

Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment

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Background: The metabolic effects of initial therapy for HIV-1 infection are important determinants of regimen selection.

Methods: Open-label study in 753 subjects randomized equally to efavirenz or lopinavir/ritonavir(r) plus two nucleoside reverse-transcriptase inhibitor (NRTI) vs. the NRTI-sparing regimen of lopinavir/r plus efavirenz. Zidovudine, stavudine, or tenofovir with lamivudine was selected prior to randomization. Metabolic outcomes through 96 weeks were lipoatrophy, defined as at least 20% loss in extremity fat, and fasting serum lipids.

Results: Lipoatrophy by dual-energy X-ray absorptiometry at week 96 occurred in 32% [95% confidence interval (CI) 25–39%] of subjects in the efavirenz plus two NRTIs arm, 17% (95% CI 12–24) in the lopinavir/r plus two NRTIs arm, and 9% (95% CI 5–14) in the NRTI-sparing arm ($P \leq 0.023$ for all comparisons). Varying the definition of lipoatrophy (≥ 10 to $\geq 40\%$ fat loss) and correction for baseline risk factors did not affect the significant difference in lipoatrophy between the NRTI-containing regimens. Lipoatrophy was most frequent with stavudine-containing regimens and least frequent with tenofovir-containing regimens ($P < 0.001$), which were not significantly different from the NRTI-sparing regimen. Total cholesterol increases at week 96 were greatest in the NRTI-sparing arm (median +57 mg/dl) compared with the other two arms (+32–33 mg/dl; $P < 0.001$). Use of lipid-lowering agents was more common (25 vs. 11–13%) in the NRTI-sparing arm.

Conclusion: Lipoatrophy was more frequent with efavirenz than lopinavir/r when combined with stavudine or zidovudine, and less frequent when either drug was combined with tenofovir. Lipoatrophy was least frequent with the NRTI-sparing regimen, but this benefit was offset by greater cholesterol elevations and the need for lipid-lowering agents.

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Introduction

Metabolic alterations, including redistribution of body fat and elevations in serum lipids, are among the most important complications of antiretroviral therapy [1–5]. Loss of limb fat (lipoatrophy) is disfiguring and lipid elevations may increase risk of cardiovascular disease. It is generally accepted that protease inhibitor-containing regimens, especially when ritonavir-enhanced, are more likely to cause lipid elevations than efavirenz-based regimens [6,7]. Lipoatrophy has been most closely linked to regimens containing stavudine, but the role of other nucleoside reverse-transcriptase inhibitors (NRTIs), including zidovudine and tenofovir, has not been compared in well powered studies of initial therapy [8–10]. Moreover, the potential value of NRTI-sparing regimens in preventing lipoatrophy has not been defined.

Thus, despite the importance of metabolic complications in the management of HIV disease, their relative frequencies are incompletely studied and NRTI-sparing regimens, specifically designed to minimize their risk, have not been evaluated.

ACTG A5142 was a randomized study designed to rigorously compare both virologic and metabolic outcomes following initial therapy of HIV-1 infection with efavirenz plus two NRTIs, lopinavir/r plus two NRTIs, or lopinavir/r plus efavirenz (NRTI-sparing regimen). The metabolic outcomes studied were changes in body fat, including trunk fat and the occurrence of lipoatrophy, changes in fasting total cholesterol, high-density lipoprotein (HDL) and non-HDL cholesterol, and triglycerides.

Methods

Study population

HIV-1-infected, antiretroviral-naive male and nonpregnant female subjects of at least 13 years of age with plasma HIV-1 RNA levels 2000 copies/ml or more, acceptable laboratory values, and any CD4 cell count were enrolled [11]. The study protocol was approved by an institutional review board or ethics committee at each participating site. All subjects provided written informed consent.

Study design

ACTG A5142 was a phase III, randomized, multicenter, open-label trial. Subjects were randomized equally to one of three treatment regimens: lopinavir/r plus efavirenz (lopinavir-efavirenz arm) or two NRTIs plus either lopinavir/r (lopinavir arm), or efavirenz (efavirenz arm) [11]. Prior to randomization, investigators selected zidovudine, stavudine extended release (investigational formulation, 100 mg once daily or 75 mg if the subjects weight was <60 kg) or tenofovir to be given with

lamivudine if the patient was randomized to an arm that included NRTI. The investigational stavudine formulation yielded concentrations similar to current marketed products [12]. Randomization was stratified based on screening plasma HIV-1 RNA, chronic hepatitis (either B or C) infection, and choice of NRTI.

