Improvement in Lipoatrophy Associated with Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus–Infected Patients Switched from Stavudine to Abacavir or Zidovudine: The Results of the TARHEEL Study

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Stavudine use is a contributing factor for lipoatrophy, whereas use of abacavir or zidovudine is less likely to cause this complication. The TARHEEL study was a 48-week, open-label study that assessed changes in lipoatrophy after abacavir (86 patients [73%]) or zidovudine (32 patients [27%]), 300 mg twice daily, was substituted for stavudine for 118 human immunodeficiency virus (HIV)–infected patients (HIV type 1 RNA level, <400 copies/mL) with virological suppression who had developed lipoatrophy after ⩾6 months of stavudine-based treatment. At week 48, full-body dual-energy x-ray absorptiometry demonstrated a median increase in arm fat of 35%, leg fat of 12%, and trunk fat of 18%, compared with the baseline level. These improvements coincided with fat gain in lipoatrophic areas that was documented by computerized tomography. Results of a "body image" questionnaire showed that a substantial percentage of patients reported some or a lot of fat gain in the arms (22%), legs (18%), buttocks (19%), and face (27%). HIV suppression was maintained over the study period. In conclusion, replacing stavudine with abacavir or zidovudine resulted in improvement in stavudine-induced lipoatrophy.

Because HIV-infected patients receiving HAART regimens must continue to receive treatment for the rest of their lives, combinations of antiretroviral agents that produce maximum viral suppression with the fewest long-term safety concerns should be sought. One long-term toxicity of HAART, lipoatrophy, is characterized by loss of subcutaneous tissue from facial pads, extremities, and buttocks [1]. It occurs most often in patients treated with nucleoside reverse-transcriptase inhibitors (NRTIs) with the greatest propensity to inhibit mDNA polymerase γ [2].

Studies of NRTIs involving enzyme assays and cell cultures have demonstrated that the hierarchy of mDNA polymerase γ inhibition is zalcitabine $\geqslant$ di-

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danosine ⩾ stavudine > lamivudine > zidovudine > abacavir [3]. Consistent with this hierarchy, the NRTI stavudine has been shown clinically to place patients at a 2.5-fold higher risk of developing lipoatrophy than does zidovudine [2], and that risk increases with duration of stavudine treatment, concurrent elevation of serum lactate levels, and concurrent administration of protease inhibitors (PIs) [4]. Stavudine is also believed to cause lipoatrophy by inducing adipocyte apoptosis [5, 6].

The disfigurement of lipoatrophy may discourage some patients from continuing their antiretroviral therapy or prompt them to seek expensive plastic surgical correction [7–9]. In view of these possible negative sequelae, some clinicians have felt that it is prudent to replace stavudine with NRTIs that have the least lipoatrophogenic effects in patients who have developed stavudine-related fat wasting [10, 11]. The primary objective of TARHEEL (Trial to Assess the Regression of Hyperlactatemia and to Evaluate the Regression of Established Lipodystrophy; GlaxoSmithKline protocol ESS40010) was to assess the regression of symptoms and/or signs of stavudine-associated lipoatrophy and hyperlactatemia in HIV-infected patients when abacavir or zidovudine is substituted for stavudine over a 48-week period. Results presented below concentrate primarily on the lipoatrophy-related objective of this study.

METHODS

Study population. Male and nonpregnant, nonlactating female subjects aged ⩾18 years were eligible for study screening if they had documented HIV infection, if they received a treatment regimen containing stavudine consistently for ⩾6 months immediately before the study, and if they had an undetectable HIV-1 RNA level (i.e., <400 copies/mL). In addition, patients were required to have ⩾1 of the following characteristics: a clinician-confirmed decrease in the level of facial fat or a decrease in the level of fat in the lower extremities or gluteal region; ⩾2 self-reported lipoatrophy signs above or 1 sign plus an elevation in the lactate level of ⩾2.2 mmol/L at the screening visit; or ⩾2 of the following, by self-report: shortness of breath on exertion, generalized weakness, fast heart beat, recent weight loss of ⩾4.5 kg within the previous 2 months, pain and/or bloating in the abdomen, nausea and/or vomiting and/or lack of appetite plus an elevation in the lactate level of ⩾2.2 mmol/L at the screening visit; or a serum lactate level of >3.2 mmol/L at the screening visit.

