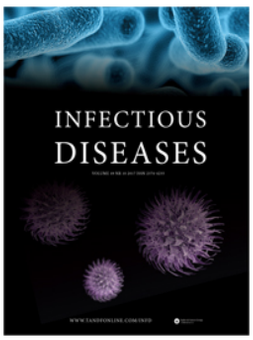

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ORIGINAL ARTICLE

Substitution of nevirapine or raltegravir for protease inhibitor vs. rosuvastatin treatment for the management of dyslipidaemia in HIV-infected patients on stable antiretroviral therapy (Nevrast study)

Leonardo Calza[a], Eleonora Magistrelli[a], Vincenzo Colangeli[a], Marco Borderi[a], Linda Bussini[a], Isabella Bon[b], Maria Carla Re[b] and Pierluigi Viale[a]

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ABSTRACT

Objectives: An observational, prospective, cohort study was performed to compare efficacy and safety of a switch from ritonavir-boosted protease inhibitor (PI/r) to nevirapine or raltegravir with that of rosuvastatin addition to current antiretroviral therapy in HIV-infected patients with hyperlipidaemia.

Methods: All HIV-infected patients receiving a stable PI/r-based antiretroviral regimen, with persistently suppressed viremia, naïve to non-nucleoside analogues and to integrase strand transfer inhibitors, with mixed hyperlipidaemia, and who underwent a switch from PI/r to nevirapine (Group A) or raltegravir (Group B) or who started rosuvastatin at 10 mg daily (group C) with unchanged antiretroviral regimen were enrolled into the study.

Results: Overall, 136 patients were enrolled: 43 patients were included in the group A, 46 in the group B, and 47 in the group C. The mean age was 46.6 years, and 108 (79.4%) were males. After 48 weeks of follow-up, a significantly greater reduction in the mean low-density lipoprotein (LDL) cholesterol level was reported in group C (-28.2%) than in group A (−10.2%; $p < .001$) and B (−12.4%; $p = .021$), while a significantly greater reduction in the mean concentration of triglycerides was observed in group A (−31.2%) and B (−35.5%) than in group C (−11.9%; $p = .034$ and $p = .004$, respectively). The incidence of adverse events was <10% and comparable across the three groups.

Conclusion: In HIV-positive subjects receiving a PI/r, the initiation of rosuvastatin treatment after 48 weeks yielded a greater decline in LDL cholesterol, while the switch from PI/r to nevirapine or raltegravir led to a greater decline in triglycerides.

KEYWORDS
Hyperlipidaemia
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Introduction

The introduction of the combination antiretroviral therapy (cART) in clinical practice has greatly reduced morbidity and mortality of the human immune deficiency virus (HIV) infection, with a significant increase in life expectancy of the HIV-infected patients [1–3]. Consequently, these patients are exposed to a greater risk of chronic non-infectious comorbidities, such as a higher cardiovascular disease risk, which represents today the second or third most frequent cause of death in this population [4–6].

The increased risk of cardiovascular disease among HIV-infected subjects descends from several factors, including HIV infection itself, chronic inflammation and immune activation, effect of some antiretroviral agents, and traditional risk factors, such as smoking, hypertension and hyperlipidaemia, which are more frequent in these patients than in the general population. Particularly, hyperlipidaemia is a common complication of the cART including a ritonavir-boosted protease inhibitor (PI/r), and it mostly includes increased levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol, in association with decreased level of high-density lipoprotein (HDL) cholesterol [7–9].

Although dyslipidaemia has been observed in subjects treated with all the boosted protease inhibitors (PIs), its prevalence appeared to be more elevated with tipranavir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir, and fosamprenavir/ritonavir. Among the newer PIs, tipranavir has been associated with a remarkable increase in the triglyceride level, while darunavir and, mostly, atazanavir seem to have a more favourable impact on the lipid profile [10–13].

An effective management of the PI/r-associated hyperlipidaemia is complex but crucial to reduce the cardiovascular disease risk in HIV-positive people. The most appropriate intervention on the lipid metabolism alterations includes four sequential steps: diet change, physical activity, modification of current cART, and lipid-lowering therapy. The switch from a PI/r to another antiretroviral drug with a less deep impact on the lipid parameters is usually an effective strategy to change cART in dyslipidemic patients, but loss of virological efficacy and occurrence of new adverse events are potential risks. Statins are effective in reducing total and LDL cholesterol levels and preventing cardiovascular events, but their use entails an increased pill burden and a potential risk of drug–drug interactions with antiretroviral agents [14,15].

The aim of our observational study was to compare efficacy and safety of substituting nevirapine or raltegravir for a PI/r with those of adding a lipid-lowering treatment with rosuvastatin to the current cART in HIV-infected patients with mixed hyperlipidaemia and stable virological suppression.

Methods

A prospective cohort analysis of HIV-1-infected adult patients followed at our Clinic of Infectious Diseases between 2012 and 2014, receiving a stable PI/r-based cART, affected by mixed hyperlipidemia and who underwent a switch from PI/r to nevirapine or raltegravir or who started a rosuvastatin treatment was performed.

