Pharmacological Interaction of Lopinavir/Ritonavir 800/200 mg BID and Rifampicin in Subjects Presenting Tuberculosis with Contraindication for an Efavirenz containing Antiretroviral Regimen

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Abstract

Rifampicin reduces plasma concentration of most HIV protease inhibitors. Lopinavir boosted with ritonavir (LPV/r) could be an option to treat TB-HIV patients. Our aim was to evaluate lopinavir interaction with rifampicin during TB-HIV therapy. TB-HIV patients who could not use efavirenz and with no genotypic resistance to lopinavir were included. Rifampicin 600 mg, isoniazid 400 mg and pyrazinamide 2000 mg were started at day one for 6 months and LPV/r plus two nucleoside/nucleotide reverse transcriptase inhibitors were introduced at day 30. LPV/r dose was started at 400/100 mg BID and escalated over 7 days to 800/200 mg BID. Pharmacokinetic sampling was performed at day 15 (rifampicin), 45, 90, 180 (rifampicin, lopinavir, ritonavir) and 210 (lopinavir, ritonavir). Viral load (VL) and CD4 counts were performed at baseline and days 30, 60, 120, and 180. Genotypic testing was done in baseline and in the last visit. Fifteen patients were enrolled. Five were excluded during exclusively TB therapy. After LPV/r introduction five patients were excluded, three due to adverse events, and two due to low adherence. Five patients finished the study, two of them with VL<50 copies/mL. LPV/r genotypic resistance was detected in one patient. Lopinavir concentrations were below 1 μg/mL in 4/10 patients (in one study point), and one in two study points. Rifampicin concentrations were above 4 μg/mL in 6/10 patients, at least in one pharmacokinetic sample.

Although target drug concentrations of lopinavir were achieved for most patients, adverse events were frequent and low adherence was observed for both TB and HIV therapies, showing how difficult it is to treat both diseases simultaneously. Hepatic and pancreatic enzymes should be routinely monitored.

Keywords: AIDS; Tuberculosis; Pharmacokinetics; Lopinavir; Rifampicin

Introduction

Despite the use of potent antiretroviral (ARV) regimens, the incidence of tuberculosis (TB) in HIV-infected people world wide remains high [1]. Because of poorer treatment outcomes when not used, rifamycin based regimens are the preferred choice for the treatment of TB, based on their proven efficacy, tolerability, and lower costs [2]. Boosted protease inhibitors are recommended if non-nucleoside reverse transcriptase inhibitors cannot be used. However, rifampicin – a potent cytochrome P450 3A4 isoform inducer – yields sub-therapeutic blood concentrations of boosted protease inhibitors (PI), with standard PI doses [3]. An alternative is to use an integrase inhibitor as part of the antiretroviral regimen while treating TB with rifampicin. A recent trial showed similar efficacy of raltegravir and efavirenz used concomitantly with rifampicin based regimens for TB [4]. However, in high burden TB countries the use of raltegravir is limited by its high cost, being unavailable in many TB programs up to now.

The use of rifabutin has been recommended with PIs, because rifabutin is a less potent cytochrome inducer than rifampicin. However, it is metabolized by cytochrome P450 3A4 isoform, of which ritonavir (RTV) is a powerful inhibitor which can result in toxicities caused by increased rifabutin concentrations. The result of these interactions is an increase in rifabutin blood concentration. In order to avoid the potential rifabutin toxicity, the reduction of rifabutin dose is recommended when co-administered with boosted PIs. However, reducing the rifabutin dose poses the risk of acquired rifamycin resistance if ARV therapy is not adequately taken. Additionally, there are no fixed-dose combinations of TB medications incorporating rifabutin, potentiating thus the risk of drug resistance if taken separately, due to the pill burden. All the issues described above make rifampicin of greater interest in terms of public health. Also, rifabutin is not readily available in resource poor areas due to cost.

Lopinavir/ritonavir (LPV/r) are drugs with increased genetic barrier to resistance [5], which may be an excellent therapeutic option for TB-HIV patients who cannot be treated with nonnucleoside reverse transcriptase inhibitors. To overcome the effects of rifampicin hepatic induction, the standard dose of LPV/r could be doubled or extra ritonavir (super boosting) used. Some studies using these strategies, either LPV/R 400/400 mg or LPV/R 800/200 mg, have shown that there is achievement of adequate pharmacokinetic parameters. The first study, conducted by LaPorte in healthy volunteers, had comparable \( C_{\text{min}} \), \( C_{\text{max}} \) and \( AUC_{\text{0-24h}} \) of lopinavir for adjusted doses of LPV/R with