Patients were not eligible for the study if they had taken hydroxyurea ⩽3 days before screening or recombinant human growth hormone, megesterol acetate, systemically absorbed glucocorticoids, or androgenic agents ⩽4 months before screening; if they had received both zidovudine and abacavir; if they had a history of intolerance or hypersensitivity reaction to abacavir; or if they had a diagnosis of diabetes mellitus or renal failure.

Study design. In this multicenter, phase IV, open-label, switch-study design, informed consent was obtained from patients before screening. On study day 1 (baseline), patients underwent a physical examination and were evaluated for determination of demographic characteristics, baseline disease severity (using the Center for Disease Control and Prevention [CDC] classification), HIV-associated conditions, and history of prior antiretroviral drug use. Subsequent study visits were conducted at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. All laboratory samples at each of these study visits were obtained after the patients had fasted for ⩾8 h before the procedure. The study was conducted from July 2000 through February 2002 at 22 outpatient treatment sites in the United States. The study protocol for ESS40010 was approved by the institutional review boards at each study site.

Treatment switch. Patient regimens could be switched from stavudine to abacavir, administered as one 300-mg tablet of Ziagen (GlaxoSmithKline), or to zidovudine, administered as one combination tablet containing 150 mg of lamivudine and 300 mg of zidovudine (Combivir; GlaxoSmithKline). Clinicians also had the option to switch up to a maximum of 2 drugs in the patient's HAART regimen, one of which had to be stavudine. Thus, for zidovudine-experienced patients, stavudine/didanosine could be switched to abacavir-lamivudine, and for zidovudine-naive patients, stavudine-zalcitabine could be switched to lamivudine-zidovudine (150-mg/300-mg fixed-dose combination tablet; hereafter, "lamivudine-zidovudine").

Assessment of body fat changes. One of 2 primary end points was change from baseline in physical signs of lipoatrophy at 48 weeks, as assessed objectively and consistently by one type of full-body dual-energy x-ray absorptiometry (DEXA) (either Hologic QDR-4500A [Hologic] or Lunar [GE Medical Systems]). The other primary end point was change from the baseline level in serum lactate concentration. DEXA measurements of physical signs of lipoatrophy were made at baseline, and changes that occurred after the switch to abacavir or zidovudine were assessed by repeated measurements using the same type of DEXA analysis and machine at study weeks 12, 24, and 48 (or at an early termination visit if the patient was withdrawn before completion of week 48). DEXA scans were sent to an external third-party central laboratory (Synarc; San Francisco, CA) for analysis, to provide standardization in methodology and ongoing instrument quality control (documented by monthly quality-control spine phantom forms) and calibration across all study sites. One DEXA analyst evaluated all scans for a given patient.

Changes in lipoatrophy were also assessed using anthropometry, body mass index, and single abdominal CT scan at the fourth lumbar vertebra (L4). The same CT technologist consistently evaluated CT scans for a given patient. To permit patient self-report of changes in lipoatrophy, patients com-

pleted a "body image" questionnaire (a nonvalidated tool developed by Glaxo Wellcome) at baseline and at weeks 12, 24, and 48. Patients rated fat changes in their face, legs, arms, and buttocks, compared with baseline, as "lost some/a lot," "no change," or "gained some/a lot."

Efficacy assessment. Plasma HIV-1 RNA levels were measured from blood samples obtained at baseline and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 using the Roche PCR assay Amplicor HIV-1 MONITOR UltraSensitive Version 1.0 (Roche Diagnostics), which has a lower limit of quantitation (LLOQ) of 50 copies/mL and a quantitation range of 50–75,000 copies/mL. If, at any point during the study, HIV-1 RNA values were >75,000 copies/mL, the Roche AMPLICOR PCR Standard 1.0 assay (LLOQ, 400 copies/mL; Roche Diagnostics) was automatically used. Loss of virologic control (i.e., "virologic breakthrough") was defined as measurement of a plasma HIV-1 RNA level of >1000 copies/mL on 2 occurrences ⩾1 week apart without confounding factors, such as any intercurrent illness or infection, vaccination, test methodology, or poor compliance with treatment. Intensification with one additional marketed antiretroviral medication (excluding stavudine) was allowed in these circumstances only after consultation with the sponsor. If the plasma HIV-1 RNA level remained >1000 copies/mL for >8 weeks after intensification, the patient was withdrawn from the study, because no substitution of study drugs, addition of background antiretroviral medications, or further switches in intensification of therapy were allowed. $CD4^+$ lymphocyte counts were measured by flow cytometry at baseline and weeks 8, 12, 24, and 48.

