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Switching Strategies to Improve Lipid Profile and Morphologic Changes

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Abstract

Metabolic alterations and body fat changes are well-recognized limitations of protease inhibitor-based regimens. Strategies of replacing protease inhibitors with nonnucleoside reverse transcriptase inhibitors or abacavir have been shown to improve metabolic abnormalities, particularly by decreasing cholesterol and triglyceride levels, and reducing cardiovascular risk. The various therapeutic options show differences in efficacy, tolerability, and metabolic outcomes. Abacavir seems to be better tolerated, at least in the only randomized trial in which the three options were compared face-to-face, but it is associated with higher virologic failure in patients with prior suboptimal nucleoside therapy. Nonnucleoside reverse transcriptase inhibitors, particularly nevirapine, result in a better lipid profile with a greater increase in HDL cholesterol and in the HDL/total cholesterol ratio, one of the most important parameters associated with a reduction in cardiovascular risk. Efavirenz has been associated with increased triglyceride levels in some studies.

Although protease inhibitor compounds as a family have been linked to metabolic and body fat alterations, new drugs such as atazanavir seem to be associated with a more favorable lipid profile.

Lipoatrophy is a stigmatizing complication in HIV-infected patients receiving HAART. There is strong evidence suggesting a prominent role of thymidine analogs, mainly stavudine, in its development. Substitution of stavudine or zidovudine for abacavir or tenofovir partially improves peripheral fat loss. In addition, the lipid profile significantly improves.

Finally, although the extended use of non-thymidine nucleoside analogs and the development of new families of antiretroviral drugs will probably result in a lower impact in lipids and morphologic changes, many patients are currently under treatment with these compounds. In this setting, switching strategies may be useful to minimize clinical and psychological consequences, improving the quality of life of HIV-infected patients treated with HAART. **(AIDS Reviews 2006;8:191-203)**

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Key words

Lipoatrophy. Simplification therapy. Switching strategies. Lipid abnormalities. Cardiovascular risk.

Introduction

The development of HAART has dramatically influenced the course of HIV disease, with decreases in morbidity and mortality in HIV-infected individuals[1,2]. Nonetheless, this treatment may be associated with metabolic disturbances and changes in body fat distribution that can affect long-term adherence to therapy[3-6]. The morphologic abnormalities, which are given the general term "lipodystrophy", consist of symmetrical loss of limb, buttock, and face fat (lipoatrophy), central fat accumulation in the abdomen, breasts, and neck (buffalo hump, lipohypertrophy), or both these conditions. The most frequent metabolic alterations related to HAART use are hypertriglyceridemia with or without hypercholesterolemia, and insulin resistance or diabetes[3-6]. Although the morphologic abnormalities often occur concurrently with any of the metabolic complications (particularly hypertriglyceridemia), it is not rare

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to find one of these entities alone. The mechanisms of interaction between these complications are not well defined.

Several studies have suggested that the dyslipidemia associated with antiretroviral therapy may increase cardiovascular risk. The DAD (Data collection on Adverse events of anti-HIV Drugs)[7] prospective observational study showed a 26% relative increase in the rate of myocardial infarction per year of exposure to HAART during the first four to six years of use. An incidence of 6% of new cases of diabetes per 1000 patients/year has also been reported in association with HAART[8]. Moreover, a comparison of different HAART regimes[9] has shown that increased protease inhibitor (PI) exposure –but not nonnucleoside reverse transcriptase inhibitor (NNRTI) exposure– is associated with an elevated risk of myocardial infarction. The HIV Outpatient Study (HOPS) cohort[10] also observed an increase in myocardial infarction with PI use, again in comparison with NNRTI.

Although the etiology of metabolic disturbances is likely to be multifactorial, growing evidence suggests a direct participation of PI. Increases in triglycerides and VLDL cholesterol have been documented after four weeks of lopinavir/r administration in healthy individuals[11] and alterations in glucose metabolism have been associated with other antiretrovirals in this family[12].

It is important to point out that these lipid alterations and morphologic abnormalities vary between the different PI[4-6]. Indinavir has been more frequently associated with insulin resistance and lopinavir/r with severe hypertriglyceridemia, whereas the use of other agents, such as nelfinavir and particularly atazanavir, results in a relatively favorable lipid profile[13].

The role of PI in fat changes remains uncertain. It seems that they may contribute considerably to central-fat accumulation (buffalo hump, "crixbelly", etc.). Many studies have suggested that thymidine nucleoside analogs, mainly stavudine and to a lesser degree zidovudine, play a major role in fat loss through a mechanism of mitochondrial toxicity[14-17]. It is likely that the interaction of both these antiretroviral families increases the risk of body changes[14-17]. In addition, it has been recently demonstrated that thymidine analogs are also involved in some lipid disorders[18,19].

Fortunately, the armamentarium against HIV is quite large and several drugs with a better associated metabolic profile are now available. Thus, switching to one or more of these drugs may improve metabolic disturbances. Various clinical trials have shown the benefit of this approach: in the earliest efforts, by switching a PI to the NNRTI nevirapine or efavirenz, or to the nucleoside analog abacavir; more recently, by replacing stavudine with tenofovir or abacavir, and also by switching several PI to atazanavir (Table 1). The changes in body fat distribution are less marked, but some improvements have been observed when stavudine is discontinued[20-23].

The aim of the present article is to review the studies published in the English literature and/or presented at international conferences investigating the strategy of switching antiretrovirals to improve metabolic alterations and/or body fat changes. Most of these studies show that the switching approach, which can also be called a "simplification strategy" when the replaced drugs have more complex regimens involving a larger number of pills than the new compounds, maintains virologic suppression in most instances after the switch. However, because of space constraints and in order to focus the present review on metabolic alterations, the virologic and immunologic outcomes generally will not be described.

Switch from a PI to a NNRTI or abacavir

Nevirapine-switch studies

Non-randomized studies

The first switch trial, reported by Carr, et al.[24], included patients on PI therapy (indinavir or saquinavir/ritonavir) with lipodystrophy symptoms and metabolic abnormalities. The patients were switched to nevirapine (n = 16) or nelfinavir (n = 12). Within six months the results favored the nevirapine group in terms of total cholesterol, triglycerides, and insulin resistance. It was a small study, but it suggested that the lipid profile might improve with a change in the PI.

Martínez, et al.[25] reported an improvement in lipodystrophy and metabolic parameters, such as total cholesterol (22%), triglycerides (57%), and glucose (15%), as well as insulin resistance (45%) in 23 patients switched from a PI to nevirapine.

Tebas, et al.[26] provided a detailed report of the metabolic alterations and morphologic changes on dual-energy X-ray absorptiometry (DEXA) scanning in 40 patients with a viral load of < 200 copies/ml who were switched from a PI to nevirapine. Median follow-up was 24 weeks. This strategy was effective in reducing lipid levels, but it was not successful in improving body fat changes.

In a 48-week observational study[27] from the Athena cohort, the risk of virologic failure was compared in patients with plasma HIV-1 RNA < 500 copies/ml, who were switched from a first PI-containing antiretroviral regimen to nevirapine or to a second-line PI. From this cohort there were 446 eligible patients, 125 in the nevirapine group and 321 in the PI group. The risk of treatment failure in the nevirapine arm was lower than in the second-line PI arm, primarily because the discontinuation rate was lower. The authors also analyzed adverse events and observed that physician-diagnosed lipodystrophy was more frequent in the PI group.