The study followed subjects for 96 weeks after the last patient was enrolled. Follow-up evaluations included safety laboratories, plasma HIV-1 RNA, and CD4 cell count every 4–8 weeks. Changes in randomized regimen or NRTI were allowed for toxicity, but were considered endpoints in the composite efficacy analysis. Body composition was measured by whole-body dual-energy X-ray absorptiometry (DEXA) at entry and again at 48 and 96 weeks using standard methods [10,13]. Scans were read centrally (Tufts University) by reviewers who were masked to treatment assignment. Clinically apparent lipoatrophy was reported as an adverse event, but standardized clinical assessments were not performed. Fasting serum levels of total cholesterol, HDL cholesterol, and triglycerides were measured at site laboratories at entry and weeks 12 and 24, and every 24 weeks thereafter. Low-density lipoprotein (LDL) cholesterol was calculated [14] as was non-HDL cholesterol.

Statistical analysis

The primary metabolic objectives were to compare, between randomized treatment arms, the prevalence of lipoatrophy at 48 and 96 weeks and the changes from baseline in serum lipids at follow-up time points (weeks 12, 24, 48, 72, and 96). The *a priori* definition of lipoatrophy was a loss in extremity fat of at least 20% (all limbs combined) from baseline by DEXA scan. Secondary objectives included comparing the percentage change in body fat measures. Sensitivity analyses defined lipoatrophy as at least 10, 30, or 40% loss in extremity fat. Comparisons among the different selected NRTI included data only from subjects randomized to the efavirenz and lopinavir arms.

Analyses were performed using intent-to-treat principles based on randomized treatment assignment; antiretroviral regimen changes, the use of lipid-lowering medications, and missing values were ignored. At each time point, analyses included all available data. Additional analyses (as-treated) were performed that censored values after a change in any component of the treatment regimen. Between-group statistical comparisons used either the Wilcoxon rank-sum or Fisher exact test, as appropriate, and were not corrected for multiple comparisons. *P* values below 0.05 were considered significant. Confidence intervals (CIs) for proportions were exact binomial. All presented CIs were 95% two-sided. Logistic regression was used to investigate the association between randomized treatment arm and NRTI choice with the odds of experiencing lipoatrophy at week 96. The

original study size of 660 subjects was predicted to have 85% power to detect a 50% reduction in the assumed prevalence of lipoatrophy between any two randomized arms. Enrollment continued after reaching 660 participants to allow enrollment at a Durban South African site ($N=20$) and into a substudy [15].

Role of the funding source

The ACTG A5142 team, including members from the sponsor (NIH) and collaborating pharmaceutical companies, contributed to the design and analysis of the study. The ACTG conducted the study, collected the data, and performed the analysis. All authors had full access to the full study report and had final responsibility for the decision to submit for publication.

Results

Accrual and patient characteristics

Of the 757 subjects enrolled between January 2003 and May 2004, four were excluded from all analyses because they never began treatment. Baseline characteristics from the 753 evaluable subjects were balanced between treatment arms [11]. Subjects were predominately men (80%) with a median age of 38 years. The majority were nonwhite with 42% non-Hispanic black, 19% Hispanic,

and 36% non-Hispanic white. The median baseline plasma HIV-1 RNA was 4.8 log₁₀ copies/ml and median CD4 cell count was 191 cells/μl. NRTI choice was 42% zidovudine, 24% stavudine, and 34% tenofovir.

DEXA scans were available at baseline for 693 (92%), at baseline and week 48 for 576 (76%), and at baseline and week 96 for 510 (68%) subjects (171, 166, and 173 in the efavirenz, lopinavir, and lopinavir–efavirenz arms, respectively). The most common reasons for missing DEXA scans were missed appointments, subjects exceeding the machine weight limit, and inoperable equipment. Fasting total cholesterol levels were obtained at baseline in 700 (93.0%) subjects and baseline plus week 96 in 492 (65%) subjects. Baseline metabolic characteristics were similar between treatment arms (Table 1). For subjects in the two arms containing NRTI, metabolic parameters were balanced among the three selected NRTIs (Table 1), even though use of these agents was not randomized. The median follow-up was 112 weeks with no differences among the treatment arms; there was no difference in time to medication change/discontinuation by study regimen or by selected NRTI [11].

Measures of fat distribution

On the basis of a *priori* definition ($\geq 20\%$ fat loss at 96 weeks), lipoatrophy was more prevalent in the efavirenz arm [32% (95% CI 25–39)] than in the lopinavir [17%

Table 1. Baseline metabolic parameters by randomized treatment arm and selected nucleoside reverse transcriptase inhibitor (NRTI).

