Efavirenz (EFV) but not Atazanavir/ritonavir (ATV/r) Significantly Reduces Atovaquone Concentrations in HIV+ Subjects

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ABSTRACT

Background: Atovaquone is an alternative agent for prophylaxis and treatment of PCP and toxoplasmosis. Previous studies have shown that average steady state atovaquone concentrations (Cavg) ≥14 µg/mL and ≥18.5 µg/mL are predictive of successful treatment of PCP and toxoplasmosis, respectively. In a recent study, atovaquone exposure following a single dose of atovaquone/proguanil was reduced by 46-75% in HIV+ patients receiving EFV, lopinavir/ritonavir (LPV/r) or ATV/r compared to HIV- controls receiving no antiretroviral therapy ART. The current study was conducted to determine if similar pharmacokinetic (PK) interactions occur at steady state in HIV+ subjects receiving atovaquone oral suspension at doses used in the treatment of PCP or toxoplasmosis.

Methods: 30 HIV+ volunteers were recruited, 10 each taking EFV-based ART, ATV/r-based ART, or no ART. Subjects were randomly assigned to atovaquone 750 mg BID with food for 14 days (Phase 1) followed (after a washout period) by atovaquone 1500 mg BID with food for 14 days (Phase 2), or vice versa. On day 14 of each phase, blood samples were collected over 12 hrs to determine atovaquone PK parameter values including area under the concentration-time curve [AUC_τ] and C_{avg} using non-compartmental methods. PK parameter values from the EFV and ATV/r arms were compared to the no ART arm using an unpaired t-test.

Results: 29 of 30 subjects (25 males; mean age: 42±11 yrs) completed both dosing cohorts. HIV-RNA was < 50 copies/mL in all subjects in the EFV and ATV/r-based ART groups. Median (range) HIV-RNA in the no ART group was 1224 (<40-26,743) copies/mL. Median (range) CD4+ counts in the EFV, ATV/r, and no ART groups were 602 (212-1321), 616 (357-916), and 585 (412-912) cells/mm3, respectively. Table 1 provides the pharmacokinetic results. Subjects on EFV-based ART had 47% and 44% lower atovaquone exposure than no ART subjects at atovaquone doses of 750 mg BID and 1500 mg BID, respectively (P<0.01 for each). Moreover, 4 of 10 subjects (40%) on EFV + atovaquone 750 mg BID had an atovaquone Cavg <14 µg/mL – the concentration associated with successful PCP treatment.

Conclusions: Coadministration of EFV significantly lower atovaquone exposure in when compared to participants not receiving ART. In contrast, when administered with ATV/r, the PK parameter values of atovaquone did not differ significantly from control group values at either of the studied doses. These data suggest that the current recommended dose of atovaquone 750 mg BID for PCP treatment may not be adequate in all patients receiving concurrent EFV.

INTRODUCTION

- Atovaquone is an alternative therapy for the treatment and prevention of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasma encephalitis (TE).
- Average steady state concentrations ($CP_{ss\ avg}$) of ≥ 14 mcg/mL and ≥ 18.5 mcg/mL have been shown to be predictive of successful treatment of PCP and TE, respectively.[1-2]
- A recent study demonstrated significant decreases in atovaquone areas under the curve (AUC) of 75%, 74%, and 46% following a single dose of atovaquone/proguanil 250/100 mg in HIV+ subjects treated with ARV regimens that included efavirenz (EFV), ritonavir-boosted atazanavir (ATV/r), or lopinavir/ritonavir (LPV/r), respectively, compared to HIV-negative controls.[3]
- If similar interactions are seen when atovaquone alone is co-administered at treatment doses for PCP or toxoplasmosis, the current recommended doses of atovaquone may not be adequate for patients receiving these ARVs concomitantly.
- The purpose of this study was to determine the influence of EFV and ATV/r on the steady-state pharmacokinetics (PK) of atovaquone oral suspension in HIV+ volunteers.

METHODS

Study Design and Treatments

- Single-center, open-label, parallel sequence, randomized, pharmacokinetic study (NCT01479361).
- Three groups of HIV+ subjects were recruited – 10 receiving EFV-based ART, 10 ATV/r-based ART, and 10 on no ART.
- Subjects were randomly assigned to atovaquone 750 mg or 1500 mg, each given as BID with food for 14 days.
- On day 14, serial blood samples were collected prior to dosing and at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose to determine atovaquone concentrations.
- After a 2-6 week washout period, each subject was crossed over to the other dosage arm, and the same dosing scheme and PK blood draw schedule was repeated.

Inclusion Criteria

- HIV+ males and females 18-70 years old meeting one of the following:
  1)On stable (≥ 3 months) ARV regimens that included EFV 600 mg daily, or ATV/r 300/100 mg daily, with CD4 cells > 200 cells/mm^3, and virologically suppressed (HIV RNA <200 copies/mL on at least 2 consecutive occasions within 6 months prior to enrollment)
  2)Not receiving ARV therapy with CD4 cells ≥350 cells/mm3
- Receiving no medications with known or suspected interaction with atovaquone

Pharmacokinetic and Statistical Analysis

- Plasma concentrations of atovaquone were analyzed by noncompartmental methods (Phoenix WinNonlin v6.3, Certara, St. Louis, MO). Geometric mean data with 90% confidence intervals (CI) are reported. Pharmacokinetic parameter values (area under the concentration or AUCτ and average plasma concentration or C_{avg}) for the EFV and ATV/r arms were compared to the no ART arm using a two-tailed, unpaired t-test. Statistical significance was defined a priori as $\alpha < 0.05$.

