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ORIGINAL ARTICLE

Efficacy and Safety of Atazanavir-Ritonavir Plus Abacavir-Lamivudine or Tenofovir-Emtricitabine in Patients with Hyperlipidaemia Switched from a Stable Protease Inhibitor-Based Regimen Including One Thymidine Analogue

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Abstract

Randomized, open-label, prospective clinical trial assessing efficacy and safety on hyperlipidemia of a switching from a regimen including one protease inhibitor and one thymidine analogue to atazanavir/ritonavir plus abacavir/lamivudine or tenofovir/emtricitabine. Adult HIV-infected patients on their first antiretroviral therapy (of at least 48-week duration), including one protease inhibitor and zidovudine or stavudine, with stable immunovirologic features, and having diagnosis of persisting hyperlipidemia, were randomized to replace current treatment with atazanavir/ritonavir plus abacavir/lamivudine (arm A) or tenofovir/emtricitabine (arm B), and were followed for 48 weeks. Eighty-nine patients were enrolled: 42 patients were randomized to arm A, and 47 to arm B. At the end of the 48-week follow-up, incidence of virologic failure was comparable in both arms, and associated with a poor drug compliance. Increase in CD4 lymphocyte count was significantly higher in arm A after a 24-week study period (62.5 versus 39.2×10^6 cells/L; $p < 0.05$), while immunologic responses were comparable at the end of 48-week follow-up (91.5 versus 83.6; $p > 0.05$). A statistically significant reduction (−15.4%) in mean triglyceridaemia versus respective baseline values was reported in both groups ($p < 0.05$), without statistically significant difference between arm A and B. Similar results were reported for total cholesterol and low-density lipoprotein (LDL) cholesterol levels. Safety and tolerability profiles were comparable in both groups. Switching from a protease inhibitor- and thymidine analogue-based antiretroviral regimen to atazanavir/ritonavir plus abacavir/lamivudine or tenofovir/emtricitabine proved effective in the management of hyperlipidemia, without significant differences in lipid-lowering effect, virologic efficacy, and safety profile between these regimens.

Introduction

Lipid metabolism abnormalities are frequently observed in HIV-infected patients receiving antiretroviral therapy, particularly in association with protease inhibitors (PIs) and thymidine nucleoside reverse transcriptase inhibitors (NRTIs).[1,2]

Because current antiretroviral regimens have led to a notable extension of life expectancy in HIV-positive patients, prolonged dyslipidemia could significantly act on the long-term prognosis and outcome of this population, so that an increasing concern is mounting, particularly about the higher risk of cardiovascular complications.[3–8] Increased plasma lipid levels are associated with higher low-density lipoprotein (LDL) cholesterol concentrations and atherogenic ratios, and recent studies have shown an increased risk of myocardial infarction and cerebrovascular events in patients treated with highly active antiretroviral therapy (HAART).[9–11]

Even though hypolipidemic diet and physical exercise may certainly improve dyslipidemia, substitution of PIs and thymidine analogues with other drugs associated with a better lipid profile, or lipid-lowering agents (such as statins or fibrates) can be considered when plasma lipid levels excessively increase or persist for long time.[12,13]

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Atazanavir is a potent PI with a pharmacokinetic profile that allows once-daily oral administration with or without ritonavir boosting. Atazanavir/ritonavir, administered at 300/100 mg daily, has shown long-term efficacy comparable to that of lopinavir/ritonavir in patients who have experienced multiple virologic failures,[14] but it seems associated with a more favorable plasma lipid profile.[15] Moreover, dyslipidemia linked to stavudine can be partly or completely reversed after the substitution by tenofovir in highly experienced patients and switch from stavudine to tenofovir seems virologically safe and associated with a lower predicted risk of cardiovascular events.[16] Abacavir represents also a virologically effective replacement for stavudine or PI and usually leads to a significant improvement in both cholesterol and triglycerides,[17] even though recent studies have demonstrated an increased risk of myocardial infarction in subjects recently exposed to abacavir or didanosine.[18]

The aim of our study was to compare efficacy and safety of replacing an antiretroviral treatment including one PI and one thymidine analogue (zidovudine or stavudine) with atazanavir/ritonavir plus abacavir/lamivudine or tenofovir/emtricitabine in HIV-infected patients with persisting hyperlipidemia and stable virologic suppression.