	Randomized treatment arm			Totals
	Efavirenz	Lopinavir	Lopinavir–efavirenz	
N (for DEXA assessments)	225	234	234	693
N (for cholesterol measurements)	239	230	231	700
Weight (kg)	74.1 (65.4, 84.0)	73.5 (65.4, 83.1)	74.0 (63.3, 88.1)	73.9 (64.5, 84.9)
Body mass index (kg/m ²)	24.8 (22.2, 27.6)	24.6 (22.0, 28.1)	24.6 (21.9, 28.6)	24.7 (22.0, 28.0)
Extremity fat (kg)	7.2 (4.6–10.3)	6.7 (4.5–10.7)	7.1 (4.8–10.5)	7.1 (4.6–10.5)
Trunk fat (kg)	8.3 (5.1–11.9)	8.0(5.0–12.3)	8.2 (5.1–12.1)	8.2 (5.0–12.2)
Total cholesterol (mg/dl)	153 (133–176)	155 (130–174)	152 (135–180)	154 (133–176)
HDL cholesterol (mg/dl)	35 (29–43)	35 (29–42)	34 (29–42)	35 (29–43)
Non-HDL cholesterol (mg/dl)	119 (99–138)	116 (93–136)	117 (102–142)	117 (99–137)
LDL cholesterol (mg/dl)	91 (73–111)	90 (70–110)	93 (75–113)	92 (72–111)
Triglycerides (mg/dl)	116 (76–175)	112 (80–164)	118 (86–158)	115 (80–163)
N on lipid lowering agent at entry (%)	5 (2)	2 (1)	4 (2)	11 (1)
	NRTI selected (efavirenz and lopinavir arms only)			
	Stavudine	Tenofovir	Zidovudine	
N (based on DEXA)	106	161	192	459
N (based on total cholesterol)	118	158	193	469
Weight (kg)	74.2 (63.5, 81.3)	71.7 (64.3, 83.9)	75.4 (66.0, 85.0)	73.8 (65.4, 83.8)
Body mass index (kg/m ²)	24.7 (22.1, 28.0)	24.7 (21.6, 27.6)	24.8 (22.4, 28.4)	24.7 (22.1, 27.9)
Extremity fat (kg)	7.1 (4.3–10.3)	6.7 (4.3–9.9)	7.1 (4.8–11.6)	6.9 (4.5–10.4)
Trunk fat (kg)	9.1 (5.1–12.5)	7.3 (4.3–10.8)	8.5 (5.7–12.9)	8.2 (5.0–12.3)
Total cholesterol (mg/dl)	156 (133–180)	154 (133–174)	151 (130–175)	154 (132–175)
HDL cholesterol (mg/dl)	35 (29–41)	37 (29–44)	35 (29–43)	35 (29–43)
Non-HDL cholesterol (mg/dl)	122 (101–141)	117 (96–134)	111 (93–137)	117 (97–137)
LDL cholesterol (mg/dl)	94 (71–114)	90 (73–110)	88 (70–109)	91 (71–110)
Triglycerides (mg/dl)	119 (77–190)	113 (76–164)	112 (79–164)	113 (78–167)

Listed values are the median (interquartile range), except where noted. Lipid measurements were obtained after overnight fasting. DEXA, dual-energy X-ray absorptiometry; Efavirenz, efavirenz + two nucleoside reverse transcriptase inhibitors arm; HDL, high-density lipoprotein; LDL, low-density lipoprotein; lopinavir, lopinavir–ritonavir + two nucleoside reverse transcriptase inhibitors arm; lopinavir–efavirenz, lopinavir–ritonavir + efavirenz arm.

