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(Original Article)

**ASSESSING THE IMPACT OF HEPATITIS C VIRUS COINFECTION ON
LOPINAVIR/RITONAVIR TROUGH CONCENTRATIONS IN HIV-INFECTED
PATIENTS**

Running head: Plasma trough concentrations of lopinavir/ritonavir in HIV/HCV-coinfected patients

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ABSTRACT

Purpose. Chronic hepatitis C represents an emerging issue in the management of HIV disease because of the same route of transmission, leading to a very high prevalence of HCV-coinfection in HIV-positive patient population. Lopinavir is extensively metabolized by the hepatic cytochrome P450 3A4, and pharmacokinetics of this protease inhibitor (PI) could be influenced by liver impairment, but data on the impact of HCV-coinfection on lopinavir plasma concentrations are very limited and conflicting still today. **Methods.** In this observational, open-label study, adult HIV-infected outpatients on stable antiretroviral treatment including two nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir for at least 4 weeks were asked to participate. The trough plasma concentration (C_{trough}) of lopinavir and ritonavir was assessed at steady state by a validated high-performance liquid chromatography (HPLC)-tandem mass spectrometry method. **Results.** A total of 65 HIV-positive patients were enrolled in the study. These patients were stratified into two groups with regard to HCV-coinfection: 45 were HIV-mono-infected (HIV+/HCV-) and 20 were HIV-HCV-coinfected (HIV+/HCV+). Lopinavir C_{trough} in plasma was comparable between HIV+/HCV+ and HIV+/HCV- subjects, without statistically significant differences (GMR 0.89, 95% CI 0.61-1.42; $p=0.581$). Similarly, mean ritonavir C_{trough} was comparable in the two considered groups. Almost all samples were found to be within the therapeutic plasma level range (97% in HIV+/HCV- group and 100% in HIV+/HCV+ group). No correlation was found between lopinavir plasma levels and adverse events (such as diarrhoea and hypertriglyceridaemia) or immunovirological parameters of HIV disease. **Conclusions.** In our study, pharmacokinetics of lopinavir/ritonavir did not show significant changes in HIV-positive patients with HCV-coinfection, and in absence of liver cirrhosis.

Key words: chronic hepatitis C, antiretroviral therapy, protease inhibitor, pharmacokinetics, therapeutic drug monitoring

INTRODUCTION

Although the introduction of highly active antiretroviral therapy (HAART) has led to a significant increase in survival of patients with human immunodeficiency virus (HIV) infection and acquired immune-deficiency syndrome (AIDS), an ongoing problem is the emergence of clinical complications associated with comorbidities.

The impact of chronic liver diseases has become of increasing concern in HIV-positive population, because the prevalence of hepatitis C virus (HCV) and HIV (HCV/HIV) co-infection is estimated to be around 25% to 30%, and the prevalence may be higher than 50% in some countries (such as Italy and Spain) and than 90% in some subpopulations (such as intravenous drug addicts) [1-3]. Moreover, liver toxicity is a common adverse event of antiretroviral agents and is expected to occur more commonly in subjects with HCV coinfection.

Lopinavir/ritonavir is a potent, peptidomimetic HIV protease inhibitor (PI) which is often included in initial therapeutic regimens. Lopinavir is extensively and rapidly metabolized by the hepatic cytochrome P450 (CYP) 3A4 isoenzyme, and its coadministration with low-dose ritonavir (100 mg daily), a potent inhibitor of CYP3A4, significantly improves its pharmacokinetic properties [4]. Particularly, CYP3A4 is the major determinant of lopinavir pharmacokinetics, far more than drug transporters P-glycoprotein or multidrug resistance protein 2 (MRP2), and both intestinal and hepatic CYP3A activity contributed importantly to low oral bioavailability of this PI [5]. Elevated and prolonged serum levels of lopinavir support twice-daily dosing, or once-daily dosing in antiretroviral-naïve patients. Liver dysfunction associated with chronic hepatitis C could impact on the absorption of the drug, its first-pass metabolism by the enteric tract and the liver, binding to plasma proteins, and plasma protein concentrations, thereby resulting in an increased exposure to lopinavir and the risk of developing adverse events [6, 7].

