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Switching to a Protease Inhibitor–Containing, Nucleoside-Sparing Regimen (Lopinavir/Ritonavir Plus Efavirenz) Increases Limb Fat But Raises Serum Lipid Levels:

Results of a Prospective Randomized Trial (AIDS Clinical Trial Group 5125s)

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Abstract

Background—Subcutaneous limb fat loss continues to be one the most troubling side effects of long-term antiretroviral regimens. Nucleoside analogues and protease inhibitors (PIs) have been linked to the development of this complication.

Methods—We evaluated the effects of nucleoside-sparing and PI-sparing regimens on fat distribution, bone mineral density, and metabolic parameters in 62 subjects, who were not selected for lipoatrophy, with advanced HIV (nadir CD4 count < 200 cells/mm³ or HIV RNA level > 80,000 copies/mL) and an undetectable HIV viral load. Participants were randomized to switch their initial successful antiretroviral regimen to open-label lopinavir/ritonavir (LPV/r) at a dose of 533/133 mg twice a day and efavirenz (EFV) at a dose of 600 mg/d (the nucleoside-sparing arm) versus EFV and 2 nucleoside analogues (the PI-sparing arm).

Findings—At week 48, the median change in limb fat in the nucleoside-sparing arm was 562 g (6%, interquartile range [IQR]: –218–1186 g) versus a loss of –242 g (–4%, IQR: –539–452 g) in the nucleoside-containing PI-sparing arm ($P = 0.086$). At the time of last observation (median = 102 weeks, IQR: 73–152 weeks), a median gain of 782 g (10%, IQR: –380–1168 g) of limb fat was noted in the nonnucleoside arm ($n = 22$) versus a loss of 850 g (–15%, IQR: –1270 to –526 g) in the nucleoside-containing arm ($n = 25$; $P = 0.002$).

Interpretation—The switch to a nucleoside-sparing combination antiretroviral regimen (LPV/r + EFV) was associated with significant improvement in limb fat. These results provide additional evidence that nucleoside analogues are important in the progressive limb fat loss that characterizes antiretroviral treatment and that switching medications can significantly improve this complication. This option has to be carefully balanced with the potential to increase serum lipid levels and the trend to increase virologic failure.

Keywords

antiretroviral switch; lipoatrophy; nucleoside sparing

The impressive success of antiretroviral therapy (ART) in reducing the morbidity and mortality associated with HIV disease has been tempered by frequent toxicities associated with chronic ART use. Lipid abnormalities, insulin resistance, increased cardiovascular risk, and lipodystrophy have been reported.¹ Lipodystrophy refers to body fat distribution changes that occur after the initiation of ART. Two distinct components have been described: limb fat atrophy (lipo-atrophy) and trunk and visceral fat accumulation. Limb lipoatrophy has become a common distinguishing characteristic associated with HIV and its treatment.^{2,3} This complication can profoundly affect the well-being of the patient, can be stigmatizing, and can be coincident with a cluster of metabolic complications.

Longitudinal studies evaluating the effect of ART initiation have demonstrated that within weeks of initiating ART, lean body mass and limb and trunk fat mass increase.^{4,5} With continued treatment for more than a year, limb fat mass slowly and progressively declines, whereas the gain in trunk fat mass is maintained.^{4,6,7} Patient-related factors that are associated with progressive limb fat mass loss include age,^{8,9} white race, female gender,⁷ low nadir CD4⁺ cell count, hepatitis C virus (HCV) coinfection,^{9–12} and specific polymorphisms in the tumor necrosis factor- α (TNF α) and ApoC3 genes.¹³ Treatment-related factors that may also contribute include exposure to stavudine (d4T)¹⁴ and, potentially, zidovudine (ZDV). Protease inhibitors (PIs) were initially thought to play a significant role in the development of lipoatrophy,¹⁵ but subsequent data have also implicated the nucleoside reverse transcriptase inhibitors (NRTIs).^{16,17} Some authors have suggested that PIs may contribute to the development of osteopenia or osteoporosis associated with HIV or its treatment,¹⁸ fat accumulation and lipid abnormalities,¹⁹ and glucose intolerance or diabetes.²⁰

