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RESEARCH ARTICLE

Boosted- lopinavir versus boosted- atazanavir plus two nucleoside reverse transcriptase inhibitors in second- line antiretroviral therapy in HIV-1 infected patients in Abidjan, Ivory Coast

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ABSTRACT

Introduction: Atazanavir is a protease inhibitor recently introduce in the therapeutic arsenal for second-line antiretroviral therapy in Ivory Coast. The objective of this study was to compare the efficacy and safety of a second-line treatment with 2 NRTIs + boosted lopinavir (LPV/r) versus 2 NRTIs + boosted atazanavir (ATV/r) in HIV-1 positive patients in Abidjan.

Patients and Methods: Retrospective, comparative, single-center study, in 194 HIV-1 positive patients (143 with LPV/r, 51 with ATV/r), failed a first-line treatment, followed in Abidjan on 1 May 2009 to 30 June 2010. The analysis focused on clinical parameters and immuno-virological data. The principal judgement criterion was the proportion of patients with undetectable viral load in both groups after 12 months of HAART. Tolerance was found on the frequency of adverse events grade 3-4 during follow-up.

Results: Clinically, improvement of the general condition and regression of opportunistic infections was similar in both groups. The average gain of CD4 after 12 months of follow-up was +357/mm^3 in the LPV/r group versus +278 mm^3 for ATV/r group ($p = 0.012$). The percentage of patients with undetectable viral load was similar in both groups (92% vs. 96% ; $p = 0.535$). The frequency of grade 3-4 adverse events was similar in both groups.

Conclusion: HAART with LPV/r is at least as efficient as with ATV/r in second-line treatment, in terms of viral load reduction, with better recovery of CD4. LPV/r is an excellent second-line treatment in resource-limited countries. *J Microbiol Infect Dis 2016;6(4): 149-155*

Keywords: Abidjan; Atazanavir; HIV; Lopinavir; Second-line; Sub-Saharan Africa

INTRODUCTION

Atazanavir is part of the drug recommended by WHO in second-line antiretroviral treatment in resource-limited settings [1,2]. This drug is known for his more favorable lipid profile than lopinavir and for its ease of use once a day and its availability in form of fixed combination with ritonavir [3-5]. According to some authors, it would be preferable to prescribe atazanavir as Protease Inhibitor (PI) for second-line because he has the advantage to cause no cross-resistance with other PIs and is not showing the problem of lopinavir, which selects the L76V mutation conferring resistance class [6-8]. On the other hand, there are other studies describing a better efficacy of lopinavir in patients for whom second-line treatment was delayed due to late failure confirmation [9-12]. Such delays are very often encountered in our context where viral load is not routinely available. Other authors also claim that it is preferable to prescribe lopinavir due to its better genetic barrier compared to atazanavir [10]. Comparative trials showed similar efficacy between these two PIs, but they have mostly been conducted in high-income countries and in naïve patients to antiretroviral treatment [13-15]. In Sub-Saharan Africa, only few studies have compared the efficacy of PIs such as lopinavir and atazanavir in the second-line [16]. These evaluations in Sub-Saharan Africa and in many low-income countries have focused on the therapeutic response after 12 months, with most regimens based on lopinavir/r [17-20]. One of the main reasons is that atazanavir has recently been

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introduced in the therapeutic arsenal in many African countries, particularly in Ivory Coast. Due to the stop of indinavir use since 2010 and more than 3 years use of atazanavir in our service, we found it useful to compare within our cohort the therapeutic response between the two combination therapies of protease inhibitors (boosted LPV versus boosted ATZ containing regimens) recommended as second-line in Ivory Coast.

PATIENTS AND METHODS

Study design and setting

This is a retrospective and comparative study on a historical cohort, consisting of two groups of HIV1-infected patients on HAART including two nucleoside reverse transcriptase inhibitors plus a ritonavir-boosted Protease Inhibitor. The one group received ritonavir-boosted atazanavir (ATZ/r), the other ritonavir-boosted lopinavir (LPV/r). All patients were treated according to the applicable World Health Organization (WHO) treatment guidelines [1]. The study was conducted between May 2009 and June 2010 in the Department of Infectious and Tropical Diseases (DITD) of the Treichville university hospital, Abidjan (Ivory Coast). It is a referral center for the management of people leaving with HIV/AIDS, working closely with several other institutions in the country, in Africa and Europe. The active patient file is 9500 seropositive patients with 4852 patients on ARTs at the end of 2010.

