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Lack of a Pharmacokinetic Interaction between Emtricitabine and Tenofovir DF when Co-administered to Steady State in Healthy Volunteers

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Introduction

- Emtricitabine (Emtriva™, FTC) is a potent new NRTI recently approved in the US for the treatment of HIV infection in adults
- As FTC will be combined with tenofovir DF (TDF) in once daily (QD) dosage regimens, a multiple dose study was conducted to evaluate the potential for a pharmacokinetic (PK) interaction when these drugs are administered together

Objective

- To evaluate the effect of FTC on steady-state tenofovir pharmacokinetics
- To evaluate the effect of TDF on steady-state FTC pharmacokinetics
- To evaluate the safety and tolerability when FTC and TDF are administered alone or together for 7 days

Methods

- This was a randomized, open-label, 3-period crossover, steady-state drug-drug interaction study in 19 healthy male and female volunteers
- Eligible subjects received each of the following three 7-day treatments over a 21-day treatment period (no washout):
  - Treatment A: 200 mg FTC QD x 7 days
  - Treatment B: 300 mg TDF QD x 7 days
  - Treatment C: 200 mg FTC + 300 mg TDF QD x 7 days
- Drug was administered 30 min after a standardized breakfast on days 1, 5, 6, and 7 of each treatment period
- Plasma PK assessments were made over a 24-hr dosing interval following the last dose of each treatment
- FTC and tenofovir plasma concentrations were simultaneously analyzed by LC/MS/MS with LOQ of 5 and 10 ng/mL, respectively
- Non-compartmental PK analysis was conducted using WinNonlin™
- A conclusion of no clinically significant difference between the test (FTC+TDF) and reference (FTC alone or TDF alone) treatments was made if the 90% confidence intervals (CIs) of test/reference ratio for the geometric least-squares mean ratio for AUC_{ss}, C_{max} and C_{min} are each within the range of 0.7 and 1.43

Results

Demographics

- 19 subjects enrolled: 4 female, 15 male
  - mean (range) age 26 yr (19 - 41 yr)
  - mean (range) weight 73.8 kg (61.7 - 94.4 kg)

Safety

- Based on clinical and laboratory evaluations FTC and TDF were well tolerated after multiple dosing alone or together. One subject discontinued for reasons unrelated to the study and one subject for an AE (moderate vomiting episodes while on FTC+TDF)

Pharmacokinetics

- Plasma concentration profiles for FTC alone and with TDF are shown in Figure 1 while FTC pharmacokinetic parameters and statistical results are presented in Table 1
- Plasma concentration profiles for tenofovir alone and with FTC are shown in Figure 2 while tenofovir pharmacokinetic parameters are presented in Table 2

Figure 1. Mean FTC Plasma Concentration-time Profiles

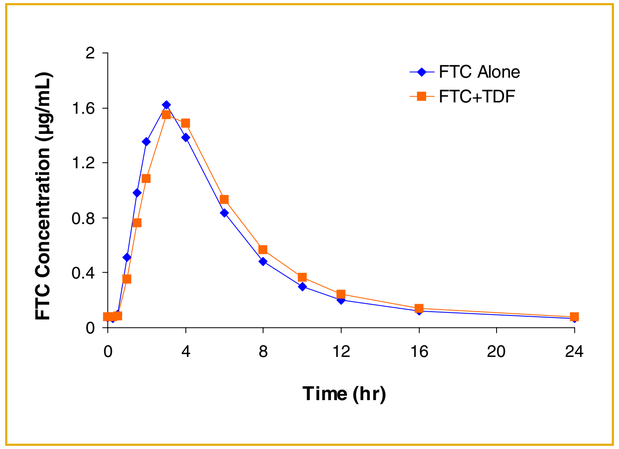

Table 1. Pharmacokinetic and Statistical Results for FTC When Administered Alone or in Combination with TDF (n=17)

PK Parameter[1]	FTC Alone	FTC + TDF	Geometric Least Squares Mean Ratio (90% CI)
AUC_{ss} (µg•hr/mL)	10.2 (19)	10.7 (11)	1.07 (1.00 - 1.14)
C_{max} (µg/mL)	1.8 (22)	1.7 (18)	0.96 (0.87 - 1.06)
C_{min} (µg/mL)	0.06 (28)	0.08 (22)	1.20 (1.12 - 1.29)
t_{max} (hr)	3.0 (29)	3.0 (20)	N/A
$t_{1/2}$ (hr)	10.6 (24)	10.7 (16)	N/A

[1] Mean (%CV)
C_{max}= Maximum plasma concentration; C_{min}= Minimum plasma concentration; t_{max}= Time to C_{max}; AUC_{ss}=Steady-state AUC; $t_{1/2}$= Terminal phase half-life

Figure 2. Mean Tenofovir Plasma Concentration-time Profiles

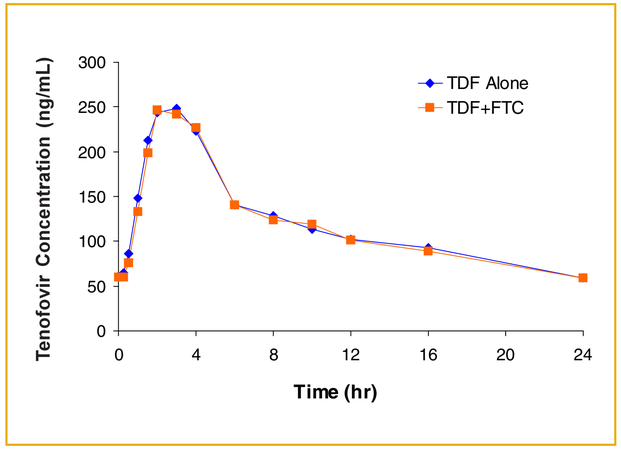

Table 2. Pharmacokinetic and Statistical Results for Tenofovir When TDF was Administered Alone or in Combination with FTC (n=17)

PK Parameter[1]	TDF Alone	TDF + FTC	Geometric Least Squares Mean Ratio (90% CI)
AUC_{ss} (ng•hr/mL)	2844 (24)	2801 (18)	1.00 (0.92 - 1.09)
C_{max} (ng/mL)	279 (21)	288 (22)	1.03 (0.95 - 1.11)
C_{min} (ng/mL)	54 (28)	54 (20)	1.02 (0.92 - 1.13)
t_{max} (hr)	2.4 (33)	2.4 (38)	N/A
$t_{1/2}$ (hr)	15.3 (30)	15.9 (24)	N/A

[1] Mean (%CV)
C_{max}= Maximum plasma concentration; C_{min}= Minimum plasma concentration; t_{max}= Time to C_{max}; AUC_{ss}=Steady-state AUC; $t_{1/2}$= Terminal phase half-life

- The 90% CI of C_{max}, C_{min} and AUC_{ss} for FTC + TDF vs. FTC were well within the range of 0.7 to 1.43
- The 90% CI of C_{max}, C_{min} and AUC_{ss} for TDF + FTC vs. TDF were well within the range of 0.7 to 1.43

Conclusions

- **Tenofovir DF had no effect on the pharmacokinetics of emtricitabine**
- **Emtricitabine had no effect on the pharmacokinetics of tenofovir**
- **Safety results from this study were consistent with previous studies conducted in healthy volunteers and raised no new safety issues for emtricitabine or tenofovir DF**