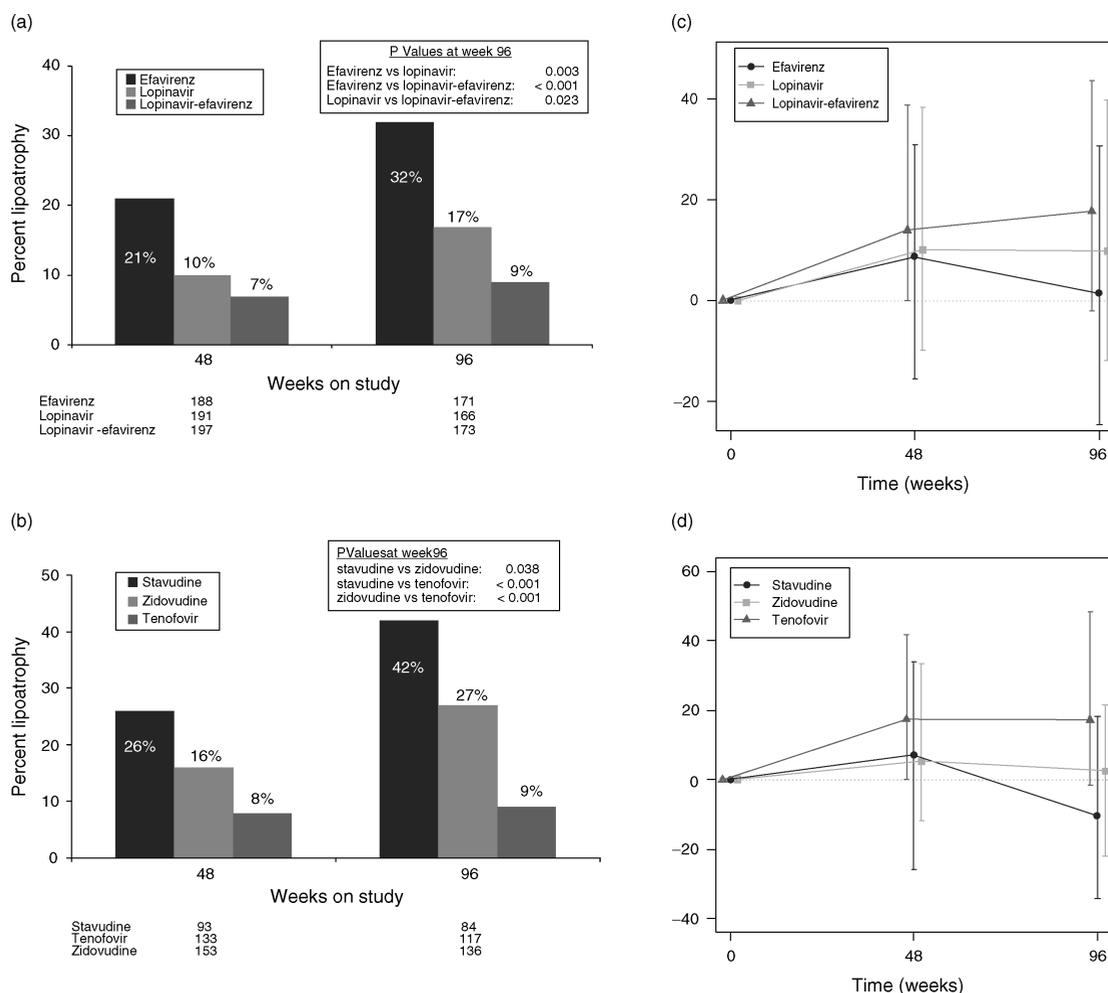


Fig. 1. Percent of subjects with lipoatrophy and median percent change in extremity fat (a) Percent of subjects with lipoatrophy (greater than 20% loss of extremity fat from baseline) by randomized treatment arm. (b) Percent of subjects with lipoatrophy (greater than 20% loss of extremity fat from baseline) by selected NRTI. (c) Median percent change in extremity fat from baseline by randomized treatment arm. Vertical bars represent interquartile range. *P* values at 96 weeks: efavirenz versus lopinavir, *P* = 0.007; efavirenz versus lopinavir-efavirenz, *P* < 0.001; lopinavir versus lopinavir-efavirenz, *P* = 0.013. (d) Median percent change in extremity fat from baseline by selected nucleoside reverse transcriptase inhibitor (NRTI). Vertical bars represent interquartile range. *P* values at 96 weeks: stavudine versus zidovudine, *P* = 0.043; stavudine versus tenofovir, *P* < 0.001; zidovudine versus tenofovir, *P* < 0.001.

(95% CI 12–24)] or the lopinavir-efavirenz arms [9% (95% CI 5–14)] (*P* ≤ 0.023 for all three pairwise comparisons; Fig. 1a). As-treated analyses yielded very similar results: lipoatrophy was present at week 96 in 31% (95% CI 23–40), 18% (95% CI 11–27), and 9% (95% CI 5–16) of the efavirenz, lopinavir, and lopinavir-efavirenz arms, respectively. The differences in lipoatrophy were not driven by overall weight gain; subjects gained a median of 3.6 kg of total body weight, with no significant differences between arms (all *P* > 0.05).

Using a continuous metric, differences in extremity fat among treatment arms were apparent at week 48 and were significant at week 96 (Fig. 1c). The median percentage increase in extremity fat at week 96 was greatest for the lopinavir-efavirenz arm [17.6%, inter-

quartile range (IQR) 4.1–43.6], followed by the lopinavir arm (9.8%, IQR –11.9 to 40.8) and least in the efavirenz arm (1.4%, IQR –24.6 to 31.9). Each pairwise comparison between treatment arms was significant (*P* ≤ 0.013). Extremity fat increased a median of 1.1, 0.7, and 0.05 kg in the lopinavir-efavirenz, lopinavir, and efavirenz arms, respectively.

