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Short Communication

Switch from unboosted protease inhibitor to a single-tablet regimen containing rilpivirine improves cholesterol and triglycerides

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ABSTRACT

This study aimed to evaluate the efficacy, tolerability and potential savings of combined antiretroviral therapy (cART) simplification from an unboosted protease inhibitor (PI) regimen with atazanavir or fosamprenavir to a single-tablet regimen (STR) based on rilpivirine/emtricitabine/tenofovir disoproxil fumarate (RPV/FTC/TDF) among HIV-1-infected patients with HIV-1 RNA <50 copies/mL. This was a retrospective, multicentre, open-label, 12-week trial. Plasma HIV-1-RNA levels, CD4+ cell counts, cholesterol, triglycerides, bilirubin, glycaemia, creatinine and physical examination were performed at baseline and at scheduled follow-up. All patient costs were calculated and were estimated for 52 weeks of therapy. Fifty-one patients were enrolled [28 male (54.9%)]. At baseline, 30 patients (58.8%) were treated with FTC/TDF, 20 (39.2%) with abacavir/lamivudine and 1 (2.0%) with lamivudine/zidovudine. Thirty-three patients (64.7%) received atazanavir. All patients maintained HIV-RNA <50 copies/mL; the median CD4+ cell count remained stable. Mean triglycerides decreased from 124 mg/dL (range, 39–625) at enrolment to 108.7 mg/dL (range, 39–561) at study end ($P = 0.25$). At baseline, mean cholesterol was 172.8 ± 38.1 mg/dL and decreased to 161.9 ± 38.6 mg/dL ($P = 0.038$); likewise, median total bilirubin decreased from 1.07 mg/dL (range, 0.2–4.7) to 0.6 mg/dL (range, 0.13–3.1) ($P < 0.001$). cART-related annual cost reduction with a STR was €3155.47 per patient (–24%). Non-cART patient management expenses were €402.68 vs. €299.10 for atazanavir or fosamprenavir and STR regimens, respectively. Switching to RPV/FTC/TDF from an unboosted PI in virologically suppressed HIV-infected patients is safe and is associated with a reduction in triglycerides, cholesterol and cART-related costs.

1. Introduction

Ritonavir-sparing regimens based on atazanavir (ATV) or fosamprenavir (FAPV) plus two nucleoside reverse transcriptase inhibitors (NRTIs) have been an option for human immunodeficiency virus (HIV)-infected patients who did not tolerate ritonavir, minimising the long-term side effects and improving the lipid profile [1–5]. In the last years, the introduction of safer, better tolerated and more active drugs has changed the antiretroviral treatment scenario [6].

In addition, a single-tablet regimen (STR) containing rilpivirine/emtricitabine/tenofovir disoproxil fumarate (RPV/FTC/TDF) may successfully reduce the pill burden, improving tolerability and decreasing combined antiretroviral therapy (cART)-related costs in virologically suppressed patients [7].

Protease inhibitor (PI)-based regimens are known to be associated with an increased risk of metabolic side effects [8,9]. The switch to a non-nucleoside reverse transcriptase inhibitor (NNRTI) from an unboosted PI in virologically suppressed patients allows maintaining virological success with a decreased risk of virological failure

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and a lower degree of systemic inflammation [10,11]. To date, no data are available on the effect of the switch from unboosted PI (ATV or FAPV) to an RPV/FTC/TDF-based STR. The aim of this study was to assess the efficacy, tolerability and potential savings of a simplification strategy from an unboosted PI regimen to a STR based on RPV/FTC/TDF among HIV-1-infected patients with HIV-1 RNA <50 copies/mL.

2. Materials and methods

This study was a retrospective, multicentre, pilot, open-label, 12-week trial aiming to evaluate the tolerability, safety, efficacy and cost savings of the switch from a regimen based on the unboosted PIs ATV or FAPV + two NRTIs to a STR based on RPV/FTC/TDF among HIV-1-infected patients with HIV-1 RNA levels <50 copies/mL. Data collection began in December 2013 and ended in December 2015. Key inclusion criteria were: age >18 years; plasma HIV-1 RNA <50 copies/mL at enrolment; and stable cART regimen since 1 year. Exclusion criteria were more than one mutation among K101E/P, E138K/A/G/Q/R/S, Y181I/V and M230I/L at historical genotyping and estimated glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation of <50 mL/min. The study was conducted at seven different infectious diseases units in Italy. All participants were evaluated at baseline and after 4 weeks and 12 weeks. Plasma HIV-1-RNA levels, CD4+ T-lymphocyte cell counts, cholesterol, triglycerides, bilirubin, glycaemia, plasma creatinine levels and physical examination were performed at baseline and at scheduled follow-up visits. Disease management costs per patient were collected; the expected disease management was calculated based on expert opinion [12]. Drug prices were based on what the National Health Service paid for them. All patient costs, including outpatient visits, blood samples, biochemical analyses and cART-related costs were collected and calculated both for PI and RPV/FTC/TDF STR regimens and were projected for 52 weeks of therapy. Furthermore, all patients were investigated for admission to hospital during the study. This study was reviewed and approved by the Liguria Regional Ethics Committee.