Safety assessment. At all study visits, patients were asked open-ended questions about the occurrence of adverse events and changes in concurrent medications, were assessed for the appearance of HIV-associated conditions, and underwent fasting (8-h) blood sampling to measure changes in standard laboratory and hematology parameters, serum lactate, and anion gap. Lipids (panel), insulin, free fatty acids, lipase, and C-peptide levels were determined at baseline and study weeks 8, 12, 24, and 48 or at an early termination visit. Bone mineral density, *t* scores, and *z* scores were assessed at baseline and at weeks 12, 24, and 48.

Statistical analysis. The primary population for analyses was the intent-to-treat (ITT) population, which consisted of all patients who were enrolled in the study and who had ⩾1 efficacy measurement. The Wilcoxon signed rank test was used to assess DEXA-determined changes from baseline in body fat for each body region (truck, arm, and leg) at week 48 for patients in the ITT population; changes from baseline in CT findings; and changes from baseline in serum lactate levels. No statistical tests were used to evaluate changes from baseline in anthropometry findings, body image questionnaire answers, or differences between responses to the switch to abacavir and zidovudine (i.e., DEXA- and CT scan–measured fat change). Differences were considered to be statistically significant if P was <.05.

RESULTS

Patient characteristics and disposition. One hundred eighteen patients with stavudine-associated lipoatrophy were enrolled in the study. Most patients were male (83%) and white (65%), with a median age of 43 years (table 1). At baseline, the median duration of prior stavudine treatment was 42 months (range, 7–87 months), and 97 patients (82%) had received stavudine for ⩾2 years before the start of the study. Screening serum lactate levels were normal (<2.2 mmol/L) in 102 patients (86%) and high (⩾2.2 mmol/L) in 16 patients (14%). Eighty-nine percent of patients had serum HIV-1 RNA levels of <400 copies/mL, including 97% of the normolactatemic patients and 38% of the hyperlactatemic patients (who had treatment interrupted for a median of 31 days [range, 1–77 days] because of their high lactate levels). The median $CD4^+$ cell count was 511 cells/mm^3. Approximately one-half of the patients had CDC category A HIV infection, 21% had category B infection, and 30% had category C infection. Besides having undergone treatment with stavudine, patients also had been exposed previously to the NRTIs zidovudine (52%) and lamivudine (90%), the NNRTIs efavirenz (33%) and nevirapine (27%), and the PIs indinavir (45%) and nelfinavir (34%). Stavudine was replaced by abacavir for 86 patients (73%) and by zidovudine (as Combivir) for 32 patients (27%).

Ninety-three patients (79%) in the ITT population completed the study and were evaluable. Twenty-five patients (21%) discontinued treatment prematurely for the reasons shown in table 1.

Body fat changes. DEXA showed that the median baseline values for arm, leg, and trunk fat were 0.994 kg, 2.148 kg, and 6.954 kg, respectively. Fat levels increased gradually in lipoatrophic body areas over 48 weeks in the study population as a whole after the switch from stavudine to abacavir or zidovudine (figure 1). Changes from baseline levels were generally small but statistically significant by week 24, at which time median increases in actual fat weight and percentage of fat gain above the baseline value were as follows: arms, 0.197 kg (25%; $P <$ .001); legs, 0.096 kg (7%; $P = .01$); and trunk, 0.613 kg (9%; $P <$ .0001). Increases above the baseline value in fat weight and percentage of fat gain in all these body areas were even greater at week 48, as follows: arms, 0.249 kg (35%); legs, 0.288 kg (12%); and trunk, 0.949 kg (18%) ($P <$ .0001 for all; table 2). In a visual comparison of DEXA results between abacavir and zidovudine recipients, median fat gain in the trunk was observed to be similar with both NRTIs, but more fat gain was

Table 1. Characteristics and dispositions of the study patients enrolled with stavudine-induced lipoatrophy: the intent-to-treat population.