By week 96, 9% (95% CI 5–16) of tenofovir, 27% (95% CI 20–36) of zidovudine, and 42% (95% CI 31–53) of stavudine-exposed subjects developed lipoatrophy (*P* < 0.001 for tenofovir vs. the other NRTI; *P* = 0.038 zidovudine vs. stavudine; Fig. 1b). The same order of frequency of lipoatrophy was observed by NRTI subgroup in both the efavirenz and lopinavir arms. Specifically, the percentage of subjects developing

Table 2. Multivariate models assessing factors associated with lipoatrophy ($\geq 20\%$ reduction from baseline in extremity fat at 96 weeks by dual-energy X-ray absorptiometry) for nucleoside reverse transcriptase inhibitor containing arms ($N = 337$).

Potential factor associated with lipoatrophy at week 96 (NRTI-containing regimens only)	Model 1 (ARV effects only)		Model 2 (full model)	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Regimen (EFV vs. LPV)	2.66 (1.54, 4.59)	<0.001	2.63 (1.49, 4.64)	<0.001
D4T vs. ZDV	1.93 (1.07, 3.49)	0.029	2.12 (1.14, 3.94)	0.018
TDF vs. ZDV	0.24 (0.12, 0.51)	<0.001	0.24 (0.10, 0.52)	<0.001
Black race (vs. all others)	–	–	0.99 (0.55, 1.82)	0.998
Sex (male)	–	–	2.85 (1.12, 7.25)	0.029
Age (for every 10 year increase)	–	–	0.72 (0.52, 1.00)	0.053
Baseline extremity fat (per kg increase)	–	–	1.09 (1.02, 1.16)	0.011
Baseline CD4 ⁺ (per 100 cell increase)	–	–	1.14 (0.98, 1.33)	0.091

95% CI, 95% confidence interval; ARV, antiretroviral; D4T, stavudine; EFV, efavirenz + two nucleoside reverse transcriptase inhibitors arm; LPV, lopinavir-ritonavir + two nucleoside reverse transcriptase inhibitors arm; OR, odds ratio; TDF, tenofovir; ZDV, zidovudine. All subjects randomized to the two nucleoside reverse transcriptase inhibitors containing regimens who had a dual-energy X-ray absorptiometry scan result available at week 96 were included in this analysis; $N = 337$.

lipoatrophy with tenofovir, zidovudine, and stavudine, respectively, were 6 (3/50), 16 (12/73), and 33 (14/43) in the lopinavir arm; and 12 (8/67), 40 (25/63), and 51 (21/41) in the efavirenz arm.

To further investigate potential interactions between randomized treatment and NRTI choice on the occurrence of lipoatrophy, multivariate logistic regression models were used. No significant interaction was found between treatment regimen and NRTI choice ($P = 0.73$), hence this interaction was not included in subsequent models. In a model that controlled for NRTI choice (Table 2), the odds of developing lipoatrophy at week 96 were higher for efavirenz than for lopinavir (odds ratio 2.66, 95% CI 1.54–4.59). A second model included other baseline covariates (Table 2). Male sex, lower age, greater baseline extremity fat, and higher baseline CD4 cell count all tended to increase the odds of lipoatrophy at 96 weeks, but the significance of efavirenz vs. lopinavir and NRTI choice was unchanged. A final model included all subjects and compared each of the six NRTI–PI and NRTI–NNRTI combinations to the NRTI-sparing lopinavir–efavirenz regimen (Table 3). In this model, the odds of developing lipoatrophy were greatest for stavudine,

followed by zidovudine, and then tenofovir. When tenofovir was given with either efavirenz or lopinavir/r, the odds of lipoatrophy at week 96 were not significantly different from the NRTI-sparing lopinavir–efavirenz regimen.

To evaluate whether the differences in lipoatrophy between the efavirenz and lopinavir arms were sensitive to the definition of lipoatrophy, analyses were repeated with lipoatrophy defined as at least 10, 20, 30, or 40% loss in extremity fat from baseline to week 96. The differences between the efavirenz and lopinavir arms were still significant regardless of the definition of lipoatrophy, with odds ratios ranging from 2.1 to 5.1 (Supplemental Digital Content 1; Supplementary Fig. 1; Table 4; $P < 0.003$). This was most apparent for zidovudine and stavudine as the selected NRTI. For tenofovir, odds ratio close to 1 and wide CIs indicate little difference in lipoatrophy between efavirenz-containing or lopinavir/r-containing regimens. As-treated analyses yielded similar results (data not shown).

For subjects randomized to receive an NRTI-containing regimen, the median percentage increase in extremity fat

Table 3. Influence of randomized treatment arm and nucleoside analog reverse transcriptase inhibitor on occurrence of lipoatrophy ($\geq 20\%$ reduction from baseline in extremity fat at 96 weeks); all patients ($N = 510$).