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rifampicin and standard doses of LPV/R without rifampicin; however, a significant number of cases of hepatotoxicity was described [6]. Later, HIV-infected people have shown better tolerance of these drugs combinations than HIV-uninfected individuals. Two studies conducted by Decloedt et al. one in HIV-infected [7], and the other in TB-HIV co-infected individuals [8], showed adequate pre-dose concentrations with much lower rates of hepatotoxicity than LaPorte. In the first study of Decloedt et al., LPV/r doses were escalated to twice the standard dose (800 mg/200 mg BID) and in their second study, as in LaPorte study, a group of patients used LPV/r 800 mg/200 mg BID and another group used LPV/r 400 mg/400 mg BID, both after escalation. However, these studies did not show the tolerance of HIV-infected patients to TB regimens before ARV therapy introduction. We conducted a prospective study to assess the pharmacokinetics of LPV/R800/200 mg in association with rifampicin-containing anti-tuberculosis regimens, in patients presenting tuberculosis that initiated TB treatment first, and later were started on antiretroviral therapy as recommended in Brazil. We also aimed to describe the adverse events observed during the tuberculosis treatment period with rifampicin, and the clinical, immunological and virological endpoints.

Method

This was a pharmacokinetic, descriptive, open-label, prospective, study, conducted at Tuberculosis Clinics of Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro. We enrolled HIV positive patients, 18 years or older, with tuberculosis, with any contraindications to use efavirenz or no genotypic resistance to LPV/ron the screening sample, who signed a written informed consent. Patients were excluded if they had resistance to rifampicin, hepatic enzymes higher than (ACTG) grade 2 (G2), hepatitis B and C or pregnancy. Tuberculosis diagnosis was based on signs and symptoms, consistent radiological abnormalities, and exclusion of other opportunistic diseases, even if the acid fast sputum smears were negative. TB was confirmed if Mycobacterium tuberculosis was identified in culture, or if after two months there was a favorable clinical response to tuberculosis treatment in the case of either negative cultures or contamination. Patients were followed up until 210 days after TB therapy initiation. A clinical resolution was considered a successful outcome of TB therapy. Study endpoints were defined as adequate plasma levels of rifampicin and LPV/R, a drop higher than 1 log10 in viral load (VL) after 90 days compared to baseline and viral suppression after 180 days, an increase in CD4 cell counts from baseline, treatment compliance measured by pill count at each visit and grade 3 and 4 adverse events. Genotyping analysis was done at D180 or at last visit if viral load was above 1,000 copies/mL. The study was approved by IPECEthics review board.

Antiretroviral treatment consisted of two nucleoside reverse transcriptase inhibitor combination or associated with a nucleotide analogue (tenofovir) and a combination of lopinavir-800 mg and ritonavir-200 mg (4 tablets of Kaletra™) BID, orally. Anti-TB medications were given in accordance with the current recommendations of the Brazilian Ministry of Health. This consisted of a 6 month regimen of rifampicin 600 mg and isoniazid 400 mg daily given in a fasting state with the addition of pyrazinamide for the first 2 months. Doses were adjusted for subjects who weighed less than 45 and 35 kg.

Patients started anti-TB treatment at D1, when all ARV drugs were discontinued. After a month, they were prescribed a LPV/r based ARV. In the first 3 days, they used two LPV/r gel tablets BID (400/100 mg); then it was escalated to three tablets BID (600/150 mg) and after three more days, to four tablets BID (800/200 mg). Escalation was done as a way to improve tolerance, and was already done before in other studies [6-8].

All formulations of LPV/r were supplied by Abbott Laboratories and rifampicin formulations were provided by the Brazilian Ministry of Health network.

The study procedures done on each visit are showed on Figure 1.

### Screening

**Questionnaire:** sex, age, alcohol abuse, use of illicit drugs, weight loss, concomitant medication, date of first positive HIV serology, history of opportunistic diseases and comorbidities, current and previous antiretroviral [ARV] therapy regimens.

**Medical history and physical exam.**

**Laboratory tests:** microscopic examination of sputum; culture of sputum, blood and other clinical specimens for mycobacteria; serologic tests for viral hepatitis (B and C), syphilis and toxoplasmosis; blood cell counts; serum levels of urea, creatinine, liver enzymes, uric acid, and albumin; chest x-rays or CT scans; pregnancy test (female patients in reproductive age).

### Day 1

**Updated medical history and comorbidities, concomitant medication, and physical exam**

**Antiretroviral drugs in use were discontinued; TB treatment was started.**

**Laboratory tests:** blood cell counts; serum levels of urea, creatinine, uric acid, liver enzymes, and albumin; lipid profile; CD4 cell count and HIV viral load; genotyping; urine pregnancy test in women of childbearing potential.