Characteristic	All patients (n = 118)	Patients with a normal lactate level (n = 102)	Patients with an elevated lactate level (n = 16)
Age, median years (range)	43 (28–59)	43 (28–59)	43 (30–59)
Sex			
Male	98 (83)	87 (85)	11 (69)
Female	20 (17)	15 (15)	5 (31)
Race			
White	77 (65)	69 (68)	8 (50)
African American	18 (15)	12 (12)	6 (38)
Hispanic	16 (14)	15 (15)	1 (6)
Asian	3 (3)	2 (2)	1 (6)
Other	4 (3)	4 (4)	0
HIV-1 RNA level, median $\log_{10}$ copies/mL (range)			
Screening	…	…	1.69 (1.69–2.28)
Baseline	1.69 (1.69–5.28)	1.69 (1.69–3.45)	3.47 (1.69–5.28)
HIV-1 RNA level of <400 copies/mL	105 (89)	99 (97)	6 (38)
$CD4^+$ cell count, median cells/mm^3 (range)	511 (128–1776)	529 (128–1776)	500 (194–910)
CDC HIV infection class			
Category A	58 (49)	47 (46)	11 (69)
Category B	25 (21)	23 (23)	2 (13)
Category C	35 (30)	32 (31)	3 (19)
Serum lactate level, median mmol/L (range)			
Screening	…	…	2.90 (2.2–5.0)
Baseline	1.40 (0.6–4.1)	1.40 (0.6–4.1)	2.05 (1.1–3.3)
Symptoms of hyperlactatemia	52 (45)[a]	46 (46)	6 (38)
Time not receiving HAART, median days (range)	…	…	31 (1–77)
Time receiving stavudine therapy			
6 months–1 year	7 (6)	6 (6)	1 (6)
1–2 years	14 (12)	12 (12)	2 (13)
>2 years	97 (82)	84 (82)	13 (81)
Stavudine replacement			
Abacavir	86 (73)	74 (73)	12 (75)
Zidovudine[b]	32 (27)	28 (27)	4 (25)
Prior antiretroviral experience			
Abacavir	3 (3)	3 (3)	0
Lamivudine-zidovudine	5 (4)	4 (4)	1 (6)
Lamivudine	106 (90)	93 (91)	13 (81)
Zidovudine	61 (52)	53 (52)	8 (50)
Efavirenz	39 (33)	33 (32)	6 (38)
Nevirapine	32 (27)	27 (26)	5 (31)
Indinavir	53 (45)	47 (46)	6 (38)
Nelfinavir	40 (34)	34 (33)	6 (38)
Cause of premature withdrawal from study	25 (21)	22 (22)	3 (19)
Adverse event	10 (8)	8 (8)	2 (13)
Consent withdrawn	7 (6)	6 (6)	1 (6)
Lost to follow-up	5 (4)	5 (5)	0
Protocol violation	2 (2)	2 (2)	0
Protocol-defined virologic failure	1 (1)	1 (1)	0

NOTE. Data are no. (%) of patients, unless otherwise indicated. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention.

[a] Data were missing for 2 patients.

[b] As Combivir (150 mg of lamivudine and 300 mg of zidovudine; GlaxoSmithKline).

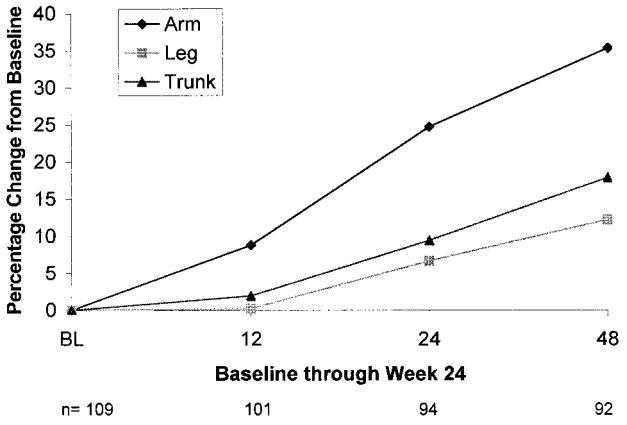

Figure 1. Changes in dual-energy x-ray absorptiometry (DEXA) results after substitution of abacavir or zidovudine for stavudine.

noted in the arms and legs of patients who switched to abacavir (table 2).

