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Duration of first-line antiretroviral therapy with tenofovir and emtricitabine combined with atazanavir/ritonavir, efavirenz or lopinavir/ritonavir in the Italian ARCA cohort

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Objectives: To explore the durability of three first-line tenofovir/emtricitabine-based regimens in combination with atazanavir/ritonavir, efavirenz or lopinavir/ritonavir in HIV-1-infected patients.

Patients and methods: A retrospective, longitudinal, multicentre analysis of adult patients enrolled in the Antiretroviral Resistance Cohort Analysis (ARCA), a national prospective observational cohort of HIV-1-infected patients followed up at more than 100 clinical and laboratory units in Italy. Patients eligible were those starting first-line antiretroviral therapy between 1 June 2004 and 15 April 2011 and who were followed up for at least 6 months. The primary endpoint was durability, defined as the time from antiretroviral therapy initiation to first treatment modification. Time-dependent events were analysed by the Kaplan–Meier approach and the Cox proportional hazard model.

Results: There are 26 000 HIV-infected patients in the ARCA database, of whom 1654 met study inclusion criteria. Six hundred and thirty-nine (38.6%) received efavirenz, 321 (19.4%) received atazanavir/ritonavir and 694 (41.9%) received lopinavir/ritonavir as a first-line regimen. Over a total observation period of 88 months, equivalent to more than 2805 person-years of follow-up, 618 patients underwent treatment modification. Lopinavir/ritonavir, given twice daily, was associated with a higher discontinuation rate than efavirenz- and atazanavir-based regimens [hazard ratio (HR) 1.83, 95% confidence interval (CI) 1.56–2.15, $P=0.001$]. Comparing the once-daily regimens, the rate of discontinuation of efavirenz was higher than that of atazanavir/ritonavir (HR 1.39, 95% CI 1.06–1.83, $P=0.016$).

Conclusions: Significant differences in treatment duration were observed among the three studied regimens. Once-daily regimens exhibited greater durability than the twice-daily regimen. Among the specific regimens examined, tenofovir/emtricitabine plus atazanavir/ritonavir showed the greatest durability.

Keywords: tenofovir/emtricitabine, durability, drug utilization, antiviral therapy, HIV/AIDS

Introduction

The introduction of highly active antiretroviral therapy (HAART) as the standard treatment for HIV infection has greatly reduced mortality and morbidity.[1,2] Current practice guidelines recommend the use of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) or integrase inhibitors for initial therapy of HIV-1 infection.[3–5]

Suppression of viral replication requires lifelong HAART, and inconsistent use of medications can lead to development of

resistance to one or more drugs included in the regimen, limiting future treatment options and compromising patient outcome.[6] However, adverse drug reactions, drug–drug interactions, co-morbidities and socioeconomic barriers may influence the safety, durability and efficacy of HAART.[7] In clinical practice, tenofovir/emtricitabine is the preferred backbone suggested in all guidelines.[3–5] Several studies have compared the efficacy and tolerability of atazanavir/ritonavir versus efavirenz,[8] atazanavir/ritonavir versus lopinavir/ritonavir[9,10] and efavirenz versus lopinavir/ritonavir,[11,12] but there are few data directly comparing the three drugs in combination with tenofovir/emtricitabine in clinical practice.

The aim of this study was to assess the durability of the most common first-line regimens—atazanavir/ritonavir, efavirenz and lopinavir/ritonavir—in combination with tenofovir/emtricitabine in previously antiretroviral-naive, HIV-infected adults followed in a large Italian cohort.

Patients and methods

Study design

This was a retrospective, longitudinal, multicentre analysis of 1654 HAART-naive, HIV-infected adults enrolled in ARCA, a national observational cohort[13] of HIV-1-infected patients followed up at more than 100 clinical and laboratory units in Italy. At the time of this study, data from more than 26000 patients in the cohort were available. Patients are enrolled in the ARCA database after giving informed consent to provide their data for academic not-for-profit studies. The data include demographics, hepatitis B and C virus status, AIDS-defining events, antiretroviral treatment, viral load, CD4+ T cell counts and HIV-1 genotype.