Patients and Methods

This was a 48-week, open-label, prospective, randomized, pilot trial in which adult HIV-infected patients with hyperlipidemia and receiving a stable PI-based antiretroviral regimen including one thymidine analogue were allocated to switch to atazanavir-ritonavir plus abacavir-lamivudine or tenofovir-emtricitabine. Prospective patients were required to be receiving their first antiretroviral treatment represented by a stable PI-containing regimen (of at least 48-week duration) with or without ritonavir and including zidovudine or stavudine, having plasma HIV RNA less than 50 copies per milliliter and CD4 lymphocyte count greater than 350 cells/mm^3 for longer than 24 weeks, and having diagnosis of hyperlipidemia for longer than 24 weeks. Hyperlipidemia was diagnosed when plasma fasting total cholesterol level was greater than 200 mg/dL, and/or plasma fasting triglyceride level was greater than 172 mg/dL. Diagnosis of lipodystrophy was indicated by physical examination and observation of peripheral fat wasting (involving face and/or buttocks and limbs), with or without abdominal, mammary, or dorsocervical ("buffalo hump") fat accumulation. The 10-year risk for myocardial infarction in all considered patients was estimate by the Framingham equation (available online at: http://hp2010.nhlbihin.net/atpiii/calculator.asp).

Patients previously treated with atazanavir, tenofovir, or abacavir, and those with a history of virologic failure while receiving PI-based HAART, or with genotype drug resistance testing showing a decreased susceptibility to atazanavir-ritonavir, abacavir-lamivudine, or tenofovir-emtricitabine were excluded from the study. Exclusion criteria included also recent diagnosis of opportunistic disease or other severe acute disease, cardiovascular disease (coronary artery disease, peripheral vascular disease or cerebrovascular disease), increased 10-year risk of coronary events ($\geq$10%), diabetes mellitus (fasting glucose concentration $\geq$126 mg/dL or current antidiabetic therapy), alcohol or drug abuse, hypothyroidism, Cushing's syndrome, acute or chronic myopathy, acute or chronic kidney diseases, acute hepatitis, liver cirrhosis, pregnancy, or undergoing treatment with corticosteroids, androgens, estrogens, growth hormone, thiazide diuretics, β-blockers, thyroid preparations, proton pump inhibitors, acid-reducing agents, or lipid-lowering drugs. All enrolled patients were randomized 1:1 to receive either atazanavir-ritonavir (300–100 mg once daily) plus abacavir-lamivudine (600–300 mg once daily, arm A) or atazanavir-ritonavir (300–100 mg once daily) plus tenofovir-emtricitabine (300–200 mg once daily, arm B) for 48 weeks. Eventual clinical adverse events and adherence to therapy were carefully checked on monthly outpatient visits, while plasma lipid levels (triglycerides, total cholesterol, LDL cholesterol and high-density lipoprotein [HDL] cholesterol), hematology, $CD4^+$ lymphocyte count, plasma HIV viral load, complete liver and kidney function tests, coagulation profile, serum creatine-phosphokinase, aldolase, and urinalysis were performed at day 0 and weeks 12, 24, 36, and 48. Plasma HIV viral load was evaluated using the bDNA Quantiplex HIV-RNA-3 assay (Chiron Corporation, Emeryville, CA), according to the manufacturer's instructions, with a lower limit of detection placed at 50 bDNA copies per milliliter.

Recruitment started in January 2006 and stopped in June 2007, and all patients provided written informed consent. Screening for HLA-B*5701 allele was not performed in patients randomized to the abacavir-based regimen because in the year 2006 it was not recommended by international and national guidelines.

