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Lipid Metabolism and Lipodystrophy in HIV-1-Infected Patients: The Role Played by Nonnucleoside Reverse Transcriptase Inhibitors

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Abstract

Dyslipidemia and lipodystrophy represent significant healthcare concerns in HIV-infected patients due to their association with diabetes mellitus and increased cardiovascular disease risk. Since the lipid effects of the nonnucleoside reverse transcriptase inhibitors are not well characterized, we systematically summarized the effects of nonnucleoside reverse transcriptase inhibitor treatment on dyslipidemia and lipodystrophy in HIV-1 infection. As with other classes of antiretroviral agents, the nonnucleoside reverse transcriptase inhibitors are associated with lipid changes, although individual agents exhibit differing effects on lipid profiles. Comparative trials have shown that the risk for hypertriglyceridemia is lower with efavirenz than with the use of ritonavir-boosted lopinavir, but there is a greater likelihood of hypercholesterolemia compared to ritonavir-boosted atazanavir. Data also suggest that efavirenz results in greater increases in plasma lipid levels than integrase inhibitors and CC-chemokine-receptor-5 antagonists. Lipid disturbances are less frequent with the newer nonnucleoside reverse transcriptase inhibitors than with efavirenz. However, in most cases, no change in the total:high-density lipoprotein-cholesterol ratio was seen between the efavirenz and comparator groups. Switching from efavirenz to etravirine or rilpivirine, or the integrase inhibitors raltegravir or elvitegravir, resulted in significant reductions in lipid levels. There appears to be minimal potential for efavirenz or rilpivirine to result in development of lipodystrophy. Overall, nonnucleoside reverse transcriptase inhibitors have a smaller impact on plasma lipids than ritonavir-boosted protease inhibitors, with the newer agents exhibiting more favorable lipid profiles than efavirenz. When considering antiretroviral regimens, awareness of the different lipid effect profiles of the third agent is important, without forgetting the critical contribution of the background antiretrovirals. **(AIDS Rev. 2015;17:21-36)**

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Key words

Efavirenz. Nevirapine. Etravirine. Rilpivirine. Lipids. Cardiovascular disease.

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Introduction

With the long-term success of antiretroviral therapy (ART), non-AIDS-related mortality and morbidity are increasing in importance; cardiovascular disease is now the second most common cause of death (after cancer) among HIV-infected patients[1].

Dyslipidemia represents significant healthcare concerns in HIV-infected patients due to its direct association with increased cardiovascular disease risk. Also, lipodystrophy, comprising abnormal central fat accumulation (lipohypertrophy) and localized loss of fat tissue (lipoatrophy), has been indirectly linked to cardiovascular disease through viral, host, and ART factors. For example, in the D:A:D study of over 23,000 HIV-infected patients, raised serum total cholesterol (TC), raised triglycerides, and the presence of diabetes were associated with an increased risk of myocardial infarction, whereas lipodystrophy was identified as a risk factor for new-onset diabetes[2,3].

Lipid metabolism and lipodystrophy

Although the etiology of dyslipidemia in HIV infection is complex and remains unclear, evidence to date suggests that dyslipidemia may result from both the HIV infection itself as well as the effects of ART. It is known that many factors may play a role in the development of dyslipidemia, including baseline demographics, HIV disease characteristics, and ART[4]. However, it should be noted that different antiretroviral regimens can differ markedly in terms of their effects on plasma lipids.

Combination ART has been shown to have opposing effects on cardiovascular disease risk. Antiretroviral agents may decrease cardiovascular disease risk by reducing immune activation and levels of inflammatory mediators through the suppression of HIV replication[5,6]. In contrast, through their association with dyslipidemia, antiretrovirals can also have pro-atherogenic/cardiovascular effects. Generally, patients treated with combination ART show an atherogenic lipid profile comprising hypertriglyceridemia, elevated low-density lipoprotein (LDL)-cholesterol and decreased high-density lipoprotein (HDL) levels (high HDL levels are associated with a decreased cardiovascular risk)[1,7].

Lipodystrophy is a condition characterized by either regional or generalized redistribution of fat stores, in particular, loss of peripheral fat stores (limbs, buttocks, face) and accumulation of truncal fat (intraabdominal fat disposition and dorso-cervical fat pad, commonly called 'buffalo hump'). Although the stigmatizing effect of these changes in physical appearance can have a significant negative impact on patients' quality of life and treatment adherence, it is the association with dyslipidemia, diabetes mellitus and other metabolic complications – also referred to as "lipodystrophy syndrome" – increasing cardiovascular disease risk which are of greatest concern[8]. For example, visceral adipose tissue has been shown to be associated with cardiovascular disease in HIV-infected patients irrespective of body mass index or waist girth[9].

The etiology of lipodystrophy is not fully understood, but is known to include metabolic alterations in addition to clinical manifestations. Several factors that affect dyslipidemia as described above may also play a role in the development of lipodystrophy. Lipodystrophy is also known to be associated with altered levels of proinflammatory cytokines, adipocyte inflammation and altered function, oxidative stress, and macrophage infiltration. In addition, mitochondrial toxicity appears to be an important factor in the development of ART-associated lipoatrophy (particularly with the nucleoside analogs)[10].

This paper analyses the potential association of NNRTI-based ART on dyslipidemia and lipodystrophy in adult HIV-1-infected patients, based on a systematic PubMed search of the literature restricted to the 10 years up to/including September 2014 (Fig. 1). We focused mainly on studies from treatment-naive patients, as data from these studies would have fewer confounding factors.

Nonnucleoside reverse transcriptase inhibitors, dyslipidemia, and lipodystrophy

Distinct changes in lipids have been seen with different classes of antiretrovirals. For instance, lipid disturbances have been reported in patients treated with nonnucleoside reverse transcriptase inhibitors (NNRTI), although use of NNRTIs appears to be less associated with the development of dyslipidemia than use of protease inhibitors (PI).

Although initial studies indicated that lipodystrophy was associated with use of the PIs and nucleoside reverse transcriptase inhibitors (NRTI), its etiology in patients receiving ART is complex, and is modulated by lifestyle factors and HIV infection itself. While NNRTIs have been shown to have a favorable safety profile in terms of lipodystrophy complications, within the NNRTI treatment class, different effects on lipids are seen.

The lipid and lipodystrophy effects of individual NNRTIs in published clinical trials are discussed in detail below.