The ARCA initiative was started in 2002 and is compliant with the Declaration of Helsinki. Each participating centre is answerable to a local ethics committee that follows national (and European where applicable) regulations.

Patients

Eligible patients were HIV-infected antiretroviral-naive adults in whom first-line HAART was initiated between 1 June 2004 and 15 April 2011 and who were followed up for at least 6 months. Patients receiving first-line treatments comprising tenofovir/emtricitabine as the backbone plus efavirenz, lopinavir/ritonavir or atazanavir/ritonavir were extracted from the ARCA database. Patients who discontinued first-line tenofovir/emtricitabine-based HAART for a short period of time and then restarted on the same regimen were excluded.

Study endpoints

The primary endpoint was the estimated duration of the three HAART regimens compared in the study, defined as time from HAART initiation to discontinuation of therapy due to any cause. The causes of treatment change recorded included side effects of HAART, virological and/or immunological failure, pregnancy, poor compliance, HAART intensification, regimen simplification and supervised interruption.

As this is an observational study, each prescribing physician establishes the modification of HAART in accordance with local guidelines, although within internationally approved rules.

A switch from tenofovir/emtricitabine to tenofovir/emtricitabine/efavirenz was not considered a treatment modification because it reflects the delayed availability of the new fixed formulation of tenofovir/emtricitabine/efavirenz in Italy in 2008.

Statistical analysis

For statistical analysis we considered the sex and age of patients, median CD4 cell count and viral load at the time of starting HAART. The χ^2 test, one-way analysis of variance (ANOVA) and Student's *t*-test were used to evaluate differences among groups.

Data were summarized as median and range in the case of quantitative variables and as absolute frequencies and percentages in the case of qualitative items. Time to event was analysed by the Kaplan–Meier method and differences among curves were evaluated by the log-rank test. A multivariable Cox regression model including sex, age, therapy and baseline viral load (>100000 versus <100000) was tested. Only therapy and viral load were significant prognostic factors. Results are given as HRs and 95% CIs and were adjusted for variables included in the model. Using logistic regression, we examined the effect of calendar year of starting HAART on the proportion of patients discontinuing each of three HAART regimens.

Results

A total of 1654 antiretroviral-naive, HIV-infected patients were included in the study. Among these patients, 639 (38.6%) received an efavirenz-based first-line regimen, 321 (19.4%) received an atazanavir/ritonavir-based first-line regimen and 694 (41.9%) received a lopinavir/ritonavir-based first-line regimen. Baseline characteristics of patients are listed in Table 1. Patients who were prescribed lopinavir/ritonavir had more advanced disease with a higher viral load and a lower CD4 cell count at baseline. During our observation period of 88 months, we had 2805 person-years of follow-up, in which 618 patients underwent treatment modification. The most frequent reason for switching was drug toxicity (Table 2). Treatment change occurred in 72 individuals over 564 person-years in the atazanavir/ritonavir group, in 190

Table 1. Baseline demographics and disease characteristics

	Efavirenz (*n*=639)	Atazanavir/ritonavir (*n*=321)	Lopinavir/ritonavir (*n*=694)	*P* value
Age (years), median (range)	39 (17–72)	41 (16–76)	40 (17–74)	0.12
Sex, *n* (%)				
males	496 (77.6)	228 (71.0)	511 (73.6)	0.06
females	143 (22.4)	93 (29.0)	183 (26.4)	
Co-infection, *n* (%)				
HCV	101 (15.8)	68 (21.2)	116 (16.7)	0.11
HBV	58 (9.1)	33 (10.3)	66 (9.5)	0.83
Mode of transmission, *n* (%)				
heterosexual	164 (25.7)	80 (24.9)	244 (35.2)	0.001
CD4+ cells/mL, median (range)	283 (3–892)	236 (3–761)	167 (1–1242)	0.001
HIV-RNA copies/mL, *n* (%)				
>100000	156 (37.9)	86 (50.6)	272 (54.1)	0.001
<100000	256 (62.1)	84 (49.4)	231 (45.9)	

HCV, hepatitis C virus; HBV, hepatitis B virus.

