Poster #21

Relationship Between Lopinavir Exposure and Virologic Response in Subjects Receiving Lopinavir/ritonavir Monotherapy After Successful Induction with Lopinavir/ritonavir Plus Zidovudine/lamivudine

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Abstract

Background: Study M03-613 was a controlled, randomized open-label study in antiretroviral-naïve subjects comparing a lopinavir/ritonavir (LPV/r) induction-maintenance strategy to efavirenz (EFV) + zidovudine/lamivudine (AZT/3TC). After successful induction treatment with LPV/r+AZT/3TC, LPV/r monotherapy (soft gel capsule 400/100 mg BID) maintained plasma HIV-1 RNA suppression ≤50 copies/mL in the majority of subjects for up to 72 weeks. However, subjects receiving LPV/r monotherapy had more confirmed HIV-1 RNA rebound >50 copies/mL compared to subjects receiving EFV+AZT/3TC. Previous analyses determined that lower adherence and lower baseline CD4+ T-cell counts were associated with lower likelihood of maintaining virologic response. We assessed potential relationships between LPV exposure and virologic response to LPV/r monotherapy in Study M03-613.

Methods: 92 of 104 subjects randomized to LPV/r+AZT/3TC achieved 3 consecutive plasma HIV-1 RNA ≤50 copies/mL, deintensified to LPV/r monotherapy, and were followed for a median of 68 weeks on monotherapy. LPV concentrations were available from 82 of these subjects with an average of 3 samples per subject. C_{trough} and AUC were estimated using Bayesian methods in NONMEM with intra-occasion variability in pharmacokinetic parameters. The primary analysis looked at the relationships between LPV measured concentration, estimated C_{trough} or AUC and log-transformed HIV-1 RNA levels using linear regression analysis. The relationships between LPV concentration, estimated C_{trough} or AUC and HIV-1 RNA levels classified as ≤50, 50–500 and >500 copies/mL were also explored using ANOVA.

Results: The PK model well-described the observed concentrations and estimated an average (range) C_{trough} and AUC of 6.1 µg/mL (2.5–18.5) and 89.2 µg*h/mL (45–235), respectively. 24 of the subjects with available LPV concentrations experienced HIV-1 RNA rebound >50 copies/mL and 6 subjects experienced HIV-1 RNA rebound >500 copies/mL. HIV-1 RNA levels measured immediately following LPV concentration measurements were not correlated with LPV estimated C_{trough}, estimated AUC or measured concentration ($p>0.15$). When HIV-1 RNA levels were classified as ≤50, 50–500 and >500 copies/mL, there was also no significant association with LPV estimated AUC, estimated C_{trough} or measured concentration ($p>0.12$).

Conclusions: In antiretroviral-naïve subjects maintained on LPV/r monotherapy after successful HIV-1 RNA suppression with LPV/r+AZT/3TC, LPV concentrations during monotherapy were not significantly associated with plasma HIV-1 RNA levels or virologic rebound at >50 or >500 copies/mL. LPV levels during monotherapy were not predictive of episodes of viremia.

Introduction

Study M03-613 was a controlled, randomized open-label study in antiretroviral-naïve subjects comparing a lopinavir/ritonavir (LPV/r) induction-maintenance strategy to efavirenz (EFV) + zidovudine/lamivudine (AZT/3TC) through 96 weeks.

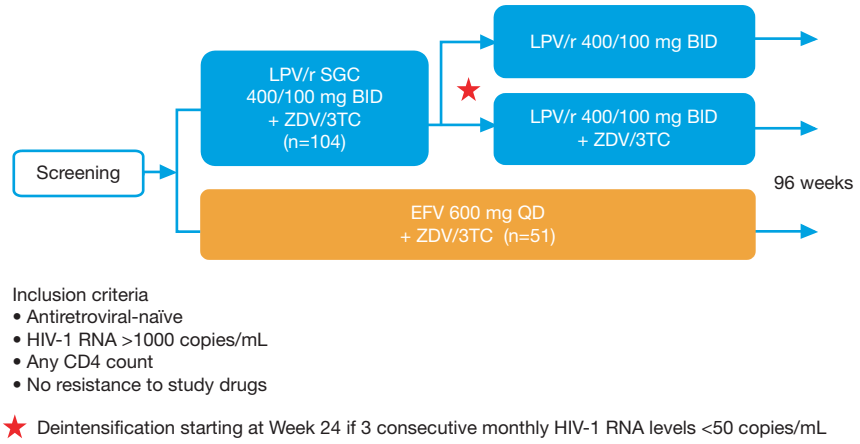
155 antiretroviral-naïve HIV-1 positive subjects were randomized 2:1 to LPV/r + ZDV/3TC induction (n=104) for at least 24 weeks, followed by maintenance LPV/r monotherapy after 3 consecutive monthly plasma HIV-1 RNA levels <50 copies/mL, or to EFV + ZDV/3TC (n=51), as described in Figure 1.