Effective interventions for managing HIV lipoatrophy have not been identified. Several studies report that substituting the PI component of ART does not improve or reverse limb lipoatrophy.²¹ Treatment with the peroxisome proliferator-activated receptor- γ (PPAR γ) agonist rosiglitazone seemed to increase limb fat mass in patients with HIV-associated

lipoatrophy,²² but these findings were not confirmed in a large prospective randomized trial.²³ Pioglitazone was only modestly active in improving subcutaneous fat in the extremities.²⁴ Switching d4T or ZDV to abacavir (ABC) or tenofovir (TDF) has been reported to increase limb fat mass,^{25–28} however, with a decrease of limb lean mass in a study by Boyd et al.²⁸ Switching to regimens without NRTIs increased mitochondrial DNA content in fat and peripheral blood mononuclear cells,²⁸ a potential mechanism implicated in the development of lipoatrophy.²⁹ If osteopenia or osteoporosis, fat accumulation, lipid abnormalities, and insulin resistance are linked to PI use, the expectation would be that clinical improvements should occur after switching to alternative regimens that do not include these drugs.

In the AIDS Clinical Trials Group (ACTG) A5125s, we examined the effects of PI-containing NRTI-sparing and NRTI-containing PI-sparing regimens on fat distribution, changes in bone mineral density (BMD), and metabolic parameters in patients who switched their currently successful antiretroviral regimen to a PI-sparing or NRTI-sparing regimen. The primary objective was to quantify the changes in limb fat mass (using regional dual-energy x-ray absorptiometry [DEXA]) within and between each of the 2 treatment arms. The secondary objectives were to quantify changes in fasting lipids (high-density lipoproteins [HDLs], low-density lipoproteins [LDLs], total cholesterol, and triglycerides), fasting glucose, insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), hip and spine BMD, and serum markers of bone metabolism after switching ART; to examine relations between changes in regional fat, lipids, and insulin resistance; and to examine relations between baseline demographic variables, CD4⁺ lymphocyte cell counts, body mass index (BMI), limb fat mass, and changes in indices of glucose metabolism, lipids, and bone metabolism after switching ART.

METHODS

ACTG A5125s was the metabolic substudy of ACTG 5116, a class-sparing and regimen simplification study for patients with advanced HIV disease (defined as baseline CD4⁺ counts < 200 cells/mm³ or plasma HIV RNA levels > 80,000 copies/mL) who had reached an undetectable viral load (defined as an HIV-1 RNA level < 200 copies/mL) while on their first potent antiretroviral regimen for at least 18 months. Most ACTG A5116 participants were previously enrolled in ACTG 388,³⁰ a study that evaluated 2 4-drug regimens compared with a 3-drug regimen in patients with advanced disease. In that study, subjects received lamivudine (3TC) plus ZDV and indinavir, EFV plus indinavir, or nelfinavir plus indinavir and were monitored for 2.1 years. Further details about ACTG 388 can be found in the original publication³⁰ and on the Web site (<http://www.clinicaltrials.gov/>). Figure 1 shows a consort diagram of the current trial.

In the metabolic substudy ACTG A5125s (as in the parental trial ACTG 5116), patients with well-controlled viral replication were randomized to switch their current antiretroviral regimen to a PI-sparing regimen of 2 NRTIs with EFV (arm I) or to an NRTI-sparing regimen of EFV with lopinavir/ritonavir (LPV/r; arm II). Arm I nucleoside options were enteric-coated didanosine (ddI-EC) plus 3TC, ddI-EC plus ZDV, ZDV plus 3TC (or Combivir; GlaxoSmithKline, Philadelphia, PA), d4T plus 3TC, or ddI-EC plus d4T. There

was no randomization to the nucleoside options (they were selected by the primary providers and the participants).

Only LPV/r, EFV, d4T, ddI-EC, ZDV, 3TC, and fixed-dose 3TC and ZDV (Combivir) were provided in the study. Individuals did not have to be lipoatrophic to enter the study.

The study was reviewed and approved by the local institutional review board at each clinical research unit. All participants signed an informed consent form.