Inclusion criteria were as follows: adult HIV-1-infected patients receiving cART for at least 24 months, unchanged cART during the last 12 months, current cART including two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus one PI/r, plasma HIV RNA $<$20 copies/mL for at least 6 months, mixed hyperlipidaemia, and switching from PI/r to nevirapine (200 mg twice daily) or raltegravir (400 mg twice daily) or beginning a lipid-lowering therapy with rosuvastatin (10 mg daily) from 1 January 2012 through 31 December 2014.

Mixed hyperlipidaemia was defined by the association of hypertriglyceridemia (plasma fasting triglyceride levels $>$200 mg/dL) with hypercholesterolemia (plasma fasting total cholesterol levels $>$200 mg/dL).

Exclusion criteria were prior treatment with any non-nucleoside reverse transcriptase inhibitor (NNRTI), prior treatment with any integrase strand transfer inhibitor (INSTIs), concomitant drug or alcohol abuse, history of genetic hyperlipidaemia, dysthyroidism, Cushing's syndrome, acute hepatitis, chronic hepatitis with serum alanine amino-transferase (ALT) $>$ 200 U/L, liver cirrhosis, acute or chronic renal disease with serum creatinine $>$1.5 mg/dL, myopathy, serum creatine kinase (CK) $>$ 200 U/L, pregnancy, lactation, concurrent treatment with lipid-lowering agents, corticosteroids, androgens, oestrogens, thiazide diuretics, beta-blockers, thyroid preparations or anticoagulants. Written informed consent was obtained from all eligible patients and the study was approved by the Ethic Committee of the S.Orsola-Malpighi Hospital.

All the enrolled subjects switching from PI/r to nevirapine were included in the group A, those switching from PI/r to raltegravir in the group B, and those starting rosuvastatin with their unchanged antiretroviral regimen in the group C. All of these enrolled patients were

prospectively followed-up at 12-week intervals for at least 48 weeks, in order to assess both efficacy and tolerability of substitution therapy and lipid-lowering treatment, according to some epidemiological, clinical, and laboratory features of HIV infection.

Eventual clinical adverse events and adherence to drug therapies were carefully checked on monthly outpatient visits, while plasma fasting triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, haematology, complete liver and kidney function tests, serum creatine-phosphokinase (CPK), aldolase, amylase, lipase, CD4 lymphocyte count, plasma HIV viral load and urinalysis, were performed at day 0 and subsequently at weeks 12, 24, 36 and 48. The HIV RNA viral load was detected using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (Roche Diagnostics, GmbH, Mannheim, Germany), in accordance with the manufacturer's instructions, and it was expressed as the number of copies per millilitre of plasma with the lowest detection limit of 20 copies/mL.

The cardiovascular risk was calculated as 10-year risk of heart disease or stroke using the atherosclerotic cardiovascular disease (ASCVD) algorithm published in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Assessment of Cardiovascular Risk [16], and available at http://www.cvriskcalculator.com.

The primary study endpoint was change in the total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels between baseline and week 48 in the three evaluated arms. The secondary endpoints included variations in cardiovascular risk, HIV viral load, and CD4 cell count, in association with the evaluation of clinical and laboratory adverse events. Moreover, we have compared efficacy in lowering plasma lipid levels of the two 'switch' Groups (A, B) vs. the 'rosuvastatin' Group (C).

Mantel-Haenszel chi-square test and Fisher's exact test were used for comparisons of proportions. Student's *t*-test was used for comparisons of quantitative variables, with significance levels placed at $p < .05$. All analyses were performed using an intent-to-treat approach, and between-group comparisons were performed with the Wilcoxon ranksum test. The aim of the study was to evaluate changes in serum concentrations of LDL cholesterol level and whether the switch strategy or the statin treatment could lead to a $\geq$10% decrease in the median concentration of the LDL cholesterol between baseline and week 48. Assuming a standard deviation of 20%, a power of 80%, a type I error of 0.05, and a 2-tailed Wilcoxon paired test, 40 patients in each group needed to be enrolled in the study.

Results

Overall, 136 patients were enrolled into the study: 43 subjects switching to nevirapine (Group A), 46 switching to raltegravir (Group B), and 47 starting the rosuvastatin treatment (Group C). A hypolipidaemic diet and regular physical exercise were persistently recommended in all considered groups. The diet recommendations include obtaining 25 to 35% of daily calories from fats, and restricting saturated fats to less than 7% of total calories and cholesterol to less than 200 mg per day.

Epidemiological, clinical and laboratory features of these patients are summarized in Table 1. The mean age ± standard deviation (SD) was 46.6 ± 8.8 years, 108 (79.4%) were men, 131 (96.3%) were Caucasian, 94 were smokers (69.1%), 35 (25.7%) had arterial hypertension, 25 (18.4%) had a chronic hepatitis B or C, and the mean cardiovascular risk ± SD was 8.5 ± 3.3%. The baseline characteristics of the enrolled patients were similar across the three groups, and there were no statistically significant differences for all the evaluated parameters (*p* not significant for all comparisons across the three groups).