Table 1. Randomized studies investigating protease inhibitor or thymidine analog switching

	Arms	Results	Comments
PI substitution (by NNRTI or abacavir)			
Ruiz L. JAIDS 2001;27:229-36[29]	– PI (n = 29) *vs.* NVP (n = 31) – Body changes evaluated by anthropometric measures and DEXA	– Significant decrease in total cholesterol and TG levels at 48 weeks of follow-up – No significant changes in body fat distribution	– Severity of lipodystrophy not reported
Barreiro P. AIDS 2000;14:807-12[28]	– PI (n = 34) *vs.* NVP (n = 104)	– No significant changes in lipid parameters at 6 months of follow-up – 70% of patients included had lipodystrophy, 50% of them improved (physician/patient opinion)	– Body fat changes assessed only according to physician/ patient perception
Katlama C. XIII IAC 2000 [abstract LbPeB7044][43]	– PI (n = 65) *vs.* EFV (n = 69)	– No differences in total cholesterol, but an increase in HDLC in EFV arm at 24 weeks of follow-up	– Small study – Body fat changes not evaluated
Becker S. 8th CROI 2001 [abstract 20][42]	– PI (n = 120) vs. EFV (n = 226)	– No differences in total cholesterol or TG levels between groups at week 48 – Trend to an increase in HDLC in EFV arm	– Body fat changes not evaluated
Martínez E. 8th CROI 2001 [abstract 668][41]	– PI (n = 47) *vs.* EFV (n = 46) in patients with lipodystrophy – Body fat evaluated by ultrasound	– Significant improvement in HDLC and insulin resistance at 12 months of follow-up in EFV group – Improvement in central body fat accumulation, but lipoatrophy continued	
Pulvirenti J. 39th A M Inf Dis, San Francisco 2001 [abstract 689][47]	ABC (n = 58) *vs.* PI (n = 29)	– Week 24: TG and cholesterol levels improved in ABC arm	– Body fat changes not evaluated
Clumeck N. AIDS 2001;15:1517-26[44]	– PI (n = 106) *vs.* ABC (n = 105)	– Proportion of patients with hypertriglyceridemia (TG > 2.3 mmol/l) and hypercholesterolemia (cholesterol > 5.2 mmol/l) decreased significantly at one year of follow-up in patients treated with ABC	– Fractionated cholesterol levels not evaluated – Body fat changes not assessed
Katlama C. HIV Med 2003;4:79-86[45]	– TRIZAL Study – PI (n = 103) *vs.* TRIZIVIR (n = 106)	– Patients treated with ABC showed a greater reduction in cholesterol and TG levels at 48 weeks of follow-up	– Fractionated cholesterol not reported – No anthropometric measurements
Opravil M. J Infect Dis 2002;185:1251-60[46]	– PI (n = 79) *vs.* TRIZIVIR (n = 84)	– After 84 weeks, non-fasting cholesterol and TG levels decreased	– Risk of virologic failure when treatment history or resistance testing suggests presence of mutations resistant to simplified regimen – Body fat changes not evaluated

Table 1. Randomized studies investigating protease inhibitor or thymidine analog switching *(Continuation)*

	Arms	Results	Comments
Negredo E. CID 2002;34:504-10[31]	– PI (n = 26) *vs.* NVP (n = 26) *vs.* EFV (n = 25) – Body fat changes assessed by DEXA and anthropometry	– Only the group treated with NVP obtained significant improvement in TG and cholesterol levels at 12 months of follow-up. Improvement resulted from decrease in LDLC levels – In patients treated with EFV, TG increased starting from month nine and reached abnormal levels – No changes in body fat between groups	
Fisac C. AIDS 2005;19:917-25[59]	– (Metabolic substudy: LIPNEFA) – NVP (n = 29) *vs.* EFV (n = 32) *vs.* ABC (n = 29) – Anthropometry and DEXA	– Patients with moderate/severe fat accumulation showed non-significant decrease; lipoatrophy may have worsened – After 24 months significant improvement in lipid profile, more marked in patients without lipodystrophy – Patients who switched to NVP or EFV presented important improvement in HDLC. Total cholesterol levels dropped significantly in patients treated with ABC because of reduction in LDLC levels – Non-significant trend toward improved insulin-resistance	– DEXA scanning done in small subpopulation (n = 28) – Number of patients per arm too small to detect differences between them – 78% of patients continued with d4T
Maggiolo F. Clin Infect Dis 2003;37:41-9[60]	– ABC (n = 69), EFV (n = 70), PI (n = 70)	– After 104 weeks of follow-up, TG and cholesterol levels increased in PI group and these patients had more lipodystrophy than the others – In EFV group there was slight increase in TG and cholesterol levels – The ABC-based therapy did not influence triglycerides levels and cholesterol levels in this group were significantly lowered than the others; the maximum decrement was observed 4 months after initiation of therapy	– Body fat changes not evaluated by DEXA or anthropometry
PI substitution (by atazanavir)			
Gatell J. Swan Study XVI IAC Toronto, 2006[50]	– PI (n = 141) *vs.* ATV (n = 278)	– After 48 weeks of follow up, TG, total cholesterol and LDLC improved significantly	– Switch from boosted PI to unboosted ATV – Body fat changes not evaluated
Thymidine analogs (stavudine or zidovudine) substitution			
Carr A. JAMA 2002;288:207-15[65]	MITOX Study Switch from d4T or AZT to ABC (n = 54) or continue treatment (n = 57) Change in peripheral fat evaluated by DEXA and abdominal visceral fat by CT	After 24 weeks there was significant peripheral fat increase in arms and legs in ABC group compared with d4T/AZT arm (+ 0.39 *vs.* + 0.08 kg; p = 0.02) However, abdominal visceral fat increased in ABC arm (+ 12.5 cm^2) and decreased in d4T/AZT arm (– 1.5 cm^2); the change was not significant (p = 0.07) Metabolic parameters did not differ between groups	Duration of follow-up only 24 weeks Results not compared according to which drug was substituted (d4T or AZT)

Table 1. Randomized studies investigating protease inhibitor or thymidine analog switching *(Continuation)*

	Arms	Results	Comments
Milinkovic A. 12th CROI 2005 [abstract 857][76]	– Three arms: switch d4T to TDF, reduce dose of d4T 30 mg/d or continue with d4T 40 mg/d – Body fat evaluated by DEXA	– At 6 months both groups (switch and reduced dose) showed improved metabolic parameters (total and fractionated cholesterol, TG and glucose) and increased body fat; however the effect was greater in the TDF-switch group	
Moyle G. 12th CROI 2005 [abstract 44LB][75]	– RAVE study – Switch d4T or AZT to ABC or TDF – Changes in peripheral fat evaluated by DEXA, and abdominal visceral fat by CT	– 48 weeks: significant increase in peripheral fat (arms/legs) in both groups – No differences between arms (ABC, +0.5 kg; TDF, +0.3 kg) – Similar results between arms in abdominal visceral fat changes – Greater improvement in lipid parameters (total cholesterol, LDLC, TG) in the TDF arm	– In the TDF arm more patients had d4T in their regimen than the other group (77 *vs.* 59%)
Switch to thymidine analog-sparing regimens			
Tebas P. 12th CROI 2005 [abstract 40][77]	– ACTG 5125s (ACTG5116 substudy) – EFV + LPV/r *vs.* 2 NRTI + EFV – Appendicular fat and mineral bone density evaluated by DEXA	– At week 48 the LPV/r + EFV group was associated with significant improvement in appendicular fat, increases in serum lipids and stable glucose metabolism and regional bone mineral density	– This study did not evaluate differences between specific NRTI
Murphy R. 12th CROI 2005 [abstract 45LB][78]	– ACTG 5110 – Switch d4T or AZT to ABC or LPV/r + NVP – Abdominal and peripheral fat evaluated by CT	– At 24 weeks subcutaneous thigh fat increased in the LPV/r + NVP group – There were significant subcutaneous abdominal adipose tissue (SAT) increases in both groups	
Negredo E. JAIDS 2005;38:47-52[79]	– NEKA Study – LPV/r + NVP *vs.* LPV/r + 2 NRTI	– At week 48: HDLC increased 10% and the mitochondrial DNA/nuclear DNA ratio showed a trend toward increasing in the NVP group	– Body fat changes not assessed
Multiple (PI, NNRTI and/or nucleoside analog) substitutions			
John M. JAIDS 2003;33:29-33[67]	– Adults on treatment with d4T or AZT, 3TC and a PI – Double switch: from d4T to AZT and from PI to ABC, or continue with the same regimen – Changes in peripheral fat evaluated by DEXA, and abdominal visceral fat by CT	– 48 weeks: significant increase in peripheral fat (legs) in switch group (+ 0.009 kg *vs.* – 0.010 kg [leg mo]; p = 0.05) – Peripheral fat in arms increased significantly in patients that switched (+ 0.014 kg [arm mo]; p = 0.004) while in remaining patients there were no changes – No differences between groups in metabolic parameters (total cholesterol, HDLC and LDLC, TG, lactate)	– Non-significant trend observed In the on-treatment analysis – Sample size too small (overall 37 patients) to detect significant differences between arms
Moyle G. JAIDS 2003;33:22-8[68]	– Adults with hypercholesterolemia and/or lipoatrophy on treatment with d4T and PI or NNRTI – Three different arms: switch d4T to ABC (group 1, n = 10), switch PI or NNRTI to ABC (group 2, n = 10), or switch d4T and PI or NNRTI to ABC + AZT (group 3, n = 10) – Morphologic abnormalities evaluated by DEXA and CT	– 48 weeks: slight improvement in total cholesterol and LDLC in groups 1 and 2 – Significant reduction in triglycerides in group 2 – Significant increase in total body fat, and in arms/legs in group 1, with decreases in the other groups – No significant changes in abdominal visceral fat in any groups	– Few patients in each arm

