**Cerebrospinal fluid drug concentrations and viral suppression in HIV-1 infected patients receiving ritonavir-boosted atazanavir plus lamivudine dual antiretroviral therapy (Spanish HIV Research Network, PrEEC-RIS39)**

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**Short Title:** CSF drug levels and HIV-1 RNA on ATV plus 3TC.

**Keywords:** HIV-1; antiretroviral therapy; cerebrospinal fluid; atazanavir; lamivudine

**Tables**: 2

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**Objective:** To assess cerebrospinal fluid (CSF) drug concentrations and viral suppression in HIV-1 infected patients on ritonavir-boosted atazanavir (ATV/r) plus lamivudine (3TC) dual therapy.

**Methods:** HIV-1 infected adults with suppressed plasma HIV-1 RNA who switched to ATV/r plus 3TC were studied. Total ATV and 3TC concentrations at the end of the dosing interval (C24h), using a validated LC-MS/MS method, and HIV-1 RNA were measured in paired CSF and plasma samples 12 weeks after switching.

**Results:** Ten individuals were included. Median (range) age was 42.5 (33-70) years, time on ART was 39.5 (11-197) months, and time with plasma HIV-1 RNA <40 c/mL was 15.5 (6-46) months. At baseline, CSF HIV-1 RNA was <40 c/mL in all patients. Twelve weeks after switching to ATV/r plus 3TC, HIV-1 RNA remained at <40 c/mL in both plasma and CSF in 9/10 patients. One patient with suboptimal adherence to ART had HIV-1 RNA rebound in both plasma and CSF. The median CSF-to-plasma concentration ratios of ATV and 3TC were 0.013 and 0.417, respectively. Median ATV C24h in CSF was 10.4 (3.7-33.5) ng/mL (in vitro ATV IC50 range, 1-11 ng/mL). Median 3TC C24h in CSF was 43.4 (16.2-99.3) ng/mL (in vitro 3TC IC50 range, 0.68-20.6 ng/mL).

**Conclusion:** Most patients maintained HIV-1 RNA in CSF <40 c/mL despite CSF ATV C24h close to or within the IC50 range in the majority. ATV PK data in CSF should be considered and rigorous patient selection is advisable to assure effective CSF viral suppression with this two-drug simplification regimen.

**INTRODUCTION**

In the context of lifelong antiretroviral therapy (ART) for HIV-infected individuals, issues such as adherence, long-term drug toxicity, and treatment cost have prompted researchers to seek treatment simplification strategies. Simplification to boosted protease inhibitor (PI) monotherapy is associated with a higher risk of virological rebound compared to standard triple-drug therapy [1]. In contrast, recent randomized clinical trials have found that some dual antiretroviral combinations have noninferior efficacy relative to triple therapy [2-7]. Most of these studies have evaluated dual therapy with a boosted PI, including ritonavir-boosted lopinavir (LPV/r), atazanavir (ATV/r) or darunavir (DRV/r), and lamivudine (3TC) [2-6].

ATV/r plus 3TC dual therapy has demonstrated to be effective for maintaining plasma viral suppression and it is considered a promising ART simplification option [4-5]. However, since previous studies showed that ATV penetration may be suboptimal in cerebrospinal fluid (CSF) [8] the antiviral activity of this combination in CSF should be also evaluated. This is first study that aimed to determine HIV-1 RNA and drug concentrations in CSF samples from HIV-1 infected patients who switched from ATV/r plus tenofovir/emtricitabine (TDF/FTC) to ATV/r + 3TC.

**METHODS**

**Study Design and Population**

The objectives of this study were to assess cerebrospinal fluid (CSF) drug concentrations and viral suppression in HIV-1 infected patients treated with ATV/r plus 3TC dual therapy.