CT results complemented the DEXA findings, with a 32% median increase in the abdominal subcutaneous fat level and a 4% median decrease in the visceral abdominal fat level observed at week 48 (figure 2*A*). CT scans also showed that more patients had increases than had decreases in the subcutaneous abdominal fat level (87% vs. 13%) and that more patients had decreases than had increases in the visceral abdominal fat level (52% vs. 48%; figure 2*B*). Anthropometry revealed no significant changes in body weight, chest size, hip size, midarm size, midthigh size, neck size, waist size, or body mass index after the switch from stavudine to abacavir or zidovudine.

Body image questionnaire answers revealed that patients reported noticeable fat gain in lipoatrophic body areas at week 24. At week 48, the majority of patients reported "no change or gain" in body fat in the arms (81% of patients), legs (79%), buttocks (82%), and face (76%) (figure 3). Fat gains appeared to be maintained long term, because a similar percentage of patients reported that they had "gained some/a lot" of fat at weeks 24 and 48 (arms, 21% and 22%, respectively; legs, 21% and 20%, respectively; buttocks, 11% and 19%, respectively; and face, 27% at both weeks). More patients reported no change or a decrease in abdominal size than reported an increase (62% vs. 39%). More patients in the abacavir subgroup reported some or a lot of fat gain in the arms and legs; a similar percentage of patients in the abacavir and zidovudine subgroups (18%–24%) reported fat gains in the buttocks and face (table 2).

Table 2. Body fat and virologic results at 48 weeks for HIV-infected patients for whom stavudine was switched to abacavir or zidovudine.

Finding	All patients (*n* = 118)	Abacavir switch group (*n* = 86)	Zidovudine switch group (*n* = 32)
Fat changes noted by DEXA, median % change from baseline (range)			
Arms	35 (−46 to 173)	38 (−37 to 174)	17 (−46 to 132)
Legs	12 (−53 to 206)	15 (−53 to 206)	7 (−33 to 97)
Trunk	18 (−49 to 162)	19 (−49 to 162)	16 (−24 to 54)
Fat changes noted by CT, median % change from baseline (range)			
Subcutaneous abdominal fat	32 (−48 to 440)	35 (−48 to 440)	25.1 (−23 to 176)
Visceral abdominal fat	−4 (−52 to 157)	−4 (−52 to 157)	−2.9 (−29 to 89)
Fat changes from baseline noted by body image questionnaire, *n/N* (%)			
Arms[a]	22/102 (21.6)	18/71 (25.4)	4/31 (12.9)
Legs[a]	20/101 (19.8)	15/70 (21.4)	5/31 (16.1)
Buttocks[a]	19/102 (18.6)	15/71 (21.1)	4/31 (12.9)
Face[a]	27/102 (26.5)	17/71 (23.9)	10/31 (32.3)
Virologic suppression, *n/N* (%)			
ITT: observed analysis,[b] HIV-1 RNA level			
<400 copies/mL	86/92 (93)	60/64 (94)	26/28 (93)
<50 copies/mL	79/92 (86)	53/64 (83)	26/28 (93)
ITT: M = F analysis,[c] HIV-1 RNA level			
<400 copies/mL	86/118 (73)	60/86 (70)	26/32 (81)
<50 copies/mL	79/118 (67)	53/86 (62)	26/32 (81)

NOTE. CT, computerized axial tomography; DEXA, dual-energy x-ray absorptiometry; ITT, intent-to-treat.

[a] Percentage of subjects reporting gains of "some or a lot" of body fat.