Table 2. Causes of discontinuation

Drugs	Adherence	Failure	Pregnancy	Addition	Interruption	Simplification	Toxicity	Other	Total
ATV/r	1 (1.4%)	4 (5.6%)	0	1 (1.4%)	3 (4.2%)	6 (8.3%)	18 (25.0%)	39 (54.2%)	72
EFV	5 (2.6%)	22 (11.6%)	5 (2.6%)	2 (1.1%)	5 (2.6%)	0	45 (23.7%)	106 (55.8%)	190
LPV/r	6 (1.7%)	13 (3.6%)	3 (0.8%)	6 (1.7%)	11 (3.1%)	91 (25.6%)	105 (29.5%)	121 (34%)	356
Total	12 (1.9%)	39 (6.3%)	8 (1.3%)	9 (1.5%)	19 (3.1%)	97 (15.7%)	168 (27.2%)	266 (43%)	618

ATV/r, atazanavir/ritonavir; EFV, efavirenz; LPV/r, lopinavir/ritonavir.

over 1046 person-years in the efavirenz group and in 356 over 1195 person-years in the lopinavir/ritonavir group. The results of univariate analysis showed a statistically significant difference in the duration of therapy between patients receiving atazanavir/ritonavir or efavirenz and those receiving lopinavir/ritonavir ($P<0.0001$). Furthermore, there was a statistically significant difference ($P=0.01$) between atazanavir/ritonavir and efavirenz (Figure 1). Treatment duration was also shorter with twice-daily lopinavir/ritonavir than with the once-daily regimens (efavirenz and atazanavir/ritonavir) ($P=0.0001$; Figure 2). At 24 months, 50% of patients were receiving the twice-daily regimen compared with 70% receiving once-daily regimens. At the time of discontinuation, 55% of patients in the atazanavir/ritonavir arm, 51% of patients in the efavirenz arm and 64% of patients in the lopinavir/ritonavir arm had an HIV-RNA viral load below 50 copies/mL. Overall, durability on therapy was better for men than for women ($P=0.03$); this difference was greater in the efavirenz group ($P=0.007$). Moreover, durability on therapy did not show significant differences according to the age of patients. According to the multivariate analysis, the risk of treatment discontinuation was greater for both efavirenz (HR 1.39, 95% CI 1.06–1.83, $P=0.016$) and lopinavir/ritonavir (HR 1.98, 95% CI 1.44–2.72, $P<0.001$) than for atazanavir/ritonavir. The risk of treatment discontinuation was higher with the twice-daily regimen than with the once-daily regimens (HR 1.83, 95% CI 1.56–2.15, $P<0.001$). The risk of lower durability was also higher among patients with a baseline viral load >100 000 copies/mL than in those with baseline viral load <100 000 copies/mL (HR 1.28, 95% CI 1.06–1.56, $P=0.007$).

Table 3 shows the prevalence of starting therapy by calendar year. The prevalence of discontinuation in the lopinavir/ritonavir and efavirenz arms increased after 2006.

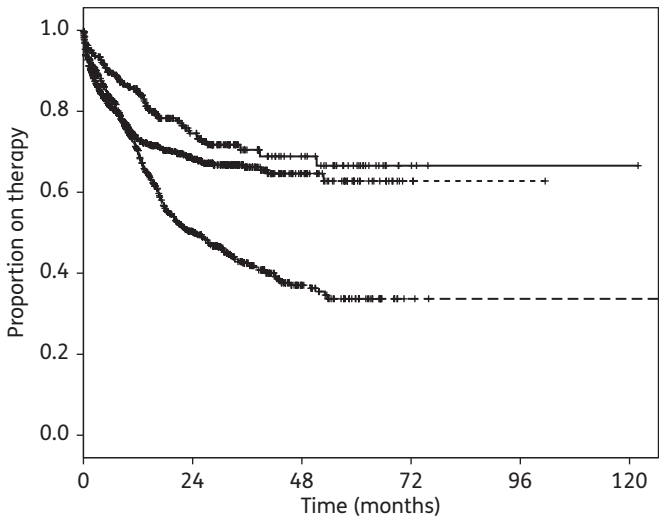

Figure 1. Time to treatment modification during the observational period after starting combination antiretroviral therapy. Top line, atazanavir/ritonavir; middle line, efavirenz; bottom line, lopinavir/ritonavir.