ABC: abacavir; AZT: zidovudine; d4T: stavudine; CT: computed tomography; DEXA: double energy X-ray absorptiometry; EFV: efavirenz; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; NNRTI: nonnucleoside reverse transcriptase inhibitors; NVP: nevirapine; PI: protease inhibitor; TDF: tenofovir; TG: triglycerides

Randomized studies

Barreiro, et al.[28] included 138 patients with a viral load < 50 copies/ml for more than six months while receiving a PI. Of these patients, 104 were switched to nevirapine and 34 continued with the same regimen. There were no significant changes in lipid parameters in either group after six months, even though 77.5 and 57.5% of the patients, respectively, had increased cholesterol and triglyceride levels at baseline. Body shape abnormalities were found in 70% of patients at randomization, but in only 50% of nevirapine patients after six months.

Another open-label, multicenter study[29], which included 106 patients with lipodystrophy, reported improvements in cholesterol and triglyceride levels in patients who were switched from a PI to nevirapine. At week 48 the nevirapine arm showed a significant decrease in cholesterol (228 to 207 mg/dl; $p < 0.05$) and triglyceride levels (270 to 217 mg/dl; $p < 0.05$), whereas, no changes were found in the PI arm. Physicians and patients noticed an improvement in lipodystrophy, although this was not confirmed by DEXA.

Efavirenz-switch studies

Non-randomized studies

The results from efavirenz-switch studies are variable and contradictory. In several studies a worsening of the lipid profile was found[30,31], in some there were no changes in metabolic alterations[32,33] or body fat[34,35,39], and in others an improvement in the metabolic parameters[36,38] and morphologic alterations[40] was described. Martínez, et al.[36] reported the results from 20 patients who had lipodystrophy with PI regimens and were changed to efavirenz. A clinical-anthropometric assessment, ultrasound study, and metabolic evaluation were done at months 0 and 6. At baseline, patients had substantial hypertriglyceridemia (85%), hypercholesterolemia (70%) and hyperglycemia (40%). A trend to an improvement in fat accumulation was observed, consisting in a reduction in the waist/hip index and visceral fat, as well as a significant reduction in triglyceride levels (31%) and in the insulin resistance index (28%). However, no significant changes in total cholesterol or cholesterol fractions were found.

The Swiss HIV cohort evaluated the strategy of switching a PI to efavirenz[37-39]. There was no evidence of major differences between the PI and NNRTI therapy with regard to body fat distribution, but a more favorable lipid profile was found in the efavirenz group.

Randomized studies

In a comparative study[41], patients were randomized to continue with a PI or change to efavirenz. After one year the efavirenz arm achieved an improvement in central body fat distribution, insulin resistance, and HDL cholesterol. Becker, et al.[42] presented 48-week data from the DMP 266-049 study, in which PI-treated patients were randomized to switch to efavirenz or continue with the PI regimen. No differences were found in total cholesterol levels, but there was a trend to an increase in HDL cholesterol in the efavirenz arm. In addition, lipodystrophy was significantly more frequent in the PI arm (3 *vs.* 0%; $p = 0.03$). In a smaller similar study[43], there were, again, no differences in total cholesterol, but an increase in HDL cholesterol was evident.

Abacavir-switch studies

In the European/Canadian CNA 30017 study[44], patients with a viral load < 50 copies/ml were randomized to continue with a PI regimen (n = 106) or to switch to abacavir (n = 105) (Fig. 1). At week 48, total cholesterol levels fell significantly and triglyceride levels were lower (NS) in the abacavir arm. In two other randomized studies[45,46], a significant decrease was also observed in total cholesterol and triglycerides after switching from a PI to abacavir or Trizivir, with no changes in HDL cholesterol. Pulvirenti, et al.[47] reported the findings from the COL30305 study. A total of 87 patients were randomly assigned to maintain their PI or switch to abacavir. Mean triglyceride and total cholesterol levels improved from baseline to a greater extent in patients who switched to abacavir. An open-label, randomized pilot study[48] compared changes in fasting lipids and HIV-1 RNA in 104 patients with PI-associated hyperlipidemia, randomized to switch to abacavir (n = 52) or continue with a PI (n = 52) for 28 weeks. The abacavir arm showed a significantly greater reduction in total cholesterol, LDL cholesterol and triglycerides, with no differences in HDL cholesterol, glucose, insulin, or insulin resistance.

Switch from PI to atazanavir

Unboosted atazanavir

In a prospective, observational study[49] including 33 HIV-infected patients with severe dyslipidemia under treatment with a PI, a significant improvement in the lipid profile was observed 24 weeks after switching to atazanavir. The 48-week results of the US Study of Women's Health Across the Nation (SWAN)[50] were reported at the last International Aids Conference in Toronto. In this multicenter open trial, stable patients were randomized to continue with lopinavir/r or to switch to atazanavir. The changes in total cholesterol, triglycerides and non-HDL cholesterol favored atazanavir (Fig. 2).

BMS AI424-044[51] is an ongoing, multicenter, open trial in which the enrolled patients came from the BMS AI424-008