Treatment	<i>N</i> per group	Multivariate odds ratio (95% CI) ^a	Multivariate <i>P</i>
Lopinavir + efavirenz (reference)	173	1.0	–
Lopinavir			
With stavudine	43	5.09 (2.22–11.65)	<0.001
With zidovudine	73	2.07 (0.92–4.68)	0.08
With tenofovir	50	0.67 (0.19–2.42)	0.54
Efavirenz			
With stavudine	41	11.1 (4.92–24.89)	<0.001
With zidovudine	63	6.93 (3.33–14.40)	<0.001
With tenofovir	67	1.43 (0.58–3.54)	0.44

95% CI, 95% confidence interval.

^aThe model contains terms (six indicator variables) for each randomized treatment and nucleoside selected combination compared with the nucleoside-sparing regimen as a reference.

Table 4. Sensitivity analysis of lipoatrophy occurrence by nucleoside analog reverse transcriptase inhibitor and treatment arm for nucleoside reverse transcriptase inhibitor containing arms (N = 337).

Selected NRTI	Randomized arm	Lipoatrophy definition (% extremity fat loss)			
		≥10%	≥20%	≥30%	≥40%
		Percentage of subjects with lipoatrophy			
TDF (N = 117)	EFV	15	12	4	3
	LPV	12	6	4	0
D4T (N = 84)	EFV	56	51	34	30
	LPV	47	33	23	12
ZDV (N = 136)	EFV	56	40	29	14
	LPV	27	16	6	1
All (N = 337)	EFV	40	32	20	13
	LPV	28	17	10	4
<i>P</i> (EFV vs. LPV overall; adjusted for NRTI choice)		0.0027	0.0004	0.0016	0.0008

95% CI, 95% confidence interval; D4T, stavudine; EFV, efavirenz + two nucleoside reverse transcriptase inhibitors arm; LA, lipoatrophy; LPV, lopinavir-ritonavir + two nucleoside reverse transcriptase inhibitors arm; OR, odds ratio; TDF, tenofovir; ZDV, zidovudine. All subjects randomized to the two nucleoside reverse transcriptase inhibitors containing regimens who had a dual-energy X-ray absorptiometry scan result available at week 96 were included in this analysis; $N = 337$.

was 17.2% (IQR -0.82 to 48.5) at week 96 with tenofovir compared with 2.4% (IQR -21.5 to 22.7) with zidovudine. By contrast, half of the subjects on stavudine lost at least 10.1% extremity fat (IQR -34.0 to 19.1; Fig. 1d). The differences between NRTI were significant for tenofovir vs. stavudine or zidovudine ($P < 0.001$, for both comparisons) and between zidovudine and stavudine ($P = 0.043$), and corresponded to median extremity fat changes of 1.2, 0.14, and -0.48 kg, for tenofovir, zidovudine, and stavudine, respectively.

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. There were no significant differences at weeks 48 or 96 by randomized treatment or NRTI selection in either percentage change in trunk fat or percentage of subjects with more than 20% gain in trunk fat.

Serum lipids

Median cholesterol and triglyceride values increased with time in all treatment arms ($P < 0.005$ for all comparisons of baseline vs. week 96; Supplemental Digital Content 1; Supplementary Fig. 2a–d). The median increases in total cholesterol, non-HDL cholesterol, and HDL cholesterol were significantly greater for the lopinavir-efavirenz arm compared with the lopinavir arm or the efavirenz arm at all time points. For example, at week 96, the median (IQR) total cholesterol increase for the lopinavir-efavirenz, efavirenz, and lopinavir arms was 57 (25–94), 33 (10–57), and 32 mg/dl (8–60), respectively. In addition, the median increase in triglycerides was larger for the lopinavir-efavirenz arm (62 mg/dl at week 96) compared with the lopinavir (46 mg/dl) and efavirenz (19 mg/dl) arms at all time points ($P \leq 0.030$ for all pairwise comparisons). The median increases in total, non-HDL and HDL cholesterol were not significantly different between the lopinavir and efavirenz arms at

most time points between weeks 24–96, but triglycerides were significantly higher in the lopinavir arm at all time points between 24 and 96 weeks. As-treated analyses gave similar results.

The total cholesterol-to-HDL cholesterol ratio was similar at baseline between randomized arms (median value 4.3, IQR 3.6–5.3) and increased in the lopinavir-efavirenz arm until week 72 (median increases 0.13–0.39), decreased in the efavirenz arm (median reductions of 0.12–0.39, $P < 0.05$ compared with the lopinavir-efavirenz arm through week 72) and remained nearly unchanged in the lopinavir arm (median reductions of 0.02–0.10, $P < 0.05$ compared with the lopinavir-efavirenz arm through week 48). The total cholesterol-to-HDL cholesterol ratio was significantly higher in the lopinavir arm than in the efavirenz at 12 and 24 weeks ($P \leq 0.013$), but not after week 24.