The primary efficacy study end point was the proportion of randomized patients who experienced virologic rebound (i.e., the proportion of randomized patients with confirmed on-study HIV-RNA $\geq$50 copies per milliliter or last on-study HIV-RNA $\geq$50 copies per milliliter followed by study discontinuation) at or prior to week 48. The study was designed with 85% power to detect a difference between week 48 virologic rebounds of 75%. Secondary efficacy end points included mean change from baseline CD4 lymphocyte through week 48, such as mean changes in plasma levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglicerydes. Safety study end points included frequency and severity of adverse events, abnormal laboratory results, and adverse event-related discontinuations.

All efficacy analyses were made on an intent-to-treat basis, whereas metabolic comparisons were made in patients on-treatment at the end of the 48-week follow-up study period. Statistical assessment was carried out by Student's t test, Mantel-Haenszel χ^2 test, or Fisher exact test (where appropriate), with significance levels placed at $p < 0.05$.

Results

Between January 2006 and June 2007, 89 patients were enrolled for the study. Isolated hypercholesterolemia was diagnosed in 13 subjects (14.6%), isolated hypertriglyceridemia in 29 (32.6%), and mixed hyperlipidemia in 47 (52.8%). Enrolled subjects were randomized to atazanavir/ritonavir plus abacavir-lamivudine (42 patients, arm A) or tenofovir-emtricitabine (47 patients, arm B), and were followed for 48 weeks. A hypolipidemic diet and regular physical exercise were persistently and consistently recommended in all considered arms. The two compared patient groups did not show any significant difference according to age and gender dis-

tribution, type of exposure to HIV infection, HIV disease stage, mean CD4 cell count, type and mean duration of antiretroviral treatment, and mean baseline plasma triglyceride and cholesterol levels (total concentration and LDL-HDL components; Table 1).

Current thymidine analogue was zidovudine in 60 cases (67.4%) and stavudine in 29 (32.6%). Ongoing PI therapy included lopinavir/ritonavir in 55 cases (61.8%), fosamprenavir/ritonavir in 22 (24.7%), saquinavir/ritonavir in 9 (10.1%), and nelfinavir in 3 (3.3%). Treatment duration ranged from 12 to 39 months, with a mean length ± one standard deviation (SD) of 23.8 ± 11.7 months. Concomitant lipodystrophy was diagnosed in 14 cases (15.7%): in detail, concurrent lipoatrophy, fat accumulation, and mixed form were shown by 5 (35.7%), 4 (28.6%), and 5 (35.7%) of 14 lipodystrophic patients, respectively.

Mean plasma triglyceride level ± SD was 283 ± 89 mg/dL, and tested significantly higher in patients treated with lopinavir/ritonavir (322 ± 159 mg/dL) compared to other boosted and unboosted PIs (261 ± 112 mg/dL; $p < 0.005$). Mean plasma total cholesterol concentration ± SD was 265 ± 134 mg/dL; mean plasma LDL cholesterol concentration ± SD was 159 ± 45 mg/dL; mean plasma HDL cholesterol concentration ± SD was 55 ± 24 mg/dL. Cholesterol levels did not show any significant difference according to the administered PI-based regimen, as well as the lipodystrophy prevalence (data not shown).

At the close of the 48-week observation period, the virologic efficacy was similar in both arms, without statistically significant differences. In detail, virologic failure occurred in 3 of 89 patients (3.3%): 1 patient of 42 in arm A (2.4%) and 2 patients of 49 in arm B (4.2%; $p = 0.22$). Only 1 of these subjects harbored primary protease resistance mutations (L10I, I54V, D30N, V77I), while in the remaining 2 individuals resistance testing disclosed only relevant mutations at the reverse transcriptase gene (M41L, K65R, K70E, L74V, M184V). Poor drug compliance was registered in all these cases, and it was thought to be the most likely reason for virologic failure in this subset of patients.

After the first 24 weeks of study period, the mean increase in CD4 lymphocyte count was significantly greater in arm A (62.5×10^6 cells/L) than in arm B (39.2×10^6 cells/L; $p = 0.028$). However, at the end of 48-week follow-up the immunologic responses were comparable in both groups: mean increases in CD4 lymphocyte counts versus respective baseline values were 91.5×10^6 cells/L in arm A, and 83.6×10^6 cells/L in arm B ($p = 0.43$).