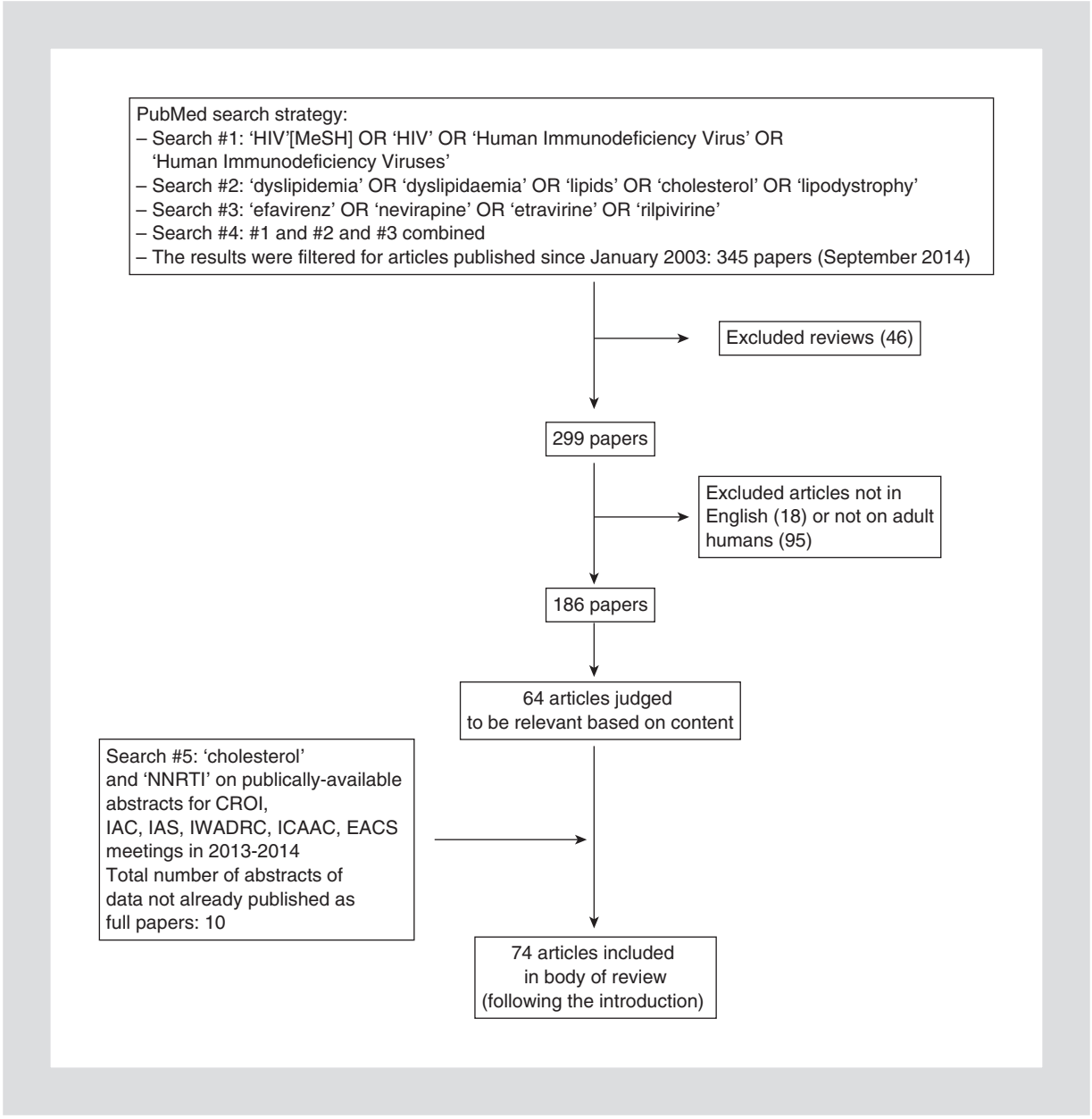

Figure 1. *Search strategy.*

Efavirenz

Dyslipidemia

Comparative trials of efavirenz with PIs have shown that the risk for hypertriglyceridemia is generally lower with efavirenz than with the PIs, but there is considerable variability. In the ACTG 5142 study, after a total of 96 weeks, although non-HDL and HDL cholesterol changes were not significantly different between the efavirenz and (ritonavir boosted; /r) lopinavir plus two NRTI treatment groups, median triglyceride increases were lower with efavirenz treatment (+19 mg/dl) than lopinavir/r (+46 mg/dl at week 96) (Fig. 2)[11]. Indeed, several other studies have also demonstrated a smaller effect of efavirenz on triglycerides compared with lopinavir/r[12-17].

Lipid effects of efavirenz have also been compared with those of atazanavir/r in ART-naive patients[18-20]. In the ACTG 5202 study, there were greater increases from baseline to week 48 in TC, LDL- and HDL-cholesterol with efavirenz than with atazanavir/r for both

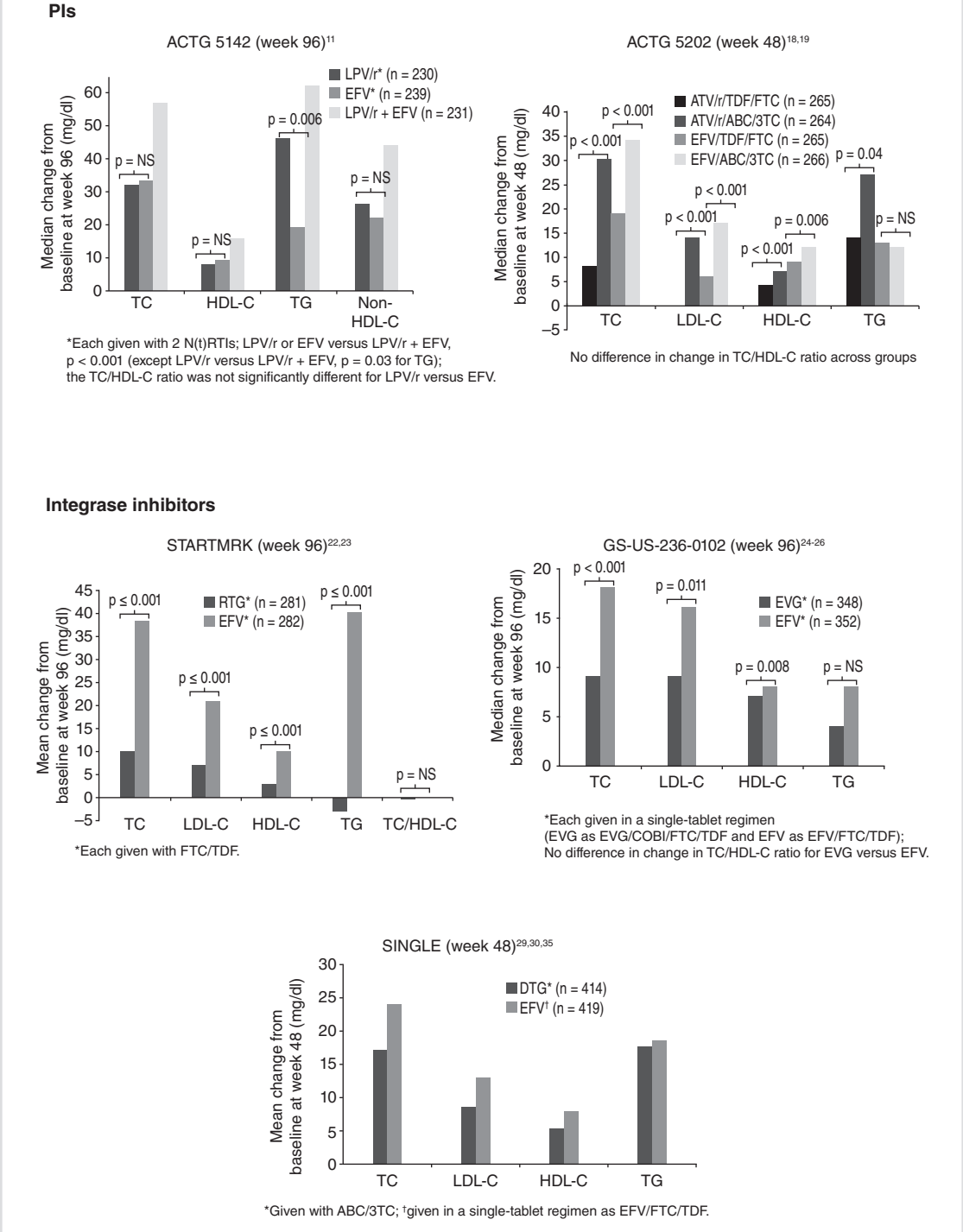

Figure 2. *Lipid changes from baseline for antiretroviral agents versus efavirenz in randomized, phase III multicenter studies of treatment-naive HIV-1-infected patients. Note that all changes are week 96 versus baseline except for the ACTG 5202 and SINGLE studies, for which week 48 changes are shown. 3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/lopinavir; COBI: cobicistat; DTG: dolutegravir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; LPV/r: lopinavir/ritonavir; NS: non-significant; N(t)RTI: nucleoside/tide reverse transcriptase inhibitor; RTG: raltegravir; TC: total cholesterol; TDF: tenofovir disoproxil fumarate; TG: triglyceride.*

tenofovir disoproxil fumarate (DF)/emtricitabine and abacavir/lamivudine background regimens (Fig. 2)[18,19]. Similar findings were reported in smaller study of efavirenz versus atazanavir/r in combination with tenofovir DF/emtricitabine[20]. Nevertheless, in both studies there was no significant difference between the efavirenz and atazanavir/r groups for the TC:HDL-cholesterol ratio.