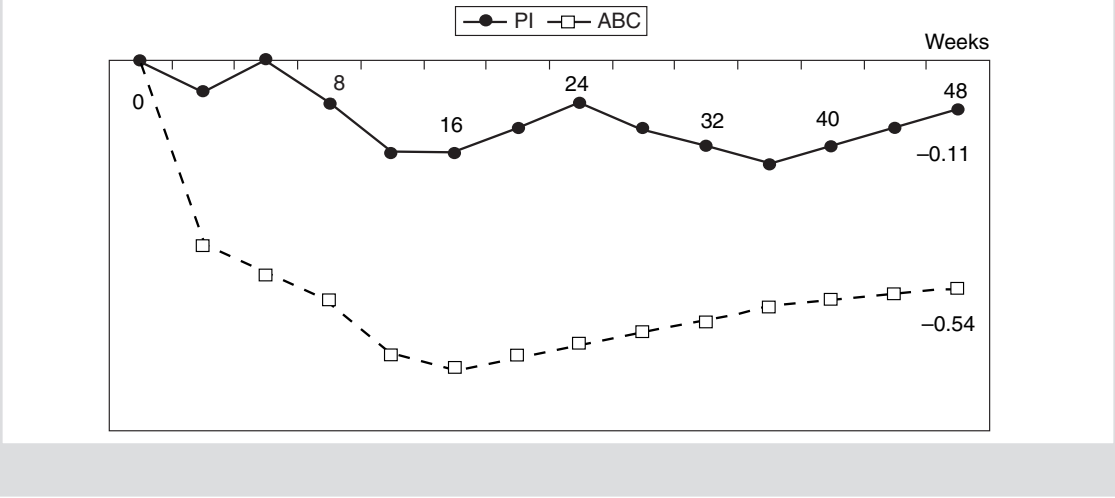
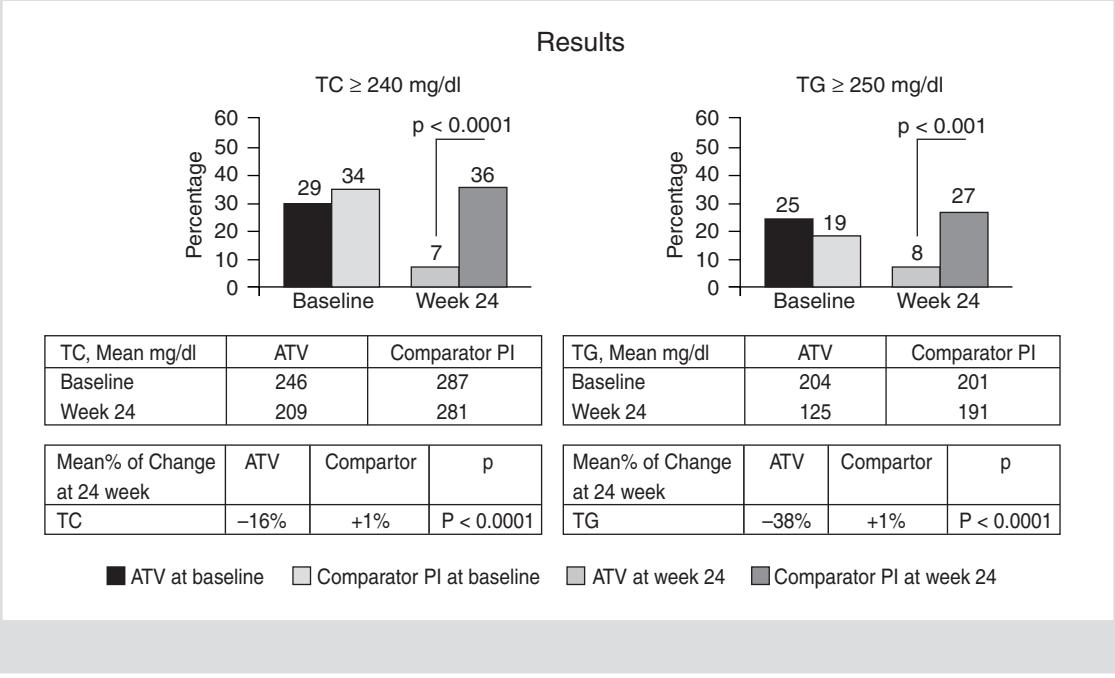


Figure 1. *Greater decrease in total cholesterol levels in patients switching to abacavir compared with those who continued with protease inhibitor-based regimens in study CNA30017*[44].

study (a 48-week trial comparing atazanavir with nelfinavir). In an extension of the study, patients were asked to switch from nelfinavir to atazanavir or to continue with atazanavir. The switch group showed a considerable decrease in lipid levels after 12 weeks (total cholesterol 16%, LDL cholesterol 21%, and fasting triglycerides 28%; p < 0.0001). Similar results were obtained after 12 weeks in another randomized study in which patients switched from a boosted or unboosted PI to atazanavir[52]. It should also be mentioned that some sporadic cases of patients in whom fat accumulation (dorsocervical fat deposits or abdominal obesity) decreased after switching from a PI to atazanavir have been recently reported[53].



TC, Mean mg/dl	ATV	Comparator PI
Baseline	246	287
Week 24	209	281

Mean% of Change at 24 week	ATV	Compartor	p
TC	–16%	+1%	P < 0.0001

TG, Mean mg/dl	ATV	Comparator PI
Baseline	204	201
Week 24	125	191

Mean% of Change at 24 week	ATV	Compartor	p
TG	–38%	+1%	P < 0.0001

Figure 2. *SWAN Study*[50]*. Lipid levels according to treatment arm: atazanavir* vs. *comparator PI. TG: triglycerides; TC: total cholesterol.*

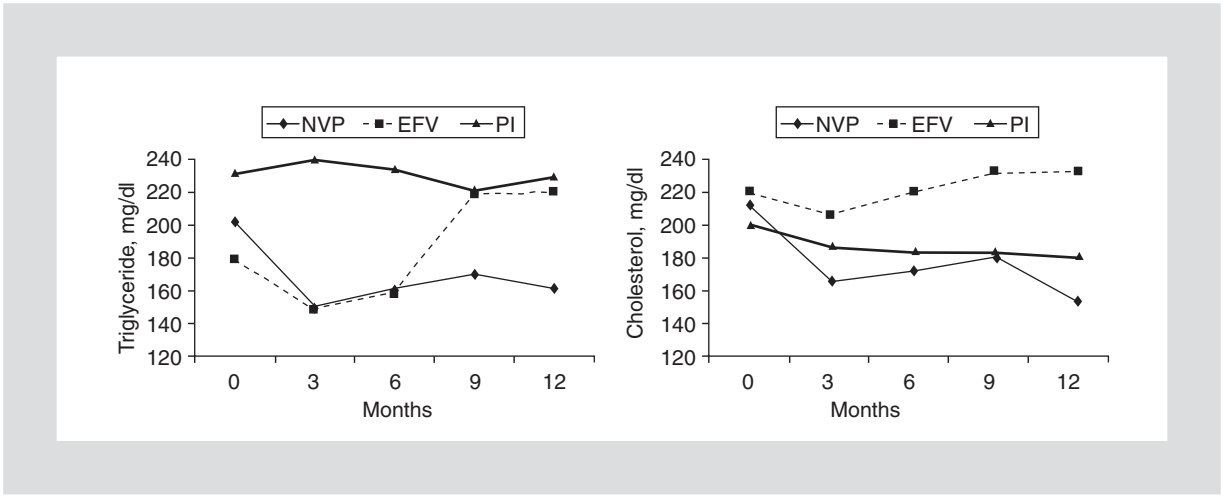


Figure 3. *Changes in triglyceride and cholesterol levels in patients who continued with protease inhibitors (PI) compared with patients switching to efavirenz (EFV) or nevirapine (NVP)[31].*

Ritonavir-boosted atazanavir

Martínez, et al.[54] described the effects of switching from a boosted PI (mainly lopinavir/r) to atazanavir/r. After six months an improvement in metabolic parameters was observed (–18% in triglycerides; $p < 0.0001$; –12% in total cholesterol; $p < 0.0001$; –10% in LDL cholesterol; $p < 0.0001$; and –3% in HDL cholesterol; $p > 0.05$).