Measurements

All patients were evaluated for safety and virologic and immunologic responses at weeks 4 and 8 and then every 8 weeks until the study ended. In addition, all patients had assessments for regional fat mass, fasting lipid profiles, fasting insulin levels, venous lactate levels, and treatment adherence at 16-week intervals. The HOMA-IR³¹ was used to monitor glucose metabolism. Assessments of whole and regional body composition (adipose and lean tissue distributions) and regional BMD (lumbar spine and proximal hip [femoral neck and trochanteric regions]) were performed at entry, at week 48, and at the final ACTG A5116 study visit. All DEXA scans were centrally analyzed at Tufts University Body Composition Analysis Center. Fasting serum markers of bone formation (osteocalcin) and destruction (NTx telopeptides) were quantified at Quest Laboratories (Baltimore, MD) using enzyme-linked immunosorbent assays (ELISAs; CIS BIO International, Bedford, MA and Wampole Laboratories, Princeton, NJ, respectively). The planned duration of the study was 48 weeks, but because of the paucity of virologic endpoints, the main study and the substudy were extended until the last patient enrolled had completed 72 weeks of follow-up.

Statistical Considerations

Descriptive statistics were used to describe the study sample. The Fisher exact test was used to examine associations between categorical variables. Within-arm evaluations were performed using Wilcoxon signed-rank tests, and between-arm comparisons were performed using Kruskal-Wallis tests. Rank tests were performed for testing the association of covariates and changes in limb fat mass while controlling for the treatment effects.³²

All significance tests were 2-sided and performed at the 0.05 level. There was no adjustment for multiple testing; therefore, any marginal results need to be interpreted cautiously. The study was powered to detect a change of 400 g of limb fat within arms and a difference of 600 g between arms (80%; $\alpha = 0.05$) at week 48. All analyses presented are intention to treat, unless stated otherwise.

Sensitivity analyses were performed to evaluate the effect of missing primary endpoint data.

RESULTS

Sixty-two HIV-infected patients with an HIV RNA level <200 copies/mL were enrolled in this substudy ($n = 31$ participants in the NRTI + EFV arm and $n = 31$ participants in the LPV/r + EFV arm). The study sample was 85% male and 60% white, with a median age of 42 years (Table 1). Baseline demographic characteristics (gender, age, race, and intravenous

drug use) were not different between the groups. Baseline median CD4⁺ counts (444 cells/mm³ for the NRTI + EFV arm and 431 cells/mm³ for the LPV/r + EFV arm) and plasma HIV RNA levels were not different between the groups. Baseline markers of glucose and lipid metabolism and body fat distribution were not different between the groups. The lumbar baseline BMD scores were slightly higher and the serum NTx concentration was slightly lower in the NRTI + EFV arm. Approximately half of the patients were on their first combination of 2 NRTIs with 1 or 2 PIs, and half were on their first combination of 2 NRTIs with 1 PI and 1 NNRTI (see Table 1). The median duration of ART treatment was more than 110 weeks. The most commonly used PI was indinavir (69%), followed by nelfinavir (14%). Overall, the groups were well matched at baseline. The combination of d4T and ddI was not used in the study. Three participants were on that combination at baseline: 2 were randomized to the LPV/r + EFV arm, and 1 randomized to the NRTI + EFV arm changed that combination to a fixed combination of ZDV and 3TC.

At week 48, the median change in limb fat in the LPV/r + EFV arm showed an increase of 562 g (6%, interquartile range [IQR]: -218-1186 g; $P = 0.05$) compared with a loss of -242 g (-4%, IQR: -539-452 g; $P = 0.628$) in the NRTI + EFV arm (between-arm comparison, $P = 0.086$). At the time of the last DEXA scan (median = 102 weeks), the LPV/r + EFV arm had gained a median of 782 g (10%, IQR: -380-1168 g; $P = 0.07$) of limb fat versus a loss of -850 g (-15%, IQR: -1270 to -526 g; $P = 0.007$) in the NRTI + EFV arm (between-arm comparison, $P = 0.002$) (Fig. 2). These results were based on observed data. After imputing missing values by last observation carried forward, similar results were observed. Thus, we concluded that the “missingness” in the data was noninformative and we could trust the results from the observed data. There were no significant changes in limb lean mass between or within arms.