At week 96, median total cholesterol had increased by 41 mg/dl (IQR 17–62) for subjects on stavudine, 33 mg/dl (IQR 8.5–54) for subjects on zidovudine, and 22.5 mg/dl (IQR 4–58) for subjects on tenofovir ($P = 0.02$ for stavudine vs. tenofovir; $P > 0.05$ for other comparisons). There were similar differences between NRTI for increases in non-HDL cholesterol at week 96. Differences between NRTI for increases in HDL cholesterol and triglycerides were less marked (data not shown).

By week 120, 124 (16%) of study subjects had taken lipid-lowering drugs at some point while on study. In the lopinavir-efavirenz arm, 63 subjects (25%) started lipid-lowering drugs, compared with 28 in the efavirenz arm (11%) and 33 (13%) in the lopinavir arm. Lipid-lowering agents were used in 15% of subjects on stavudine, 12% on zidovudine, and 11% on tenofovir.

Discussion

The need for lifelong antiretroviral therapy of HIV-1 disease argues for the use of first-line regimens with the most favorable efficacy and safety profiles. The current study (ACTG 5142) identified important differences in the metabolic effects of two first-line regimens – efavirenz or lopinavir/r with two NRTIs – recommended by the US DHHS guidelines for treatment of HIV-1 infection in adolescents and adults [16]. Each component of these regimens – NRTI, efavirenz and lopinavir/r, contributed to the important differences in metabolic outcomes. Specifically, lipoatrophy was more frequent with efavirenz plus two NRTIs than with lopinavir/r plus two NRTIs. This unexpected difference was observed with zidovudine or stavudine plus lamivudine as the NRTI, but not with tenofovir plus lamivudine. These findings are relevant to the selection of initial treatment regimens, particularly in resource-limited settings, where stavudine or zidovudine plus lamivudine are often the only NRTI available. The study also determined that the NRTI-sparing regimen of lopinavir/r-efavirenz had the lowest risk of lipoatrophy, but the greatest likelihood of serum lipid elevations and resulted in more frequent use of lipid-lowering agents. This profile should restrict the use of lopinavir/r-efavirenz for initial therapy to circumstances in which NRTI cannot be used.

The study used an *a priori* defined, objective measure of lipoatrophy ($\geq 20\%$ decline from baseline to week 96 in extremity fat). The findings were not due to differential discontinuations of either randomized regimen or NRTI component, were consistent across different definitions of lipoatrophy (10–40%) in sensitivity analyses, and were not altered by inclusion of baseline covariates. As-treated analyses that censored information after regimen/NRTI change yielded concordant results to ITT. Statistical testing confirmed that the effect of randomized regimen component (efavirenz vs. lopinavir) was independent of NRTI. Most of the lipoatrophy differences between efavirenz and lopinavir were seen in the strata that received zidovudine and stavudine, though a small sample size in the stavudine stratum may have limited statistical power. A previous small prospective study suggested that efavirenz caused less lipoatrophy than a PI-based regimen (nelfinavir); this study does not support that finding [17].

In other studies, patients initiating stavudine or zidovudine regimens lost subcutaneous fat at a rate of 12–15% per year [8]. Several years of fat loss would be required before lipoatrophy was visibly evident in most patients. Consistent with previous studies, in ACTG A5142, lipoatrophy was most frequent and cumulative in incidence over time in stavudine-containing regimens [8,10,18–21]. The pathogenesis of lipoatrophy is incompletely defined, but the prevailing hypothesis is that NRTI-mediated mitochondrial dysfunction in adipocytes leads to fat cell apoptosis and depletion

[22–24]. Results from the present study support this model as there was a clear gradation in incidence of lipoatrophy (defined both by categorical and continuous DEXA metrics) that parallels the impact of NRTI on mitochondrial DNA and RNA *in vitro*: stavudine > zidovudine > tenofovir. Previous studies of tenofovir-containing regimens also found significantly less lipoatrophy than was seen in stavudine-containing regimens [25–27] and the infrequent occurrence of lipoatrophy in subjects on the NRTI-sparing regimen of ACTG 5142 is also consistent with this model.