Integrase inhibitors (twice-daily raltegravir and once-daily elvitegravir and dolutegravir), the CC-chemokine-receptor-5 (CCR5) antagonist maraviroc dosed twice daily, and the once-daily dual CCR5/CCR2 antagonist cenicriviroc, are novel classes of antiretrovirals[21]. Agents in these classes have a smaller effect on lipid metabolism compared with efavirenz. Studies in which the effects of efavirenz have been compared with those of integrase inhibitors in treatment-naive patients include: (i) the phase III STARTMRK trial, comparing raltegravir and efavirenz each with emtricitabine/tenofovir DF)[22,23]; (ii) the phase III GS-US-236-0102 trial, comparing a once-daily tablet of elvitegravir coformulated with cobicistat plus emtricitabine/tenofovir DF and efavirenz/emtricitabine/tenofovir DF)[24-26]; and (iii) the phase IIb SPRING-1 study[27,28] and the phase III SINGLE study, comparing dolutegravir and efavirenz administered with either tenofovir DF/emtricitabine or abacavir/lamivudine[29,30]. These dolutegravir studies and others in treatment-naive patients (SPRING-2 and FLAMINGO comparing dolutegravir to raltegravir and darunavir, respectively) all showed similar dolutegravir lipid patterns[31].

In the phase III STARTMRK trial, although changes in plasma lipids were greater during efavirenz than during raltegravir treatment, no differences between groups were seen in the TC:HDL-cholesterol ratio (efavirenz has no adverse effect on the TC:HDL ratio since it increases HDL in proportion to its effect on TC) (Fig. 2)[22,23]. In two randomized trials, switching from efavirenz to raltegravir, each in combination with an NRTI background regimen, significantly improved lipid levels[32,33]. In the phase III GS-US-236-0102 study, TC and LDL-cholesterol increases at week 96 were significantly lower in patients receiving a once-daily tablet of elvitegravir coformulated with cobicistat plus emtricitabine/tenofovir DF than efavirenz/emtricitabine/tenofovir (Fig. 2)[24-26]. Again, no differences between groups were seen in the TC:HDL-cholesterol ratio. In the randomized, open-label, phase IIIb STRATEGY-NNRTI study, virologically-suppressed HIV-1-infected patients on an NNRTI (74% on efavirenz/emtricitabine/tenofovir DF) switching to the once-daily tablet of elvitegravir coformulated with cobicistat plus emtricitabine/tenofovir, experienced small decreases from baseline in TC, LDL- and HDL-cholesterol[34]. In the phase IIb SPRING-1 study, the effects on lipids were smaller with dolutegravir treatment than with efavirenz, but there were no differences either from baseline or between drugs in the TC:HDL-cholesterol ratio[27,28]. The larger phase III SINGLE study compared these two regimens[29, 30] and again the effects on lipids appeared smaller with dolutegravir than with efavirenz (Fig. 2)[35]. A Bayesian network meta-analysis including phase III/IV randomized controlled clinical trials (up to August 2013) of treatment-naive HIV-1-infected patients was conducted to provide estimates of relative efficacy and safety for dolutegravir versus atazanavir/ritonavir, darunavir/ritonavir, efavirenz, elvitegravir/cobicistat, lopinavir/ritonavir, raltegravir and rilpivirine. Adjusting for the effect of the NRTI backbone, dolutegravir resulted in significantly lower associated TC, HDL- and LDL-cholesterol increases than efavirenz, with no difference in triglyceride levels[31].

The phase III MERIT trial data compared efavirenz with those of the CCR5 antagonist maraviroc, both agents administered with zidovudine/lamivudine in treatment-naive patients. Maraviroc was not associated with elevations in TC, LDL-cholesterol, or triglycerides and showed beneficial effects on these lipid parameters compared with efavirenz at week 96[36] (Fig. 3). In a post hoc analysis of lipid effects at baseline by the National Cholesterol Education Program (NCEP) group, among patients with TC and LDL-cholesterol levels[37] below NCEP treatment thresholds at baseline, a significantly greater proportion of efavirenz- versus maraviroc-treated patients exceeded those thresholds at 96 weeks (TC: 35 vs. 11%, $p < 0.0001$; LDL-cholesterol: 23 vs. 8%, $p < 0.0001$). For the TC:HDL-cholesterol ratio, median interquartile ranges were comparable between treatment groups: maraviroc, baseline: 4.1 (3.3-4.9); at week 96: 3.9 (3.1-4.8) vs. efavirenz, baseline: 4.0 (3.2-5.0); at week 96: 3.9 (2.9-4.8). In a phase IIb, double-blind, double-dummy, 48-week study comparing the once-daily dual CCR5/CCR2 antagonist cenicriviroc with efavirenz, each with emtricitabine/tenofovir DF, in treatment-naive patients, TC and LDL-cholesterol decreased significantly with cenicriviroc but increased with efavirenz ($p < 0.05$)[38].

Table 1. Body fat distribution analyzed by dual-energy x-ray absorptiometry in treatment-naive HIV-1-infected patients in randomized, phase III multicenter studies of antiretroviral agents versus efavirenz

Study	Treatments	DEXA assessments	Proportion of patients with lipoatrophy	Change in limb fat versus baseline	Change in trunk fat versus baseline
ACTG 5005s[41]	Patients (n = 157) randomized (double-blind) to: – NFV (n = 47) – EFV (n = 51) – NFV + EFV (n = 59) Administered with zidovudine/lamivudine or stavudine/didanosine	DEXA at baseline and every 16 weeks until week 144	Not reported	Median % (absolute) change at week 144 (p value vs. baseline) – NFV: –23.8% (–0.8 kg) (p = NS) – EFV: +2.4% (+2.0 kg) (p = NS) – NFV + EFV: –21.4% (–2.0 kg) (p = 0.05) – NFV/EFV + EFV: –23.8% (–1.9 kg) (p = 0.05)	Median % (absolute) change at week 144 (p value vs. baseline) – NFV: +2.7% (+0.3 kg) (p = NS) – EFV: +32% (+3.5 kg) (p = 0.01) – NFV + EFV: +6.9% (+0.6 kg) (p = NS) – NFV/EFV + EFV: +6.4% (+0.3 kg) (p = NS)
ACTG 5142[11]	Patients (n = 693, DEXA) randomized (open-label) to: – LPV/r (n = 234) – EFV (n = 225) – LPV/r + EFV (n = 234) Administered with lamivudine and zidovudine, stavudine or tenofovir	DEXA at baseline and weeks 48 and 96	> 20% loss of limb fat – LPV/r: 17% – EFV: 32% – LPV/r + EFV: 9% ($p \leq 0.023$ pair-wise comparison between treatment groups)	Median % (absolute) change at week 96 – LPV/r: +9.8% (+0.7 kg) – EFV: +1.4% (+0.05 kg) – LPV/r + EFV: +17.6% (+1.1 kg) ($p \leq 0.013$ pair-wise comparison between treatment groups)	Trunk fat increased from a median of 8.2 kg (IQR: 5.0-12.2) at entry to 10.4 kg (IQR: 6.8-14.4) at week 96 (p = NS pair-wise comparison between treatment groups)
ACTG 5224s[42]	Patients (n = 269) randomized to blinded ABC/3TC versus TDF/FTC: – ATV/r/TDF/FTC (n = 65) – ATV/r/ABC/3TC (n = 65) – EFV/TDF/FTC (n = 69) – EFV/ABC/3TC (n = 70)	DEXA at baseline and weeks 24, 48, 96, 144 and 192	> 10% loss of limb fat (primary endpoint of substudy) – ATV/r/TDF/FTC: 15.6% – ATV/r/ABC/3TC: 16.3% – EFV/TDF/FTC: 14.3% – EFV/ABC/3TC: 18.9% (p = NS ATV/r vs. EFV) > 20% loss of limb fat (post hoc analysis) – ATV/r/TDF/FTC: 0% – ATV/r/ABC/3TC: 6.1% – EFV/TDF/FTC: 8.9% – EFV/ABC/3TC: 3.8% (p = NS ATV/r vs. EFV)	Mean % (absolute) change at week 96 (secondary endpoint of substudy) – ATV/r: +30.4% (+1.88 kg) – EFV: +16.5% (+0.96 kg) ($p \leq 0.01$ ATV/r vs. EFV)	Mean % (absolute) change at week 96 (post hoc analysis) – ATV/r: +36.5% (+2.42 kg) – EFV: +21.1% (+1.33 kg) ($p < 0.05$ ATV/r vs. EFV)
STARTMRK[25]	Patients (n = 111, DEXA substudy) randomized (double blind) to: – RTG (n = 55) – EFV (n = 56) Administered with TDF/FTC	DEXA at baseline and weeks 48 and 96	> 20% loss of appendicular fat – RTG: 8% (3/37) – EFV: 5% (2/38)	Mean % change in appendicular fat at week 96 – RTG: +18.2% – EFV: +17%	Mean % change at week 96 – RTG: +21.6% – EFV: +25.5%