2.1. Statistical analysis

The mean ± standard deviation (S.D.) or the median and range were reported for continuous variables. Paired samples *t*-tests were used for cholesterol, triglycerides, glycaemia and creatinine, and non-parametric Wilcoxon matched-pairs signed-rank tests were used for all other parameters to statistically test the change of values between baseline and 12 weeks. To test whether baseline characteristics (age, sex, PI) influenced the change at 12 weeks, a mixed model with random intercept was performed. Before performing the mixed model, particularly skewed variables (plasma bilirubin, triglycerides) were transformed using a cube root function. Stata software v.13 (StataCorp LP, College Station, TX) was used for the computation.

3. Results

A total of 51 patients were enrolled in the study [28 male (54.9%)]. The mean ± S.D. patient age was 49.1 ± 7.9 years. In 31 patients (60.8%) the route of HIV infection was intravenous drug use. Baseline characteristics are reported in Table 1. Genotypic resistance tests were available in 15 (29.4%) of the 51 patients. Two patients presented K103N mutation (one associated with Y181C) and one patient presented E138A mutation. K103N mutation is a non-polymorphic mutation that causes high-level resistance to nevirapine and efavirenz but does not affect RPV susceptibility. E138A is a polymorphic mutation that is weakly selected by etravirine and RPV. According to the RPV package insert, the presence of E138A prior to therapy may reduce the antiviral activity of RPV.

Table 1
Baseline demographic characteristics of patients ($n = 51$).

Characteristic	Data
Age (years) (mean ± S.D.)	49.1 ± 7.9
Male sex [*n* (%)]	28 (54.9)
Intravenous drug use [*n* (%)]	31 (60.8)
Backbone [*n* (%)]	
Emtricitabine/tenofovir disoproxil fumarate	30 (58.8)
Abacavir/lamivudine	20 (39.2)
Zidovudine/lamivudine	1 (2.0)
Protease inhibitor [*n* (%)]	
Atazanavir	33 (64.7)
Fosamprenavir	18 (35.3)
Peak HIV-1-RNA (copies/mL) [median (range)]	100,000 (10,000–1,200,000)
Nadir CD4+ cell count (cells/mm^3) [median (range)]	217 (6–456)
No. of therapeutic lines [median (range)]	4 (1–20)

S.D., standard deviation.

The cART regimens were based on FTC/TDF in 30 patients (58.8%), whereas 20 patients (39.2%) were on abacavir/lamivudine and 1 patient (2.0%) was on zidovudine/lamivudine. The third drug was ATV in 33 patients (64.7%). Before the switch, the median number of therapeutic lines administered was 4 (range, 1–20) and the median nadir CD4+ cell count was 217 cells/mm^3 (range, 6–456 cells/mm^3). The median peak HIV-1-RNA was 100,000 copies/mL (range, 10,000–1,200,000 copies/mL). At Week 12, HIV-1 RNA was <50 copies/mL in all patients [13]. Patients with K103N and E138A mutations were also evaluated at Week 24: HIV-RNA was <50 copies/mL in all three patients.

At baseline, the median CD4+ cell count was 698.5 cells/mm^3 (range, 187–1764 cells/mm^3) and it remained stable after 12 weeks (median, 708.5 cells/mm^3; range, 202–1696 cells/mm^3). Median plasma triglycerides were 124 mg/dL (range, 39–625 mg/dL) at baseline compared with 108.7 mg/dL (range, 39–561 mg/dL) at the end of the study (linear mixed model, $P = 0.25$). Mean ± S.D. plasma cholesterol was 172.8 ± 38.1 mg/dL at baseline and decreased significantly to 161.9 ± 38.6 mg/dL (linear mixed model, $P = 0.038$) at Week 12 (Fig. 1). The change was not significantly different ($P = 0.73$) comparing ATV and FAPV. Similarly, mean creatinine at baseline was 0.84 mg/dL and increased significantly (linear mixed model, $P = 0.026$) to 0.90 mg/dL after 12 weeks of RPV-based STR regimen without significant differences between ATV and FAPV ($P = 0.21$).

The Modification of Diet in Renal Disease (MDRD) study equation [14] estimated glomerular filtration rate decreased from 94.8 ± 20.8 mL/min/1.73 m^2 at baseline to 86.2 ± 16 mL/min/1.73 m^2 at Week 12 ($P = 0.004$). The MDRD change was not statistically significant ($P = 0.98$) comparing patients with or without TDF as previous treatment. Median total plasma bilirubin changed significantly from 1.07 mg/dL (range, 0.2–4.7 mg/dL) at baseline to 0.6 mg/dL (range, 0.13–3.1 mg/dL; $P < 0.001$, linear mixed model) at the end of the study (Fig. 1). The difference was remarkable (linear mixed model, P for interaction = 0.011) comparing ATV or FAPV: in fact, a consistent decrease was observed in patients previously on an ATV-based regimen, but not in patients on an FAPV-based regimen. The difference in plasma bilirubin at Week 12 was mainly caused by a significant difference ($P = 0.006$) between baseline plasma bilirubin levels. A slight increase of glycaemia was detected but it was not statistically significant. No other metabolic side effects were detected. Male patients showed a significantly smaller decrease in bilirubin value ($P = 0.016$; median, –0.1 mg/dL, $r = –2.5–0.7$) compared with females (median, –0.5 mg/dL, $r = –4.3–0.3$). No rash or other adverse reactions due to RPV/FTC/TDF administration were