We undertook a single-arm, open-label study at the HIV outpatient clinic of Bellvitge University Hospital (Barcelona, Spain) between October 2014 and February 2016. Eligible patients were HIV-1 infected adults (≥18 years) with plasma HIV-1 RNA suppression (<40 copies/mL) for 6 months or longer while receiving a stable ART regimen of ATV/r 300/100 mg plus TDF/FTC 300/200 mg coformulated as a single tablet once daily (Truvada®). The exclusion criteria were resistance to 3TC and/or protease inhibitors, chronic HBV hepatitis, need for proton-pump inhibitor treatment, moderate or severe hepatic impairment, and active malignancies. At baseline, participants were switched from their former regimen to ATV/r 300/100 mg once daily plus 3TC 300 mg once daily.

The study protocol was approved by the ethical review committee of Bellvitge University Hospital in accordance with the principles of the 2008 Declaration of Helsinki and the Spanish regulatory authorities. Written informed consent was obtained from all participants before any study procedures were performed. This study is registered at the EU Clinical Trials Registry (EudraCT 2014-000496-64).

**Procedures and laboratory methods**

Paired blood and CSF samples were obtained at baseline and 12 weeks after switching to ATV/r plus 3TC. HIV-1 RNA was determined in blood plasma and CSF samples at baseline and week 12, whereas ATV and 3TC concentrations were measured in plasma and CSF at week 12. CSF samples were collected by lumbar puncture using pencil-point needles.

HIV-1 RNA levels in plasma and CSF were measured using a real-time polymerase chain reaction (PCR) assay (Abbott RealTime HIV-1) with a quantification limit of 40 copies/mL.

Total ATV and 3TC concentrations were determined at the end of the dosing interval (C24h). After confirming that the last dose of ATV/r and 3TC had been taken correctly and at the right time, blood and CSF were obtained at the end of the dosing interval (24 h post-dose ±1 h and before the next dose). Plasma ATV and 3TC concentrations were measured at the Department of Molecular and Clinical Pharmacology, University of Liverpool (Liverpool, United Kingdom), using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods previously described [9-10]. ATV concentrations in CSF were measured as follows. Briefly, freshly prepared standards and quality control samples (prepared in artificial CSF) and clinical samples (100 µL) were extracted via protein precipitation using acetonitrile (200ml) with the addition of a stable isotopically labelled (SIL) internal standard (ATV-D5; Toronto Research Chemicals, Canada). ATV and SIL internal standard were resolved on a reverse-phase Fortis C18 column (3mm: 100 mm 2.1 mm) using a step-wise gradient of 0.1% Formic Acid (aqueous) and Acetonitrile (organic). Quantification was performed using a Thermo Vantage Triple Quadrupole mass spectrometer using selective reaction monitoring in positive ionisation mode. The lower and upper limits of quantification were 1.96 and 250 ng/mL respectively. 3TC concentrations in CSF were analysed off an 11-point calibration curve made using artificial CSF and validated for the range 0.28-100 ng/mL. Extraction was by protein precipitation, using 15N2, 13C-Lamivudine (Toronto Research Chemicals, Canada) as internal standard. An aliquot of the supernatant was evaporated to dryness in a nitrogen stream and reconstituted in water:ACN mixture (99:1). This was then analysed on a Thermo Vantage Triple Quadrupole mass spectrometer in positive ionisation mode.

**Statistical Methods**

 Quantitative variables are reported as the mean and standard deviation (SD) and median and range. Qualitative variables are expressed as the number and percentage. The Spearman test was used to determine associations between variables, and the coefficient of variation was used to assess within-group variability. SPSS software for Windows, version 18.0 (SPSS, Chicago, IL) was used for the statistical analyses.

**RESULTS**

 Ten patients were included in the study (4 men, 6 women). Median (range) age was 42.5 (33-70) years; time on ART, 39.5 (11-197) months; time with plasma HIV-1 RNA <40 c/mL, 15.5 (6-46) months; nadir CD4 count, 289 (79-580) cells/μL; and current CD4 count, 740 (357-1380) cells/μL.