The observed variations in antiretroviral pharmacokinetics which result in a wide range of individual patient drug exposures, has led to increasing interest in the clinical use of therapeutic drug monitoring (TDM) as an approach to individualize drug dosing, particularly in subjects with liver or renal dysfunction. Additional rationale for the clinical use of TDM includes potential, numerous pharmacokinetic interactions between antiretroviral agents and other drugs that may influence their plasma levels. TDM of PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) is straightforward and reproducible, and benefits with regard to optimal drug concentration for full viral suppression and avoidance of drug toxicity have been demonstrated [8-10].

Data on the impact of HCV co-infection on lopinavir plasma levels are controversial still today. They are currently based on a few studies including a small number of patients and have led to

conflicting conclusions. Aim of this study was to evaluate plasma trough concentration of lopinavir/ritonavir in HIV-HCV-coinfected patients (without liver cirrhosis), and in a control group of HIV-infected subjects without HCV co-infection.

METHODS

In this observational, open-label study, HIV-infected outpatients attending the Division of Infectious Diseases of S. Orsola-Malpighi Hospital in Bologna between April 2006 and March 2007 and who were on stable antiretroviral treatment including two nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir for at least 4 weeks were asked to participate. The study was approved by the Ethics Committee of S.Orsola-Malpighi Hospital, and written informed consent was obtained from each patient before enrollment.

On the day of blood sampling for pharmacokinetics analysis, epidemiological data (sex, age, race, risk factors for HIV infection, and HIV disease stage) and anthropometric measurements [body weight, height, and body mass index (BMI)] were assessed. At the same time, clinical evaluation, CD4+ lymphocyte count, plasma HIV viral load (obtained by a branched-DNA assay; Bayer Diagnostic, Milan, Italy, with a lower limit of 50 copies/mL), liver and renal function tests, and serum concentrations of glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were collected. Exclusion criteria were an age <18 years, a recent history of alcohol or drug abuse, acute hepatitis, chronic hepatitis B (defined by the persistent positivity of hepatitis B surface antigen), liver cirrhosis (defined by clinical, biochemical and/or histopathological features), recent and uncontrolled opportunistic disease, acute severe diseases, renal dysfunction (serum creatinine >1.2 mg/dL), diabetes mellitus, pregnancy or breast-feeding, adherence levels to HAART treatment <95%, current therapy with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or other protease inhibitors (PIs), current lipid-lowering or antidiabetic treatment, and concomitant administration of medications or herbal supplements known to affect lopinavir or ritonavir pharmacokinetics. HCV coinfection was diagnosed by the persistent positivity of HCV serum antibodies and HCV-RNA, and according to this evaluation the enrolled patients were stratified into two groups: without HCV co-infection (HIV+/HCV-), *versus* subjects with HCV co-infection (HIV+/HCV+).

Lopinavir/ritonavir therapy was administered by capsules at the standard dose of 400/100 mg twice a day after a standardized continental breakfast and after a moderate fat meal for lunch. The trough plasma concentration (C_{trough}) of lopinavir and ritonavir was assessed at steady state (>4 weeks after treatment initiation), with blood samples obtained before the morning dose and 10-14 hours after the previous evening dose. The precise times of the predose sample and of the previous evening

intake were recorded to ensure accurately timed blood sampling. Trough levels were considered to within an acceptable sampling timeframe if they fell within a defined time range for lopinavir every 12 hours within 10 to 14 hours after the last dose. Blood samples were collected in 3.0 mL Vacuette EDTA-containing tubes and were centrifuged (600 g for 10 minutes) to obtain plasma samples within two hours of collection. The plasma samples were frozen at -20°C and were sent on dry ice to the Central Laboratory of the S. Orsola-Malpighi Hospital to assess the C_{trough} of lopinavir. After thawing, HIV was inactivated at 56°C for 30 minutes, then the plasma samples were extracted and subjected to a validated high-performance liquid chromatography (HPLC)-tandem mass spectrometry method, as described by Dickinson et al. [11]. Internal standard (cimetidine) and acetonitrile (400 μL) were added to aliquots (100 μL) of calibrators, quality controls, and patient ultrafiltrate. After mixing, centrifugation, and addition of ammonium formate buffer (100 μL ; 20 mM), samples were analyzed by HPLC-tandem mass spectrometry (10 μL). Fragmentation of parent molecules into daughter ions occurred by electrospray ionization; ions were separated according to their m/z ratio and quantified by the intensity of their respective daughter ions. Suggested minimum target C_{trough} of lopinavir for inhibiting wild-type virus is within the range of 1,000-10,000 ng/mL and has used as a guideline for analyzing the data [9,10,12].