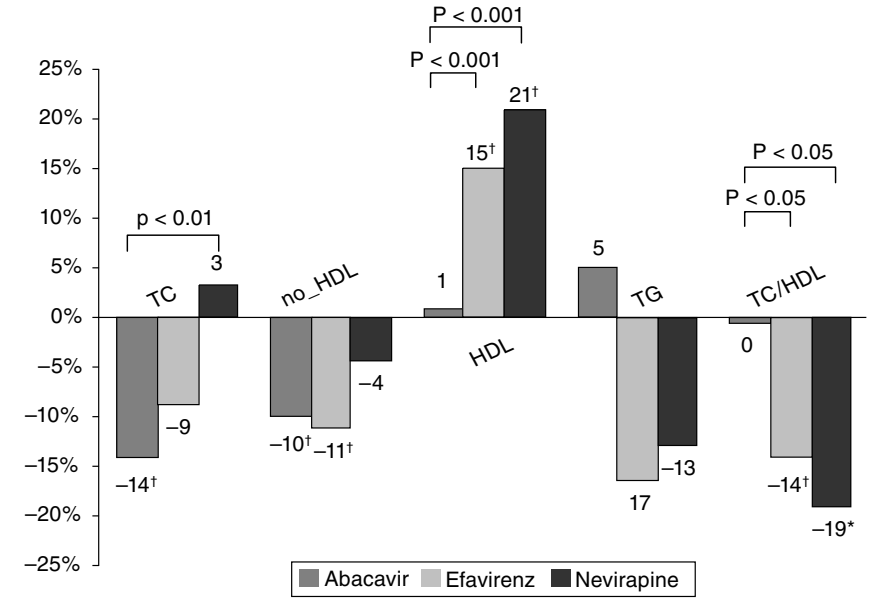
Multidrug-switch studies

One prospective, non-randomized study[55] included 100 patients under treatment with a PI. The PI regimen was changed because of toxicity or intolerance, to any of the NNRTI (efavirenz or nevirapine). After one year a reduction in total cholesterol (241 to 206 mg/dl; $p < 0.001$) and triglycerides (286 to 194 mg/dl; $p < 0.001$) was observed, but there were no favorable changes in the morphologic alterations.

Negredo, el al.[31] conducted a randomized, prospective, open study comparing continuation of PI treatment (n = 26) with a switch from the PI to nevirapine (n = 26) or efavirenz (n = 25). The patients' viral load was < 80 copies/ml and CD4+ cell count was > 300 cells/µl. At baseline, 75% of patients had lipodystrophy as assessed by DEXA scan. Metabolic abnormalities were not severe (nevirapine: 203 and 223 mg/dl triglycerides and cholesterol, respectively; efavirenz: 178 and 227 mg/dl; PI: 231 and 207 mg/dl) (Fig. 3). A significant improvement in total cholesterol, LDL cholesterol, and triglycerides was observed starting from month three in the nevirapine group, but no changes in HDL cholesterol were reported, in contrast to many studies[56,57]. In the efavirenz group, there was no improvement in lipid parameters and an increase in triglyceride levels above normal values after nine months. No body fat changes were observed in this study.

The NEFA study[58] was the first randomized study comparing the three possible options to simplify a PI regimen: nevirapine, efavirenz, and abacavir. A total of 460 patients with a viral load < 200 copies/ml for at least six months were included, and the 48-week data were published. A substudy (LipNEFA) with 90 patients, consisting in a more detailed evaluation of the metabolic and body fat changes after two years of follow-up, was conducted by our medical unit in collaboration with Hospital Vall d'Hebron[59]. Metabolic parameters were evaluated at baseline and every three months, while body fat distribution changes were assessed clinically by DEXA and by anthropometric measurements. Overall, the simplification strategy was associated with a notable improvement in the lipid profile, with several important differences between the arms, particularly regarding the NNRTI and abacavir. Whereas abacavir reduced total cholesterol and LDL cholesterol to a greater extent than the NNRTI, both NNRTI increased HDL cholesterol levels (Fig. 4). During the first year, triglycerides significantly decreased in the three arms, but in the second year they rose again up to baseline values. A non-significant trend to an improvement in insulin resistance as evaluated by the homeostasis model assessment (HOMA) index was observed (abacavir –2%, efavirenz –20%, nevirapine –5%). Overall, a trend to a decrease in lipo-accumulation and an increase in peripheral fat loss was found, the latter probably related to the high proportion of patients continuing with stavudine as part of their HAART regimen.

In a 104-week randomized study, Maggiolo, et al.[60] evaluated patients assigned to continue with their PI or to replace it with abacavir or efavirenz. In the PI group, there was a greater increase in triglycerides and cholesterol levels and more cases of lipodystrophy than in the other two groups. A slight increase in these lipid parameters was also observed



Data are stated as the median of the change percentage. TC: total cholesterol; HDL: cholesterol transported by high density lipoproteins; TG: triglycerides; TC/HDL: ratio between TC and HDL. Statistical significance of change within each arm: *p < 0.01, †p ≤ 0.001.

Figure 4. *Lipid changes observed in LipNEFA study[59] 24 months after the substitution of protease inhibitors by abacavir, efavirenz or nevirapine.*

in the efavirenz group. In the abacavir group, total cholesterol was significantly lower as compared with the other two groups, but no changes in triglycerides were found.

Nucleoside reverse transcriptase inhibitor-switch studies

Many data suggest that the thymidine-analog stavudine, and to a lesser degree zidovudine, are associated with the development of lipoatrophy through a mechanism of mitochondrial toxicity. The strategy of switching from stavudine to a non-thymidine nucleoside analog such as tenofovir or abacavir has been examined in several studies in order to improve metabolic disturbances and fat loss.

Abacavir-switch studies

Non-ra ndomized studies

In the TARHEEL study[61], an increment in peripheral fat (legs +18%, arms +35%) was observed after 48 weeks of switching from stavudine to abacavir or zidovudine. Computed tomography demonstrated a 32% increase in subcutaneous fat and a 4% decrease in visceral fat. Patients with hyperlactatemia presented a significant reduction in lactate concentrations (from 2.9 to 1.3 mmol/l). There were no changes in the remaining metabolic parameters such as total cholesterol, HDL cholesterol and LDL cholesterol, triglycerides, insulin, glucose, or peptide C.

In another similar trial[62] in which stavudine was replaced by abacavir or zidovudine, 16 patients with lipoatrophy showed peripheral fat increase (arms 21%, legs 11%) at week 48. There was a decrease in lactate concentrations and in adipocyte apoptosis, but again no changes in lipid parameters were reported.

A third study[63] involving this same substitution showed increased apoptosis in patients receiving stavudine and an improvement after 48 weeks of switching. In this case there was no metabolic evaluation.

Finally in another study, patients with lipoatrophy continued with stavudine (n = 63) or were switched to abacavir (n = 49). The anthropometric parameters improved in the abacavir arm and there was a reduction in lactate levels after six and 12 months of follow-up[64].

Randomized studies

The Australian Mitochondrial Toxicity (MITOX) study[65] included 111 patients with undetectable viral loads and moderate to severe lipoatrophy while taking stavudine or zidovudine.

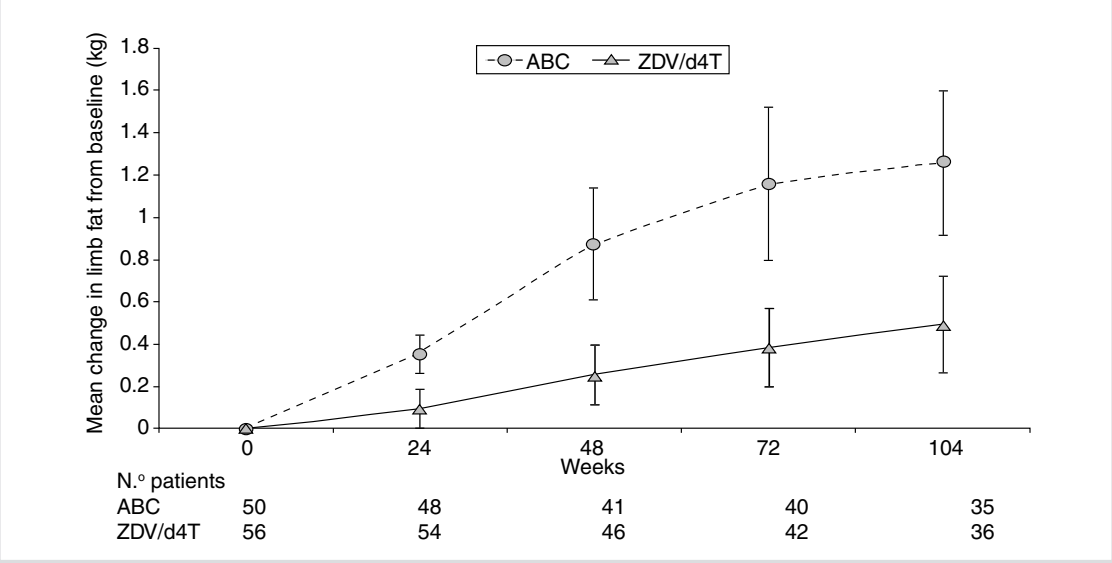


Figure 5. *Limb fat increase observed in MITOX study[65] after the substitution of stavudine or zidovudine by abacavir (ABC), compared with continuing with thymidine analogs (ZDV/d4T).*

At week 24, patients who switched to abacavir showed a slight improvement in lipoatrophy. There were no differences between the groups in visceral fat or metabolic parameters (lactate, glucose, total and fractionated cholesterol, peptide C, triglycerides, and insulin). In the 104-week extension of this study[66], the lipoatrophy improvement persisted (Fig. 5).