After the first 24 weeks of follow-up, the reduction of mean plasma triglyceride levels versus baseline respective values was 40 mg/dL (14%) in arm A, and 47 mg/dL (16.8%) in arm B. These results were maintained after 12 months without relevant modifications (Table 2). Reductions of mean triglyceride concentrations versus respective baseline values were statistically significant in both arms ($p = 0.031$ in arm A, $p = 0.027$ in arm B), while no statistically significant differences of therapeutic responses were observed between these groups ($p = 0.71$).

At the same time, the mean reduction of plasma total cholesterol levels versus baseline values after the first 6 months

Table 1. Demographic, Epidemiologic, and Laboratory Characteristics of the Eighty-Nine Enrolled Patients

Arms	*A (ATV/r ABC 3TC)*	*B (ATV/r TDF FTC)*
No. of patients	42	47
Males/females	30/12	32/15
Mean age ± SD (years)	36.3 ± 13.1	37.2 ± 13.9
MSM/heterosexuals/injection drug use	20/12/10	24/15/8
Mean duration of HIV infection ± SD (years)	4.1 ± 2.2	4.3 ± 2.5
Mean duration of antiretroviral therapy ± SD (months)	24.5 ± 11.6	22.7 ± 10.9
No. of patients with AIDS diagnosis	0	0
No. of patients with chronic HBV infection (%)	2 (4.8)	3 (6.4)
No. of patients with chronic HCV infection (%)	11 (26.2)	13 (27.7)
Mean CD4 lymphocyte count ± SD (cells/mm^3)	658 ± 272	611 ± 209
Mean duration of HIV RNA < 50 copies/mL ± SD (months)	19.2 ± 7.5	17.9 ± 6.2
No. of patients with isolated hypercholesterolemia (%)	6 (14.3)	7 (14.9)
No. of patients with isolated hypertriglyceridemia (%)	15 (35.7)	14 (29.8)
No. of patients with mixed hyperlipidemia (%)	21 (50)	26 (55.3)
Mean concentration of total cholesterol ± SD (mg/dL)	268 ± 45	278 ± 52
Mean concentration of LDL cholesterol ± SD (mg/dL)	155 ± 39	163 ± 47
Mean concentration of HDL cholesterol ± SD (mg/dL)	53 ± 21	57 ± 26
Mean concentration of triglycerides ± SD (mg/dL)	285 ± 92	279 ± 81
Mean concentration of glucose ± SD (mg/dL)	84 ± 38	79 ± 32
No. of patients with lipodystrophy syndrome (%)	6 (14.3)	8 (17)
No. of patients (%) taking:		
Zidovudine	29 (69.1)	31 (65.9)
Stavudine	13 (30.9)	16 (34.1)
Lopinavir/ritonavir	25 (59.5)	30 (63.8)
Fosamprenavir/ritonavir	9 (21.4)	13 (27.7)
Saquinavir/ritonavir	6 (14.3)	3 (6.4)
Nelfinavir	2 (4.7)	1 (2.1)

ATV/r, atazanavir/ritonavir; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine; SD, standard deviation; MSM, men who have sex with men; PI, protease inhibitors; HBV, hepatitis B virus (or positivity for HBs antigen); HCV, hepatitis C virus (or positivity for anti-HCV antibodies); LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Mean Changes (Absolute Values and Percentages) in Serum Lipid Levels at the End of Forty-Eight-week Follow-Up versus Respective Baselines Values

Arms	*A (ATV/r ABC 3TC)*	*B (ATV/r TDF FTC)*	p
Triglycerides, mg/dL (%)	−44 (−15.4)	−43 (−15.4)	n.s.
Total cholesterol, mg/dL (%)	−39 (−14.5)	−44 (−16)	n.s.
LDL cholesterol, mg/dL (%)	−25 (−16.1)	−29 (−17,8)	n.s.
HDL cholesterol, mg/dL (%)	−3 (−5.6)	−4 (−7)	n.s.