### Follow up visits (D15, D30, D45, D60, D90, D120, D150, D180, and D210)

**Medical history, comorbidities, physical exam, adverse events concomitant medication.**

**Hematologic test and blood chemistry; pregnancy test in urine (in women of childbearing potential).**

### D30, D60, D120, D180

**CD4+ and CD8+ lymphocyte counts and viral load evaluation**

**D30, D60, D180, D210**

**Chest x-ray**

**D180 or last study visit**

**HIV genotype in case of VL>1,000.**

**D15**

**Rifampicin PK**

**D45, D90, D180**

**Rifampicin, Lopinavir and Ritonavir PK**

**D210**

**Lopinavir and Ritonavir PK**

**Figure 1:** Study procedures.
Follow-up visits were scheduled every 15 days for the first two months (D60) after enrollment and then monthly until D210. TB medications were suspended on D180. Adverse events were recorded according to the AIDS table for grading severity and adult adverse experience [9]. Treatment compliance was evaluated by tablet accountability and patient compliance history at every clinical evaluation.

Patients were hospitalized at D15 to collect blood samples for rifampicin PK, at D45, D90 and D180 for lopinavir, ritonavir, and rifampicin PK, and at D210 for lopinavir and ritonavir pharmacokinetics (Figure 2). In the case of pharmacokinetic values (AUC0-12) higher than 125 μg.h/mL at D45, LPV/R dose was decreased to 600/150 mg (3 tablets) BID at D60 and lopinavir and ritonavir pharmacokinetics were repeated at D90. TB medication and ARV doses were supervised during hospitalization. For pharmacokinetic analysis, blood samples (4 mL) were drawn for predose and 1, 2, 4, 6, 8, 10, and 12 hours after drug administration, centrifuged (14,440 rpm×10 min) at −20°C (-68°F) until analysis. To obtain plasma, which was stored in tubes containing ascorbic acid (0.030 g) at −20°C (-68°F) until analysis.

Lopinavir and rifampicin were assayed in plasma using a LC-MS/MS validated method. Chromatographic analysis was carried out on a Varian 1200 L quadrupole LC-MS/MS system equipped with an electrospray ion source, operated in the positive mode. The ion spray voltage and source temperature were 5850 V and 400°C, respectively. Chromatographic separation was achieved on a Pursuit C18 (Varian 5 μm, 100×2.0 mm i.d.) column at ambient temperature, using acetonitrile–water containing formic acid 0.1% (70/30, v/v) as mobile phase at a flow rate of 0.3 mL/min.

Prior to the chromatographic analysis, 50 μL of plasma samples containing IS solution (carbamazepine and clozapine 0.6 μg/mL) were deproteinized by the addition of 400 μL acetonitrile, vortexed for 1 min and centrifuged at 14400 rpm for 5 min. The supernatant was diluted (1:4) in acetonitrile/water containing formic acid 0.048% (70/30 – v/v) and 10 μL was injected into the LC-MS/MS system. For the lopinavir analysis, after deproteinization, 100 μL methanol 50% (in water) was added to the supernatant and then was performed the dilution in acetonitrile/water containing formic acid 0.048% and LC-MS/MS analysis.

Quantification was performed by monitoring the decay of the mass-to-charge (m/z) ratio 629.70→447.30 for lopinavir, m/z 823.8→791.8 for atazanavir, indinavir, saquinavir, nelfinavir, ritonavir. The values of peak concentration (Cmax) and low concentration (Cmin) of drugs in plasma were determined directly from the individual concentration-time data. Statistical analysis was performed using software R, version 2.14 (α=0.05).

This study was approved by the Committee on Ethics in Research of Instituto de Pesquisa Clinica Evandro Chagas, Fundação Oswaldo Cruz (CAAE 003.1.009.000-07).

Results

Fifteen HIV patients, already HAART experimented; consented to participate in the study which was conducted from September 9th 2008 to April 19th 2010. The group had a low median CD4 cell count (121 cells/mm³) and median VL of 4.6 log10 copies/mL. Nine of the fifteen patients were using lopinavir based ARV regimens when TB diagnosis was made, which of three had undetectable viral load, and none of patients who had a VL>1000 copies/mm³ had virologic resistance to lopinavir/r. TB diagnosis was made by positive culture in 7/15, and pulmonary TB was the most frequent diagnosed form. Alcohol abuse was reported by 5/15 and illicit drug use by 3/15. BMI was <18.5 in 7/15, BMI<18.5

* VL in patients presenting detectable values(n = 8/15);
**without resistance;
***atazanavir, indinavir, saquinavir, nelfinavir, ritonavir.

