Introduction: Atazanavir (ATV) is a protease inhibitor that can be administered at 400 mg once daily (unboosted) or 300 mg with a 100-mg dose of ritonavir once daily (boosted). Plasma concentrations are commonly considered as an indicator of drug exposure but the antiretroviral activity of protease inhibitors may correlate better with intracellular concentrations. The aim of this study was to evaluate ATV accumulation in PBMCs and to compare unboosted and boosted ATV treatments.

Materials and Methods: Patients were recruited in Torino (Italy). Sampling was performed after written informed consent was obtained in accordance with local ethics committee indications. Patients receiving ATV as part of their antiretroviral therapy were included in the study. Main inclusion criteria were, no concomitant interacting drugs (except TDF), no hepatic or renal impairment and self-reported adherence > 95%. Ctrough was measured in samples collected 22-26 h after dosing. Plasma sample were analysed by a validated HPLC-PDA method and intracellular samples were analysed using a validated HPLC-MS method plus a Coulter Counter for cells count and mean cellular volume (MCV) quantification. The ratio of the intracellular Ctrough/plasma Ctrough was calculated to determine cellular drug accumulation.

Results: 29 patients were included in the study, 14 treated with unboosted and 15 treated with boosted ATV. Median (IQR) ATV intracellular Ctrough was higher than median plasma Ctrough, 328 ng/ml (168-440) vs 132 ng/ml (111-184), p = 0.001, for unboosted ATV and 1032 ng/ml (819-3091) vs 543 ng/ml (393-1081), p = 0.005, for boosted ATV. However, plasma and intracellular concentrations were not correlated in either treatment group (rho = 0.44, p = 0.11 for unboosted ATV and rho = 0.23, p = 0.41 for boosted ATV). Median (IQR) ATV intracellular Ctrough was higher for boosted ATV compared to unboosted ATV, 1032 ng/ml (819-3091) vs 328 ng/ml (168-440), p = 0.001. Cellular drug accumulation was comparable between the two treatment groups, 1.9 (1.2-2.3) for unboosted ATV vs 2 (1.5-4.9) for boosted ATV, p = 0.5.

Conclusions: Intracellular ATV concentrations were higher than plasma concentrations, indicating an accumulation of ATV in PBMCs. Patients treated with boosted ATV had a higher intracellular exposure but cellular drug accumulation was similar in the two treatment groups. The lack of a clear correlation between plasma and intracellular concentrations suggest a potential role for uptake and/or efflux transporters in regulating intracellular accumulation of ATV.

No conflict of interest