Two randomized studies have investigated the benefit of double switching of nucleoside reverse transcriptase inhibitor (NRTI) and PI-containing regimens[67,68]. In one of them, patients were taking stavudine with lamivudine and a PI[67]. Some of the participants (n = 15) continued this therapy, whereas others (n = 22) were switched from stavudine to zidovudine and from the PI to abacavir. At week 48 there was an average fat-mass gain in the arms and legs of switch patients *versus* a loss in the controls as evaluated by DEXA (p = 0.04, on-treatment analysis). No significant effects on intraabdominal fat were detected by computed tomography. Lastly, total and fractionated cholesterol, triglycerides, and lactate did not change significantly in the switch group.

In the other study[68], 27 HIV-1-infected patients, with a viral load < 50 copies/ml on treatment with stavudine and either a PI or NNRTI, and with high total cholesterol levels (> 5.2 mmol/l or > 180 mg/dl) and/or lipoatrophy were randomized into three groups: 1) stavudine was switched to abacavir; 2) the PI or NNRTI was switched to abacavir; and 3) stavudine and the PI/NNRTI were changed to zidovudine and abacavir. Patients were followed-up by fasting blood analysis, DEXA scanning, and computed tomography studies for 48 weeks. Total and LDL cholesterol levels fell significantly in the second and third groups. Triglycerides also improved significantly in the second group. In contrast, arm and leg fat mass on DEXA increased significantly in the first group. No changes in intraabdominal fat were observed by computed tomography.

Tenofovir-switch studies

Non-randomized studies

The Spanish LIPOTEST study enrolled 53 patients with undetectable viral load and moderate to severe lipoatrophy[69] while receiving stavudine. This drug was switched to tenofovir and patients were prospectively followed. After 48 weeks, patients gained fat mass and subcutaneous malar fat thickness, as determined by bioelectrical impedance analysis and sonography, respectively. There was also a decrease in total cholesterol and lactate levels, as well as an increase in mitochondrial DNA in peripheral blood mononuclear cells (Fig. 6).

The 903 study[70] demonstrated that the combination of tenofovir/lamivudine/efavirenz was highly effective and comparable to stavudine/lamivudine/efavirenz in naive patients. It was also observed that patients allocated to the stavudine arm had a significantly greater increase in cholesterol and triglyceride levels than the tenofovir patients. After 144 weeks of follow-up, 85 patients receiving stavudine were rolled-over into a 96-week open-label extension-phase (903E) in which they were switched from stavudine to tenofovir[71]. At week 48, significant decreas-

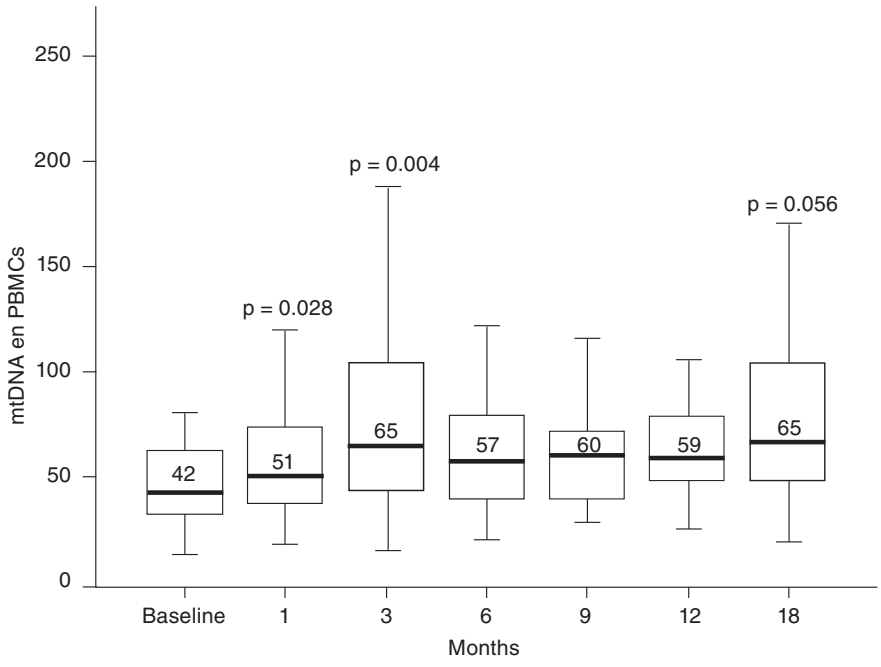


Figure 6. *Increase in PBMC mitochondrial DNA concentrations observed in LIPOTEST study[69] after the substitution of stavudine by tenofovir.*

es in total cholesterol (38 mg/dl), LDL cholesterol (16 mg/dl) and triglycerides (72 mg/dl) ($p < 0.001$) were documented, as well as an important improvement in lipoatrophy (limb fat increased 0.42 kg; $p < 0.001$). A slight decrease in HDL cholesterol levels also occurred (1 mg/dl; $p = 0.048$).

The RECOVER study from Spain was a prospective, multicenter study in which tenofovir substituted stavudine[72]. At week 12, the lipid parameters showed a substantial improvement, while at week 48[73] fasting cholesterol and triglycerides continued decreasing. Moreover, in a sub-study (LIPO-REC)[74], a statistically significant decrease was found in the overall 48-week cardiovascular risk estimated with the Framingham equation.

Randomized studies

The British RAVE study[75] is the only trial (although small) in which zidovudine or stavudine substitution for abacavir (n = 53) or tenofovir (n = 52) was investigated. At week 48, there was a significant increase in limb fat from baseline values in both groups (abacavir 0.5 kg; tenofovir 0.3 kg). Changes in lipid parameters significantly favored tenofovir (total cholesterol –0.46 *vs.* 0.31 mmol/l; $p = 0.01$; LDL cholesterol –0.25 *vs.* 0.10 mmol/l; $p = 0.05$; and triglycerides –0.49 *vs.* 0.46; $p = 0.01$).

In another small randomized study[76], maintaining a standard regimen of stavudine dose 40 mg twice daily (n = 20) was compared with reducing the stavudine dose to 30 mg twice daily (n = 18) or switching from stavudine to tenofovir (n = 18). Fasting plasma glucose, triglycerides, lactate, and total HDL and LDL cholesterol were assessed at baseline and at one, three, and six months. Mitochondrial oxidative activity (polarography) and body fat (DEXA) were evaluated at baseline and at six months. Reducing the stavudine dose and switching to tenofovir were both effective in improving total cholesterol and triglyceride status. Both approaches were also associated with increases in body fat, but the effect of switching to tenofovir was greater than that of reducing stavudine.

Switching to nucleoside analog-sparing regimens

Several trials (ACTG5125s[77], ACTG5110[78]) have recently suggested that switching a thymidine analog to a nucleoside analog-sparing regimen including a boosted PI plus a NNRTI may partially revert lipoatrophy. Although the gain in peripheral fat was modest –but statistically significant– at least it suggests that changing therapy may halt fat loss.

In the NEKA pilot study[79], a switch to a regimen of lopinavir/r plus nevirapine was associated with a reduction in mitochondrial toxicity and an improvement in lopinavir/r-associated lipid abnormalities.