At baseline, CSF HIV-1 RNA was <40 c/mL in all patients. Twelve weeks after switching to ATV/r + 3TC, HIV-1 RNA remained at <40 c/mL in both plasma and CSF in 9 of the 10 participants. One patient had HIV-1 RNA rebound in both plasma (2658 copies/mL) and CSF (1233 copies/mL) at week 12 (Table 2). The patient was asymptomatic and confirmed referred suboptimal adherence to ART during some weeks before week 12. Virologic failure was confirmed 2 weeks later (plasma HIV-1 RNA 341 copies/mL) and ART was changed empirically to abacavir (ABC), 3TC, dolutegravir (DTG), and DRV/r. Plasma viral re-suppression was achieved within one month. Genotypic resistance testing at failure showed no selection of resistance-associated mutations, and the ART regimen was simplified to ABC/3TC/DTG.

The median CSF-to-plasma concentration ratios of ATV and 3TC were 0.013 and 0.417, respectively. Median ATV C24h in CSF was 10.4 (3.7-33.5) ng/mL (in vitro ATV IC50 range for wild type HIV-1, 1-11 ng/mL [8]). Median 3TC C24h in CSF was 43.4 (16.2-99.3) ng/mL (in vitro 3TC IC50 range for wild type HIV-1, 0.68-20.6 ng/mL [11]) (**Table 1 and Figure 1**). The interindividual variability of CSF ATV concentrations was higher than that of 3TC concentrations (coefficient of variation 76% and 56%, respectively) (**Table 1**).

CSF ATV concentrations were significantly lower in female individuals compared to male individuals (median C24 5.33 ng/mL, range 3.71-17.07 ng/mL vs 25.82 ng/mL, range 10.96-33.94 ng/mL, in women and men respectively; p=0.019). In this regard, it is worthy of note that only 1 of the 6 female participants had CSF ATV concentrations above IC50 range. BP ATV concentrations were also lower in women compared to men, although this difference did not reach statistical significance (median C24 621.78 ng/mL, range 296.45-1247.37ng/mL vs 1354.60 ng/mL, range 867.33-1850.02ng/mL, in women and men respectively; p=0.114). No gender-related differences were found in 3TC concentrations in either CSF or BP.

**DISCUSSION**

The activity of ARV drugs in the central nervous system (CNS) may be limited by the natural barriers to drug penetration. The ability of drugs to penetrate into the CNS depends on many variables including the molecule size, lipophilicity, electric charge, plasma protein binding, and active transport route [12]. Although CSF drug concentrations are not necessarily indicative of brain drug exposure, CSF levels are usually used as a surrogate marker of drug penetration into CNS.

Protease inhibitors tend to have a low CSF/blood ratio, although the measured concentrations of these drugs vary. While lopinavir (LPV) and darunavir (DRV) achieve CSF concentrations above the IC50 for the wild-type virus [12-13], ATV concentrations in CSF do not consistently exceed the wild-type IC50 [8, 16].

Several ritonavir-boosted PIs in combination with 3TC have demonstrated noninferior efficacy compared to boosted PIs plus 2 nucleoside analog reverse transcriptase inhibitors (NRTIs) in virologically suppressed patients [2-6]. Although these dual combinations may avoid the potential toxicity of other NRTIs [14-15] and reduce treatment cost, there are some concerns about the effectiveness of these strategies to suppress HIV replication in the CNS.

As it was observed in a previous study assessing the efficacy of ATV/r monotherapy [16], low CSF drug concentrations can facilitate viral escape in this compartment. Therefore, because of the potentially serious consequences of HIV replication in the CNS [17-18], the antiviral efficacy of ATV-based drug-sparing maintenance therapies in CSF should be explored. It is worthy of note that neurocognitive function has been evaluated in those clinical trials assessing the efficacy and safety of ATV/r plus 3TC as switching strategy in virologically suppressed patients and no significant differences were found compared to triple therapy after 1 or 2 years of follow up [19-20]. However, these sub-studies only included a subgroup of participants and did not include information about viral suppression or drug concentrations in CSF.