The statistical analysis was performed considering lopinavir and ritonavir C_{trough} separately. Variables with normal distribution were described as mean (standard deviation, or SD) and compared by an unpaired t-test. Median and interquartile range were employed to describe variables that did not follow a normal distribution and these were compared with the Mann-Whitney non-parametric test. Percentages were compared with the χ^2 test or Fisher's exact test, as appropriate. Lopinavir and ritonavir C_{trough} were described as the geometric mean, and inter-individual variability in drug concentrations was expressed as the coefficient of variation (CV%), which was calculated by dividing the SD by the mean. Lopinavir and ritonavir C_{trough} were compared between HIV-HCV-coinfected and HIV-monoinfected patients using the geometric mean ratio (GMR) and the 95% confidence interval (CI). In order to account for the potential influence of sex, BMI, or albumin concentrations in plasma on drug exposure, multiple regression models including these variables were tested. The minimum sample size to detect a difference of 30% or greater in lopinavir C_{trough} between HIV+HCV+ and HIV+HCV- patients was 20 in each group, when accepting an α risk of 0.005 and a β risk of 0.20 [13, 14].

RESULTS

A total of 65 adult Caucasian HIV-positive patients were enrolled into the study. These patients were stratified into two groups with regard to HCV-coinfection: 45 were HIV-mono-infected

(HIV+/HCV-) and 20 were HIV-HCV-co-infected (HIV+/HCV+). The demographic, anthropometric, clinical, and laboratory characteristics of the 65 enrolled patients are summarized in Table 1.

Persistently elevated serum levels of transaminases (alanine amino-transferase or ALT > 40 UI/L in at least two blood tests obtained in the last 6 months), were registered in 16 out of 20 (80%) HIV-HCV-co-infected subjects and only in 4 out of 45 (8.8%) HIV-mono-infected persons. Among the HIV-HCV-co-infected subjects, 9 (45%) have previously received an antiviral therapy for HCV infection (interferon or pegylated interferon and ribavirine) with viral breakthrough or relapse, and all these patients were currently positive for serum HCV-RNA. Liver biopsy was previously performed in 10 subjects showing a minimal or slight chronic hepatitis (Ishak's score ranging from 1 to 9) in 6 patients, and a moderate chronic hepatitis (Ishak's score ranging from 10 to 15) in 4 individuals. All patients were at steady-state for lopinavir/ritonavir treatment at the standard dose of 400/100 mg twice daily, as part of a HAART regimen including two nucleoside reverse transcriptase inhibitors (NRTIs). Antiretroviral agents associated with lopinavir/ritonavir are reported in Table 2.

There were no statistically significant differences between the two patient groups in terms of demographic, anthropometric, and HIV-related clinical and laboratory characteristics, except for biochemical parameters reflecting the HCV-related hepatic disease. Particularly, mean values of serum alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase were significantly higher in HIV-HCV-coinfected subjects than in HIV-monoinfected ones. With regard to serum protein and metabolism parameters, there were no statistically significant differences between the two groups as to serum levels of glucose, albumin, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, while mean insulin concentration was significantly greater in HIV+/HCV+ patients than in HIV+/HCV- subjects. Duration of current antiretroviral therapy and total exposure to lopinavir/ritonavir were comparable in both groups, such as immune-virological parameters. Plasma HIV viral load was undetectable (<50 copies/mL) in 80% and 75% of HIV+/HCV- and HIV+/HCV+ patients, respectively, while mean (SD) HIV viral load in patients with detectable viremia was 5,500 (3,200) copie/mL and 2,800 (1,900) copies/mL, respectively (p=0.51).

Plasma concentrations showed a great interindividual variability in both groups, but almost all samples were found to be within the therapeutic plasma level range (97% in HIV+/HCV- group and 100% in HIV+/HCV+ group). The geometric mean plasma C_{trough} of lopinavir was 5,931 ng/mL (118%) in HIV+/HCV- patients and 6,872 ng/mL (173%) in HIV+/HCV+ ones, as showed in Figure 2. Therefore, the presence of HCV co-infection was considered to be not significant (GMR

0.89, 95% CI 0.61-1.42; $p=0.581$). No significant relationship between lopinavir C_{trough} and sex, BMI, or albumin concentration were observed (Table 3).