References

1. Palella F, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced HIV infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853-60.
2. Mellors J, Munoz A, Giorgi J, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997;126:946-54.
3. Carr A, Cooper D. Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.
4. Chen D, Misra A, Garg A. Lipodystrophy in HIV-infected patients. J Clin Endocrinol Metab 2002;87:4845-56.
5. Dube M, Fenton M. Lipid abnormalities. Clin Infect Dis 2003;36(Suppl 2):S79-83.
6. Gelato M. Insulin and carbohydrate dysregulation. Clin Infect Dis 2003;36(Suppl 2):S91-5.
7. Holmberg S, Moorman A, Greenberg A, Friis-Moller N. The DAD Study group. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003;349:1993-2003.
8. Sabin C, Friis-Moller N, Reiss P, et al. Risk factors for new onset diabetes mellitus in HIV patients. 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil 2005. [abstract TuPe2.2B28].
9. Friis-Moller N, Reiss P, El-Sadr W, et al. Exposure to PI and NNRTI and risk of myocardial infarction: Results from the DAD Study. 13th CROI, Denver 2006. [abstract 144].
10. Holmberg S, Moorman A, Williamson J, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 2002;360:1747-8.
11. Lee G, Seneviratne T, Norr M, et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. AIDS 2004;18:641-9.
12. Noor M, Lo J, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. AIDS 2001;15:F11-18.
13. Goldsmith D, Perry C. Atazanavir. Drugs 2003;63:1679-93.
14. Van der Valk M, Gisolf E, Reiss P, et al. Increased risk of lipodystrophy when nucleoside analog reverse transcriptase inhibitors are included with PI in the treatment of HIV-1 infection. AIDS 2001;15:847-55.
15. Mallal S, John M, Moore C, James I, et al. Contribution of nucleoside analog reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 2000;14:1309-16.
16. Saves M, Chene G, Suissa S. Lipodystrophy and nucleoside analog therapy in HIV-infected patients: important question, few valid answers. JAIDS 2000;25:96-7.
17. Bogner J, Vielhauer V, Beckmann R, et al. Stavudine *versus* zidovudine and the development of lipodystrophy. JAIDS 2001;27:237-44.
18. St Marc T, Touraine J. The effects of discontinuing stavudine therapy on clinical and metabolic abnormalities in patients suffering from lipodystrophy. AIDS 1999;13:2188-9.
19. Saint Marc T, Partisani M, Poizor-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 2000;14:37-49.
20. Montaner J, Reiss P, Cooper D, et al. A randomized double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, the Netherlands, Canada and Australia study. JAMA 1998;279:930-7.
21. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (The Combine Study). Antivir Ther 2002;7:81-90.
22. Staszewski S, Morales-Ramirez J, Tashima K, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med 1999;341:1865-73.
23. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine *vs.* indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. JAMA 2001;285:1155-63.
24. Carr A, Thorisdottir A, Samaras K, et al. Reversibility of PI lipodystrophy syndrome on stopping PI and switching to nelfinavir. 6th CROI, Chicago 1999 [abstract 641].
25. Martinez E, Lozano L, Conget I, et al. Reversion of lipodystrophy after switching HIV-1 PI to nevirapine. AIDS 1999;13:805-10.
26. Tebas P, Yarashesky K, Powderly W, et al. A prospective open-label pilot trial of maintenance nevirapine-containing regimens in patients with undetectable viral loads on PI regimens for at least 6 months. 7th CROI, San Francisco 2000 [abstract 45].
27. Dieleman J, Sturkenboom M, Ferdinand W, et al. Low risk of treatment failure after substitution of nevirapine for PI among HIV-infected patients with virus suppression. The Journal of Infectious Diseases 2002;185:1261-8.
28. Barreiro P, Soriano V, Blanco F, Casimiro C, de la Cruz J, González-Lahoz J. Risk and benefits of replacing PI by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. AIDS 2000;14:807-12.
29. Ruiz L, Negredo E, Domingo P, et al. Clinical, virologic and immunologic benefit of switching the PI by nevirapine in HAART-experienced patients suffering lipodystrophy: 48-weeks follow-up. JAIDS 2001;27:229-36.
30. Moyle G, Baldwin C, Mandalia S, Comitis S, Burn P, Gazzard B. Changes in metabolic parameters and body shape after replacement of PI with efavirenz in virologically controlled HIV-1-positive persons: single-arm observational cohort. J Acquir Immune Defic Syndr 2001;28:399-401.
31. Negredo E, Cruz L, Paredes R, et al. Virologic, immunologic and clinical impact of switching from PI to nevirapine or to efavirenz in patients with HIV infection and long-lasting viral suppression. Clin Infect Dis 2002;34:504-10.
32. Viciana P, Alarcon A, Martin D, et al. Partial improvement of lipodystrophy after switching from HIV-1 PI to efavirenz. 7th CROI. San Francisco 2000 [abstract 48].
33. Estrada V, De Villar N, Larrad M, Lopez A, Fernandez C, Serrano-Ríos M. Long-term metabolic consequences of switching from PI to efavirenz in therapy for HIV-infected patients with lipoatrophy. Clin Infect Dis 2002;35:69-76.
34. Rozenbaum W, Adda N, Nguyen T, et al. Prospective follow-up substitution of PI for efavirenz in patients with HIV-related lipodystrophy syndrome. 1st International Workshop on Adverse Drugs Reactions and Lipodystrophy in HIV. San Diego, 1999.
35. Bonnet E, Lepec R, Bluteau M, et al. Evolution of lipodystrophy syndrome and lipid profile in HIV patients after switching from PI to efavirenz. 7th CROI. San Francisco 2000 [abstract 49].
36. Martinez E, García-Viejo M, Blanco J, et al. Impact of switching from HIV-1 PI to efavirenz in successfully treated adults with lipodystrophy. Clin Infect Dis 2000;31:1266-74.
37. Hirschel B, Flepp M, Bucher H, et al. Switching from PI to efavirenz: differences in efficacy and tolerance among risk groups: a case-control study from the Swiss HIV Cohort. AIDS 2002;16:381-5.
38. Young J, Weber R, Rickenbach M, et al. Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV Cohort Study. Antiviral Therapy 2005;10:585-91.
39. Young J, Rickenbach M, Weber R, et al. Body fat changes among antiretroviral-naive patients on PI- and NNRTI-based HAART in the Swiss HIV Cohort study. Antiviral Therapy 2005;10:73-81.
40. Harris M, Larsen G, Montaner J, et al. Replacing PI for efavirenz for management of PI toxicity. 1st International Workshop on Adverse Drugs Reactions and Lipodystrophy in HIV. San Diego, 1999.
41. Martinez E, Romeu J, García-Viejo M, et al. An open randomized study on the replacement of HIV-1 PI by efavirenz in chronically suppressed HIV-1 infected patients with lipodystrophy. 8th CROI, Chicago 2001 [abstract 668].
42. Becker S, Rachlis A, Gill J, et al. Successful substitution of PI with efavirenz in patients with undetectable viral loads. A prospective, randomized, multicenter, open-label study (DMP 049). 8th CROI, Chicago 2001 [abstract 20].
43. Katlama C. Successful substitution of PI with Sustiva (efavirenz) in patients with undetectable plasma HIV-1 RNA levels: results of a