Subjects discontinued their NRTIs if they achieved 3 consecutive HIV-1 RNA levels <50 copies/mL. This occurred between Weeks 24 and 48.

92 of 104 subjects randomized to LPV/r + ZDV/3TC achieved 3 consecutive HIV-1 RNA levels <50 copies/mL, deintensified to LPV/r monotherapy, and were followed for a median of 68 weeks on monotherapy.

Introduction Continued

Figure 1. Study M03-613 Study Design

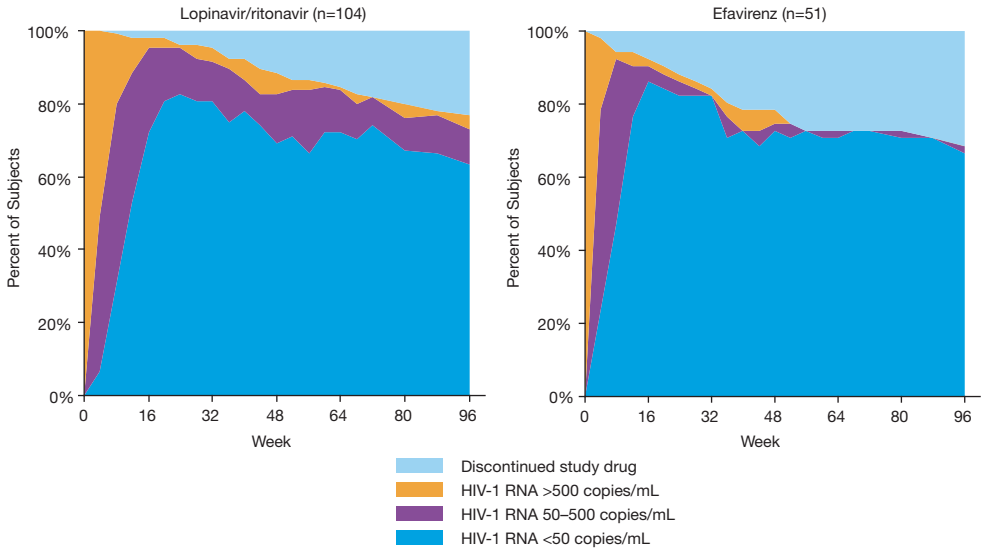


Pharmacokinetic samples were to be drawn at Weeks 4, 12, 20, 48, 72 and 88. The time and date of the two previous doses were to be recorded. Lopinavir concentrations were measured for subjects who deintensified to LPV/r monontherapy.

Most subjects in both treatment groups achieved and maintained virologic response, although those subjects who deintensified to LPV/r monotherapy were more likely to demonstrate confirmed HIV-1 RNA rebound >50 copies/mL (generally between 50 and 500 copies/mL) than EFV-treated subjects (Figure 2). At Week 96, 60% of LPV/r and 63% of EFV subjects had HIV-1 RNA <50 copies/ml (ITT, NC=F).[1]