There was no evidence that baseline covariates (limb fat mass, gender, age, race, CD4⁺ cell count, and d4T drug use) were associated with limb fat change over time, adjusting for the treatment effect.

Within the NRTI + EFV arm, we conducted a post hoc comparison of limb fat changes at week 48 between the patients who continued on d4T ($n = 6$) versus those who were not on d4T (mainly ZDV; $n = 19$). There was no evidence of a significant difference in limb fat change within and between patients using d4T or not using d4T. At the time of the final visit, there was a significant decrease in limb fat in the patients using d4T ($P = 0.01$). There was no significant difference in the percentage of limb fat change between patients who stayed on d4T versus patients who did not stay on d4T (-22.40% vs. -13.28%; $P = 0.105$), however. These results should be interpreted with caution, because the study was not powered to detect differences between different NRTIs.

Trunk fat mass remained stable in both arms of the study. It was not significantly changed from baseline in within-or between-arm comparisons (Fig. 3).

There was no evidence of a difference in change of total BMD between the NRTI + EFV and LPV/r + EFV arms from baseline to week 48 ($P = 0.974$) and to the final visit ($P = 0.670$) (see Fig. 3B). Neither was there a significant change in BMD when the data obtained

from regional DEXA (lumbar spine and hip) or bone markers (osteocalcin and NTx) were evaluated (data not shown).

There were no significant changes within each arm or differences between arms in glucose, insulin, or HOMA-IR levels ($P = 0.74$, $P = 0.68$, and $P = 0.63$, respectively; Fig. 4).

At week 48, the LPV/r + EFV group had greater increases in triglycerides (85 vs. 11 mg/dL; $P = 0.01$), total cholesterol (19 vs. -7 mg/dL; $P = 0.009$), and non-HDL cholesterol levels (13 vs. -10 mg/dL; $P = 0.011$) compared with the NRTI + EFV group (Fig. 5). The percentage of participants with triglycerides greater than 500 mg/mL 48 weeks after the switch was 4% in the NRTI-containing arm and 8% in the LPV/r + EFV group. Changes in HDL cholesterol and free fatty acid levels were similar in both groups. There was an interaction between treatment arm and time for the measurement of cholesterol ($P < 0.0001$) and triglycerides ($P < 0.0001$), which suggests differences between the 2 treatment arms in these measurement changes over time (see Fig. 5). There was no evidence of an interaction between treatment arm and time to LDL cholesterol ($P = 0.09$) or HDL cholesterol ($P = 0.83$) measurements.

We also explored relations between changes in regional fat mass and measures of fasting lipids and insulin resistance. There were no relations between the changes in limb fat with the changes in glucose or lipid metabolism. At week 48, changes in limb lean mass, total body mass, and total body lean mass were directly related to the week 48 changes in fasting insulin concentration ($P = 0.004$, $P = 0.042$, and $P = 0.016$, respectively) and week 48 changes in HOMA-IR ($P = 0.004$, $P = 0.032$, and $P = 0.017$, respectively) and were inversely related to the week 48 changes in HDL cholesterol levels ($P = 0.084$, $P = 0.071$, and $P = 0.053$, respectively). At week 48, the change in LDL cholesterol levels were directly related to age ($P = 0.044$). At week 48, changes in total cholesterol, HDL cholesterol, and triglyceride levels were inversely related to baseline BMI ($P = 0.035$, $P = 0.051$, and $P = 0.009$, respectively) and baseline lean body mass ($P = 0.047$, $P = 0.052$, and $P = 0.01$, respectively).

The safety of this medication switch was evaluated in the context of the larger sample of ACTG 5116 participants. In that study, 236 participants were randomized (118 to each arm). After a median follow-up of 2.1 years, there was a higher toxicity discontinuation rate among individuals randomized to the LPV/r + EFV arm than to the NRTI + EFV arm (40 vs. 19 discontinuations, respectively; $P < 0.001$). The discontinuations in the LPV/r + EFV arm were mainly driven by increased triglyceride levels ($P = 0.0021$), and there was a trend toward increased virologic failure in the LPV/r + EFV arm versus the NRTI + EFV arm (14 vs. 7 virologic failures, respectively; time to virologic failure, $P = 0.09$).