Ongoing PI/r therapy included darunavir/ritonavir (800/100 mg daily), atazanavir/ritonavir (300/100 mg daily), or lopinavir/ritonavir, while ongoing NRTI therapy included tenofovir/emtricitabine (245/200 mg daily) or abacavir/lamivudine (600/300 mg daily) (Table 1). Treatment duration ranged from 31 to 59 months, with a mean length ± SD of 48 ± 18 months.

Changes in lipid values

Mean plasma triglyceride level ± SD was 276 ± 98 mg/dL, mean plasma total cholesterol concentration ± SD was 256 ± 87 mg/dL, mean plasma LDL cholesterol level ± SD was 163 ± 56 mg/dL, and mean plasma HDL cholesterol concentration ± SD was 43 ± 16 mg/dL. The percentages of patients with severe hypercholesterolemia (total cholesterol >300 mg/dL) or severe hypertriglyceridemia (triglycerides >500 mg/dL) were 14% and 5.9%, respectively.

The switch from PI/r to nevirapine or raltegravir led to a significant reduction in serum triglycerides both at week 24 and at week 48, while the rosuvastatin treatment did not produce a significant decrease in serum triglyceride level. After the first 24 weeks of follow-up, the mean change ± SD in plasma triglyceride level was

Table 1. Baseline epidemiological, clinical, and laboratory features of the 136 enrolled patients distributed among the three groups.

Groups	A	B	C
Type of treatment	Switch to nevirapine	Switch to raltegravir	Rosuvastatin
No. of patients	43	46	47
No. of males (%)	36 (83.7)	38 (82.6)	34 (72.3)
No. of Caucasian patients (%)	42 (97.7)	45 (97.8)	44 (93.6)
Mean age ± SD (years)	45.5 ± 9.1	47.6 ± 8.7	48.1 ± 8.9
Homo-bisexuals/heterosexuals/i.v. drug users	19/17/7	18/21/7	20/17/10
No. of smokers (%)	28 (65.1)	32 (69.6)	34 (72.3)
No. of patients with arterial hypertension (%)	10 (23.2)	12 (26.1)	13 (27.6)
No. of patients with diabetes mellitus (%)	3 (7)	2 (4.3)	2 (4.2)
Mean BMI ± SD (Kg/m^2)	24.6 ± 3.4	24.8 ± 3.5	24.5 ± 3.1
Mean cardiovascular risk[a] ± SD	8.4 ± 2.7	8.6 ± 3.1	8.3 ± 3.5
No. of patients with HCV coinfection (%)	6 (13.9)	6 (13)	8 (17)
No. of patients with HBV coinfection (%)	2 (4.6)	1 (2.2)	2 (4.2)
Mean CD4+ lymphocyte count ± SD (cells/μL)	562 ± 124	586 ± 149	607 ± 161
Mean duration of HIV infection ± SD (years)	5.6 ± 1.8	6.3 ± 2.1	5.9 ± 1.7
Mean total duration of antiretroviral therapy ± SD (years)	5.2 ± 1.6	5.9 ± 1.7	5.5 ± 1.4
Mean duration of current cART ± SD (months)	49 ± 16	47 ± 17	46 ± 18
Current PI/r at study entry (%)			
Darunavir/r (800/100 mg once daily)	17 (39.5)	14 (30.4)	18 (38.3)
Atazanavir/r (300/100 mg once daily)	14 (32.6)	15 (32.6)	18 (38.3)
Lopinavir/r (400/100 mg twice daily)	13 (30.2)	15 (32.6)	12 (25.5)
Current NRTIs at study entry (%)			
Tenofovir/emtricitabine (245/200 mg once daily)	28 (65.1)	25 (54.3)	29 (61.7)
Abacavir/lamivudine (600/300 mg once daily)	15 (34.9)	21 (45.7)	18 (38.3)
Mean plasma triglycerides ± SD (mg/dL)	269 ± 94	278 ± 104	283 ± 97
Mean plasma total cholesterol ± SD (mg/dL)	253 ± 76	248 ± 85	266 ± 89
Mean plasma LDL cholesterol ± SD (mg/dL)	164 ± 45	159 ± 54	167 ± 62
Mean HDL cholesterol ± SD (mg/dL)	42 ± 15	44 ± 18	45 ± 18
No. of patients with total cholesterol >300 mg/dL (%)	6 (13.9)	6 (13)	7 (14.9)
No. of patients with triglycerides >500 mg/dL (%)	2 (4.6)	3 (6.5)	3 (6.4)

SD: standard deviation; BMI: body mass index; HCV: hepatitis C virus; HBV: hepatitis B virus; cART: combination antiretroviral therapy; PI/r: ritonavir-boosted protease inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

[a]10-year risk of atherosclerotic cardiovascular disease. Available from: http://my.americanheart.org/cvriskcalculator.