ATV/r, atazanavir/ritonavir; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine; LDL, low-density lipoprotein; HDL, high-density lipoprotein; n.s., not significant.

of treatment was 33 mg/dL (12.3%) in arm A, and 39 mg/dL (14%) in arm B. Similarly, at the end of the 1-year follow-up, reductions of mean total cholesterol concentrations versus respective baseline levels were statistically significant in both arms ($p = 0.042$ in arm A, $p = 0.038$ in arm B), while no statistically significant differences of therapeutic responses were observed between these groups ($p = 0.65$). Temporal changes in mean triglyceride and total cholesterol levels in both arms are shown in Figures 1 and 2.

With regard to LDL cholesterol, the mean reduction of plasma levels versus baseline values after the first 24 weeks of treatment was 22 mg/dL (14.2%) in arm A and 24 mg/dL (14.7%) in arm B. At the end of the 48-week follow-up, decreases in mean LDL cholesterol concentrations versus respective baseline levels were statistically significant in both arms ($p = 0.041$ in arm A, $p = 0.033$ in arm B), while no statistically significant differences of therapeutic responses were observed between these groups ($p = 0.82$).

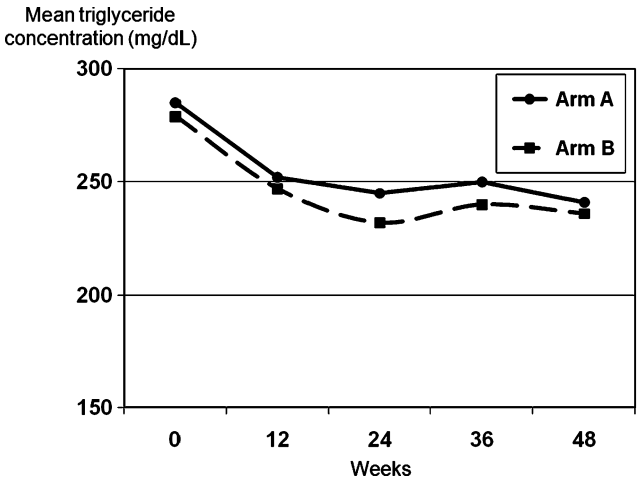

FIG. 1. Trend of mean fasting plasma triglyceride levels of patients randomized to arm A (abacavir/lamivudine plus atazanavir/ritonavir) or arm B (tenofovir/emtricitabine plus atazanavir/ritonavir) at baseline and after 12, 24, 36, and 48 weeks of follow-up.

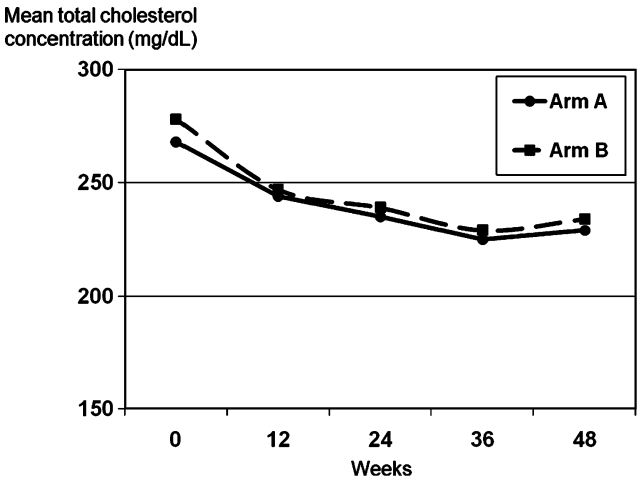

FIG. 2. Trend of mean fasting plasma total cholesterol levels of patients randomized to arm A (abacavir/lamivudine plus atazanavir/ritonavir) or arm B (tenofovir/emtricitabine plus atazanavir/ritonavir) at baseline and after 12, 24, 36, and 48 weeks of follow-up.

The mean reduction of plasma HDL cholesterol levels versus baseline values after the first 6 months of treatment was 2 mg/dL (3.7%) in arm A and 3 mg/dL (5.2%) in arm B. At the end of the 1-year follow-up, reductions of mean HDL cholesterol concentrations versus respective baseline levels were no statistically significant in both arms ($p = 0.61$ in arm A, $p = 0.058$ in arm B). No statistically significant differences of therapeutic responses were observed between these groups ($p = 0.89$).