Possible correlations between trough plasma concentration of lopinavir and some drug-related adverse events were also investigated. The geometric mean C_{trough} of lopinavir in patients experiencing recent diarrhoea (≥ 3 evacuations daily with watery feces in the last 2 days) or hypertriglyceridemia (serum triglyceride >250 mg/dL in at least 2 blood tests in the last 6 months), were compared with those of subjects without diarrhea and hypertriglyceridemia. The geometric mean plasma C_{trough} of lopinavir was 6,121 ng/mL (91%) in subjects with diarrhoea and 6,787 ng/mL (117%) in those without this symptom, and no statistically significant difference were found (GMR 0.94, 95% CI 0.51-1.38; $p=0.471$). At the same time, the geometric mean plasma C_{trough} of lopinavir was 6,118 ng/mL (79%) in subjects with hypertriglyceridemia and 6,915 ng/mL (141%) in those with normal serum triglyceride concentrations, without statistically significant differences (GMR 0.65, 95% CI 0.43-1.25; $p=0.618$). Moreover, no statistically significant correlations were found between mean C_{trough} of lopinavir and immune-virological parameters, different kind of nucleoside analogues, presence of lipodystrophy, and plasma concentrations of total cholesterol, LDL cholesterol and glucose (data not shown).

Finally, the geometric mean plasma C_{trough} of ritonavir tested 258 ng/mL (81%) in HIV+/HCV- patients and 274 ng/mL (106%) in HIV+/HCV+ ones, without statistically significant difference (GMR 0.97, 95% CI 0.65-1.38; $p=0.712$). Similarly, no significant relationship between ritonavir C_{trough} and sex, BMI, or albumin concentration were registered (Table 3).

DISCUSSION

It is not clear whether enzyme induction or inhibition is likely to be affected in patients with hepatic dysfunction, and the final pharmacokinetic changes of PIs associated with chronic hepatitis are unknown still today. The effects of liver disease on pharmacokinetics are highly variable because the pathogenetic mechanisms are complex, and not well understood. Liver dysfunction may include a wide range of pathophysiologic abnormalities, such as reduction in blood flow, extrahepatic or interhepatic blood shunting, hepatocyte dysfunction, quantitative and qualitative changes in serum proteins, and changes in biliary flow.

Data on the consequences of chronic hepatitis C on lopinavir serum levels in HIV-infected patients are currently based on a few studies including a small number of subjects and has resulted in conflicting results.

An observational, open-label study assessed pharmacokinetics of lopinavir/ritonavir in 24 HIV-infected patients receiving a stable antiretroviral treatment for at least two weeks prior to and during

the study: 12 subjects with mild or moderate liver impairment (associated with chronic hepatitis C or chronic alcoholism), and 12 subjects with normal hepatic function. Chronic liver disease was associated with a significant increase in plasma exposure to lopinavir: the maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve from 0 to 12 hours (AUC_{12}) were increased 20% to 30% compared to the control group. Moreover, liver impairment increased unbound lopinavir AUC_{12} by 68% and C_{max} by 56% [15].

Plasma drug levels of nevirapine, efavirenz, lopinavir/ritonavir and atazanavir were measured in 268 HIV/HCV-coinfected patients. Overall, drug levels of efavirenz and nevirapine were significantly higher in subjects with hepatic cirrhosis than in those without cirrhosis, while plasma levels of lopinavir and atazanavir did not differ significantly between patients with and those without cirrhosis. Therefore, hepatic insufficiency was found to be associated with a significant impairment in the liver clearance of NNRTIs, particularly efavirenz, while no similar effects were observed for PIs [16].

The impact of substance use and hepatitis virus coinfection on plasma PI trough concentrations was evaluated in 60 HIV-infected patients established on atazanavir/ritonavir or lopinavir/ritonavir containing regimen. Substance use was associated with a marked decrease in lopinavir C_{trough} , and significantly lower lopinavir trough levels were also noted among patients with active chronic hepatitis C evaluated as an independent variable. On the contrary, substance use and HCV-coinfection showed limited effects on atazanavir trough levels. In this cohort, despite the wide interindividual variability of PI trough concentrations, substance use and active chronic hepatitis C were significantly associated with a lower C_{trough} of lopinavir [17].

However, this association was not found in other reports. In an observational, prospective study involving 78 HIV-monoinfected and 71 HIV/HCV-coinfected non-cirrhotic patients, liver function tests and steady-state lopinavir C_{trough} values were obtained at 1, 3, 6 and 12 months. Incidence of moderate to severe increase in transaminases was significantly higher in HCV-coinfected subjects, but the pharmacokinetics of lopinavir-ritonavir, as assessed by serial measurements of C_{trough} , showed no differences in the two groups, and no association was found between the serum concentration of lopinavir and the development of hepatotoxicity [18].