(Continue)

Table 1. Body fat distribution analyzed by dual-energy x-ray absorptiometry in treatment-naive HIV-1-infected patients in randomized, phase III multicenter studies of antiretroviral agents versus efavirenz *(Continued)*

Study	Treatments	DEXA assessments	Proportion of patients with lipoatrophy	Change in limb fat versus baseline	Change in trunk fat versus baseline
ECHO/ THRIVE DEXA substudy[74]	Patients (n = 413, DEXA substudy) randomized (double blind) to: – RPV (n = 209) – EFV (n = 204) Administered with FTC/TDF (60%), ZDV/3TC (30%) or ABC/3TC (10%)	DEXA at baseline and weeks 48 and 96	> 10% loss of limb fat (primary endpoint of substudy) – RPV: 15.6% – EFV: 17.2% (p = NS RPV vs. EFV) > 20% loss of limb fat (secondary endpoint of substudy) – RPV: 6.9% – EFV: 10% (p = NS RPV vs. EFV)	Median change at week 96 (secondary endpoint of substudy) – RPV: +12% (+0.73 kg) – EFV: +11% (+0.70 kg) (Within groups changes at week 96, p < 0.001 Wilcoxon signed-rank test; p = NS for RPV vs. EFV)	Median change at week 96 (secondary endpoint of substudy) – RPV: +16% (+1.29 kg) – EFV: +14% (+1.01 kg) (Within groups changes at week 96, p < 0.001 Wilcoxon signed-rank test; p = NS for RPV vs. EFV)

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; DEXA: dual-energy x-ray absorptiometry; EFV: efavirenz; FTC: emtricitabine; IQR: interquartile range; LPV/r: lopinavir/ritonavir; NFV: nelfinavir; NS: not significant; RPV: rilpivirine; RTG: raltegravir; TDF: tenofovir disproxil fumarate; ZDV: zidovudine.

Lipodystrophy

In vitro studies suggested that efavirenz may have some lipodystrophy effects, relating to an effect on adipocytes. Efavirenz has been shown to impair adipocyte differentiation and to produce an anti-adipogenic and proinflammatory response pattern *in vitro*[39]. These *in vitro* changes may suggest a role in lipodystrophy since high levels of proinflammatory cytokines are known to promote dyslipidemia and lipodystrophy[40]. However, in general, the trial data examining the relationship between efavirenz and lipodystrophy are variable, although the overall findings suggest that efavirenz has a minimal-to-neutral effect in terms of lipodystrophy. Results of different trials seem to be contradictory to some extent, which may be the result of differential effects of the background regimens within antiretroviral combinations.

Several clinical trials have reported the effects on body fat composition of efavirenz versus PIs, using objective measures of fat distribution such as dual-energy x-ray absorptiometry (DEXA)[11,25,41-43]. In the ACTG 5005 study, patients in the efavirenz group showed less lipoatrophy than those receiving a PI regimen (Table 1); there was an additional decrease in limb fat of 8.7% per year for the combined nelfinavir and nelfinavir plus efavirenz group compared with the efavirenz group (p = 0.03; adjusted for nucleoside backbone)[41]. Among the subgroup of patients receiving zidovudine/lamivudine, after week 32 there was a 2.7% increase in limb fat per year with efavirenz versus a 7.9% decrease per year for the combined nelfinavir and nelfinavir plus efavirenz group (p = 0.03).

In contrast, in the ACTG 5142 study, lipoatrophy was more frequent with efavirenz than with lopinavir/r when combined with stavudine or zidovudine and less frequent when either agent was combined with tenofovir DF compared with stavudine or zidovudine; it was least frequent with the nucleoside/tide reverse transcriptase inhibitor (N[t]RTI)-sparing efavirenz plus lopinavir/r regimen[11], consistent with previous data[4] suggesting that NRTIs play a principal role in lipodystrophy. In ACTG 5142, the median increases in limb fat from baseline to week 96 (1.4 vs. 9.8 vs. 17.6%, for efavirenz plus two N(t)RTIs vs. lopinavir/r plus two N(t)RTIs vs. efavirenz plus lopinavir/r, respectively) and incidences of lipoatrophy (> 20% loss in limb fat; 32 vs. 17 vs. 9%) were significantly different among treatment groups (Table 1).

Other studies have shown no difference between efavirenz and PI-containing regimens. In the ACTG 5224 study (substudy of 5202: abacavir/lamivudine vs. emtricitabine/tenofovir DF in combination with efavirenz or atazanavir/r) at week 96, although the estimated mean increase from baseline in visceral adipose tissue as assessed by CT scan was lower with efavirenz versus atazanavir/r (12.4 vs. 26.6%; p = 0.09), the percentage change in visceral:total adipose tissue was similar in the two groups[42]. Further, the abacavir/lamivudine and tenofovir DF/emtricitabine-based regimens all increased limb and visceral fat, with a similar prevalence of lipoatrophy (Table 1). The reported increases in trunk fat on efavirenz treatment in the above studies were not significantly different to those seen on PI therapy. A more recent study comparing efavirenz with lopinavir/r when combined with tenofovir DF and emtricitabine showed both regimens were associated with an increased expression of proinflammatory cytokine genes and with an increase in subcutaneous fat[43].

The effects of efavirenz on lipodystrophy have also been compared with those of the integrase inhibitor raltegravir (each administered with tenofovir DF/emtricitabine) in the STARTMRK study[25]. Most patients experienced modest gains in body fat at week 96, which were similar in the two treatment groups (Table 1).

Nevirapine

Dyslipidemia

Use of nevirapine appears to be associated with fewer lipid disturbances than efavirenz[44-46]. The 2NN study compared the lipid effects of nevirapine and efavirenz, both administered in combination with stavudine and lamivudine, over 48 weeks of treatment[44]. The observed increase in non-HDL-cholesterol was smaller for patients receiving nevirapine than among those receiving efavirenz, as were increases in triglycerides and in LDL-cholesterol (Fig. 3). The observed increase in the HDL-cholesterol level was significantly greater for patients receiving nevirapine (n = 417, 42.5%) than for patients receiving efavirenz (n = 289, 33.7%; p = 0.036). The increase in TC was lower with nevirapine than efavirenz (26.9 vs. 31.1%; p = 0.073), resulting in a 4.1% decrease in the TC:HDL-cholesterol ratio for patients receiving nevirapine, whereas patients receiving efavirenz experienced a 5.9% increase in the TC:HDL-cholesterol ratio (p < 0.001).