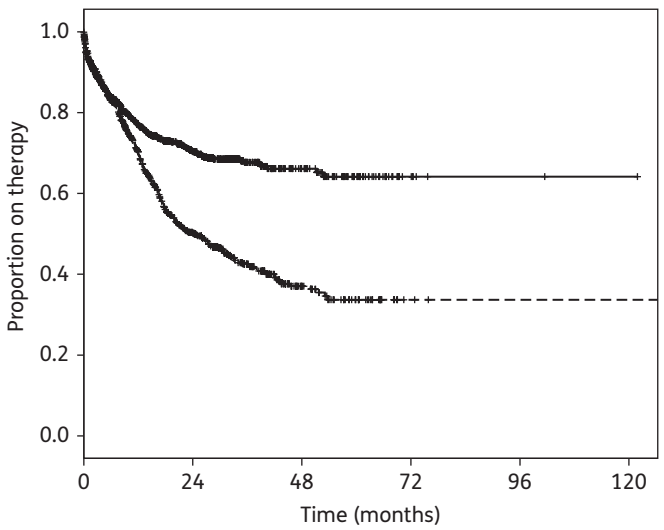

Figure 2. Time to treatment modification during the observational period after starting a once-daily or twice-daily regimen. Top line, once-daily regimens (atazanavir/ritonavir or efavirenz plus tenofovir/emtricitabine); bottom line, twice-daily regimen (lopinavir/ritonavir plus tenofovir/emtricitabine).

Discussion

In this analysis of 1654 patients starting their first HAART regimen between 1 June 2004 and 15 April 2011, changes to initial therapy with tenofovir/emtricitabine combined with atazanavir/ritonavir, efavirenz or lopinavir/ritonavir were relatively frequent. These findings are consistent with those of a previous study.[6,7] Initial treatment with atazanavir/ritonavir was associated with a longer duration of treatment than first-line therapy with lopinavir/ritonavir and, to a lesser extent, efavirenz. Our results are in agreement with the data reported in the open-label, non-inferiority study comparing once-daily atazanavir/ritonavir with twice-daily lopinavir/ritonavir, each in combination with tenofovir/emtricitabine, in 883 antiretroviral-naive participants.

Table 3. Treatment discontinuation rate by calendar year of starting antiretroviral therapy

Year of starting	Atazanavir (%)	Efavirenz (%)	Lopinavir/ritonavir (%)
2005	4.9	4.6	3.6
2006	11.1	11.4	16.8
2007	9.3	15.6	23.3
2008	15.1	23.0	27.8
2009	30.6	23.1	17.8
2010	22.2	18.8	8.3
2011	6.8	3.5	2.4

The analysis at 48 weeks[9] and at 96 weeks[10] demonstrated similar virological and CD4+ T cell responses in participants receiving the two regimens.

Furthermore, our study reaffirms an increased risk of discontinuation because of toxicity or simplification in the case of lopinavir/ritonavir-based therapy.[14,15] The vast majority of patients who discontinued because of simplification were in lopinavir/ritonavir arm; the reason for this choice was reduction in the pill burden and dosing frequency.

In our study, patients on efavirenz also switched treatment more frequently than those on atazanavir/ritonavir. Treatment failure and adverse events were the main reason for discontinuation of efavirenz; women in particular were more likely to modify their efavirenz-based regimen (Figure 3).