In our study, CSF HIV-1 RNA was maintained at <40 c/mL in most patients 12 weeks after switching to ATV/r+3TC. As has been reported in previous studies [8], ATV penetration in CSF was poor (CSF:plasma ratio 0.013) and the ATV C24h concentration was close to or within the protein-free IC50 range in the majority of patients. In contrast, 3TC showed good penetration into CSF, with a CSF:plasma ratio of 0.417, and 3TC CSF concentrations were above the upper limit of the protein-free IC50 range in 8/10 patients. The high CSF 3TC concentrations may have contributed to maintain HIV-1 RNA suppression in this compartment. Of note, ATV CSF ATV concentrations were significantly lower in women compared to men and only 1 of 6 female participants had CSF ATV C24h above the IC50 range. Nevertheless, since this is a small study and gender-related differences in ATV pharmacokinetics have not been described previously [21], this observation must be interpreted with caution.

It is worthy of note that ATV clearance is increased when it is co-administered with TDF [22], and therefore, ATV levels may increase after the switch to ATV/r plus 3TC. However, low ATV concentrations were observed in CSF even in the absence of TDF.

Our study has some limitations that should be pointed out. The small sample size and single determination of ATV and 3TC make the results more susceptible to the influence of interindividual and intraindividual variability. Moreover, a larger sample size might confirm or rule out the differences observed in ATV concentrations between women and men. In addition, 12 weeks of follow up might not be enough to evaluate the capability of this strategy to control viral replication in CSF. Indeed, CSF viral escape has been described after 6 months in patients receiving monotherapy with ATV/r [16] and a case of encephalitis associated to HIV replication in CSF has been reported in a patient who had been on monotherapy with LPV/r during 9 months [18]. Nevertheless, the design and sample size is similar to that reported in other studies evaluating ARV concentrations in CSF [23-24].

In this study, the first study assessing CSF viral suppression and drug concentrations after simplification to ATV/r plus 3TC dual therapy, we observed that 12 weeks after switching to ATV/r plus 3TC, CSF HIV-1 RNA was maintained at <40 c/mL in most patients. However, CSF ATV C24h was close to or within the IC50 range in the majority. Larger studies with a longer follow-up are needed to assess the capability of ATV/r plus 3TC dual therapy for maintaining HIV suppression also in the CSF. In the meantime, ATV pharmacokinetic data in CSF should be taken into account and rigorous patient selection and optimal adherence are advisable to assure effective CSF viral suppression with this dual antiretroviral simplification regimen.

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**Conflicts of interest**:

A.I. has received financial compensation for lectures, consultancies, and educational activities, as well as research funding for from AbbVie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dome, and ViiV Healthcare.

J.N. has received financial compensation for lectures and research from Abbott Molecular.

S.K. has received funding from Merck Gilead Sciences Jannsen and ViiV Healthcare for research and support of the HIV drig interactions website.

J.M.T. has received financial compensation for lectures, consultancies, and educational activities, as well as research funding for from AbbVie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dome, and ViiV Healthcare.

E.F. has received honoraria for advisories and/or conferences from Viiv, BMS, Abbott, Gilead, Janssen, and Merck.

D.P. has received research grants and/or honoraria for advisories and/or conferences from Viiv, BMS, Abbott, Gilead, Janssen, and Merck.

A.A, L.A., B.G., A.V. declare no conflicts of interest regarding this article.

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Authors’ contributions: A.I. and D.P. designed the study; A.I., E.F. and D.P. recruited participants; A.I., B.G. and A.V. conducted the study visits; J.N. performed the microbiological procedures. A.A. and S.K. performed LCMS/MS to measure ATV and 3TC concentrations in blood plasma and CSF; L.A. assisted in data collection and study coordination; A.I., J.M.T. and D.P. analyzed and interpreted the results; A.I. drafted the manuscript and J.M.T., E.F., S.K., and D.P. reviewed it. All authors revised the manuscript for important intellectual content and contributed to the final version.

This study was presented in part as a poster in the 9th IAS Conference on HIV Science (IAS 2017) that will take place in Paris, France on 23-26 July 2017.

