

# Assessment of Bioequivalence of Tenofovir, Emtricitabine and Efavirenz (Atripla) Fixed Dose Combination Tablet Compared with a Compounded Oral Liquid Formulation Derived from the Tablet

Poster number 605  
17th Conference on Retroviruses  
and Opportunistic Infections  
San Francisco, CA  
February 16-19, 2010

Jennifer R. King<sup>1</sup>, Matthew McCall<sup>1</sup>, Anthony Cannella<sup>2</sup>, Michael Anne Markiewicz<sup>1</sup>, Amanda James<sup>1</sup>, and Edward P. Acosta<sup>1</sup>

<sup>1</sup>University of Alabama at Birmingham, Birmingham, AL, <sup>2</sup>University of California at San Diego, San Diego, CA

Jennifer R. King, Pharm.D.  
1530 3rd Avenue South  
Shelby Building 1113  
Birmingham, AL 35294  
jking@uab.edu  
Phone: 205-934-2696  
Fax: 205-934-6201

## BACKGROUND

- Atripla is a fixed dose combination (FDC) tablet containing efavirenz (EFV), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF).<sup>1</sup>
- The tablet may be taken alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.<sup>2</sup>
- A major advantage of this FDC tablet is its ability to reduce pill burden, which may increase patients' adherence to an antiretroviral regimen.
- Administration of Atripla is limited to patients who can swallow tablets. A liquid formulation of Atripla may benefit those unable to swallow tablets, however, there is no such formulation commercially available.
- The goal of this study was to determine the bioequivalence of the FDC tablet and a compounded liquid formulation derived from the FDC tablet.

## METHODS

### Study Subjects and Design

- Subjects were HIV-negative men and women between 19 and 65 years of age, in good health based upon medical history, physical examination and laboratory screening.
- IRB approval was obtained at the University of Alabama at Birmingham and all subjects gave informed consent prior to study enrollment.
- Subjects were randomized to a single-dose, open-label, 2-period, crossover bioequivalence study.
- The reference formulation was an Atripla FDC tablet containing TDF 300 mg, FTC 200 mg and EFV 600 mg.
- The test formulation was an Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral vehicle. The solution was prepared within 24 hours of administration to ensure drug stability in solution (unpublished data).
- Subjects took an observed dose of either the test or reference formulation with 240 mL of water after fasting overnight.
- Plasma samples for drug quantitation were collected within 15 minutes before the dose and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 and 48 hours after observed ingestion of the study medication.
- After a minimum 14 day washout, subjects took an observed dose of the alternative formulation and sampling for plasma concentrations of TDF, FTC and EFV was repeated.

### Sample Size

- The target sample size for the study was 14 subjects, which was consistent with the FDA guidance on bioequivalence testing.<sup>3,4</sup>
- IRB approval to enroll up to 16 subjects was obtained to ensure enrollment of at least 14 subjects with useable data.
- Any participant who dropped out of the study was not included in the pharmacokinetic and bioequivalence analyses.

### Bioanalytical, Pharmacokinetic and Statistical Methods

- TDF and FTC were quantitated using a validated LC-MS/MS method linear over a concentration range of 10 to 5,000 ng/mL.
- EFV was quantitated using a validated HPLC method linear over a concentration range of 25 to 20,000 ng/mL.
- AUC<sub>t</sub>, AUC<sub>∞</sub>, and t<sub>1/2</sub> of TDF, FTC and EFV were determined using a non-compartmental approach with WinNonlin version 5.1.1, Pharsight Corp., Mountain View, CA.
- Maximum plasma concentration (C<sub>max</sub>) and time to C<sub>max</sub> (T<sub>max</sub>) were determined from each subject's concentration-time curve data.
- WinNonLin Professional Bioequivalence Program for Two-Period Crossover Studies, Version 5.1.1 was used to determine the ratio of the test to reference formulation mean C<sub>max</sub> and AUC<sub>∞</sub>.
- Individual pharmacokinetic data were natural log-transformed; the means and standard deviations calculated.
- The ratio of the test to reference formulation geometric mean C<sub>max</sub> and AUC<sub>∞</sub> for each drug and the 90% confidence intervals around each geometric mean ratio were determined.
- Average bioequivalence was met if the 90% confidence intervals around the C<sub>max</sub> and AUC<sub>∞</sub> geometric mean ratios for each drug all fell within the FDA's predefined limits of 0.80 to 1.25.