−77 ± 19 mg/dL in Group A (−28.6 ± 13.5%; $p = .021$), −85 ± 24 mg/dL in Group B (−30.6 ± 14.7%; $p = .008$), and −28 ± 11 mg/dL in Group C (−9.9 ± 4.6%; $p = .059$). The mean change in triglycerides was significantly higher in the two 'switch' groups than in the 'rosuvastatin' group (A vs. C, $p = .023$; B vs. C, $p = .017$), while it was comparable between Groups A and B ($p = .377$).

These results were maintained after 12 months without relevant modifications (Figure 1). At week 48, the mean change ± SD in plasma triglyceride level was -84 ± 25 mg/dL in group A, −97 ± 29 mg/dL in group B, and −34 ± 18 mg/dL in group C. The mean percentage changes are reported in Table 2. The mean reduction in triglycerides was significantly higher in the two 'switch' groups than in the 'rosuvastatin' group (A vs. C, $p = .034$; B vs. C, $p = .004$), while it was comparable between groups A and B ($p = .502$). At the same time, the percentage of patients who reached at week 48 a normal value of serum triglycerides (or rather <200 mg/dL) was significantly higher in groups A and B than in group C, without significant difference between the 'switch' groups (Table 2; A vs. C, $p = .004$; B vs. C, $p = .015$; A vs. B, $p = .089$).

The beginning of rosuvastatin led to a significant reduction in serum total and LDL cholesterol both at week 24 and at week 48, while the switch from PI/r to nevirapine or raltegravir did not produce a significant decrease in serum total and LDL cholesterol levels.

After the first 24 weeks of follow-up, the mean change ± SD in serum total cholesterol level was −20 ± 12 mg/dL in Group A (−7.9 ± 4.2%; $p = .411$), −27 ± 15 mg/dL in Group B (−10.9 ± 5.7%; $p = .344$), and −64 ± 29 mg/dL in Group C (−24.1 ± 9.2%; $p = .005$). The mean decrease in total cholesterol was significantly higher in the 'rosuvastatin' group than in the two 'switch' groups (C vs. A, $p = .002$; C vs. B, $p = .021$), while it was comparable between groups A and B ($p = .088$).

These results were maintained after 12 months without relevant modifications. At week 48, the mean change ± SD in total cholesterol level was −24 ± 15 mg/dL in Group A, −26 ± 19 mg/dL in Group B, and −65 ± 24 mg/dL in Group C. The mean percentage changes are reported in Table 2. The mean change in total cholesterol was significantly higher in the 'rosuvastatin' group than in the two 'switch' groups (C vs. A, $p = .037$; C vs. B, $p = .045$), while it was comparable

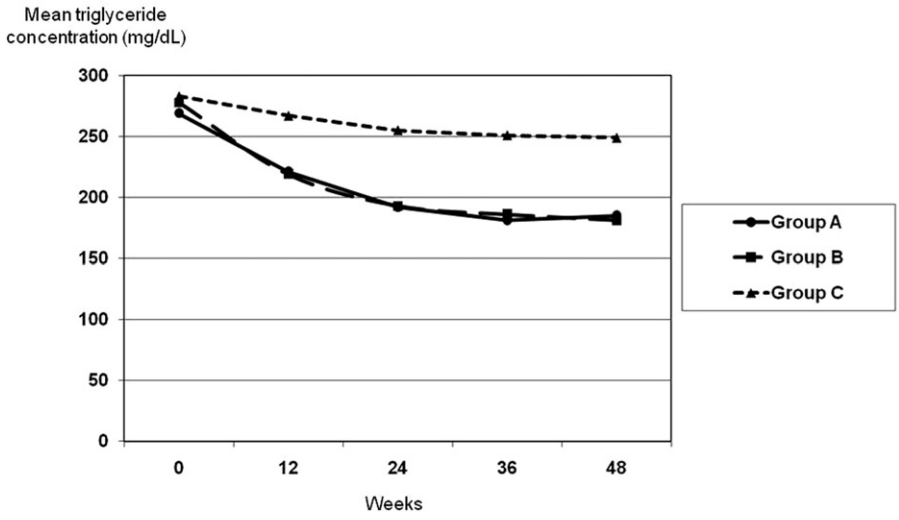

Figure 1. Trend of mean plasma triglyceride levels of the evaluable patients switched from ritonavir-boosted protease inhibitor to nevirapine (group A) or raltegravir (group B), or treated with rosuvastatin (group C) during the 48-week follow-up.

Table 2. Changes in plasma lipid levels vs. respective baseline values at the end of the 48-week follow-up.