prospective, randomized, multicenter, open-label study (DMP 266-027). XIII IAS, 2000 [abstract LbPeB7044].
44. Clumeck N, Goebel F, Rozenbaum W, et al. Simplification with abacavir-based triple nucleoside therapy *versus* continued PI-based HAART in HIV-1 infected patients with undetectable plasma HIV-1 RNA. AIDS 2001;15:1517-26.
45. Katlama C, Fenske S, Gazzard B, et al. TRIZAL study: switching from successful HAART to TRIZIVIR (abacavir-lamivudine-zidovudine combination tablet): 48 weeks efficacy, safety and adherence results. HIV Med 2003;4:79-86.
46. Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine and zidovudine in HIV infection. J Infect Dis 2002;185:1251-60.
47. Pulvirenti J, Goodwin D, Slater L, et al. Simplification of PI-containing HAART regimens with abacavir maintains viral suppression and favorable adherence in HIV-1 infected adults (COLA 30305). Program and abstract of the 39th Annual Meeting of the Infectious Diseases Society of America, 2001, San Francisco [abstract 689].
48. Keiser P, Sension M, DeJesus E, et al. Substituting abacavir for hyperlipidemia-associated PI in HAART regimens improves fasting lipid profiles, maintains virologic suppression and simplifies treatment. BMC Infect Dis 2005;5:2.
49. Moebius U, Lubach-Ruitman M, Castro-Frenzel B, et al. Switching to atazanavir improves metabolic disorders in antiretroviral-experienced patients with severe hyperlipidemia. JAIDS 2005; 39:174-80.
50. Gatell J, Branco T, Sasset L, et al. Efficacy and safety of atazanavir-based HAART in virologically suppressed subjects switched from lopinavir/ritonavir treatment (Subset Analysis of the Swan Study) AIDS 2006 XVI International AIDS Conference, Toronto, Canada.
51. Wood R, Phanuphak P, Cahn P, et al. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or atazanavir. J Acquir Immune Defic Synd 2004;36:684-92.
52. Sension M, Grinsztejn B, Molina J. Improvement in lipid profiles after 12 weeks of switching to atazanavir from boosted or unboosted PI in patients with no previous PI virologic failure and hyperlipidemia at baseline. 12th CROI, Boston, USA, 2005.
53. Haerter G, Burkhard J, Mueller M, et al. Regression of lipodystrophy in HIV-infected patients under therapy with the new PI atazanavir. AIDS 2004;18:952-4.
54. Martínez E, Azuaje CJ, Antela A, et al. Effects of switching to ritonavir-boosted atazanavir on HIV-infected patients receiving antiretroviral therapy with hyperlipidemia. 12th CROI, Boston, USA 2005.
55. Casado J, Arrizabalaga J, Antela A, et al. Long-term efficacy and tolerance of switching the PI for NNRTI: A 52 week, multicenter, prospective study. 8th CROI, Chicago 2001 [abstract 673].
56. Van de Valk M, Kastelein J, Murphy R, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 2001;15:2407-14.
57. Fisac C, Virgili N, Ferrer E, et al. A comparison of the effects of nevirapine and nelfinavir on metabolism and body habitus in antiretroviral-naive HIV-infected patients: a randomized controlled study. J Clin Endocrinol Metab 2003;88:5186-92.
58. Martinez E, Arnaiz J, Podzamczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for PI in patients with HIV infection. N Engl J Med 2003;349:1036-46.
59. Fisac C, Fumero E, Crespo M, et al. Metabolic benefits 24 months after replacing a PI with abacavir, efavirenz or nevirapine. AIDS 2005;19:917-25.
60. Maggiolo F, Ripamonti D, Ravasio L, et al. Outcome of two simplification strategies for the treatment of HIV-1 infection. Clin Infect Dis 2003;37:41-9.
61. McComsey G, Ward D, Hessenthaler M, et al. Improvement in lipoatrophy associated with HAART in HIV-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. Clin Infect Dis 2004;38:263-70.
62. McComsey G, Paulsen D, Lonergan J, et al. Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine. AIDS 2005;19:15-23.
63. Cherry C, Lal L, Thompson K, et al. Increased adipocyte apoptosis in lipoatrophy improves within 48 weeks of switching patient therapy from stavudine to abacavir or zidovudine. J Acquir immune Defic Syndr 2005;38:263-7.
64. Garcia-Benayas T, Blanco F, De la Cruz J, et al. Replacing stavudine by abacavir reduces lactate levels and may improve lipoatrophy. AIDS 2003;17:921-4.
65. Carr A, Workman C, Smith D, et al. Abacavir substitution for nucleosides analogs in patients with HIH lipoatrophy. JAMA 2002; 288:207-15.
66. Martin A, Smith D, Carr A, et al. Reversibility of lipoatrophy in HIV-infected patients two years after switching from thymidine analog to abacavir: The Mitox Extension Study. AIDS 2004;18:1029-36.
67. John M, McKinnon E, James I, et al. Randomized, controlled, 48-week study of switching stavudine and/or PI to Combivir/abacavir to prevent or reverse lipoatrophy in HIV-infected patients. J Acquir immune Defic Syndr 2003;33:29-33.
68. Moyle G, Baldwin C, Langroudi B, et al. A 48-week, randomized, open-label comparison of three abacavir-substitution approaches in the management of dyslipidemia and peripheral atrophy. J Acquir immune Defic Syndr 2003;33:22-8.
69. Ribera E, Paradiñeiro J, Sauleda S, et al. Improvements in subcutaneous fat, lipid profile and parameters of mitochondria toxicity in patients with peripheral lipoatrophy when stavudine is switched to tenofovir (LIPOTEST study). Program and abstracts of the 12th CROI, 2005, Boston, USA [abstract 860].
70. Gallant J, Staszewski S, Pozniak A, et al. The 903 Study Group. Efficacy and safety of tenofovir DF *vs.* stavudine in combination therapy in antiretroviral-naive patients. JAMA 2004;292:191-201.
71. Madruga J, Cassetti I, Suleiman J, et al. Improvement in lipoatrophy and lipid abnormalities following switch from stavudine to tenofovir in combination with lamivudine and efavirenz in HIV-infected patients: a 48 week follow-up from study 903e. Program and abstracts of the 3rd IAS Conference on HIV Pathogenesis and Treatment, 2005, Rio de Janeiro, Brazil [abstract TuPe2.2B12].
72. Domingo P, Labarga P, Palacios R, et al. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. AIDS 2004;18:1475-7.
73. Llibre J, Domingo P, Perez M, et al. Recover Study Group. Improvements in dyslipidemia at 48-weeks following substitution of stavudine with tenofovir DF. 7th International Workshop on Adverse Drug Reactions & Lipodystrophy in HIV. Dublin, Ireland, 2005.
74. Llibre J, Domingo P, Palacios R, et al. The LIPO-REC Study Group. Sustained improvement of dyslipidemia in HAART-treated patients replacing stavudine with tenofovir. AIDS 2006;20:1407-14.
75. Moyle G, Sabin C, Cartledge J, et al. A 48-week, randomized, open-label comparative study of tenofovir DF *vs.* abacavir as substitutes for a thymidine analog in persons with lipoatrophy and sustained virologic suppression on HAART. Program and abstracts of the 12th CROI, Boston, USA [abstract 44LB].
76. Milinkovic A, Lopez S, Vidal S, et al. A randomized open study comparing the effect of reducing stavudine dose *vs.* switching to tenofovir on mitochondrial function, metabolic parameters, and subcutaneous fat in HIV-infected patients receiving antiretroviral therapy containing stavudine. 12th CROI, 2005 [abstract 857].
77. Tebas P, Zhang J, Yarasheski K, et al. Switch to a PI-containing/NRTI-sparing regimen increases appendicular fat and serum lipid levels without affecting glucose metabolism or bone mineral density. The results of a prospective randomized trial, ACTG5125s. 12th CROI. Boston 2005 [abstract 40].
78. Murphy R, Zhang J, Hafner R, et al. Switching to a thymidine analog-sparing or a nucleoside-sparing regimen improves lipoatrophy: 24-week results of a prospective randomized clinical trial, ACTG5110. 12th CROI. Boston 2005 [abstract 45LB].
79. Negredo E, Molto J, Burger D, et al. Lopinavir/ritonavir plus nevirapine as a nucleoside-sparing approach in antiretroviral-experienced patients (NEKA study). J Acquir Immune Defic Syndr 2005;38:47-52.