These differences remained, or even increased, after adjusting for changes in HIV-1 RNA and $CD4^+$ cell levels, indicating an effect of the drugs on lipids over and above that which might be explained by suppression of HIV-1 infection. The higher HDL-cholesterol combined with a lower TC:HDL-cholesterol ratio, as has been observed in patients receiving nevirapine but not efavirenz[44,45], in the general population would be associated with a decrease in cardiovascular disease risk.

Two studies have also demonstrated improvements in patients' lipid profiles following a switch from efavirenz to nevirapine in their ART regimens. In a randomized, controlled study the switch from efavirenz to nevirapine was associated with a significant decrease in the patients' LDL-cholesterol level at one year compared with continuation of efavirenz therapy (p < 0.04)[47]. In the second study, a retrospective analysis of data from patients treated at an HIV-specialty private practice in the USA, patients who were switched from efavirenz to nevirapine because of neuropsychiatric side effects or elevated plasma lipids showed significant improvements in their lipid levels (all changes p < 0.05)[48].

With some exceptions[49], nevirapine has also been shown to have a more favorable lipid profile versus PIs in clinical trials[47,48,50-55]. For example, in a study in which patients switched PI therapy for nevirapine without changing nucleoside analogs, patients who had serum triglyceride levels > 400 mg/dl showed a 75% decrease at 12 months versus level at switch (p < 0.02) and this change from baseline remained statistically significant over three years (p < 0.04)[51]. Serum cholesterol levels also showed a marked initial reduction (–25%; p < 0.02) and remained lower at the end of the follow-up period (p < 0.015). However, at the three-year evaluation, complete normalization of mean serum cholesterol and triglyceride levels had not been achieved. In another study which evaluated the metabolic effects at 24 months following a switch from the PI to nevirapine (or efavirenz or abacavir) in the ART regimen, the patients' HDL-cholesterol level increased by 21% (p < 0.001) and the TC:HDL-cholesterol ratio decreased by 19% (p < 0.01)[53]. Although there was a significant decrease in triglyceride levels during the first year, by 24 months most of this initial loss had been regained. A further switch study in which patients either continued with their PI regimen (n = 79) or

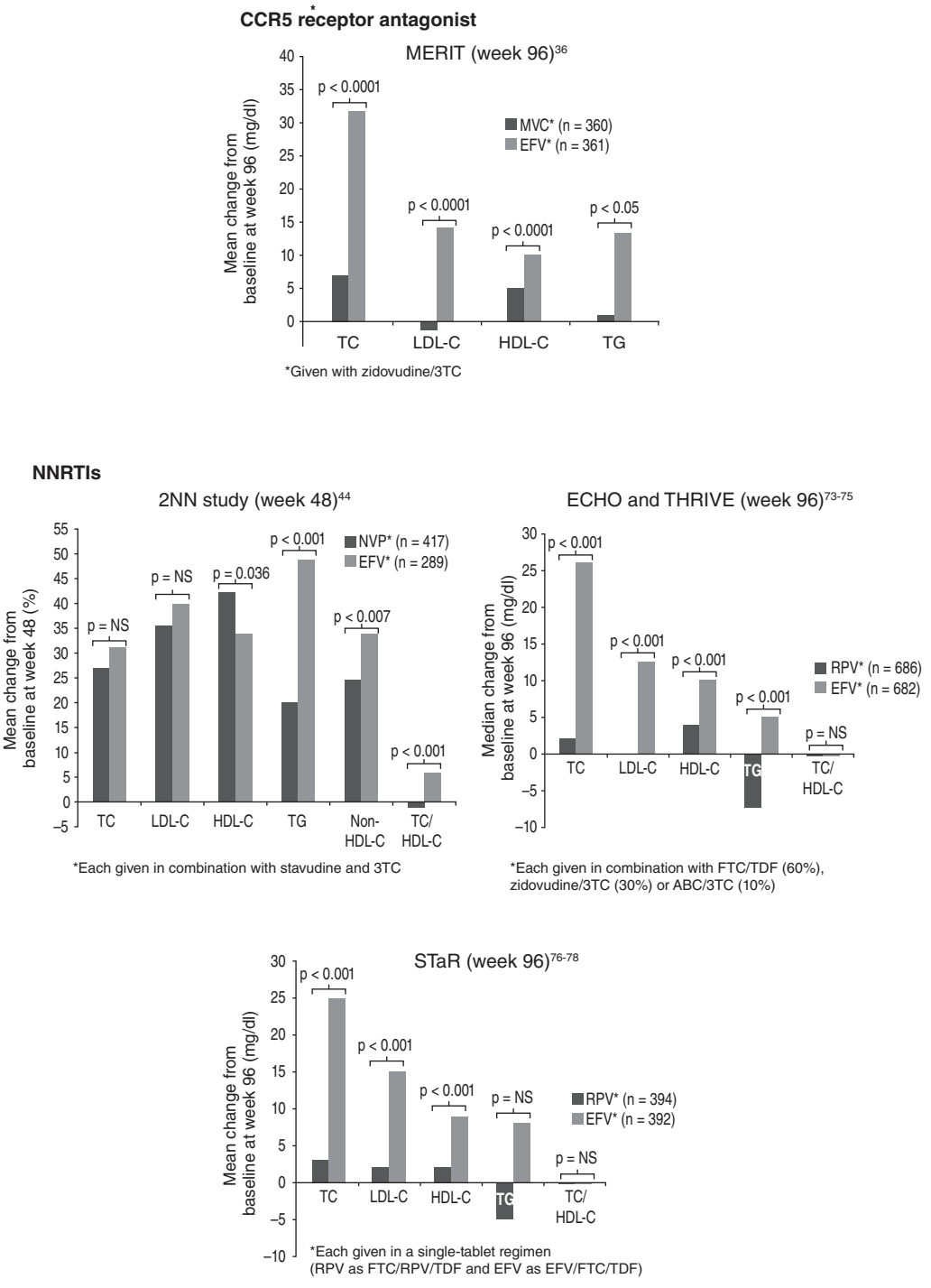

Figure 3. *Lipid changes from baseline for antiretroviral agents versus efavirenz in randomized, phase III multicenter studies of treatment-naive HIV-1-infected patients. Note that all changes are week 96 versus baseline except for the 2NN study, for which week 48 changes are shown. All changes from baseline are in mg/dl except for the 2NN study, for which the changes are in percentage. 3TC: lamivudine; ABC: abacavir; EFV: efavirenz; FTC: emtricitabine; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; MVC: maraviroc; NS: non-significant; NVP: nevirapine; RPV: rilpivirine; TC: total cholesterol; TDF: tenofovir disoproxil fumarate; TG: triglyceride.*