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**Figure Legends**

**Figure 1**

Atazanavir and lamivudine concentrations in plasma and cerebrospinal fluid.





|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **ATV concentrations, ng/mL** | **3TC concentrations, ng/mL** |
| **Patient** | **Gender** | **Plasma** | **CSF** | **CSF:plasma ratio** | **Plasma** | **CSF** | **CSF:plasma ratio** |
| 1 | F | 680.71 | 3.98 | 0.006 | 80.06 | 23.06 | 0.288 |
| 2 | F | 562.86 | 4.79 | 0.009 | 36.71 | 16.20 | 0.441 |
| 3 | M | 867.33 | 25.91 | 0.030 | 69.78 | 99.33 | 1.423 |
| 4 | M | 1794.65 | 25.73 | 0.014 | 65.72 | 60.84 | 0.926 |
| 5 | F | 1544.08 | 5.88 | 0.004 | 110.09 | 33.37 | 0.303 |
| 6 | F | 392.75 | 9.82 | 0.025 | 51.79 | 58.98 | 1.139 |
| 7 | M | 914.55 | 10.96 | 0.012 | 48.36 | 18.73 | 0.387 |
| 8 | F | 296.45 | 3.71 | 0.013 | 33.69 | 33.31 | 0.989 |
| 9 | M | 1850.02 | 33.44 | 0.018 | 173.97 | 65.72 | 0.378 |
| 10 | F | 1247.37 | 17.07 | 0.014 | 136.21 | 53.47 | 0.393 |
|  |  |  |  |  |  |  |  |
| **Median**MeanSDCV, % | **890.94** | **10.39** | **0.013** | **67.75** | **43.42** | **0.417** |
| 1015.08 | 14.13 | 0.014 | 80.64 | 46.30 | 0.667 |
| 566.73 | 10.81 | 0.008 | 45.96 | 26.15 | 0.412 |
|  56 | 76 | 57 | 57 | 56 | 62 |

**Table 1**. Atazanavir and lamivudine concentrations in Blood plasma and Cerebrospinal fluid

ATV IC50 range for wild type HIV-1: 1-11 ng/mL [8]. 3TC IC50 range for wild type HIV-1: 0.68-20.6 ng/mL [9].

3TC, lamivudine; ATV, atazanavir; CSF, cerebrospinal fluid; CV, coefficient of variation; F, female; M, male; SD, standard deviation

**Table 2.** Cerebrospinal fluid characteristics and HIV-1 RNA at Baseline and Week 12

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Baseline**  | **Week 12** |
| **Patient** | **Gender** | **CSF WBC (cells/μL)** | **CSF Proteins (g/L)** | **CSF HIV-1 RNA****(copies/mL)** | **Blood plasma****HIV-1 RNA****(copies/mL)** | **CSF WBC (cells/μL)** | **CSF Proteins (g/L)** | **CSF HIV-1 RNA****(copies/mL)** | **Blood plasma** **HIV-1 RNA** **(copies/mL)** |
| 1 | F | <0.001 | 0.25 | <40 | <40 | 0.001 | 0.20 | <40 | <40 |
| 2 | F | <0.001 | 0.30 | <40 | <40 | 0.001 | 0.25 | <40 | <40 |
| 3 | M | <0.001 | 0.38 | <40 | <40 | 0.004 | 0.55 | <40 | <40 |
| 4 | M | <0.001 | 0.32 | <40 | <40 | <0.001 | 0.25 | <40 | <40 |
| 5 | F | <0.001 | 0.23 | <40 | <40 | <0.001 | 0.26 | <40 | <40 |
| 6 | F | <0.001 | 0.36 | <40 | <40 | <0.001 | 0.37 | <40 | <40 |
| 7 | M | <0.001 | 0.42 | <40 | <40 | <0.001 | 0.41 | <40 | <40 |
| 8 | F | <0.001 | 0.29 | <40 | <40 | 0.008 | 0.26 | 1,233 | 2,658 |
| 9 | M | <0.001 | 0.33 | <40 | <40 | <0.001 | 0.38 | <40 | <40 |
| 10 | F | <0.001 | 0.50 | <40 | <40 | <0.001 | 0.58 | <40 | <40 |
|  |  |  |  |  |  |  |  |  |  |

CSF: Cerebrospinal fluid; F, female; M, male; WBC: white blood cells;