The percentage of patients who reached normal triglyceride levels after a 48-week follow-up was comparable in both groups: 8 of 36 (22.2%) in arm A, and 9 of 40 (22.5%) in arm B ($p = 0.61$). Similarly, difference in percentage of patients who reached normal total cholesterol levels was no statistically significant between the two compared groups: 7 of 27 (25.9%) in arm A, and 9 of 33 (27.3%) in arm B ($p = 0.87$).

No appreciable changes of either prevalence or severity of clinical signs of fat redistribution syndrome (lipoatrophy, fat accumulation and mixed form) were reported throughout the study.

Both antiretroviral regimens showed a favorable tolerability profile, and in all the evaluated arms there were not appreciable differences in the onset of side effects, as reported spontaneously by the patients and observed by physical examination and laboratory tests (Table 3). Mild gastroenteric signs and symptoms (nausea, dyspepsia, abdominal pain, flatulence, and diarrhea) were found with similar incidence in the two evaluated arms (19% in arm A, and 21.3% in arm B; $p = 0.68$), and they did not require any therapy modification or suspension. Three cases of fever and maculo-papular skin rash were observed in arm A (7.1%); genotype testing for HLA-B*5701 allele proved positive in all these cases and confirmed an abacavir-induced hypersensitivity reaction. At the same time, an atazanavir-related mild-to-moderate increase in total bilirubin concentration (ranging between 1.2 and 6 mg/dL) was reported in 17 patients in arm A (40.5%) and in 20 subjects in arm B (42.5%): incidence of hyperbilirubinemia was comparable in both groups ($p = 0.59$). No cases

Table 3. Number of Patients (%) with Clinical and Laboratory Adverse Events in Arms A and B Reported During the Forty-Eight-Week Study Period

Arms	*A (ATV/r ABC 3TC)*	*B (ATV/r TDF FTC)*	p
Gastrointestinal signs and symptoms	8 (19)	10 (21.3)	0.67
Headache	10 (23.8)	9 (19.1)	0.78
Fatigue	12 (28.6)	15 (31.9)	0.87
Anxiety	6 (14.3)	9 (19.1)	0.71
Sleep disturbances	3 (7.1)	5 (10.6)	0.76
Increased serum creatinine (>1.2 mg/dL)	0	0	n.a.
Hypophosphatemia (<2.5 mg/dL)	0	0	n.a.
Increased serum alanine aminotransferase (>40 and <120 U/L)	8 (19)	10 (21.3)	0.75
Increased serum total bilirubin (>1.2 and <6 mg/dL)	17 (40.5)	20 (42.5)	0.69
Jaundice	2 (4.7)	3 (6.4)	0.48
Hypersensitivity reaction (fever and skin rash)	3 (7.1)	0	0.07
Treatment discontinuation	3 (7.1)	2 (4.2)	0.26

ATV/r, atazanavir/ritonavir; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine; n.s., not significant; n.a., not applicable.

of tenofovir-related hypophosphatemia or renal function abnormalities were observed in arm B.

Three patients (7.1%) in arm A and 2 subjects (4.2%) in arm B discontinued antiretroviral therapy because of nonserious adverse events, and no statistically significant differences were found with regard to the frequency of therapy discontinuation in both compared groups ($p = 0.61$). Treatment interruptions in arm A were related to abacavir-induced hypersensitivity reaction in all three cases, while in arm B therapy was discontinued because of hyperbilirubinemia with jaundice in one case and persisting insomnia and anxiety in the other case.

Discussion

Atazanavir is a once-daily PI that showed efficacy similar to that of efavirenz and nelfinavir in clinical trials involving antiretroviral-naïve HIV-infected patients. In antiretroviral-experienced subjects, atazanavir was found to be inferior to lopinavir/ritonavir unless it was coadministered with low-dose ritonavir. Atazanavir commonly causes increased levels of unconjugated bilirubin, but did not negatively impact the lipid profile in contrast to comparators, and may be particularly helpful in patients with dyslipidemia.[19,20] Particularly, in subjects with stable virologic suppression who were receiving other PIs, switching to an atazanavir-based regimen usually provided similar or better immunovirologic efficacy and improved lipid parameters.