## RESULTS

Table 1. Mean ± SD Pharmacokinetics (n=14)

Drug	Formulation	C <sub>max</sub> (mg/L)	T <sub>max</sub> (h)	AUC <sub>0-∞</sub> (mg*h/L)	AUC <sub>0-t</sub> (mg*h/L)	t <sub>1/2</sub> (h)
EFV	Liquid	1.4 ± 0.4	4.4 ± 3.0	29.2 ± 12.6	63.2 ± 44.3	50.9 ± 25.2
	Tablet	1.6 ± 0.6	4.1 ± 1.7	30.7 ± 12.5	65.4 ± 33.7	52.8 ± 18.8
FTC	Liquid	2.1 ± 0.4	0.9 ± 0.2	10.6 ± 1.8	10.9 ± 1.7	12.4 ± 5.2
	Tablet	1.9 ± 0.6	2.2 ± 1.1	10.8 ± 2.7	11.1 ± 2.7	10.7 ± 2.8
TDF	Liquid	0.3 ± 0.1	0.8 ± 0.3	1.9 ± 0.6	2.3 ± 0.6	17.4 ± 3.0
	Tablet	0.2 ± 0.1	1.4 ± 0.5	1.5 ± 0.6	1.9 ± 0.7	16.3 ± 4.2

Table 2. Bioequivalence; Geometric Mean Ratio; 90% CI (n=14)

Drug	Formulation	C <sub>max</sub> (mg/L)		AUC <sub>0-∞</sub> (mg*h/L)	
		GM (%CV)	Ratio of GM Liquid vs. Tablet (90% CI)	GM (%CV)	Ratio of GM Liquid vs. Tablet (90% CI)
EFV	Liquid	1.3 (28.8)	0.86 (0.75-1.04)	56.7 (80.0)	0.97 (0.82-1.26)
	Tablet	1.5 (39.0)		58.7 (57.5)	
FTC	Liquid	2.1 (21.0)	1.15 (0.97-1.25)	10.8 (15.9)	0.99 (0.91-1.05)
	Tablet	1.8 (32.3)		10.9 (24.7)	
TDF	Liquid	0.3 (27.7)	1.38 (1.12-1.70)	2.2 (36.3)	1.21 (1.07-1.40)
	Tablet	0.2 (47.8)		1.8 (29.2)	

## CONCLUSIONS

- The 90% CI for FTC C<sub>max</sub> and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met.
- The 90% CI for EFV C<sub>max</sub> fell below the range of bioequivalence while EFV AUC<sub>∞</sub> fell slightly above the range and TDF C<sub>max</sub> and AUC<sub>∞</sub> fell above the range.
- TDF C<sub>max</sub> and AUC<sub>∞</sub> were approximately 40% and 20% higher, respectively with the liquid formulation.
- These data suggest both formulations are not bioequivalent for two of the three drugs; the clinical implications of these data are unknown.
- Possible risks/benefits for HIV-infected patients should be carefully considered before crushing Atripla tablets to construct a compounded oral solution.

## REFERENCES

- Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) [package insert]. Princeton, NJ: Bristol-Myers Squibb and Gilead Sciences; January 2010.
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- Sixteen HIV-negative adults (7=male, 9=female) were enrolled between March and August 2009.
- One male dropped out of the study due to a scheduling conflict with the second PK visit and one female dropped out of the study due to nausea and vomiting after the tablet administration during the first PK visit.
- Safety findings from this study were similar to other studies.<sup>1</sup>
- Mean ± SD age and weight for subjects completing the study were 33.3 ± 10.9 years and 85.7 ± 18.4 kg, respectively.

Figure 1. Mean Efavirenz Concentrations (n=14)

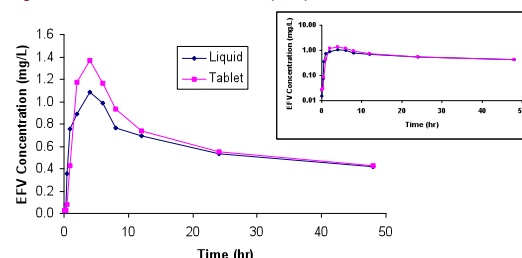


Figure 2. Mean Emtricitabine Concentrations (n=14)

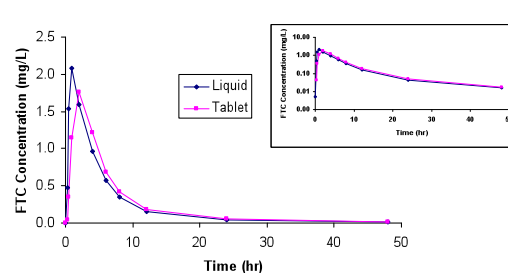


Figure 3. Mean Tenofovir Concentrations (n=14)

