

Title: The pharmacokinetics of Lopinavir/Ritonavir in combination with Atazanavir in HIV-infected Subjects

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## Abstract

Since its introduction in 2000, lopinavir/ritonavir has become the preferred protease inhibitor for patients initiating antiretroviral therapy due to its high rate of success, tolerability, and retention of antiviral activity. Combination of lopinavir/ritonavir with other protease inhibitors (indinavir, saquinavir, amprenavir) has been used to improve viral suppression in heavily treatment experienced patients. Initial dosing of these combinations has been largely empiric and not based on formal pharmacokinetic studies. Subsequent reports of suboptimal serum concentrations when lopinavir/ritonavir and (fos)amprenavir or tipranavir are combined highlight the need to characterize the drug interaction potential among these combinations prior to their widespread use. Failure to account for such interactions could result in increased virological failure or drug toxicity for patients.

Treatment with once-daily HAART regimens is also a high priority for clinicians to improve patient adherence. Atazanavir is a once-daily protease inhibitor with a favorable lipid profile and is now being explored in combination with other protease inhibitors. Lopinavir/ritonavir and atazanavir may prove to be a potent and well-tolerated combination; however, limited information exists about the drug interaction potential between these agents. A preliminary study conducted in 16 HIV-infected patients demonstrated no apparent effect on trough concentrations for either drug. Another study conducted in 28 heavily pretreated patients likewise demonstrated no major interaction and was associated with virological suppression. Lopinavir trough concentrations were observed to be decreased by 35% after atazanavir coadministration in 13 subjects. Limitations of these studies include their limited pharmacokinetic sampling, inadequate statistical power, and use of lopinavir/ritonavir soft gelatin capsule formulation. Lopinavir/ritonavir is now available in a new tablet (meltrex formulation) that achieves more consistent serum concentration when compared with the soft gelatin capsule. Since the meltrex tablet will replace the soft gelatin capsule, the resultant serum concentrations obtained with lopinavir/ritonavir and atazanavir are presently unknown.

Lopinavir/ritonavir is currently FDA-approved for once-daily (treatment-naïve patients) or twice daily (treatment-naïve or –experienced patients) dosing. Our study will examine the implications of both once-daily and twice daily dosing of lopinavir/ritonavir meltrex formulation with atazanavir, reflecting the potential scope of this combination's use in medical practice. We will also compare trough concentrations obtained with these agents to determine whether they exceed clinically relevant concentrations for therapy. Median protein binding-corrected 95% inhibitory concentrations have been determined for both atazanavir and lopinavir and will serve as important clinical thresholds to interpret minimally effective serum concentrations when these agents are used in combination. The ability to safely and effectively administer lopinavir/ritonavir with atazanavir once-daily would be an important discovery, making it easier for patients to administer the two agents because of the dosing symmetry.

HIV-seropositive individuals will be used in this study and will provide an effective means to assess the potential for pharmacokinetic interaction under controlled conditions. Use of seropositive individuals will control for potential disease-related effects on drug clearance. The present study design provides a rational and effective means to assess the magnitude of any pharmacokinetic interaction between lopinavir and atazanavir and possesses adequate statistical power to assess clinically important changes in drug exposure. Results from this study will provide valuable empiric dosing information to clinicians when using this combination and can guide the development of subsequent studies to determine optimal dosage adjustment should they be deemed necessary.