[b] No imputations are made for missing values

[c] All missing values are considered failures

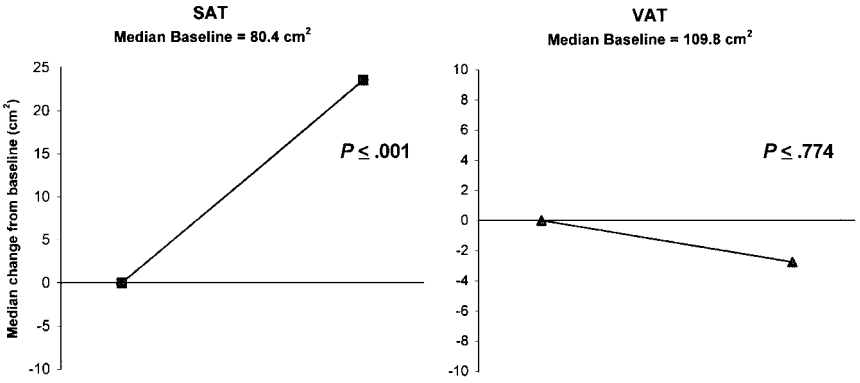

Figure 2. Median change from baseline in subcutaneous and visceral abdominal fat levels, as observed on the CT scans *(A)*, and percentage of subjects with changes in subcutaneous and visceral abdominal fat levels from baseline to week 48 *(B)*. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Efficacy. ITT:observed analysis (i.e., no imputations are made for missing values) showed that at 24 weeks, 95% (92/97) of the entire study cohort had HIV-1 RNA <400 copies/mL and 84% (81/97) had HIV-1 RNA <50 copies/mL. This degree of viral load suppression was maintained at week 48: 93% (86/92) <400 copies/mL and 86% (79/92) <50 copies/mL. The ITT: M = F results (i.e., all missing values are considered failures) also showed that most patients had undetectable HIV-1 RNA at 24 and 48 weeks (<400 copies/mL: 78% [92/118] and 73% [86/118]; <50 copies/mL: 69% [81/118] and 67% [79/118]). One patient underwent treatment intensification to didanosine, 1 to efavirenz, and 1 to lopinavir/ritonavir, with subsequent regain of virologic suppression. No differences in virologic suppression were observed between patients who switched to abacavir versus those who switched to zidovudine (table 2).

Ten of 16 patients who were hyperlactatemic had their antiretroviral treatment interrupted for a median of 31 days (range, 1–77 days) because of this condition. The median HIV-1 RNA level was elevated at baseline (3.47 $\log_{10}$ copies/mL), but it decreased once abacavir or zidovudine therapy was started. At week 48, the HIV-1 RNA level was reduced by 2.06 $\log_{10}$ copies/mL less than the baseline level.

At week 48, the median $CD4^+$ cell count was 9 cells/mm^3 greater than the baseline level for the total population, 2 cells/mm^3 greater than the baseline level for the normolactatemic group, and 199 cells/mm^3 greater than the baseline level for the hyperlactatemic group.

Safety. The treatment-related adverse events reported in >5% of patients were nausea (18%), fatigue (13%), and diarrhea (6%). The only serious adverse event that was reported by >1 patient was an allergic reaction to medicinal substances (8 patients [7%]). DEXA data showed no significant changes in bone mineral density. New-onset neck fat deposition (i.e., "buffalo hump") was observed in 3 patients (it was considered to be possibly drug-related in 2 patients), central fat accumulation was observed in 1 patient, and nonspecific lipodystrophy was observed in 1 patient. The median serum lactate level decreased only in the 16 hyperlactatemic patients (from 2.9 mmol/L to 1.3 mmol/L). Between baseline and week 48, clinically important changes in serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, free fatty acid, C-peptide, glucose, and insulin levels and anion gap were not observed.