DISCUSSION

There has been considerable controversy about the relative role, if any, that each component of potent antiretroviral regimens plays in the development of HIV lipoatrophy. We evaluated the impact of an NRTI-sparing regimen versus a PI-sparing regimen on changes in limb fat

mass. These results provide additional evidence that NRTIs are important in the progressive limb fat loss that characterizes HIV lipoatrophy.

Lipoatrophy in the extremities affects up to half of the patients receiving ART, and the number of therapeutic options is limited. Other than the cosmetic improvements of facial injections of polylactic acid,³³ the only treatment strategy that has resulted in modest but statistically significant improvements has been switching some NRTIs to ABC^{25–27} or to TDF.³⁴

Clinical lipoatrophy was not a requirement for enrollment in this study. Participants had a median of 6 kg of limb fat, which is less than the 8 kg that typically sized non-HIV-infected individuals have on average^{35,36} but more than the 3 to 4 kg of limb fat of individuals enrolled in clinical lipoatrophy studies.^{34–36} Our findings, if confirmed in individuals with more significant fat loss, identify a potential new therapeutic option for the management of HIV lipoatrophy in some individuals. The nucleoside-sparing regimen (LPV/r + EFV) was associated with significant improvements in limb fat when compared with maintaining an NRTI-containing regimen. Except for limb fat mass, there were no other significant changes in regional fat mass between study groups.

So far, newer NRTIs such as TDF and ABC seem to be less associated with the development of lipoatrophy. Large prospective trials that used TDF-containing or ABC-containing regimens have reported fewer instances of severe lipoatrophy, even in patients followed for prolonged periods.³⁷ This, combined with once-daily dosing for TDF and ABC, has led to the preferential use of these medications in initial regimens in the developed world. Thus, in the future, it is possible that lipoatrophy associated with HIV and ART may become less frequent in industrialized countries. ZDV or d4T in combination with 3TC is still the main nucleoside in antiretroviral regimens that are being implemented in the developing world, however.³⁸ Unless an unlikely genetic difference protects these populations from developing HIV lipoatrophy, progressive limb fat loss should be expected to be a significant problem that may limit the long-term utility of ART in these countries and may be associated with an increased risk of stigmatization. Identifying treatment options to ameliorate fat loss is important to avoid the potential negative impact of this complication.

The LPV/r + EFV regimen increased limb fat mass at the expense of a significant increase in fasting serum triglycerides as well as total and non-HDL cholesterol levels without significantly affecting glucose or bone metabolism. This increase in serum lipid levels might increase the risk for cardiovascular disease in these individuals. To our surprise, however, after a significant increase during the first 8 weeks, total cholesterol and triglycerides tended toward baseline levels during the rest of the follow-up period (see Fig. 5). We considered 2 different alternatives to explain this unexpected finding. The first was that this was an artifact of the intention-to-treat statistical analysis. There were more dropouts in the LPV/r + EFV group; thus, it is possible that individuals who developed higher lipid levels would preferentially stop the ART regimen and that their lipid levels would have declined as a consequence. To rule out that possibility, we repeated the analysis as an “on-treatment analysis,” considering only the results obtained while the participant was on the original treatment regimen, and also as a “last observation carried forward analysis,” with the

assumption that the lipids had not changed from the time the individual discontinued the original regimen. In both analyses, the trend of decline in lipid levels after week 8 persisted. We also considered the possibility that this decline was attributable to the fact that lipid-lowering agents were permitted in this study, although their use was minimal. We repeated the analysis censoring the lipid values measured after any lipid-lowering agents were initiated. Again, the decrease in lipid levels persisted. Therefore, it is possible that the trend in lipid levels seen here could represent a true biologic phenomenon or the effect of an unmeasured change in the diet or physical activity of the patients.