Study population

For the study, patients were selected fulfilling the following criteria: HIV-1; at least 15 years old; followed in DITD; having received ATV/r or LPV/r in combination antiretroviral therapy since at least 6 months and being in the situation of first-line antiretroviral treatment failure. Patients had initiated antiretroviral treatment either at WHO clinical stage 3 and CD4 count lower 350 cells/mm^3 or at WHO clinical stage 4 or at CD4 count lower 200 cells/mm^3. The first-line regimen consisted of an NNRTI (nevirapine or efavirenz) and two NtRTIs. First-line failure was defined as the occurrence of opportunistic infections or in the absence of concurrent infections at least 50% decrease in CD4 count compared to the previous rate or two consecutive viral loads >1000 copies/ ml after at least 6 months of ART.

Procedures

The enrollment of patients was based on the database of the National AIDS Program of Ivory Coast, and the database of the DITD pharmacy. We identified patients under HAART combining two nucleoside inhibitors plus ATV/r or LPV/r. Patients enrolled in the study had followed a series of visits according to national guidelines, including a baseline visit and routine visits at least every 12 weeks for clinical assessments and every 24 weeks for clinical and biological assessments. Data collected include: 1) Baseline demographics data: birth date, gender, HIV clinical stage (WHO or CDC stage), ART initiated, clinical assessment, medical history, 2) Follow-up: clinical assessment (other diseases/infection, HIV clinical stage, weight, medications such as antiretroviral drugs and cotrimoxazole), 3) Biological data: CD4, hemoglobin, serum chemistry, liver function tests, plasma HIV RNA viral load, and 4) Outcomes: death, loss to follow up, and treatment changes. CD4 counts were measured by FACS Count Flow cytometers (*Fascan Becton-Dickinson™, San Carlos, CA, USA*). Plasma HIV-1 RNA levels were quantified with *Amplicor 1.5 Roche®* (threshold of 200 copies/ml). Primary endpoint was the proportion of patients with HIV RNA of less than 200 copies/ml at month 12 (or week 48). Secondary efficacy endpoints were the log reduction in HIV RNA by week 48, the average CD4 gain after 12 months of follow-up. Safety endpoints included the frequency and quality of adverse events, serious adverse events, laboratory abnormalities, and changes from baseline in laboratory results over time.

Statistical Analysis

A database was created with Epi-Data, and data were analyzed using Epi-info™ (*version 3.5.3, 2011; CDC, Atlanta, USA*). The results were presented as the frequencies or means with standard deviations. A comparison of the frequencies was performed with Chi-squared test, and a comparison of the mean or median values was performed with Student's *t*-test or a nonparametric test. The difference was statistically significant for $p < 0.05$.

RESULTS

Cohort description

During the study period, we analyzed 220 cases of patients meeting our inclusion criteria and 194 cases were selected. The reasons for non-inclusion of patients were as follows: 22 patients with tuberculosis after initiation of second-line treatment, 3 patients with first-line treatment with NNRTI and one patient on PI without first-line treatment failure. Among the included 194 patients, 51(26.3%) received 2 NRTIs

plus ATV/r (ATV/r group) and 143 (73. 7%) 2 NRTIs plus LPV/r (LPV/r group).

