INTRODUCTION
Liver transplantation (LTx) is a definitive therapeutic option for HIV-infected patients with end-stage liver disease (ESLD). Pharmacokinetic (PK) interactions between antiretroviral therapy (ARVT), protease inhibitors (PIs) in particular, and immunosuppressive agents (IS) are critical elements in the management of patients with HIV infection who undergo LTx. Currently, no standard guidelines exist regarding IS dose adjustments necessary once ritonavir (RTV) boosted or unboosted PIs are initiated after LTx in HIV-infected patients.

PATIENTS, METHODS AND OBJECTIVES
This is a single-center, open-label, cross-sectional pilot PK study of consecutive HIV-infected subjects who underwent LTx. The study population was divided in two groups: patients undergoing PIs boosted with RTV (group A) and patients undergoing unboosted PIs (group B).

The primary objective was the IS drug dosage decrease in group A and B when comparing IS doses pre- versus post-ARVT resumption (after LTx) necessary to achieve therapeutic window (TW). The secondary objective was the median time necessary to gain IS TW in both groups after dose adjustment at 48 hours from ARVT re-initiation.

IS drug PK assays were performed using MEIA whole blood quantification. PIs plasma C\textsubscript{T} levels were measured by a modified HPLC method and they were compared with minimal effective concentration (MEC) values.
**RESULTS**

Twelve consecutive HIV-infected adult patients (11 males, 1 female) were enrolled. Group A included 4 patients receiving boosted PIₘ (3 LPV/RTV, 1 APV/RTV) and group B 8 subjects receiving unboosted PIₘ (7 ATV, 1 fosamprenavir -fosAPV-). After transplantation all patients re-initiated the same pre-LTₓ ARVT regimen as soon as liver function stabilized.

More rapid increases in plasma levels of IS were noted 48 hours after the resumption of boosted PIₘ post-LTₓ. The median fold decrease in IS dosage required to achieve the IS TW was 7.5 (range= 6-14) in group A and 2.9 (range= 2-4) in group B. Difference between the two groups resulted significant with a p-value of 0.0065.

The median time required to achieve IS concentrations within the TW after dose adjustment was 4.5 days (range 0-13) in group A and 3.5 days (range 0-15) in group B. At the time of IS TW achievement, plasma Cₜ levels of PIₘ were above the MEC in 10 of 12 patients (83.3%). Difference in the median time to gain TW between group A and B did not result significant (p-value= 0.93).

Grade III-IV drug-related laboratory toxicities were not observed during the first 48 hours after restarting ARVT. Seven patients, 3 belonging to group A, and 4 to group B developed acute renal failure.

**DISCUSSION**

Although the optimal timing of ARVT resumption after surgical procedure is not clear, we encourage an early ARVT re-initiation as soon as normal graft function is achieved and IS Cₜ levels can be stabilized within their TW.

Unboosted PIₘ had fewer IS PK interactions and were easier to use compared to boosted PIₘ in the post-LTₓ period.

Given the extent of drug-drug interactions involved and the inter-patient variability, the routine utilization of therapeutic drug monitoring for both PIₘ and IS management is mandatory after LTₓ.