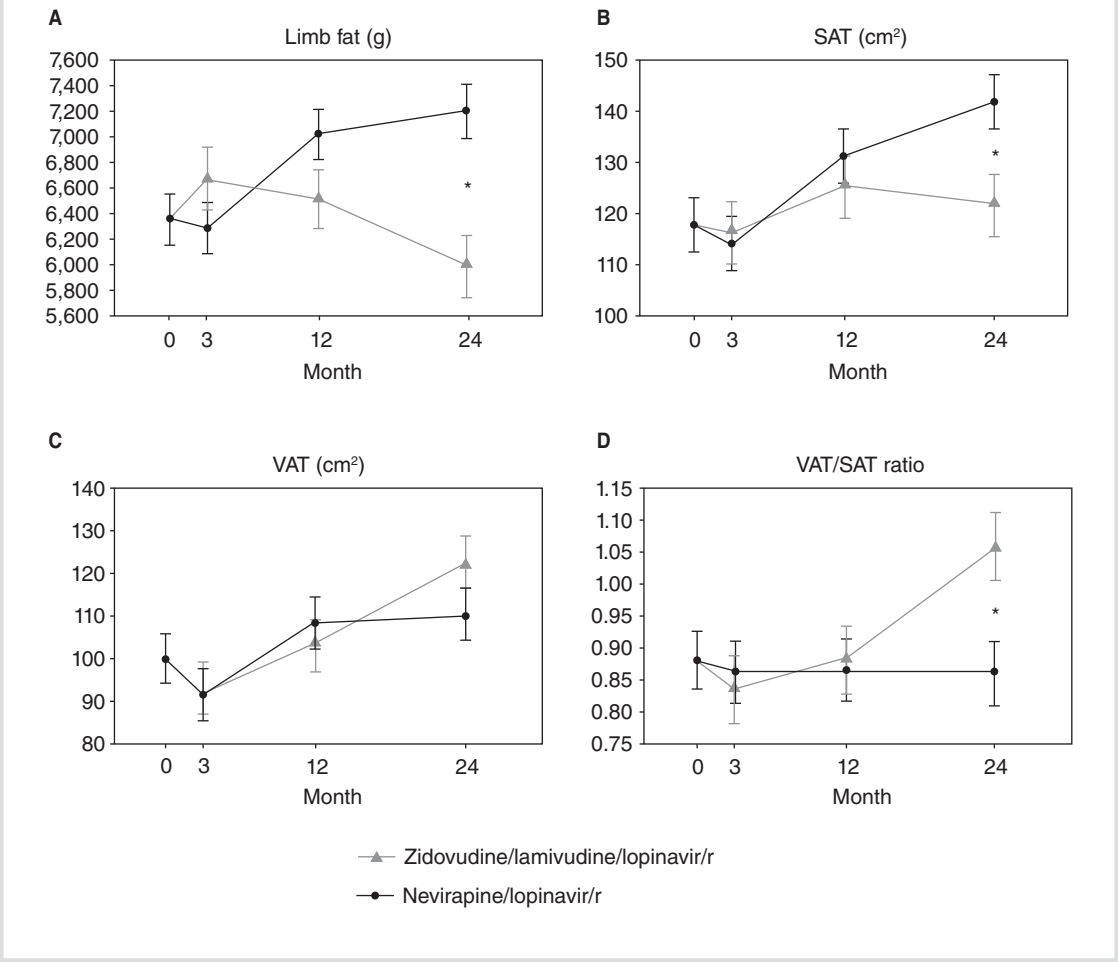

Figure 4. *Changes in body fat composition in patients receiving zidovudine/lamivudine plus lopinavir/r or nucleoside/tide reverse transcriptase inhibitor-sparing antiretroviral therapy with nevirapine plus lopinavir/r*[60]. SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.

replaced the PI with nevirapine (n = 81) showed that while, after 48 weeks, the number of patients with severe hypertriglyceridemia (triglycerides > 400 mg/dl) had increased from four to 11 in the PI group, in the nevirapine group it decreased from 11 to six patients[52].

Lipid effects of nevirapine have also been compared with those of atazanavir/r, each combined with emtricitabine/tenofovir DF, in antiretroviral-naive patients. In ARTEN, a randomized, open-label, noninferiority trial[56,57], increases from baseline in HDL-cholesterol (9.7 vs. 3.9 mg/dl; p < 0.0001) and apolipoprotein A1 (0.18 vs. 0.08 g/l; p < 0.0001) were significantly greater with nevirapine than with atazanavir/r, while triglycerides increased less with nevirapine than with atazanavir/r (0.02 vs. 27.80 mg/dl; p = 0.0001). Mean changes from baseline in the TC:HDL-cholesterol ratio were –0.24 for nevirapine versus 0.13 for atazanavir/r (p = 0.0001). NEWART, a randomized phase IV trial[58], also demonstrated a greater increase in HDL-cholesterol at week 48 on nevirapine versus on atazanavir/r treatment (9.6 vs. 3.5 mg/dl; p = 0.016). The changes in TC:HDL-cholesterol ratio at week 48 were –0.38 for nevirapine and –0.02 for atazanavir/r (p = 0.038).

Lipodystrophy

As with efavirenz, available clinical trial data regarding the impact on lipodystrophy of switching

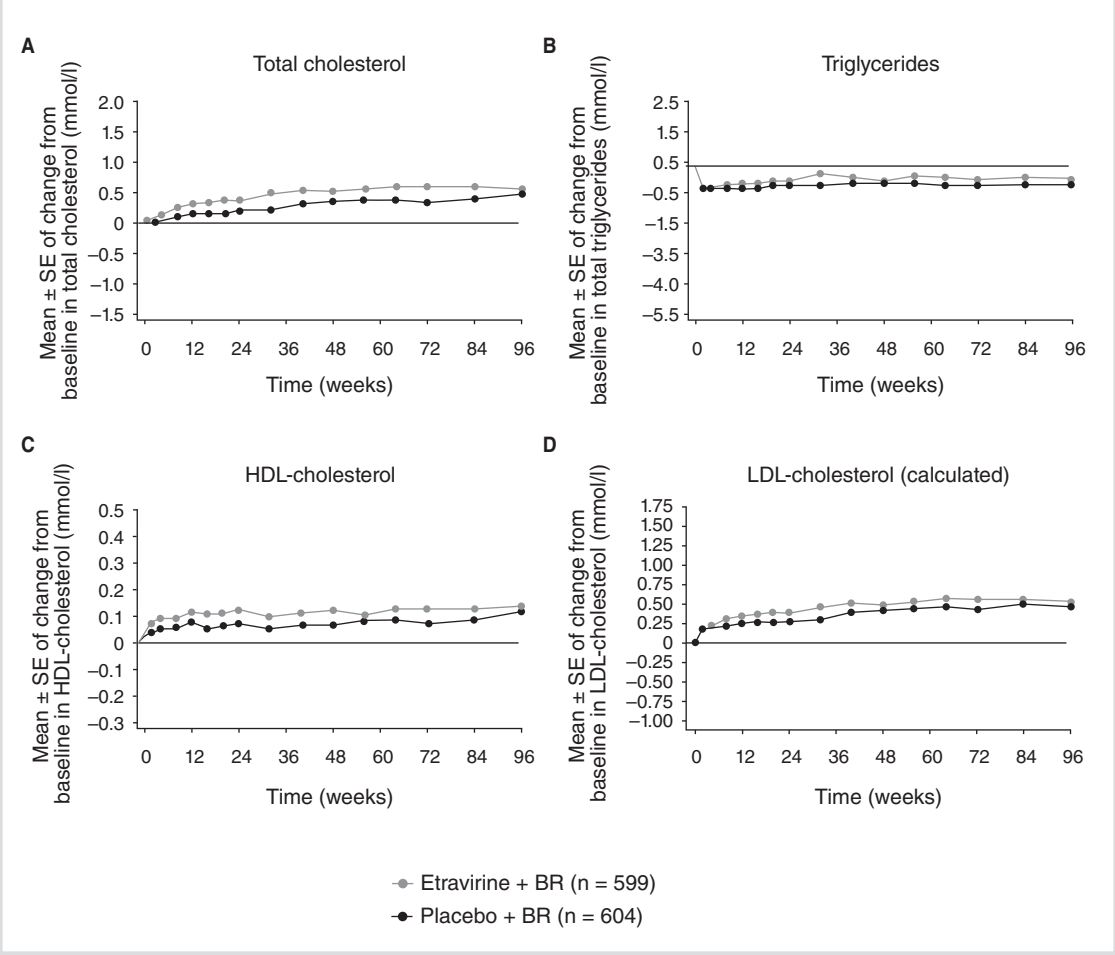

Figure 5. *Mean changes in fasted lipids over 96 weeks with etravirine vs. placebo treatment in the DUET trials[63]. HDL: high-density lipoprotein; LDL: low-density lipoprotein; SE: standard error; BR: background regimen* (reproduced with permission from Pierre-Marie Girard).

from a PI– to a nevirapine-based regimen are conflicting, and may be a consequence of the contribution of the background N(t)RTI agents in the regimens and study durations. Further, some of the studies are in a small number of patients and should therefore be interpreted with caution.