Table 1: baseline characteristics of patients included in the study.

| Variables                        | Number =15 |
|----------------------------------|------------|
| Sex                              | Male       |
|                                  | 10         |
| Baseline CD4 (median [IQR])      | 121 (45-158) |
| Baseline VL log* (median [IQR])  | 4.6 (3.7-4.9) |
| TB diagnosis                     |            |
| Culture                          | 8          |
| Clinical, radiological           | 4          |
| Histopathological                | 3          |
| TB clinical forms                |            |
| Pulmonary                        | 9          |
| Extrapulmonary                   | 4          |
| Disseminated                     | 2          |
| Previous ARV use                 |            |
| Naive                            | 1          |
| NNRTI regimens**                 | 9          |
| LPV/r regimens**                 | 9          |
| Regimens with other PIs***       | 4          |
| Alcohol abuse                    | 5          |
| Illicit drugs use                | 3          |
| BMI<18.5                         | 7          |

* VL in patients presenting detectable values (n = 8/15);

Additional data includes CD4/VL, virological resistance, and drug interactions. Pediatric patients were not included in the study. All patients were treated with lopinavir, ritonavir and rifampicin.
pancreatitis, both related to the study drug. At D180, TB therapy was suspended and only five patients remained in the study. Two of them had undetectable viral load (Table 2). Pharmacokinetics of LPV/r alone was performed in 4/5 patients at D210.

Table 2 shows the CD4 counts and viral load for each study visit for those who completed 180 days of TB therapy. An improvement of CD4 cell counts from baseline to D60 was observed. However, from D60 to D180 all CD4 counts declined. Observing the favorable effect of lopinavir therapy on viral load, it was unclear why an increase in CD4 counts was not observed from baseline to D180 as expected. Only two out of five patients achieved undetectable viral load at D180.

Lopinavir genotypic resistance was detected in one patient at D60, when he dropped out from the study. This patient had baseline out of five patients achieved undetectable viral load at D180. Two of them had undetectable VL and had used 4 different ARV regimens before a D60, when he dropped out from the study. This patient had baseline out of five patients achieved undetectable viral load at D180.

Low adherence (2)
Pancreatitis (1)
Hepatotoxicity (2)
HCV co-infection (1)

Table 2: CD4 counts and viral load for each study visit.
Figure 4: Median steady-state plasma profiles of rifampicin (RIF) and lopinavir (LPV) on the study days 15, 45, 90, 180 and 210. Error bars indicate interquartile ranges.
patient received the study drugs and recovered. Our conclusion was that the patient did not take the medicines at home. Two other patients were discontinued during TB therapy because they did not come to the scheduled visits after many calls.

**Discussion**

Concomitant therapy for TB and HIV is still a challenge because of pill burden, drug-drug interaction and a consequent low adherence to both treatments. Few studies have been done to explore these issues. In countries where rifabutin is not available it is not clear how to introduce anti-TB drugs to HIV patients using PI with undetectable viral load. LPV/R is one of the few PI combination options to use with rifabutin and still needs a dose adjustment. Start a TB treatment and maintain antiretrovirals being used with a LPV/R double standard dose could lead to a higher frequency of adverse events and a need of both treatments interruption. In 2008 it was not known which the best moment to initiate antiretroviral therapy in HAART naïve patients, after TB treatment start, was. Then, antiretroviral interruption to start TB treatment and subsequent HAART reintroduction 30 days later with PI doses adjustment was the strategy considered to be used and adopted in this study. Until nowadays, there is no answer on how to proceed with HIV patients previously HAART experimented, especially those with efavirenz resistance, who start TB therapy with rifabutin as part of it. Detectable viral load in patients using LPV/R could occur because of no adherence, what was corroborated in the study since we did not found resistance in baseline genotyping, a reason for reintroducing LPV/R to these patients after TB treatment start.

Recently, a study was published by Decloedt and colleagues to evaluate concomitant therapy for TB-HIV patients with lopinavir 800/200 mg BID in South Africa [8]. The authors showed an overall good virologic control and compliance contrasting with our results, however, in their study; patients were enrolled after being established on tuberculosis treatment which excluded those who had early adverse events related to TB drugs. In our study, patients had a high incidence of adverse events to TB therapy, prior to the initiation of HAART. Compliance was also a limitation for both therapies as well as adverse events, even though the majority of the patients had already used LPV/r before TB diagnosis. In some cases adverse events, such as pancreatitis and hepatotoxicity related to study drugs, were barriers to adherence. Adverse events were controlled by the interruption of both therapies resulting in improvement in all cases. Unfortunately, one patient died after being discontinued due to hepatotoxicity, during a Scan with contrast when the adverse event was almost resolved. We did not observe a correlation between adverse events and a higher LPV/r blood concentration.