In an open-field, 24-week, prospective, observational cohort study including 33 antiretroviral-experienced patients with hyperlipidemia, a rapid and significant decrease of 46% in triglyceride levels was shown after switch to an atazanavir-containing HAART. Similarly, a sustained improvement of 18% was reported in total cholesterol, while HDL and LDL cholesterol levels did not change significantly, as did CD4 cell count and HIV viral load.[21]

The SLOAT study was a prospective, open-label, comparative trial in which 189 patients treated with lopinavir/ritonavir and having undetectable HIV viral load for longer than 24 weeks were randomized to continue on the same therapy or switch to boosted or unboosted atazanavir. A significant reduction in median fasting total cholesterol (−19 mg/dL) and triglycerides (−80 mg/dL) was observed after 48 weeks of atazanavir switching, although lipid levels remained relatively stable in the lopinavir/ritonavir group. Greater reductions in fasting total cholesterol and triglycerides were seen in subjects on unboosted atazanavir in comparison with those receiving atazanavir/ritonavir. Incidence of virologic failure and changes in CD4 cell counts from baseline were comparable between treatment arms.[22]

In a multicenter, noncontrolled, retrospective study assessing 36 patients switched from a PI-based HAART to an atazanavir/ritonavir based regimen without changes in NRTIs, significant reductions were observed in total cholesterol (−9%), LDL cholesterol (−13%), and triglycerides (−23%) after a 6-month follow-up. In addition, 33% more patients achieved their National Cholesterol Education Panel (NCEP) Adult Treatment Panel (ATP) III cholesterol goals, while no appreciable changes were noted in median CD4 lymphocyte count or in number of patients with undetectable HIV viral load.[23]

The SWAN study was a 48-week, open-label trial involving HIV-positive patients with persisting virologic suppression who were receiving stable PI-based regimens and who were randomized 2:1 to switch to atazanavir (278 patients) or to continue to receive current PI treatment (141 patients). The proportion of randomized patients with confirmed virologic rebound through week 48 was significantly lower for those who switched to atazanavir than for those who received the comparator PI (7% versus 16%), while changes in CD4 cell count from baseline were comparable in the two treatment groups. Moreover, subjects who switched to atazanavir therapy experienced significantly fewer total cholesterol, triglycerides, and non-HDL cholesterol elevations than did patients in the comparator PI regimen.[15]

Previous studies have shown improvements in lipoatrophy and dyslipidemia after a switch from thymidine analogues to either tenofovir or abacavir.[24] In randomized Phase 3 trials, first-line treatment with tenofovir leads to lower rates of clinically diagnosed lipoatrophy and lipid elevations, relative to either stavudine or zidovudine.[25,26]

In a STACCATO trial substudy, 35 antiretroviral-naïve Thai patients with stable HIV RNA suppression were switched from stavudine/didanosine to tenofovir/lamivudine while receiving saquinavir/ritonavir once daily. After a 48-week study period, there were significant reductions in lipid and lactate levels, in association with reversal of lipoatrophy. The immune-virologic efficacy was maintained at week 48, and the mitochondrial DNA content rose significantly, showing a partial improvement of mitochondrial damage.[27]

Study 934 was a randomized, open-label trial that compared efficacy and tolerability of two antiretroviral regimens consisting of efavirenz with fixed-dose zidovudine/lamivudine or tenofovir/emtricitabine. Through 144 weeks,

significantly more patients in the tenofovir/emtricitabine arm reached and maintained an undetectable HIV viral load, with a trend toward greater CD4 cell count increase, in comparison with the zidovudine/lamivudine group. Moreover, patients in the tenofovir-treated group had smaller increase in fasting total cholesterol and triglycerides than those in the zidovudine arm. At the same time, total limb fat was significantly greater and incidence of lipoatrophy significantly lower in those treated with tenofovir/emtricitabine compared to those receiving zidovudine/lamivudine.[28]