Groups	A		B		C	
Type of treatment	Switch to nevirapine		Switch to raltegravir		Rosuvastatin	
No. of patients	43	*p*	46	*p*	47	*p*
Total cholesterol	−9.4 ± 4.6%	.308	−10.6 ± 5.9%	.075	−24.6 ± 10.8%	.012
LDL cholesterol	−10.2 ± 4.5%	.098	−12.4 ± 5.6%	.119	−28.2 ± 10.3%	.008
HDL cholesterol levels	+5.1 ± 2.3%	.781	+1.8 ± 0.4%	.822	+2.2 ± 0.7%	.576
Triglyceride levels	−31.2 ± 14.5%	.002	−35.5 ± 17.4%	.011	−11.9 ± 6.8%	.066
N. of patients who reached normal triglyceride levels[a] (%)	27 (62.8)	n.a.	30 (65.2)	n.a.	15 (31.9)	n.a.
N. of patients who reached normal total cholesterol level[b] (%)	11 (25.6)	n.a.	14 (30.4)	n.a.	31 (65.9)	n.a.

All values are reported as mean percentage changes ± standard deviation.
All the *p* values refer to comparison between baseline value and value at week 48 in each group.
LDL: low-density lipoprotein; HDL: high-density lipoprotein; n.a.: not applicable.
[a]Normal triglyceride level: triglycerides <200 mg/dL.
[b]Normal total cholesterol level: total cholesterol <200 mg/dL.

between groups A and B ($p = .289$). At the same time, the percentage of patients who reached at week 48 a normal value of total cholesterol (or rather <200 mg/dL) was significantly higher in group C than in groups A and B, without significant difference between the 'switch' groups (Table 2; C vs. A, $p < .001$; C vs. B, $p < .001$; A vs. B, $p = .549$).

After the first 24 weeks of follow-up, the mean change ± SD in serum LDL cholesterol level was −16 ± 9 mg/dL in Group A (−9.6 ± 4.2%; $p = .623$), −18 ± 11 mg/dL in Group B (−11.3 ± 5.9%; $p = .279$), and −45 ± 21 mg/dL in Group C (−26.9 ± 10.1%; $p = .009$). The mean decrease in LDL cholesterol was significantly higher in the 'rosuvastatin' group than in the two 'switch' groups (C vs. A, $p = .011$; C vs. B, $p = .018$), while it was comparable between groups A and B ($p = .306$).

These results were maintained after 12 months without relevant modifications (Figure 2). At week 48, the mean change ± SD in LDL cholesterol level was −17 ± 10 mg/dL in Group A, −20 ± 12 mg/dL in Group B, and −47 ± 26 mg/dL in Group C. The mean percentage changes are reported in Table 2. The mean change in LDL cholesterol was significantly higher in the 'rosuvastatin' group than in the two 'switch' groups (C vs. A, $p < .001$; C vs. B, $p = .021$), while it was comparable between groups A and B ($p = .506$).

No significant changes in the mean HDL cholesterol level were reported in each group between baseline and weeks 24 and 48, and variations in HDL cholesterol were comparable across the three groups (Table 2).

During the study, blood pressures remained similar to baseline values, and no patients changed their smoking status in all the groups. The rosuvastatin treatment led to a significantly reduction in the mean 10-year cardiovascular risk, while the switch to nevirapine or raltegravir did not lead to a significant risk change. At week 48, the mean change ± SD in the cardiovascular risk was −1.6 ± 0.7% in Group A ($p = .623$), −1.8 ± 0.9% in Group B ($p = .556$), and −3.8 ± 1.7% in Group C ($p = .034$). The mean decrease in cardiovascular risk was significantly higher in the 'rosuvastatin' group than in the two 'switch' groups (C vs. A, $p = .004$; C vs. B, $p = .021$), while it was comparable between groups A and B ($p = .709$).

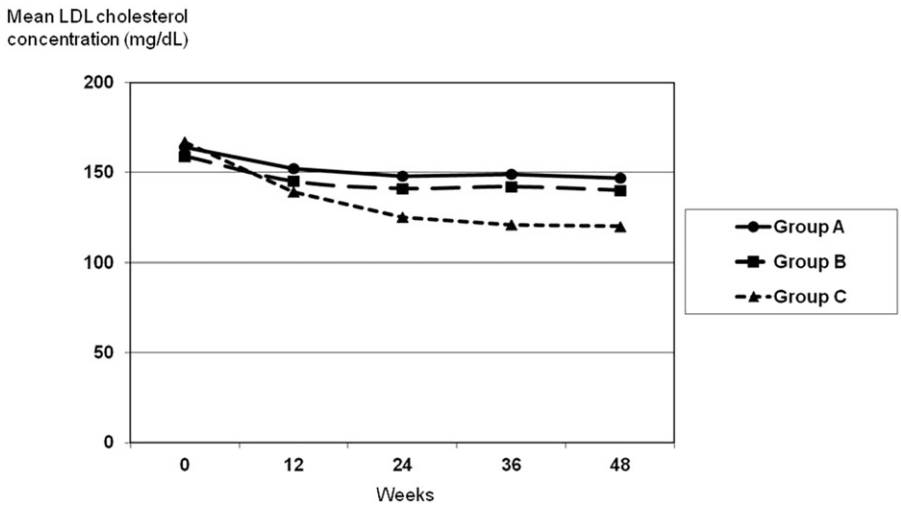

Figure 2. Trend of mean plasma low-density lipoprotein (LDL) cholesterol levels of the evaluable patients switched from ritonavir-boosted protease inhibitor to nevirapine (group A) or raltegravir (group B), or treated with rosuvastatin (group C) during the 48-week follow-up.