Data have shown that such a switch can lessen lipodystrophy body-shape changes[52]. In this study, while lipodystrophy changes increased by 15% in patients who continued on PI treatment (n = 79), they decreased by 4% among patients who switched to nevirapine (n = 81)[52]. However, other studies have shown no beneficial impact on lipodystrophy of such a switch[53,59].

Data from clinical trials of N(t)RTI-sparing regimens using nevirapine showed improvements in lipodystrophy[60-62]. In a study in which treatment-naive patients were randomized to treatment with zidovudine/lamivudine plus lopinavir/r or nevirapine plus lopinavir/r, the N(t)RTI regimen (but not the N[t]RTI-sparing regimen) was associated with lipoatrophy and greater relative intraabdominal lipohypertrophy[60]. In the small zidovudine/lamivudine plus lopinavir/r subset (n = 22), limb fat decreased progressively by a mean of 684 g (p = 0.02) up to 24 months while abdominal fat increased, but exclusively in the visceral compartment (+21.9 cm^2; p = 0.008). In contrast, in the nevirapine plus lopinavir/r group (n = 26), a generalized increase in fat mass was observed (Fig. 4). After two years, limb fat in patients in the nevirapine plus lopinavir/r group was 1,223 g higher than in patients in the zidovudine/lamivudine

plus lopinavir/r group (p = 0.0002). Another study in which patients switched to nevirapine plus lopinavir/r treatment demonstrated an improvement in mitochondrial parameters, although there were no significant improvements in DEXA scan results versus lopinavir/r plus two NRTIs at 48 weeks[61]. In a study in which patients with lipoatrophy switched from a thymidine analog-containing regimen to nevirapine plus lopinavir/r, there were significant (p < 0.01) increases at 48 weeks following switching in subcutaneous thigh fat (+17%) and subcutaneous abdominal tissue (+33%) and an 11% decrease in the visceral:total adipose tissue ratio[62].

Etravirine

Dyslipidemia

The randomized DUET studies showed that the etravirine and placebo groups had generally similar changes from baseline in lipid levels at week 96[63]. Patients stable on virologically failing treatment with documented NNRTI resistance and ≥ 3 PI resistance mutations were randomized to receive twice-daily etravirine or placebo (each with darunavir/r, optimized NRTIs, and optional enfuvirtide). Figure 5 shows the mean changes in fasted TC, HDL-, LDL-cholesterol, and triglyceride levels over 96 weeks from the pooled DUET-1 and -2 study data. Lipid changes on etravirine treatment were comparable with those in patients who received placebo. The incidence of lipid abnormalities over 96 weeks was low and generally similar in the etravirine and placebo groups, although there was a trend towards an increased frequency of grade 3 TC elevations (9% of etravirine patients vs. 6% with placebo) and grade 3 or 4 triglyceride elevations (11% etravirine vs. 7% with placebo) with etravirine. The TC:HDL-cholesterol ratio was also generally similar over time in the etravirine and placebo groups. A phase IIb, single-arm, open-label, multicenter, 48-week US trial investigated the N(t)RTI-sparing regimen of etravirine 400 mg once daily and darunavir/r 800/100 mg once daily in HIV-1-infected, treatment-experienced patients or treatment-naive patients with transmitted resistance to ART (INROADS)[64]. While there were increases in LDL-, HDL-cholesterol, TC, and triglycerides from baseline to week 48, the TC:HDL-cholesterol ratio remained relatively unchanged.

In the UK Switch study, switching from efavirenz plus two N(t)RTIs to etravirine plus two N(t)RTIs resulted in significant reductions in TC and LDL-cholesterol[65]. Also, in the Switch EE study, there was a significant decline in TC, LDL-cholesterol, and triglyceride levels after replacing efavirenz with etravirine[66]. In the Spanish Etraswitch study, patients who switched to etravirine showed statistically significant reductions in TC, HDL-cholesterol, and triglycerides versus no significant changes in patients who continued on PIs[67]. Similarly, in two prospective cohort studies, one of switching from PI or NRTI regimens to etravirine plus raltegravir[68] and the other switching from efavirenz or ritonavir-boosted PIs to an etravirine-containing regimen[69], and a retrospective case review of switching from other efavirenz-containing regimens (predominantly Atripla®, efavirenz/emtricitabine/tenofovir DF) or PI-based regimens to etravirine plus two N(t)RTIs[70], switching to an etravirine-based regimen resulted in an improvement in lipid profiles.

While etravirine treatment is not indicated in treatment-naive patients, data from the SENSE study, in which such patients received either once-daily etravirine 400 mg (n = 79) or efavirenz 600 mg (n = 78) plus two nucleoside analogs (abacavir/lamivudine or zidovudine/lamivudine), showed that lipid elevations at 48 weeks were smaller on etravirine versus efavirenz treatment[71]. There were significantly larger increases in TC (+0.61 mmol/l; p < 0.0001), HDL-cholesterol (+0.15 mmol/l, p = 0.004), LDL-cholesterol (+0.35 mmol/l; p = 0.005) and triglycerides (+0.33 mmol/l; p = 0.03) at week 48 in the efavirenz group versus etravirine. There were also fewer grade 3/4 elevations in TC, LDL-cholesterol and triglycerides in the etravirine group (2, 1, and 0 patients, respectively) versus efavirenz (8, 6, and 2 patients, respectively).

Lipodystrophy

To date there has been no evidence of a link between the use of etravirine and lipodystrophy syndrome, and no full articles have been published on etravirine and lipodystrophy. In the single-arm, open-label, phase IIb INROADS study of etravirine 400 mg once daily and darunavir/r 800/100 mg once daily, median changes from baseline to week 48 in limb fat (+7.9 to +9.0 kg) and abdominal fat (+12.0 to +12.3 kg) were not considered clinically relevant. From baseline to week 48, 10 patients (29%) experienced > 20% loss of limb fat and 10 patients (29%) experienced > 20% gain in trunk fat[72].

Rilpivirine

Dyslipidemia

Two phase III clinical trials, ECHO and THRIVE, demonstrated a superior lipid profile with rilpivirine versus efavirenz treatment[73-75]. In these studies, treatment-naive, HIV-1-infected adults received once-daily rilpivirine 25 mg (n = 686) or efavirenz 600 mg (n = 682), with background tenofovir DF/emtricitabine (ECHO), or tenofovir DF/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine (THRIVE). While levels of TC, LDL-, HDL-cholesterol and triglycerides remained close to baseline throughout the 96-week treatment period in the rilpivirine group, in the efavirenz group there were significantly greater increases in all four of these lipid measures at week 96 (Fig. 3). This was reflected in the incidences of grade 3/4 treatment-emergent lipid abnormalities (TC: 0.1% of rilpivirine-treated patients vs. 3% for efavirenz, $p < 0.0001$; LDL-cholesterol: 1% rilpivirine vs. 6% efavirenz, $p < 0.0001$; triglycerides: 0.6% rilpivirine vs. 3% efavirenz, $p = 0.0002$). In addition, proportions of patients with at least one fasted lipid value classified as abnormal using NCEP cutoff values were lower in the rilpivirine group than the efavirenz group (TC above normal: rilpivirine 22%, efavirenz 52%, $p < 0.0001$; LDL-cholesterol above normal: rilpivirine 21%, efavirenz 44%, $p < 0.0001$; HDL-cholesterol below normal: rilpivirine 58%, efavirenz 47%, $p = 0.0186$; triglycerides above normal: rilpivirine 40%, efavirenz 55%, $p < 0.0001$). However, there was no difference in the TC:HDL-cholesterol ratio between groups ($p = 0.17$). The benefits were consistent by N(t)RTI background regimen, although the differences between treatment groups were more pronounced in patients receiving tenofovir DF/emtricitabine (n = 1096) compared with zidovudine/lamivudine (n = 204) or abacavir/lamivudine (n = 68). The 96-week data from the STaR study comparing rilpivirine versus efavirenz (both as single-tablet regimens including emtricitabine/tenofovir DF) showed that rilpivirine was associated with lesser changes from baseline in TC (+3 vs. +25 mg/dl), LDL-cholesterol (+2 vs. 15 mg/dl), and triglycerides (–5 vs. +8 mg/dl) than efavirenz (Fig. 3). However, again the change from baseline in TC:HDL-cholesterol at week 96 was similar (–0.2 mg/dl) in both groups[76-78].