Baseline characteristics

Baseline demographic and clinical characteristics are presented in Table 1. In overall, the median age at second-line initiation was 41 years [interquartile range (IQR): 36–50 years], 63.9% of the patients were women and the baseline clinical CDC stage was B for 45% and C for 41 % of the patients. There were more female in the LPV/r group than in the ATV/r group (69% versus 49%; p <0.05), and baseline median age was significantly lower in the LPV/r group compared to the ATV/r group (39 years versus 46 years, p <0.05). However, no significant difference in viral load at baseline between the groups (4.71 $\log_{10}$ copies/ml versus 4.56 $\log_{10}$ copies/ml; $p = 0.40$). A total of 28 (54%) patients received tenofovir (TDF) plus emtricitabine (FTC) in the ATV/r group and 78 (54%) for the LPV/r group. The combination abacavir (ABC) + didanosine (DDI) was the second most prescribed scheme (19.6 % versus 35%) in the two groups.

Table 1. Baseline characteristics of patients in ATV/r group vs LPV/r group

Parameters	Over all, n=194 (%)	ATV/r, n=51 (%)	LPV/r, n=143 (%)	p-value
Age at baseline(years) Median (IQR)	41(36-50)	46(40-52)	39(34-47)	0.001
Gender (F)	124 (63.9)	25 (49.0)	99 (69.2)	0.010
CDC Stage				
A	27 (13.9)	10 (19.6)	17 (11.9)	
B	87 (44.9)	20 (39.2)	67 (46.9)	NA
C	80 (41.2)	21 (41.2)	59 (41.2)	
Cotrimoxazole prophylaxis	158 (81.5)	34 (66.7)	124 (86.7)	0.02
CD4 cell count of patients				
350-200	90 (46.4)	24 (47)	66 (46.2)	0.9
<200	104 (53.6)	27 (53)	77 (53.8)	
Base line RNA loads, N(%) of patients				
<100000	24 (12.4)	12 (23.5)	12 (8.4)	0.0048
>100000	170 (87.6)	39 (76.5)	131 (91.6)	
NRTIs (%)				
TDF+FTC	106 (54.6)	28 (54.9)	78 (54.5)	
ABC+DDI	60 (30.9)	10 (19.6)	50 (35)	0.013
Others	28 (14.5)	13 (25.5)	15 (10.5)	

Primary outcome

The proportion of patients with HIV RNA of less than 200 copies/ml at week 48 was not significantly different in the two groups (92 % in the ATV/r group versus 96 % in the LPV/r group, p=0.535) (Fig. 1).

Secondary outcomes

The mean reductions of viral load were 1.87 $\log_{10}$ for ATV/r group versus 1.98 $\log_{10}$ for the LPV/r group, p= 0.184 (Figure 2). CD4 cell count distributions and the change from baseline at week 48 were different in the two groups. At week 48, the median increase from baseline was 279 cells/mm^3 in the ATV/r group and 357 cells/mm^3 in the LPV/r group (p=0.012) (Figure 3).

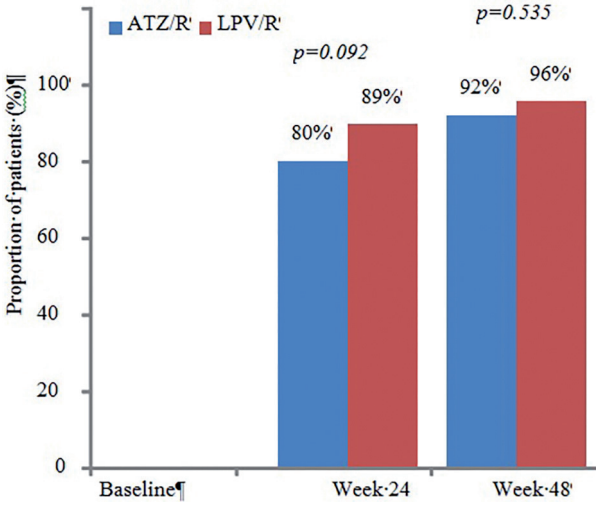

Figure 1. Evolution of virologic response in both treatment groups during follow-up