Table 3. Treatment discontinuations and treatment-related clinical and laboratory adverse events reported during the 48-week follow-up.

Groups	A	B	C
Type of treatment	Switch to nevirapine	Switch to raltegravir	Rosuvastatin
No. of patients	43	46	47
Treatment discontinuations owing to adverse events [*n* (%)]	6 (13.9)	2 (4.3)	3 (6.4)
Serious adverse events [*n* (%)]	1 (2.3)	0	0
Clinical adverse events [*n* (%)]			
Nausea, loss of appetite	5 (11.6)	3 (6.5)	2 (4.2)
Diarrhoea	4 (9.3)	3 (6.5)	5 (10.6)
Headache	3 (7)	2 (4.3)	4 (8.5)
Fatigue	3 (7)	4 (8.7)	4 (8.5)
Skin rash	4 (9.3)	0	0
Myalgia	0	2 (4.3)	5 (10.6)
Laboratory adverse events [*n* (%)]			
Increased ALT level (>100 U/L)	5 (11.6)	0	0
Increased CK (>300 U/L)	0	3 (6.5)	4 (8.5)

ALT: alanine amino-transferase; CK: creatine kinase.

Tolerability, treatment discontinuations and changes in immune-virological parameters

After 48 weeks, the incidence of treatment discontinuation was similar across the three groups. Overall, 16 discontinuations (11.8%) were observed: 7 discontinuations in Group A, 4 in Group B, and 5 in Group C. So, the overall incidence of drop-out using the intent-to-treat analysis was higher in Group A (16.3%) than in Group B and C (8.9% and 10.6%, respectively), but this difference was not statistically significant (A vs. B, $p = .068$; A vs. C, $p = .102$; B vs. C, $p = .381$).

Treatment discontinuations due to adverse events are summarized in Table 3 and were more frequent in group A than in group B and C, but this difference did not reach a statistical significance (A vs. B, $p = .059$; A vs. C, $p = .077$; B vs. C, $p = .288$).

Four discontinuations associated with adverse events in the Group A were due to a hypersensitivity reaction to nevirapine with a maculo-papular skin rash. The skin rash was not accompanied by fever or other symptoms, did not require hospitalization, and totally disappeared within 7 days after the discontinuation of the nevirapine-based regimen. Other two discontinuations in this group were due to a significant increase in the serum transaminases (ranging from 100 to 500 U/L). Two discontinuations in group B were caused by the occurrence of myalgia with increased CK level (ranging from 300 to 700 U/L), while three discontinuations in group C were due to persistent diarrhea (2 cases) or increased CK level (one case, ranging from 300 to 600 U/L).

Overall, both the 'switch' groups and the 'rosuvastatin' group showed a favourable tolerability profile, and in all the evaluated arms there were no significant differences in the onset of serious and non-serious adverse events, as reported spontaneously by the patients and observed by physical examination and laboratory tests.

Mild gastroenteric signs and symptoms (nausea, loss of appetite and diarrhoea), headache and fatigue were the most frequent adverse effects, they were found with similar incidence in the three evaluated groups, and did not require any therapy modification or suspension (Table 3).

Treatment discontinuations due to virological failure were 5 (3.7%): one in Group A (2.3%), 2 in Group B (4.3%), and 2 in Group C (4.2%), without significant differences across the three groups. In all cases the patient's adherence to cART was lower than 95% but genotypic analysis at the time of virological failure demonstrated no resistance mutations. Overall, virological success at week 48 in the intent-to-treat analysis was 83.7% in Group A, 91.3% in Group B, and 89.4% in Group C, without significant differences across the three groups (A vs. B, $p = .068$; A vs. C, $p = .102$; B vs. C, $p = .381$).

The mean changes in the CD4 + T lymphocyte count ± SD from baseline to week 48 were also similar across the three groups, without statistically significant differences (Group A: +49 ± 19 cells/mm^3; Group B: +58 ± 26 cells/mm^3; Group C: +41 ± 15 cells/mm^3) (A vs. B, $p = .744$; A vs. C, $p = .498$; B vs. C, $p = .317$).

Discussion

A change in current cART by switching from a PI/r to a different antiretroviral drug with a more favourable impact on the lipid parameters should be considered when diet and lifestyle changes are insufficient to correct the hyperlipidaemia. However, the necessary requisite of any new antiretroviral regimen is to maintain a full virological efficacy, so a change in current cART must be ruled out if there is a risk of virological failure.