A cross-sectional, comparative study assessed lopinavir and ritonavir pharmacokinetics in 26 HIV-mono-infected patients and 22 HIV/HCV-coinfected subjects; moreover, HCV-positive subjects were grouped according to the presence of an underlying advanced hepatic fibrosis, or not. Lopinavir and ritonavir pharmacokinetics were comparable between HCV-negative and HCV-positive patients without liver function impairment, but PI plasma levels show significant differences in HCV-positive group with advanced liver disease. The apparent volume of distribution

after oral administration of lopinavir was 125% higher in HCV-positive subjects with advanced liver fibrosis than in HCV-negative individuals, and 107% higher than in HCV-positive subjects without advanced fibrosis. For ritonavir, AUC_{12} and maximum and minimum plasma concentrations in HCV-positive patients with advanced fibrosis were 63%, 86% and 100% higher, respectively, when compared with these parameters in HCV-negative controls [19].

A prospective, open-label study evaluated the pharmacokinetics of total and unbound lopinavir in 56 HIV-infected patients (24 HIV-monoinfected, 23 HIV/HCV-coinfected, and 9 HIV/HCV-coinfected with liver cirrhosis). No significant differences in AUC_{12} , C_{trough} or apparent oral clearance of total and unbound lopinavir were observed among the three groups. However, chronic liver impairment produced a slight, although not significant, decrease in plasma protein binding, and the free-fraction of lopinavir increased from 0.97% in HIV-mono-infected patients to 1.18% in HIV/HCV-coinfected patients with liver cirrhosis. No significant changes in pharmacokinetics of total and unbound lopinavir were showed in patients with liver dysfunction and morphologic evidence of cirrhosis, possibly because of the potent inhibitory effect of ritonavir on lopinavir metabolism [20].

In our study, mean plasma trough concentrations of lopinavir and ritonavir were comparable in HIV-mono-infected and HIV/HCV-coinfected patients without liver cirrhosis, and pharmacokinetics of these PIs was not significantly influenced by the presence of HCV coinfection, even though plasma drug concentrations showed a great inter-individual variability in both groups. Similarly, no statistically significant correlations were found between mean C_{trough} of lopinavir and commonly encountered adverse effects (such as diarrhoea and hypertriglyceridaemia), immunovirological parameters of HIV disease, different kind of nucleoside analogues, presence of lipodystrophy, plasma concentrations of total cholesterol, LDL cholesterol and glucose. Despite a large variation of antiretroviral drug plasma levels, single-measurement TDM may be sufficient in the routine management to assess if the PI C_{trough} is within the therapeutic plasma level range, as showed by Donnerer et al. [21].

Chronic liver disease is usually associated with chronic hepatocyte damage and decreased cell function, with a 50% reduction in cytochrome P450 content. In general, chronic hepatic dysfunction and changes in hepatocellular mass may produce a reduction in intrinsic clearance of several drugs, leading to a marked increase in their plasma levels and risk of potential toxicity. The absence of significant changes in lopinavir plasma concentrations among HIV-infected patients with chronic hepatitis C could be explained by the distinguishing pharmacokinetics of co-formulated lopinavir/ritonavir. Because ritonavir usually inhibits the liver metabolism of lopinavir and thus

decreases the lopinavir hepatic clearance, the reduction in lopinavir intrinsic clearance in subjects with hepatic impairment may be absent or less pronounced.

These pharmacokinetic data suggest that no adjustment of lopinavir/ritonavir dosing is requested in HIV/HCV-coinfected patients without liver cirrhosis, even though caution is always necessary for the administration of PIs in subjects with chronic liver diseases, and notably with hepatic cirrhosis. Further, enlarged studies are certainly required to better investigate the pharmacokinetic changes of PIs in HIV-infected patients with HCV-coinfection.

TABLES

Table 1. Demographic, anthropometric, clinical, and laboratory characteristics of the 65 patients enrolled in our study.