DISCUSSION

The results of this study show that stavudine-associated lipoatrophy improves over 48 weeks after stavudine is replaced by either abacavir or zidovudine in HAART regimens, that virus load suppression and $CD4^+$ cell count increases are maintained

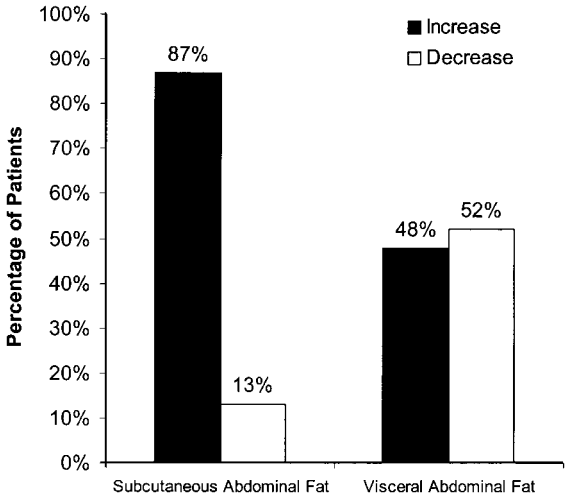

Figure 3. Changes in body image questionnaire responses after substitution of abacavir or zidovudine for stavudine in HAART.

while this improvement occurs, and that the switch is well tolerated. These findings corroborate those of an earlier, small-scale study involving 59 subjects; that study showed abdominal and midthigh CT scan–based evidence of improvement in stavudine-induced peripheral fat wasting in 83% of patients receiving all-NRTI regimens and in 71% of those receiving PI-containing regimens for whom stavudine was switched to abacavir or zidovudine for 12 months [12]. The DEXA results from our study are also consistent with those reported recently in a shorter-term (24-week) study by Carr et al. [10] in which a significant increase in limb fat mass ($P = .002$) was observed after abacavir was substituted for stavudine. The slightly greater improvement noted with abacavir may have been related to its lesser effect on mDNA polymerase γ, compared with zidovudine [3].

As has been reported elsewhere [4], fat gain after discontinuation of stavudine therapy may proceed at different rates and to different degrees, depending on the body area monitored. Thus, in our study, DEXA revealed greater fat gain in the arms than in the legs or trunk, whereas CT revealed increased subcutaneous fat levels but decreased visceral fat levels after the switch to abacavir or zidovudine. The reduction in abdominal visceral fat seen in our study would be expected to lower cardiovascular risk [13]; no changes in serum lipid levels occurred to further influence this risk. Patient self-assessment results on the body image questionnaire generally confirmed DEXA and CT findings. However, because one-half to two-thirds of patients did not notice a change in fat level, fat changes may have had to be large in many patients to make them realize they had occurred at all. This underscores the importance of relying on objectively measured fat assessment rather than solely on subjective methods. Discordance between patient self-assessments of fat changes and DEXA results has been reported previously [14]. Anthropometry did not detect a significant fat gain, consistent with another study in which this method detected only a trend for fat increase in lipoatrophic body areas over a 12-month period after switching from stavudine to abacavir [15].

Saint-Marc et al. [16] have shown that peripheral fat wasting can be expected to be observed in ~63% of patients after they have received stavudine for a median duration of 14 months. Other risk factors that have been shown in multivariate analyses to predispose to NRTI-induced lipoatrophy (e.g., longer duration of HIV disease, advanced HIV disease, longer time receiving HAART, greater NRTI experience in general, older age, lower pretherapy fat content, white race, and elevated triglyceride levels) also need to be factored into a long-term treatment strategy [17–22]. The results of our study suggest that, if patients develop lipoatrophy while receiving stavudine, switching as early as possible to either abacavir or zidovudine would be prudent, because more-advanced cases of lipoatrophy may take longer to reverse or may only partially reverse. However, it is noteworthy that switching to either abacavir or zidovudine may mean a trade-off in adverse events (e.g., risk of anemia associated with zidovudine and risk of hypersensitivity reaction with abacavir).

This study had a limitation in that it did not include a control arm. A control arm would have been valuable to confirm whether body fat levels fluctuate with continued stavudine treatment. However, results from the Western Australian HIV Cohort Study [23] and a study by García-Benayas et al. [15], which did include a control group, suggest no change or worsening of lipoatrophy with continued stavudine treatment. Longer-term studies need to be performed to see whether stavudine-associated lipoatrophy is totally reversible and to better understand the change in the long-term safety profile after substitution of stavudine with abacavir or zidovudine.

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