However, this study revealed complex interactions between the NRTI component of the regimen and efavirenz or lopinavir/r. The frequency of lipoatrophy was greater with efavirenz than lopinavir/r when stavudine or zidovudine were used. The mechanism of greater lipoatrophy with stavudine or zidovudine plus efavirenz compared with lopinavir/r is not clear. A recent randomized comparison of atazanavir with or without ritonavir, given with stavudine and lamivudine, suggested that ritonavir may mitigate the limb fat loss of the regimen. After 96 weeks, the group with ritonavir had 20% less lipoatrophy (defined by DEXA scan as in A5142), a reduction from 49 to 29% ($P < 0.05$) [28]. Potential mechanisms that could explain these results include a protective effect from the mitochondrial toxicity of NRTI by ritonavir (or lopinavir and ritonavir) or efavirenz-related enhancement of the effect.

This study also found that baseline factors can influence the development of lipoatrophy independent of regimen and NRTI used. Male subjects had 2.85-fold greater odds of lipoatrophy compared with women ($P = 0.029$). Unexpectedly, subjects with higher baseline CD4 cell counts tended to have more lipoatrophy, a finding that contrasts with previous reports, which found either no association [21] or more lipoatrophy associated with lower CD4 cell count [19,20]. Subjects with greater initial limb fat were not protected from lipoatrophy. Race and baseline lipids did not add to the prediction of those at risk for lipoatrophy. In some, but not all previous, mostly retrospective, cross-sectional studies of nonrandomized antiretroviral therapy, increasing age was associated with a greater risk of lipoatrophy [20]. In this study, a borderline protective effect (odds ratio 0.7; $P = 0.054$) of age was found after accounting for other factors. Differences between our study and others can be explained by different populations and study designs – prospective, randomized in this study vs. observational cohorts in previous studies.

Serum lipids increased in all study arms after the initiation of antiretroviral therapy. Unexpectedly, this study found no significant difference in cholesterol fractions between the lopinavir and efavirenz arms of the study. There was also no difference in the use of lipid-lowering agents between the lopinavir and efavirenz arms throughout the study.

However, triglycerides were uniformly higher among subjects receiving lopinavir/r-containing regimens. Consistent with prior data, stavudine was associated with the greatest lipid elevations among the NRTI. Although the study was too short in duration to detect clinical consequences, the magnitude of total cholesterol changes seen in this study is similar to that seen in cohort studies where an association between lipids and an increased risk of cardiovascular events was found [29,30]. In one study, an increased myocardial infarction relative rate of 1.3 was seen per 39 mg/dl increase in total cholesterol [29].

There are limitations of this study. NRTI choice was not randomized, but selected prior to randomization, although the distribution of the NRTI chosen was not different across the arms nor was duration of exposure to NRTI agents. The open-label design could have affected the use of lipid-lowering agents, and the study had inadequate follow-up to discern whether differences in lipid abnormalities would result in increased risk for clinical events such as cardiovascular or cerebrovascular disease. There is no universally agreed upon definition for clinical lipoatrophy and this study did not include a case definition or data collection instrument to capture clinically apparent fat loss primarily because such definitions contain significant subjective bias. However, our measure (DEXA) of lipoatrophy was objective, and hence the open-label design is unlikely to have significantly influenced these data. Furthermore, clinically defined lipoatrophy would have been subject to ascertainment bias, particularly with prior data suggesting that one treatment, that is, stavudine, was associated with lipoatrophy. As changes in extremity fat measured by DEXA have been associated with clinically defined lipoatrophy in previous studies [21,25,31,32], the magnitude and significance of the lipoatrophy findings suggest they would be clinically relevant.

This study provides important new information for clinicians and patients on the relative risk and benefits of available antiretroviral regimens for initial therapy of HIV-1 infection. The risk of lipoatrophy can be minimized with a NRTI-sparing regimen or one containing tenofovir and lamivudine as the NRTI component. Although lipoatrophy was infrequent on lopinavir/r plus efavirenz, this combination was suboptimal because of greater increases in triglycerides and use of lipid-lowering agents, and more frequent selection of efavirenz resistance [11]. Unexpectedly, lipoatrophy was less common with lopinavir/r than efavirenz regimens containing zidovudine or stavudine, but cholesterol increases were similar and triglyceride increases were greater with lopinavir/r. These findings re-affirm the central role of tenofovir as a component of NRTI-containing regimens for initial therapy and question the use of stavudine or zidovudine in combination with lamivudine and an NNRTI, which are among the most commonly used regimens worldwide [16]. Indeed, after the study was fully enrolled, stavudine

was moved from a preferred to an alternative recommended agent in the US DHHS guidelines (10/29/2004 version) [33]. This report adds to the analyses of virologic outcome from ACTG 5142, which showed significantly shorter time to virologic failure for lopinavir/r than for efavirenz given with two NRTIs [11]. Careful selection of regimen components can minimize the risk of lipoatrophy and may improve the risk-to-benefit ratio of treatment, favoring earlier initiation of antiretroviral therapy.

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