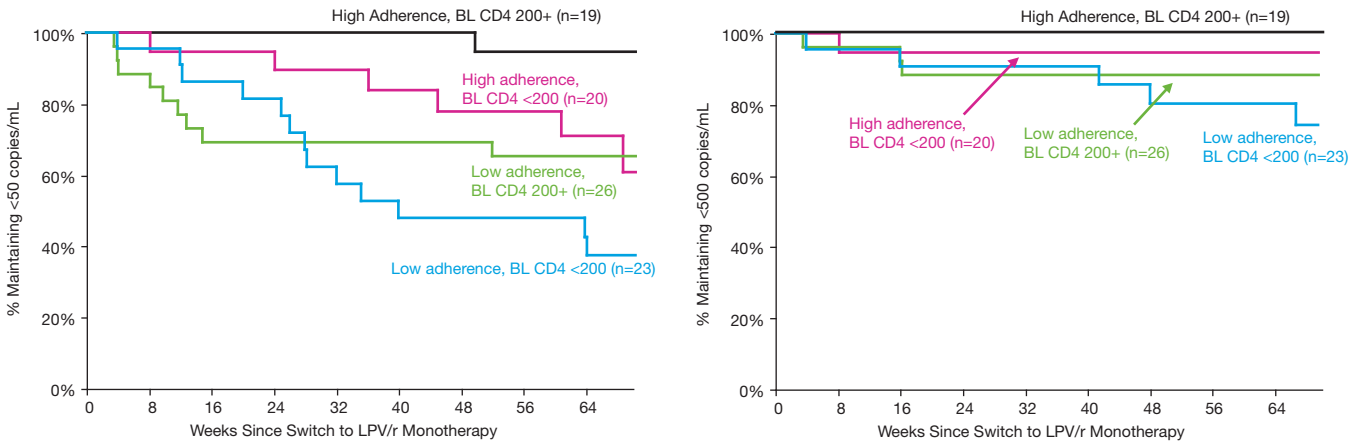
In a prior analysis, it was determined that higher levels of adherence to the LPV/r monotherapy regimen were associated with a higher likelihood of maintaining virologic suppression. In addition, lower baseline CD4+ T-cell counts were associated with lower likelihood of maintaining virologic suppression (Figure 3).[2]

Figure 2. Efficacy Through Week 96



Introduction Continued

Figure 3. Time to Loss of Virologic Response >50 Copies/mL and 500 Copies/mL by Adherence and Baseline CD4 Cell Count



Objective

To assess the potential relationships between lopinavir exposure and virologic response to LPV/r monotherapy in Study M03-613.

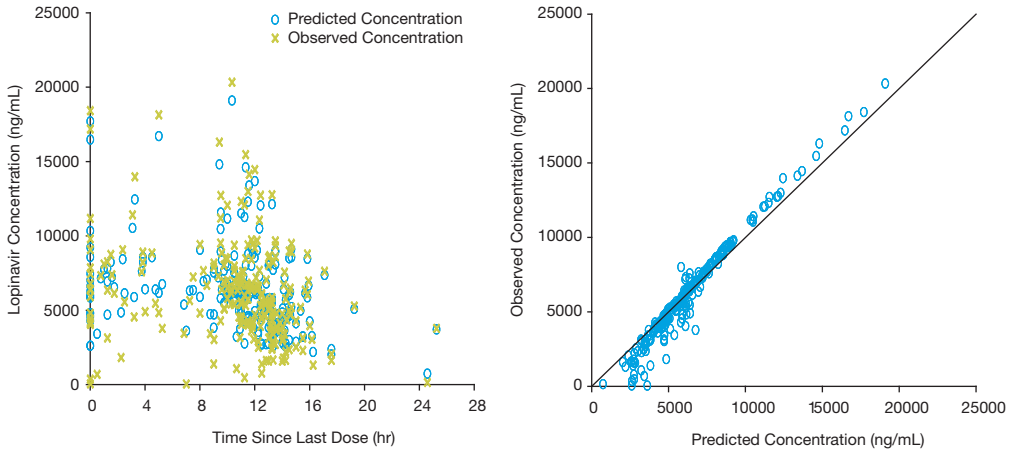
Methods

- Lopinavir concentrations were available from 82 of the 92 subjects (89%) following deintensification with an average of 3 samples per subject.
- Lopinavir C_{trough} and AUC were estimated using Bayesian methods in NONMEM with a one-compartment absorption model with intra-occasion variability in pharmacokinetic parameters.
- The primary analysis looked at the relationships between lopinavir measured concentration, estimated C_{trough} or AUC and log-transformed HIV-1 RNA levels from the same visit using linear regression analysis and accounting for time on monotherapy.
- The relationships between LPV concentration, estimated C_{trough} or AUC and HIV-1 RNA levels classified as ≤50, 50–500 and >500 copies/mL were also explored using ANOVA.