Rilpivirine/tenofovir DF/emtricitabine single-tablet regimen studies have also demonstrated favorable effects on lipids with rilpivirine when switching from efavirenz or a boosted PI. In study GS111, switching from efavirenz/emtricitabine/tenofovir DF to rilpivirine/emtricitabine/tenofovir DF in virologically suppressed patients resulted in an improvement in 48-week fasting lipid profiles, including TC, LDL-cholesterol, triglycerides, and the TC: HDL-cholesterol ratio[79]. Fasting TC fell by 0.62 mmol/l from baseline and LDL-cholesterol by 0.41 mmol/l (both $p < 0.001$). The TC:HDL-cholesterol ratio decreased by 0.35. In an multicenter, open-label study of suppressed individuals on efavirenz/emtricitabine/tenofovir DF with CNS toxicity switching to rilpivirine/emtricitabine/tenofovir DF, significant improvements were seen at week 24 for TC (–0.9 mmol/l; $p < 0.001$), LDL cholesterol (–0.57 mmol/l; $p < 0.001$), and triglycerides (–0.35 mmol/l; $p < 0.001$)[80]. In the GS106 (SPIRIT) study, switching from a PI/r plus two N(t)RTIs to rilpivirine/emtricitabine/tenofovir DF similarly resulted in an improvement in 24-week fasting lipid profiles (e.g. triglycerides showed a 54 mg/dl decrease with rilpivirine/emtricitabine/tenofovir DF versus 3 mg/dl increase in the PI-based group; $p < 0.001$)[81]. The TC:HDL-cholesterol ratio was lower for emtricitabine/rilpivirine/tenofovir DF versus the PI/r (–0.27 vs. +0.08; $p < 0.001$), and the NCEP classification and 10-year Framingham risk score showed significantly greater improvement in the emtricitabine/rilpivirine/tenofovir DF group versus the PI/r plus two N(t)RTIs ($p \leq 0.001$)[81].

In the aforementioned Bayesian network meta-analysis of phase III/IV randomized controlled clinical trials in treatment-naive HIV-1-infected patients[35], and adjusting for NRTI backbone, dolutegravir was not significantly different from rilpivirine for changes in cholesterol or triglyceride levels.

Lipodystrophy

Although rilpivirine has been shown *in vitro* to produce an anti-adipogenic and proinflammatory response pattern in adipocytes, unlike efavirenz, the concentrations of rilpivirine required to induce such responses are not seen *in vivo*[39]. A DEXA substudy analysis of body fat changes on rilpivirine versus on efavirenz treatment in the ECHO and THRIVE studies[74] showed that patients receiving rilpivirine had slightly more limb fat gain than those receiving efavirenz (median changes from baseline: 0.73 vs. 0.7 kg at week 96; both $p < 0.0001$) (Table 1). Comparable median limb fat increases were recorded at week 96 in the subgroup of patients who received background emtricitabine/tenofovir DF treatment, but there were limb

fat decreases in those who received zidovudine/lamivudine (rilpivirine –0.41 kg, efavirenz –0.81 kg). The efavirenz data reported in this substudy are consistent with ACTG 5142 (Table 1). Comparable proportions of patients in the rilpivirine and efavirenz groups had a ≥ 10% (15.6 vs. 17.2%, respectively) or ≥ 20% (6.9 vs. 10.0%) decrease from baseline in limb fat.

Clinical perspective

As with other classes of antiretroviral agents, NNRTIs are associated with lipid changes, though individual agents exhibit different effects. Trial data show that the selection of background N(t)RTIs has a significant impact on the degree of dyslipidemia and lipodystrophy that may be expected with a given NNRTI-based regimen.

Dyslipidemia

Comparative trials of efavirenz with PIs have shown that the risk for hypertriglyceridemia is lower with this NNRTI than with the use of lopinavir/r in the phase III ACTG 5142 study[11]. However, there is a greater likelihood of hypercholesterolemia with efavirenz versus atazanavir/r[18-20], findings that could also be influenced by the lopinavir/r regimen requiring twice the ritonavir dose than the atazanavir/r regimen. Use of efavirenz was also associated with significantly greater increases in plasma TC, LDL-cholesterol, and triglyceride levels compared with the newer NNRTI rilpivirine in the phase III clinical trials, ECHO, THRIVE, and STaR[73-78]. Data also indicate that efavirenz has a greater effect on plasma lipid levels than the integrase inhibitors: (i) raltegravir in the phase III STARTMRK trial[22,23]; (ii) elvitegravir in the phase III GS-US-236-0102 trial[24-26]; and (iii) dolutegravir in the phase IIb SPRING-1 study[27,28], the phase III SINGLE study[29,30,35] and in a meta-analysis[31]. Efavirenz also has a greater effect on plasma lipid levels than the CCR5 antagonist maraviroc in the phase III MERIT trial[36]. However, in most cases there was no difference in the change of the TC:HDL-cholesterol ratio between the efavirenz group and the comparator group[11,18-20,22-28,36-37,73-78]. Switching from efavirenz to the NNRTIs etravirine[65-70] or rilpivirine[79-81], or the integrase inhibitors raltegravir[32,33] or elvitegravir[34] has been shown to result in significant reductions in lipid levels. Furthermore, it should be noted that the background antiretroviral agents in the treatment regimens also play a considerable role in the development of dyslipidemia.

Lipodystrophy

Efavirenz has been shown to be associated with a similar gain in limb fat as PIs in the majority of head-to-head trials, except for study ACTG 5142 in which the increase in limb fat was lower than that observed with lopinavir[11]. Treatment with efavirenz or rilpivirine resulted in similar increases in limb fat in the ECHO and THRIVE DEXA substudy[74]. Also, increases in appendicular fat were similar in the efavirenz and raltegravir treatment groups in the STARTMRK study[25]. The effects of the background N(t)RTI regimen in the ECHO and THRIVE DEXA substudy (more limb fat loss with zidovudine/lamivudine than with emtricitabine/tenofovir DF) were consistent with those of previous trials. As such, there appears to be minimal potential for efavirenz or rilpivirine to result in the development of lipodystrophy, the choice of background N(t)RTIs being more important in this regard. Indeed, the influence of background N(t)RTIs is a confounding factor in lipodystrophy studies. For example, background regimens that include the thymidine analogs stavudine or zidovudine (stavudine > zidovudine) tend to be associated with a greater loss of limb fat than regimens including tenofovir DF or abacavir[41,57,82-84]. Also, use of thymidine analog-sparing regimens or a switch from a thymidine analog to tenofovir DF or abacavir have been shown to result in an increase in limb fat[11]. Another confounding factor in assessing the relative contributions of individual antiretrovirals is differences in the methodology (some studies used DEXA versus CT scan to measure fat distribution) and differing endpoints used in clinical trials (e.g. changes in limb fat of > 10, > 20 or > 30%).

Conclusions

The association between dyslipidemia and NNRTIs seems weaker than with ritonavir-boosted PIs. Within the NNRTI class, the newer agents have a more favorable effect on some lipid parameters than efavirenz. Increases in plasma lipid levels are also greater for efavirenz than the newer classes of antiretrovirals, the integrase inhibitors and CCR5 antagonists. However, the contribution of the background components of the antiretroviral regimen is clearly significant, so it is important to be aware of the different lipid effect profiles of all individual agents as well as the third agent. The choice of background N(t)RTI rather than the third agent appears to be the more important factor for the development of lipodystrophy.

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