The absence of changes in BMD and glucose metabolism suggests that the contribution of PIs to the development of these complications is limited or that these changes, once they occur, are irreversible. The trend to increased virologic failure in the nucleoside-sparing arm stresses the importance of only conducting switches of ART with caution in a well-controlled environment. The recently presented data from ACTG 5142 that compared a regimen of 2 NRTIs + EFV with a regimen of 2 NRTIs + LPV/r and with a regimen of LPV/r + EFV are reassuring and suggest that LPV/r + EFV (a regimen without nucleoside analogues) is virologically equivalent to an NRTI + EFV regimen in antiretroviral-naïve patients.³⁹

In summary, this study shows that the switch to the NRTI-sparing regimen LPV/r + EFV can be a therapeutic option for individuals with significant limb fat loss. This option has to be carefully balanced with the potential to increase serum lipid levels and the trend to increase virologic failure. Decisions about the management of patients with lipoatrophy should be individualized. Alternative nucleoside-sparing regimens that might produce the same effect on limb fat mass but with a better lipid profile should be explored.

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FIGURE 1.

ACTG 5125s consort diagram. There were no significant differences between participants who enrolled in ACTG A5125s and those who did not enroll with regard to gender, race, age, CD4⁺ cell count at baseline, and HIV-1 RNA levels at baseline (data not shown).

FIGURE 2. Changes in limb fat measured by DEXA (median, IQR). The #*P* values refer to the between-arm comparisons. The **P* values refer to the within-arm comparisons. The numbers at the bottom represent the number of subjects at each time point.

FIGURE 3.

Changes (median, IQR) in trunk fat and total BMD measured by whole-body DEXA. There were no significant differences within or between arms.

FIGURE 4.

Change (median, IQR) in fasting serum glucose and insulin levels.

FIGURE 5.
Changes (median, IQR) in serum lipid parameters.

TABLE 1

Baseline Characteristics

	LPV/r + EFV Arm (n = 31)	NRTI + EFV Arm (n = 31)	P
Male (%)	84	87	NS
White (%)	61	58	NS
Hx IVDU (%)	3	10	NS
Age (y)	41	42	NS
CD4 ⁺ count (cells/mm ³)	431	444	NS
% HIV RNA level < 200 copies/mL	97	100	NS
% on d4T (n)	19 (6)	25 (8)	NS
% NRTIs + 1 or 2 PIs (n)	45 (14)	52 (16)	NS
% NRTIs + PI and NNRTI (n)	52 (16)	39 (12)	NS
% Other (n)	3 (1)	9 (3)	NS
Median time on ART (wk)	109	127	NS
Glucose (mg/dL)	90 (82–95)	89 (84–102)	NS
Insulin (IU/mL)	8 (5–1)	7 (5–10)	NS
HOMA (units)	1.62 (0.96–2.28)	1.37 (0.99–1.98)	NS
Weight (kg)	74.3 (66.3–82.7)	78.7 (70.2–91.8)	NS
Lean body mass (kg)	52.3 (49.0–64.6)	57.5 (52.2–63.4)	NS
Limb fat (kg)	6.4 (3.9–10.1)	6.0 (4.7–8.9)	NS
Trunk fat (kg)	10.2 (6.2–13.0)	10.6 (7.4–14.6)	NS
Lumbar <i>t</i> score	−0.8 (−1.7–0.2)	0.1 (−1.0–0.2)	0.046
N-telopeptide (nM BCE)	19.2 (14.5–22.9)	13.8 (12.2–17.05)	0.01
Osteocalcin (ng/mL)	17.35 (13.7–20)	17.3 (13.6–18.9)	NS
Cholesterol (mg/dL)	204 (174–231)	196 (184–236)	NS
HDL cholesterol (mg/dL)	40 (33–49)	43.5 (37–54)	NS
Non-HDL cholesterol (mg/dL)	154 (116–237)	151.5 (139–174)	NS
Triglycerides (mg/dL)	144 (116–237)	123 (92–308)	NS
Free fatty acids (mmol/L)	0.47 (0.2–0.63)	0.46 (0.36–0.6)	NS

Median and (IQR) unless stated otherwise.

Hx indicates history; IVDU, intravenous drug use; NS, not significant.