Result

The goodness of fit of the pharmacokinetic model with intra-occasion variability is shown in Figure 4.

Figure 4. PK Model Goodness of Fit



Result Continued

Using linear regression, lopinavir AUC, C_{trough} and measured concentration were not significantly correlated to observed HIV-1 RNA levels (p = 0.1520, 0.1960 and 0.8456, respectively). Lopinavir exposure did not predict HIV-1 viral load at the measured time points. These data are shown in Figures 5, 6 and 7, respectively.

Figure 5. Estimated Lopinavir AUC vs. HIV-1 Viral Load

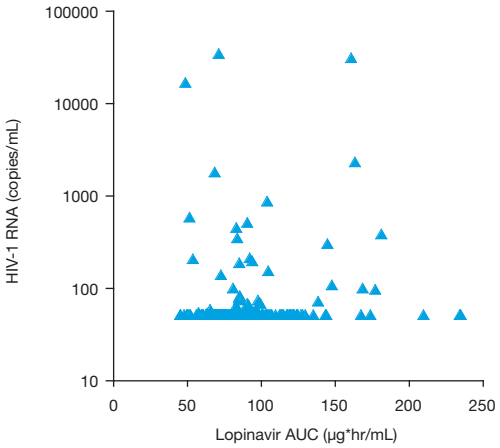


Figure 6. Estimated Lopinavir C_{trough} vs. HIV-1 Viral Load

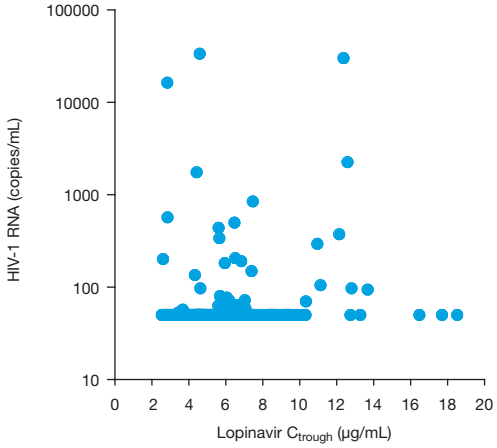
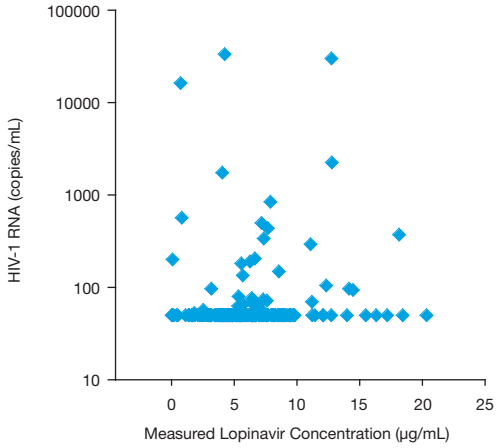


Figure 7. Measured Lopinavir Concentration vs. HIV-1 Viral Load



A secondary analysis examining HIV-1 RNA levels by category (≤50, 50–500 and >500 copies/mL) similarly did not find an overall correlation with lopinavir AUC, C_{trough} or measured lopinavir concentration (p=0.1229, 0.1529 and 0.4128, respectively).

The only cateogorical relationship detected was that subjects with HIV-1 RNA ≤50 copies/mL had lower lopinavir AUC values (p=0.0409) than subjects with HIV-1 RNA between 50–500 and >500 copies/mL. This was considered to be a spurious result.

Conclusions

In antiretroviral-naïve subjects maintained on LPV/r monotherapy after successful HIV-1 RNA suppression with LPV/r+AZT/3TC, lopinavir concentrations during monotherapy were not significantly associated with plasma HIV-1 RNA levels or virologic rebound at >50 or >500 copies/mL.

Lopinavir levels during monotherapy were not predictive of episodes of viremia.

References

1. Cameron et al. Oral abstract #THLB0201. IAC 2006
2. Campo et al. Abstract # 514. CROI 2007

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