The low rifampicin plasma levels observed in our study are consistent with results previously reported for HIV-infected patients in literature [10-13] and could be explained by the malabsorption observed in advanced HIV infection [10,14]. Although the low exposure to rifampicin was detected, it did not compromise patients' outcomes. One explanation would be post antibiotic effect of rifampicin [15]. TB treatment resulted in therapeutic success for all adherent patients.

Lopinavir plasma levels showed adequate concentrations of drugs for the majority of patients. Although lopinavir concentrations were below 1 µg/mL in 4/10 patients during the study, two of them, finished the study with undetectable viral load. Considering the target to resistant virus, 6/10 patients had minimum concentrations above 4 µg/mL during the study (5 of them were previously exposed to PI), but none of them showed LPV resistance. These results indicate that the increased dose of LPV/r (800/200 mg BID) when administered concomitantly to rifampicin was enough to achieve LPV therapeutic levels.

A study conducted at South Africa discussed the importance of adjusting lopinavir dose in patients with low weight (<50 Kg) to achieve an adequate serum concentration and to prevent overdose [16]. In our study, only one out of three patients who dropped out due to adverse events weighed<50 kg. Moreover, 3/10 patients taking lopinavir full dose (800 mg) showed an AUC over the target limit, without any signs of overdose. Therefore, it seems that low weight was not a parameter to adjust lopinavir dose in our study population.

The main limitation of the study was the small number of participants, with an elevated number of drop outs what had an impact in the analysis.

In conclusion, LPV/r 800/200 mg dose showed adequate concentration to treat a wild type virus, although low adherence was observed in several patients during TB and HIV therapies, concomitant or not. Adverse events and no compliance with the elevated number of pills for both treatments were limitations to finish the study. CD4 counts and viral load were improving just at the beginning of the therapy, not sustained through the end of the study. Although low adherence was remarkable, only one case of resistance to LPV/r occurred in the study. Other options for concomitant treatment of TB and HIV patients with resistance to efavirenz could facilitate adherence. Unfortunately, drugs

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**Table 3:** Summary of the pharmacokinetic for rifampicin and lopinavir, by treatment stage (median, IQR).

| Drug   | Study day | AUC (µg/mL*h) | Cmax (µg/mL) | tmax (h) | Cmin (µg/mL) | tmin (h) |
|--------|-----------|---------------|--------------|---------|--------------|---------|
| Rifampicin | D 15 | 27.64 (13.19-39.77) | 5.05 (3.30-6.23) | 3.00 (2.00-4.00) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) |
|         | D 45     | 34.35 (22.39-58.19) | 5.05 (4.22-8.21) | 1.50 (1.00-2.00) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) |
|         | D90      | 34.39 (32.71-61.80) | 5.88 (5.81-8.50) | 2.00 (1.50-2.00) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) |
|         | D180     | 40.40 (37.84-58.26) | 6.51 (6.33-10.81) | 2.00 (2.00-4.00) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) |
| Lopinavir | D 45    | 142.95 (112.88-168.85) | 14.71 (13.02-20.39) | 4.00 (3.50-4.50) | 4.64 (2.65-9.85) | 12.00 (0.00-12.00) |
|         | D90     | 179.38 (140.16-182.99) | 18.91 (16.37-21.16) | 4.00 (3.00-4.00) | 6.65 (4.33-10.01) | 1.00 (0.50-6.50) |
|         | D180*   | 123.05 (88.47-154.56) | 16.65 (12.04-18.91) | 2.00 (1.50-2.00) | 0.74 (0.37-5.92) | 12.00 (12.00-12.00) |
|         | D180**  | 173.95 (146.06-201.63) | 18.94 (15.86-22.03) | 5.00 (3.50-6.50) | 9.34 (7.60-11.07) | 11.00 (10.50-11.50) |
|         | D 210   | 119.14 (101.56-133.91) | 12.13 (10.58-14.18) | 4.00 (4.00-4.50) | 4.82 (3.25-6.16) | 6.00 (0.00-12.00) |

* median values of patients receiving LPV/r 600/150 mg
** median values of patients receiving LPV/r 800/200 mg
like rifabutin and raltegravir are expensive and not available in most low-income countries. While governments do not make access to these drugs possible, LPV/r continues to be an option for these patients.

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