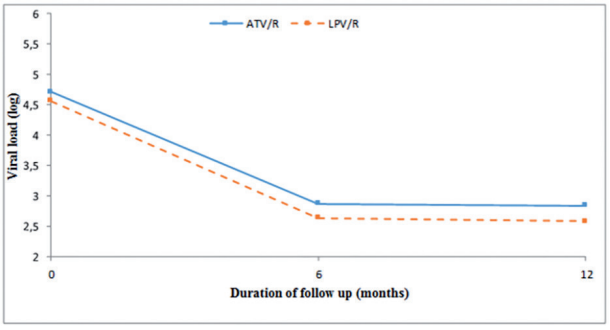

Figure 2. Proportion of patients with undetectable viral loads (< 200 copies/ml) during follow-up

Treatment-related adverse events (AEs) occurred in 11.8 % ATV/r group and 10.5% in LPV/r group. The majority of AEs in LPV/r were clinical AEs, although the main AEs were laboratory abnormality in ATV/r group. More patients on LPV/r group experienced grade 2-4 treatment-related nausea and diarrhea. However, AEs related to ATV was dominated by hepatic transaminase elevation. Serious adverse events were reported in less than 2 % of patients on either regimen within exception of peripheral subcutaneous lipodystrophy, which was reported by 2 (1%) in the two group.

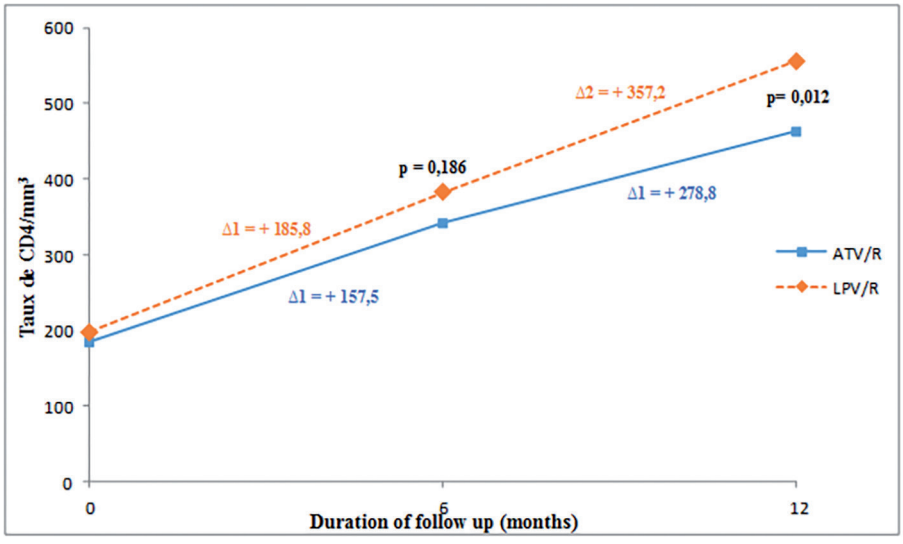

Figure 3. Evolution of CD4 in both treatment groups during follow-up at week 48.

DISCUSSION

This is the first study in West Africa, particularly in Ivory Coast evaluating immunologic and virological efficacy of two regimens of antiretroviral therapy with second-line PIs boosted by ritonavir. An assessment of the unboosted atazanavir with ritonavir was conducted in Senegal, but only in HIV patients on first-line antiretroviral therapy [21]. Atazanavir demonstrated significant antiviral potency and well tolerated in our study at 48 weeks when administrated at 300 mg once daily, in combination with an optimized antiretroviral regimen in treatments-experienced patients failing their antiviral regimen. The virological responses did not differ in patients who received ATV/r versus those received LPV/r (*p= 0.535*).

In general, our results are comparable with those observed in previous studies while they were conducted in developed countries and in HIV-infected patient's naïve to antiretroviral therapy. Indeed, the Castle study showed at week 48, 343 (78%) of 440 patients receiving ATZ/r and 338 (76%) of 443 patients receiving LPV/r had achieved a viral load of less than 50 copies per ml. In the same study, there was no difference between groups in log reduction in HIV RNA from baseline and week 48. These results are consistent with those in the literature [13,14]. Besides, to the difference of the recent WHO guidelines, the majority of studies previously conducted especially in northern countries, analyzed the switch from other PIs to atazanavir-containing regimens. Maintenance of virological efficacy has clearly been demonstrated in a number of well-designed randomized trials, in particular, for patients coming from LPV/r regimen [22-24].This therapeutic approach could be considered in our African context where metabolic and cardiovascular diseases are very common.