The antiretroviral classes associated with the less deep effect on the lipid parameters include NNRTIs and INSTIs. The substitution of the PI/r with some non-nucleoside analogues (such as nevirapine, etravirine and rilpivirine) [17–20] or some integrase inhibitors (such as raltegravir and elvitegravir/cobicistat) [21,22] is usually associated with an improvement in cholesterol and triglyceride levels, maintenance of viral suppression, and good tolerability profile.

Among the NNRTIs, the 'lipid-friendly' effects of the nevirapine are well known for a long time. In some early clinical trials, the nevirapine-based cART was associated with a significant increase in serum levels of HDL cholesterol, apolipoprotein A1, and lipoprotein A1, with a significant reduction in the total cholesterol/HDL cholesterol ratio. Moreover, the nevirapine-based regimens led to a significantly smaller elevation in total cholesterol, LDL cholesterol and triglycerides in comparison with those including efavirenz or a PI/r. Overall, the nevirapine use resulted in changes in plasma lipids and lipoproteins associated with a lower cardiovascular risk profile in the general population [23–26]. Patients treated with nevirapine also showed higher concentrations of adiponectin (an anti-inflammatory protein) and lower concentrations of soluble CD14 (an inflammatory marker) compared to those receiving efavirenz, indicating a lower inflammatory profile associated with nevirapine treatment [27].

The INSTI raltegravir has shown a better lipid profile in comparison with protease inhibitors in several switch studies. The SWITCHMRK-1 and -2 studies are two randomized, double-blind, multicentre trials including 702 adult patients with undetectable HIV RNA for at least 3 months while on a lopinavir/ritonavir-based regimen and who were randomized to switch from lopinavir/ritonavir to raltegravir or to maintain the PI/r. After 24 weeks, a significant decrease in total cholesterol, non-HDL cholesterol, and triglycerides was observed in the raltegravir group in comparison with the lopinavir/ritonavir-group, even if the virological efficacy was lower in raltegravir-treated subjects than in those receiving the PI/r [28].

In the SPIRAL multicentre, open-label, randomized trial, 273 adult patients with undetectable plasma viral load for at least 6 months on PI/based cART were randomized to switch from PI/r to raltegravir or to continue on current PI/r-based regimen. After 48 weeks, switching to raltegravir led to a significant reduction in plasma lipids and total-to-HDL cholesterol ratio in comparison with maintaining current PI/r. Moreover, in this study the substitution of raltegravir for PI/r showed a noninferior virological efficacy in comparison with the unchanged PI/r based regimen [29].

The RASTA randomized pilot study evaluated safety and efficacy of a treatment switch to raltegravir plus tenofovir/emtricitabine or abacavir/lamivudine in 40 patients with persistently suppressed HIV RNA and treated with stable PI-, NNRTI-, or nucleoside reverse transcriptase inhibitor (NRTI)-based cART. After 48 weeks, a significant decrease in total cholesterol, non-HDL cholesterol, and triglycerides was reported, in association with a significant CD4 + cell count increase and a rare virological failure [30].

In addition to its favourable impact on the lipid parameters, raltegravir has demonstrated a favourable

effect on the inflammation and immune-activation markers in some clinical studies. The substitution of raltegravir for PI/r or NNRTI was associated with a significant decline in plasma levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and soluble CD14 (sCD14), which are markers of systemic inflammation and monocyte activation, and were found to be associated with increased mortality in HIV-positive people [31,32].

The efficacy and safety of a switch from PI/r to elvitegravir/cobicistat, another boosted INSTI, was assessed in the STRATEGY-PI randomized, open-label trial. In this study, 433 adult patients with HIV RNA <50 copies/mL for at least 6 months and treated with tenofovir/emtricitabine plus a PI/r were randomised either to switch to coformulated tenofovir/emtricitabine/elvitegravir/cobicistat or to continue the current cART. Switching to the elvitegravir/cobicistat-based treatment was associated with a significant decrease in triglycerides in comparison with the PI/r-based treatment, and the simplified regimen showed also a significant superiority in the virological efficacy caused by a higher proportion of subjects discontinuing treatment for adverse events in the PI/r-treated group [33].

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, represent the first-line therapy for hypercholesterolemia, but their use is problematic in HIV-infected persons receiving cART because of potential drug-drug interactions with some antiretroviral agents, the risk of adverse events and the reduced compliance to multiple pharmacologic treatment [14].

A recent systematic review evaluated 18 clinical trials concerning the use of statins in 736 HIV-infected patients receiving cART and showed that rosuvastatin 10 mg daily and atorvastatin 10 mg daily provided the largest reduction in total cholesterol concentration, in association with low rates of adverse events [34].

Moreover, statins also show pleiotropic effects which are not dependent on lowering cholesterol concentration, and have been associated with anti-inflammatory and immunological properties. In the HIV-positive people, these drugs have been shown to decrease serum levels of several inflammatory biomarkers, and to slow the progression of atherosclerosis, even though data about their anti-inflammatory and immunological effects are still limited [35–38].