Study 903 is a Phase 3 trial with a completed 144-week, double-blinded phase comparing tenofovir with stavudine in combination with lamivudine and efavirenz, and an ongoing 336-week open-label extension phase in which a subset of patients was allowed to switch from stavudine to tenofovir. At 144 weeks after the switch, percentage of patients with virologic suppression and mean increase in CD4 cell count were comparable in both groups. On the contrary, patients switched to tenofovir experienced a significant decrease in mean fasting total cholesterol and triglycerides, in association with a significant increase in mean limb fat.[29]

The RECOVER study was a prospective, multicenter trial assessing the 12-month evolution of lipid profile in 873 HIV-infected virologically suppressed subjects substituting tenofovir for stavudine. At 48 weeks, there was a significant, sustained reduction in median serum levels of total cholesterol, LDL cholesterol, and triglycerides, while HDL cholesterol remained roughly unchanged. Particularly, the greatest decrease in triglycerides was observed in patients with severe hypertriglyceridemia at baseline, while the estimated 10-year cardiovascular risk decreased in all subjects, and to a higher extent in those with baseline hyperlipidemia.[30]

In the COMET study, the impact of switching from twice-daily zidovudine/lamivudine to once-daily tenofovir/emtricitabine with efavirenz was evaluated in 402 virologically suppressed HIV-infected patients. At 24 weeks, subjects switched to tenofovir/emtricitabine maintained virologic suppression and experienced a significant decrease in fasting lipid concentrations.[31]

The nucleoside analogue abacavir showed also a more favorable impact on the plasma lipid profile than stavudine or PIs. In a prospective, randomized, open-label trial, 237 antiretroviral-naïve patients were assigned to receive abacavir or stavudine plus lamivudine and efavirenz. At 96 weeks, similar virologic and immunologic responses were reported in both arms, but the lipid profile in abacavir patients presented more favorable changes in levels of triglycerides, HDL cholesterol, and apolipoprotein AI.[32] At the same time, substituting abacavir for PIs in subjects with persisting undetectable HIV viral load and HAART-associated dyslipidemia usually improves serum lipid concentrations and maintains virologic suppression.[17–33]

However, recent or current, but not cumulative or past use of abacavir or didanosine was associated with an increased rate of myocardial infarction in 33,347 patients enrolled in the DAD Study. Relative rate was 1.9 with abacavir and 1.49 with didanosine compared with those with no recent use of these drugs, while rates were not significantly increased in subjects who stopped these agents more than 6 months previously compared with those who had never received these drugs. The heightened risk of myocardial infarction with recent abacavir exposure was accentuated in persons who had pre-existing risk factors for cardiovascular diseases.[18] Abacavir was associated with an excess risk of cardiovascular diseases compared with other NRTIs also in the SMART Study. This drug may cause vascular inflammation which may precipitate a cardiovascular event, because high-sensitivity C-reactive protein and interleukin-6 plasma levels were 27% and 16% higher for individuals receiving abacavir compared with those treated with other NRTIs.[34]

Although conflicting data exist regarding cardiovascular risk associated with abacavir therapy, this drug should be use with caution in individuals at higher risk for cardiovascular disease.[35]

In our study, switching from a protease-inhibitor and thymidine analogue-based antiretroviral regimen to atazanavir/ritonavir plus abacavir/lamivudine or tenofovir/emtricitabine proved effective and safe in the management of hyperlipidemia. No significant differences in lipid-lowering effect, virologic efficacy, and safety profile were reported between these regimens. Particularly, both switching treatments obtained a significant decrease in serum levels of triglycerides, total cholesterol, and LDL cholesterol, but only approximately 22%–27% of patients reached normal lipid levels after the 48-week follow-up. No appreciable changes of either prevalence or severity of clinical signs of fat redistribution syndrome (lipoatrophy, fat accumulation and mixed form) were reported throughout the study. Final immunologic responses were also comparable in both arms, but a more rapid increase in CD4 cell count was observed in patients taking abacavir/lamivudine.

Finally, nonthymidine analogues and atazanavir may represent an effective therapeutic option in HIV-infected patients with PI-related dyslipidemia, but further larger studies are certainly requested in order to better investigate efficacy and safety of these antiretroviral combinations.

Author Disclosure Statement

No competing financial interests exist.

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