ng/mL)	60.8 (32.9)	91.8 (35.3)	151 (137, 166)
T_{max} (hr)*	1.51 (1.50 – 2.00)	1.50 (1.50 – 2.50)	NA
$T_{1/2}$ (hr)*	14.0 (12.5 – 17.3)	14.2 (13.0 – 16.4)	NA

AUC_{ss}= steady state area under the curve over the dosing interval; C_{max} = maximum plasma concentration;
C_τ = minimum (trough) plasma concentration; T_{max} = time to C_{max}; $T_{1/2}$ = elimination half-life
Data expressed as arithmetic mean ± SD or *median (IQR)
% Geometric Mean Ratio is the model-based anti-log of the difference of the treatment of TDF + LPV/r vs. TDF alone
(90% confidence interval of the ratio)

Pharmacokinetic Study Safety Results

- No serious adverse events were reported in this study
- 23 (85%) subjects experienced at least 1 treatment-emergent AE
- Most common AE was diarrhea (67% of subjects reported at least one episode)
  - TDF alone (n = 4), LPV/r alone (n = 13), TDF + LPV/r (n = 14)
  - 2 subjects withdrew consent due to diarrhea
  - Other frequent AEs were: headache (52%), nausea (32%), and abdominal pain (26%)
  - One subject experienced elevated liver function tests attributed to LPV/r
  - One subject experienced tachycardia attributed to both TDF and LPV/r

Table 3. Study GS-908 TDF Compassionate Access Study (N=296)

Baseline Characteristics	
Mean (SD) HIV RNA (log_{10} c/mL)	4.9 (0.4)
Mean CD4 Cell Count/(cells/mm^3)	36 (51)
Prior AIDS diagnosis	93%
Mean Age (yrs)	42 (7)
Male (%)	93%
Race (%)	
Caucasian	70%
African American	16%
Hispanic	12%
Asian	2%

- LPV/r was used in 271/296 (94%) of patients
  - Mean duration of concomitant use: 63 weeks (maximum 96 weeks)

Table 4. Long Term Safety of TDF + LPV/r in Compassionate Access Study (N=271)

Maximum Toxicity Grade Mean Duration of Concomitant Use: 63 Weeks (Maximum 96 Weeks) Incidence of Abnormality n (%)				
Grade	Serum Creatinine (mg/dL)		Serum Phosphorus (mg/dL)	
1	≥ 0.5 Δ from BL	27 (10%)	2.0 - < 2.2	9 (3%)
2	2.1 – 3.0	2 (<1%)	1.5 – 1.9	12 (3%)
3	3.1 – 6.0	0	1.0 – 1.4	1 (<1%)
4	> 6	0	< 1.0	1 (<1%)

- The incidence of confirmed changes in serum creatinine to > 2.0 mg/dL or serum phosphorus < 1.5 mg/dL was < 1%
- Five subjects experienced serum creatinine changes leading to tenofovir DF discontinuation
  - One patient developed Fanconi's syndrome (also experienced during prior use of high dose adefovir dipivoxil)

Conclusions

- **LPV and RTV PK were unaffected by TDF**
- **Tenofovir exposures were increased (+32%) when TDF was co-administered with LPV/r**
  - **Similar increase to that observed in previous study (+34%)**
- **Co-administration of TDF + LPV/r was generally safe and well tolerated**
  - **Gastrointestinal AEs were most common and occurred with greater frequency in study arms containing LPV/r**
- **Laboratory evidence of clinically significant nephrotoxicity or TDF discontinuation was infrequent (< 1%, and < 2%) with long term use of TDF + LPV/r in patients with advanced HIV disease**
  - **Changes in serum creatinine and phosphorus were similar to the background incidence reported in an advanced patient population[5]**
- **PK findings and clinical experience indicate that TDF and LPV/r are not involved in a clinically significant drug-drug interaction**

References

[1] Kearney BP, et al. 8th ECCATH. 2001. #171
[2] Flaherty JF, et al. 1st IAS Conference on HIV Pathogenesis and Treatment. 2001. #336
[3] Chiu Y-L, et al. 2nd IAS Conference on HIV Pathogenesis and Treatment. 2003. #839
[4] Poirier JM, et al. 42nd ICAAC. 2002. #H-1715
[5] Fisher EJ, et al. AIDS 15:1695-1700. 2001