	HIV+/HCV- (n=45)	HIV+/HCV+ (n=20)	p value
N. of males (%)	37 (82.2)	12 (60)	0.65
Mean age \pm SD (years)	43.2 \pm 4.9	45.1 \pm 5.7	0.81
Mean body weigh \pm SD (Kg)	66.2 \pm 25.4	68.1 \pm 26.5	0.58
Mean body mass index \pm SD (Kg/m ²)	21.6 \pm 3.7	24.7 \pm 4.6	0.51
Heterosexual/homosexual/i.v. drug user	19/9/17	8/7/5	0.62
N. of patients with a previous AIDS diagnosis (%)	6 (13.3)	3 (15)	0.48
Mean duration of current antiretroviral therapy \pm SD (months)	29.4 \pm 9.5	26.8 \pm 8.1	0.61
Mean time of exposure to lopinavir \pm SD (months)	30.2 \pm 11.4	28.4 \pm 10.7	0.23
Mean total duration of antiretroviral therapy \pm SD (months)	60.2 \pm 28.4	55.7 \pm 24.9	0.35
Mean CD4 T-lymphocyte count \pm SD (cells/mm ³)	609 \pm 285	685 \pm 307	0.29
N. of patients with HIV RNA levels < 50 copies/mL (%)	36 (80)	15 (75)	0.37
Mean serum concentration \pm SD of			
- alanine aminotransferase (ALT) (UI/L)	21 \pm 7	46 \pm 18	0.02
- aspartate aminotransferase (AST) (UI/L)	19 \pm 9	41 \pm 10	0.01
- total bilirubin (mg/dL)	0.58 \pm 0.21	0.71 \pm 0.38	0.45
- albumin (g/dL)	4.4 \pm 0.9	4.2 \pm 0.8	0.31
- alkaline phosphatase (UI/L)	242 \pm 85	261 \pm 98	0.28
- gamma-glutamyltransferase (UI/L)	36 \pm 11	71 \pm 39	0.02
- total cholesterol (mg/dL)	192 \pm 89	181 \pm 65	0.48
- LDL cholesterol (mg/dL)	108 \pm 72	94 \pm 51	0.56
- HDL cholesterol (mg/dL)	45 \pm 22	50 \pm 24	0.25
- triglycerides (mg/dL)	201 \pm 195	176 \pm 127	0.51
- glucose (mg/dL)	89 \pm 47	94 \pm 49	0.49
- insulin (μ U/mL)	9.7 \pm 4.8	35.2 \pm 21.4	0.002
- creatinine (mg/dL)	0.89 \pm 0.24	0.92 \pm 0.26	0.33

SD, standard deviation; i.v., intravenous; AIDS, acquired immune-deficiency syndrome

Table 2. N. of patients taking different antiretroviral agents in association with lopinavir/ritonavir in their current HAART regimen.

	HIV+/HCV- (n=45)	HIV+/HCV+ (n=20)	p value
Lamivudine (%)	29 (64.4)	15 (75)	0.45
Tenofovir (%)	19 (42.2)	8 (40)	0.38
Emtricitabine (%)	15 (33.3)	4 (20)	0.61
Zidovudine (%)	10 (22.2)	4 (20)	0.39
Abacavir (%)	8 (17.7)	3 (15)	0.59
Didanosine (%)	5 (11.1)	2 (10)	0.31
Stavudine (%)	3 (6.6)	4 (20)	0.19

HAART, highly active antiretroviral therapy

Table 3. Lopinavir and ritonavir trough concentrations in HIV-monoinfected (HIV+/HCV-) and HIV-HCV-coinfected (HIV+/HCV+) patients. Data are presented as geometric mean (coefficient of variation %).

Variables	Lopinavir C _{trough}		p	Ritonavir C _{trough}		p
	HIV+/HCV-	HIV+/HCV+		HIV+/HCV-	HIV+/HCV+	
Overall	5,931 (118%)	6,872 (173%)	0,58	258 (81%)	274 (106%)	0,71
Men	5,412 (135%)	6,144 (182%)	0,49	221 (107%)	249 (98%)	0,59
Women	6,218 (95%)	7,312 (144%)	0,61	269 (132%)	291 (127%)	0,65
BMI ≥ 25	5,118 (106%)	5,774 (109%)	0,32	231 (79%)	255 (89%)	0,61
BMI < 25	6,185 (91%)	6,945 (87%)	0,51	272 (104%)	288 (134%)	0,46
Albumin ≥ 3,5	5,725 (112%)	6,418 (109%)	0,71	241 (82%)	259 (91%)	0,38
Albumin < 3,5	6,106 (139%)	7,098 (106%)	0,49	267 (118%)	285 (104%)	0,59

BMI, body mass index (Kg/m²); albumin, albumin plasma concentration (g/dL).

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