Although the replacement of PI/r and the statin treatment are the leading interventions to lower total cholesterol, non-HDL cholesterol and other lipid values, only two randomized studies to date have compared these strategies in HIV-infected patients on cART and with dyslipidaemia [39,40].

In a randomized, open-label trial, we have evaluated the efficacy of a switch from PI/r to nevirapine or efavirenz in comparison with a lipid-lowering treatment with pravastatin or bezafibrate in 130 HIV-infected subjects with mixed hyperlipidaemia. The enrolled patients were subjects receiving their first cART (including two NRTIs plus one PI/r), with HIV RNA <50 copies/mL for at least 6 months, and with total cholesterol >250 mg/dL and triglycerides >200 mg/dL. These patients were randomized to switch from current PI/r to nevirapine or efavirenz or to start a treatment with pravastatin (20 mg daily) or bezafibrate (400 mg daily) with the unchanged cART. After 12 months, a significantly greater reduction in triglycerides and total cholesterol was reported in patients treated with pravastatin (−41.2% and −45.8%, respectively) and bezafibrate (−46.6% and −37.6%, respectively) than in those switched to nevirapine (−25.2% and −27.1%, respectively) or to efavirenz (−9.4% and −10.2%, respectively). So, drug therapy with pravastatin or bezafibrate proved significantly more effective in the management of mixed dyslipidemia than the switching therapy, but the switch from PI/r to nevirapine proved more effective than that to efavirenz. The tolerability profile was similar across the four study groups [39].

In a recent randomized, open-label trial, 43 adult HIV-infected subjects on stable PI/r-based cART with HIV RNA <50 copies/mL for at least 6 months, hypercholesterolemia (total cholesterol >5.5. mmol/L), and elevated cardiovascular risk score were randomized to switch from PI/r to another drug or to start rosuvastatin (10 mg daily). The commonest PI/substitutes were raltegravir (45% of cases) and rilpivirine (20%). After 12 weeks, a significantly greater decline in total and LDL cholesterol was reported in patients treated with rosuvastatin (−21.4% and −29.9%, respectively) than in those who had replaced the PI/r (−8.7% and −1%, respectively). However, the reduction in triglycerides was significantly higher in the switching patients (−34.1%) than in those treated with rosuvastatin (-9.8%). Moreover, a higher incidence of adverse events (mostly nausea and diarrhoea) was observed in association with the PI/r switch than with the rosuvastatin treatment [40].

In the present study, both the switch from PI/r to nevirapine or raltegravir and the beginning of a rosuvastatin treatment with unchanged antiretroviral regimen were effective in reducing lipid values in patients on

stable PI/r-based cART and with mixed hyperlipidaemia. However, the statin therapy proved more effective in decreasing total and LDL cholesterol concentrations, in association with the 10-year cardiovascular disease risk, while the switching strategy was more effective in reducing triglycerides. The effects of nevirapine and raltegravir on the lipid parameters were comparable, and the incidence of adverse events was low and similar across the three study groups. Our study has provided to the current evidence a further demonstration that the statin treatment has a higher efficacy in reducing cholesterol levels compared to switching strategies, while the switch from PIs to NNRTIs or integrase inhibitors shows a higher efficacy in reducing triglyceride levels than the statin therapy. So the conclusions of the present study are unanimous with those of previously published studies [39,40] and lead to a useful suggestion for the clinical practice, or rather that statins are the most effective intervention to treat the hypercholesterolemia after diet and lifestyle changes.

Obviously, several limitations are present in our study, so the results must be interpreted with caution. First, the lack of a randomization and the observational design, with some confounding factors which could potentially influence the choice of treatment, even though the baseline characteristics of patients were comparable across all treatment groups. Moreover, the limited sample size, the short duration of the observation period, and the data extraction from the medical records which can be occasionally incomplete or inaccurate. Despite the same recommendations about diet and exercise were given to all enrolled subjects, it is possible that some patients may have adhered to these recommendations less stringently. We have examined only two antiretroviral regimens and only one statin, then we cannot state if other antiretroviral regimens and other statins may produce similar or greater effects. Particularly, the impact of newer integrase inhibitors (such as elvitegravir and dolutegravir) on the lipid metabolism in comparison with raltegravir was not evaluated. Finally, the rosuvastatin treatment and the PI/r switch to nevirapine or raltegravir could be employed simultaneously with a superior efficacy, but this strategy was not evaluated in our study.

In conclusion, in adults receiving a PI/r-based cART, switching from PI/r to nevirapine or raltegravir or starting rosuvastatin with unchanged cART are two effective approaches to improve mixed hyperlipidaemia, even though the switch proved more effective in reducing triglycerides while the statin treatment proved more effective in decreasing total and LDL cholesterol. Further, enlarged, randomized trials are certainly needed in order to define the best clinical intervention in treated patients with dyslipidaemia.

Disclosure statement

No potential conflict of interest was reported by the authors.

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