Sample Size Determination

- A difference in atovaquone AUC of at least 40% was considered to be clinically relevant. A standard deviation of 40 was assumed for a mean of 100. With α set at 0.05, a total of 30 subjects was required to detect a statistically significant difference of 40% in atovaquone AUC_τ with EFV or ATV/r compared to no ARVs with > 90 % power (SYSTAT).

Atovaquone Analysis

- Atovaquone concentrations in human plasma were determined using a high performance liquid chromatography (HPLC) liquid-liquid extraction method.
- Percent errors, as a measure of accuracy, were <7.44%, and the inter- and intra-assay coefficients of variation for atovaquone were 1.86-7.9% and 4.61-6.28%, respectively.

RESULTS

Twenty-nine of 30 subjects (25 males) met inclusion criteria and completed the study. The mean age of the participants was 42 yrs. (±11 yrs.).

Table 1

	Concurrent EFV	Concurrent ATV/r	No Concurrent ARVs (Control)	GMR (EFV: Control)	GMR (ATV/r: Control)
Atovaquone 750 mg twice daily x 14 days					
AUC, (µg*hr/mL) 90% CI *P* vs Control	178 (157-198) 0.001	306 (231-380) 0.4	364 (296-432)	0.53 (0.43 - 0.64)	0.90 (0.67 - 1.21)
C_{avg} (µg/mL) 90% CI *P* vs Control	14.8 (13.1-16.5) 0.001	25.5 (19.3-31.7) 0.4	30.3 (24.6-36.0)	0.53 (0.43 - 0.64)	0.90 (0.67 -1 .21)
Atovaquone 1500 mg twice daily x 14 days					
AUC, (µg*hr/mL) 90% CI *P* vs Control	256 (237-274) 0.01	431 (327-535) 0.8	455 (351-558)	0.56 (0.43 – 0.73)	0.95 (0.65 – 1.38)
C_{avg} (µg/mL) 90% CI *P* vs. Control	21.3 (19.7-22.9) 0.01	35.9 (27.2-44.6) 0.8	37.9 (29.2-46.5)	0.56 (0.43 – 0.73)	0.95 (0.65 – 1.38)

Figure 1A.

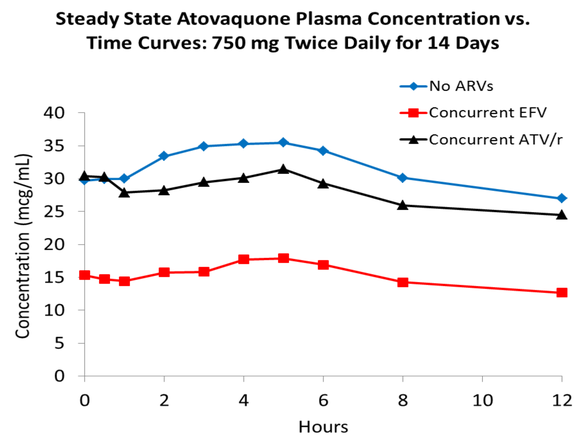
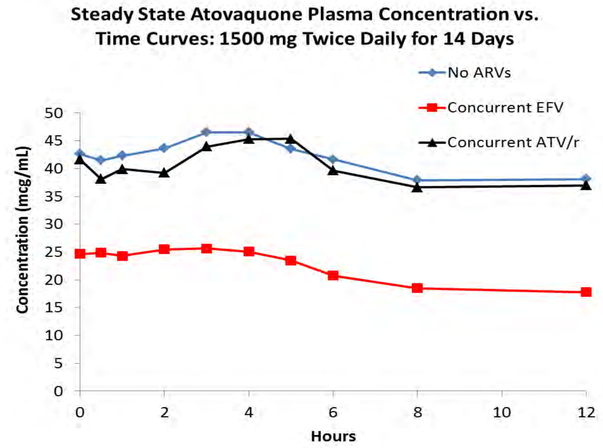


Figure 1B.



DISCUSSION and CONCLUSION

- Under steady-state conditions, concurrent EFV + atovaquone is associated with significantly reduced (~50%) atovaquone plasma concentrations (AUC and C_{avg}) at both 750 mg and 1500 mg atovaquone doses (p=0.001 and p=0.01, respectively).
- In contrast, ATV/r PK parameter values did not differ significantly from control group values at either of the studied doses.
- In subjects receiving atovaquone 750 mg BID, atovaquone Cavg was < 14 µg/mL in 4/10 subjects taking EFV and in 1/10 subjects receiving no ARV therapy; suggesting that higher atovaquone doses (1500 mg BID) may be necessary for the treatment of PCP in HIV+ patients receiving concurrent EFV.
- In subjects receiving atovaquone 1500 mg BID, atovaquone Cavg was < 18.5 µg/mL in 1/10 subjects taking EFV and in 0/9 subjects receiving no ARV therapy; suggesting the adequacy of this dose for the treatment of TE.

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