In term of immunologic response, the mean increases from baseline in CD4 cell count were lower in the ATZ/r group than LPV/r group (+279 cells/ml *versus* +357 cells/ml), with a significant difference (p =0,012). The poorer response in the ATZ/r could be explained by the influence of age on the immune response. Indeed, patients in ATZ/r group had a higher mean age, and a poorer immune response as confirmed by numerous studies [25,26]. The interpretation of *Balestre and al* is that there is a continuous effect of age (following thymic atrophy) that has a substantial impact on CD4 response as early as from 40 years [27]. Although, this assertion is rejected by some authors that exclude any influence of age on the immune response [28].

At the same time, the safety of atazanavir has been demonstrated in previous studies and the most frequent side effect of atazanavir-containing ART is hyperbilirubinemia (HBR), which is defined as any elevation of bilirubin above the normal range (usually up to 1.0 mg/dl or 21 µmol/l). Visible hyperbilirubinemia (icterus) in skin and sclera is a less common clinical finding. These reversible indirect (unconjugated) bilirubin elevations are caused by the competitive UDP-glucuronosyltransferase (UGT) inhibition by atazanavir [29]. In large studies, grade 3-4 HBR, had occurred in 23 % of patients on unboosted and 55% of patients on boosted atazanavir [30]. In our study and overall, atazanavir is well tolerated and no jaundice has been reported during the period of follow-up. Adverse events grade 1-2 such as increase of alanine aminotransferase and aspartate aminotransferase occurred in 8% of patients, but were not clinically significant. Furthermore, no increase in bilirubin was found. This difference could be explained by the fact that bilirubin is not performed systematically in our context during the laboratory monitoring. This exam is paid by the patient, at the request of the physician and that depending on the clinical context. Rotger et al assessed the utility of genotyping and hyperbilirubinaemia and found that chronic hepatitis C and hepatitis B infection were associated with higher bilirubin levels [31]. The authors suggested that pre-treatment screening for UGT1A1*28 genotype would reduce the prevalence of jaundice from 22% to 5%. However, testing is expensive and impractical in routine practice and may result in avoidance of use of ATV in patients who would potentially benefit from its use. Other factors had been identified, namely, the methadone use and concomitant use of tenofovir which were independently associated with a smaller change in bilirubin. The low incidence of both clinical and biological serious adverses effects limit the number of treatments discontinuations, as observed in our study, corroborating data from ATAZIP and SLOAT studies. [22,24].

Furthermore, recent data support the use of ATV/r in pregnant women with HIV; in this observational study, atazanavir and lopinavir showed safety and activity in pregnancy, with no difference in the main pregnancy outcomes [32]. Atazanavir use was associated with a better lipid profile and higher bilirubin levels [3,4,33,34]. Overall, this study finding confirms that these two HIV protease inhibitors represent equally valid alternative options.

Some limitations in our study need to be considered: firstly, the relatively small sample size in the ATV/r group and its retrospective nature, corrected by the statistical tests. Secondly, there was no data regarding the adherence although the fact that the majority of our patients had an undetectable viremia would suggest adequate adherence. Finally, the absence of ATV/r lipid profile would have allowed us to check the reputation of good lipid profile which of this drugs. The antiretroviral therapy in this study had proven generally effective and only three patients were lost-follow up with one death after 48 weeks.

Conclusion

The results of this study support WHO guidelines on the use of antiretroviral drugs for treating and preventing HIV, especially in the treatment of patients infected with HIV in second-line antiretroviral therapy [1,2]. Using a boosted PI plus two NRTI combinations is recommended as the preferred strategy for second-line ART for adults, adolescents and for children when NNRTI-containing regimens were used in first-line ART. Moreover, heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART. A subsequent prospective, large, multicenter, randomized study would be helpful to better assess the second-line treatment in Ivory Coast.

Declaration of conflicting interests

The authors declare that they have no conflict of interest.

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