We noted an increase in discontinuations by calendar year up to 2006 for efavirenz and lopinavir/ritonavir. These observations are likely to be attributable, at least in part, to approval of atazanavir/ritonavir as a once-daily option for first-line therapy in the USA and European Union.[16]

In agreement with several studies showing daily dosing is an important component of regimen complexity, we found a significant difference in the duration of once-daily (atazanavir/ritonavir or efavirenz) versus twice-daily (lopinavir/ritonavir) combination antiretroviral therapy.[17,18] Once-daily dosing is considered a key contributor to treatment success, improving quality of life, adherence and patient satisfaction with therapy.[19,20] In our study we observed that patients with lower CD4+ T cell counts received PI-based regimens more frequently. Our finding is not supported by statistical analysis, but in a retrospective longitudinal analysis by Torti *et al.*,[11] comparing lopinavir/ritonavir- and efavirenz-based regimens, the group who received lopinavir/ritonavir-containing regimens had significantly lower CD4+ counts at baseline. In these patients, the preference for first-line treatment with lopinavir/ritonavir is justified by the ACTG 5142 study, in which patients receiving regimens containing lopinavir/ritonavir experienced greater increases in CD4+ T cell counts than did those receiving efavirenz plus two NRTIs.[12]

The difference we found in persistence with efavirenz treatment between males and females (Figure 3) can be explained by the lower weight in the latter group, resulting in increased frequency of dose-dependent toxic effects.[15,21]

Toxicity remains a major cause of treatment discontinuation, with more than one-quarter of patients stopping therapy because of the occurrence of an adverse event. Although the reason for treatment change is recorded, one limitation of our analysis is an inability to determine the nature of the adverse event as this type of data is not recorded in the ARCA database, which is not focused on the toxicity of antiretrovirals. Another limitation is the lack of data about interruption of tenofovir/emtricitabine. In contrast, a strength of this study is the fact that we have 7 years of data from multiple real-world practices and we found a high discontinuation rate. As in a few large randomized controlled clinical trials, we found atazanavir/ritonavir to be a well-tolerated once-daily regimen and more durable than lopinavir/ritonavir. Better-tolerated regimens or strategies to improve tolerability remain a critical goal of antiretroviral therapy.

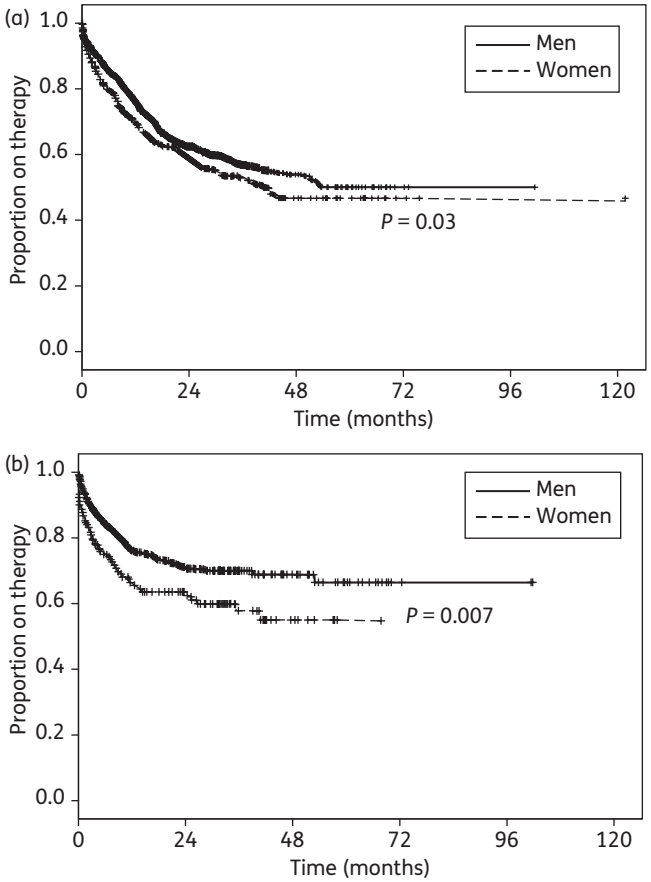

Figure 3. (a) Durability of first-line therapy for all regimens in men and women. (b) Durability of the first-line efavirenz-based regimen in men and women.

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Author contributions

A. D. B., R. P., D. G. and F. M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A. D. B. and F. M. Statistical expertise: D. G. Drafting of the manuscript: A. D. B., R. P. and D. G. Critical revision of the manuscript for important intellectual content: F. M., G. S., A. D. B. and R. P. All authors approved the final version of the manuscript.

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