

# Abacavir Substitution for Nucleoside Analogs in Patients With HIV Lipoatrophy

## A Randomized Trial

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**L**IPODYSTROPHY (PERIPHERAL lipoatrophy, central fat accumulation, and lipomata) is common in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy and is significantly associated with dyslipidemia, insulin resistance, and lactic acidemia.<sup>1-7</sup> Lipoatrophy in HIV-infected adults is disfiguring and potentially stigmatizing and has been associated with poorer adherence to antiretroviral therapy.<sup>8</sup> Lipodystrophy was initially attributed to protease inhibitor therapy on the basis of cohort studies, a finding confirmed by in vitro adipocyte studies.<sup>9-11</sup> The type and duration of nucleoside reverse transcriptase inhibitor (NRTI) therapy were subsequently linked to lipoatrophy,<sup>12-16</sup> with these findings also confirmed in vitro.<sup>17</sup> The NRTI-related lipoatrophy may be

**Context** Peripheral lipoatrophy may complicate antiretroviral therapy of human immunodeficiency virus (HIV) infection, often related to duration and type of nucleoside analog therapy, and may have a mitochondrial pathogenesis. No proven therapy exists for lipoatrophy, but abacavir is a nucleoside analog that may be less toxic to mitochondria.

**Objective** To determine if substitution of stavudine or zidovudine with abacavir improves HIV lipoatrophy without affecting control of HIV replication.

**Design** Randomized, open-label 24-week study.

**Setting** Seventeen hospital HIV outpatient clinics and primary care centers in Australia and England, with randomization from June 2000 through January 2001.

**Participants** A total of 111 adults (109 men) with moderate or severe lipoatrophy who were receiving stavudine (n=85) or zidovudine (n=26) and had stable plasma HIV RNA levels below 400 copies/mL and no prior abacavir therapy.

**Intervention** Patients were randomly assigned to switch from stavudine or zidovudine to abacavir, 300 mg twice per day, while continuing all other antiretroviral therapy (n=54) or to continue all antiretroviral therapy (n=57).

**Main Outcome Measures** The primary end point was limb fat mass, measured by dual-energy x-ray absorptiometry; key secondary end points were plasma HIV RNA levels, adverse events, physician-assessed (via subjective measures) lipodystrophy severity, total and central fat mass, and fasting metabolic (lipid, glycemic, and lactate) levels.

**Results** There was a significant increase in limb fat in the abacavir group relative to the stavudine/zidovudine group (0.39 vs 0.08 kg; mean difference, 0.31; 95% confidence interval [CI], 0.06-0.57 kg), as well as significant relative increases in subcutaneous thigh ( $P=.01$ ), arm ( $P<.001$ ), and abdominal ( $P=.001$ ) fat areas on computed tomography. Switching had no significant effect on secondary end points, including plasma HIV RNA (for unadjusted comparison between groups at week 24, odds ratio, 1.38; 95% CI, 0.48-3.96). Change in limb fat mass at week 24 did not correlate with change in subjectively determined perceived lipoatrophy severity ( $r=-0.06$ ;  $P=.53$  by Spearman correlation). Hypersensitivity to abacavir was seen in 5 patients (10%).

**Conclusions** In this sample of lipoatrophic HIV-infected adults, switching from stavudine or zidovudine to abacavir for 24 weeks led to significant, albeit modest, objectively measured increases in limb fat. Clinical lipoatrophy, as assessed subjectively, did not resolve, however, and at the rate of increase observed may take years to resolve with use of this strategy. Longer-term follow-up is needed.

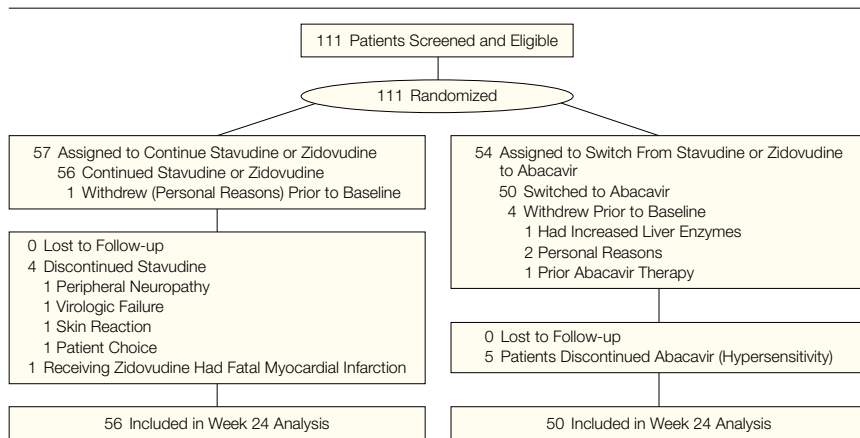
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**Figure 1.** Trial Profile



a result of mitochondrial toxicity: lipoatrophy is associated with lactic acidemia<sup>15</sup>; lipoatrophy may develop more rapidly in adults with asymptomatic, low-level lactic acidemia<sup>18</sup>; and mitochondrial DNA depletion has been found in atrophic peripheral adipocytes of recipients of NRTIs, most commonly stavudine and zidovudine.<sup>19</sup>

No proven treatment exists for HIV lipoatrophy, and no study has found that limb fat increases spontaneously over time in patients with lipoatrophy. A randomized protease inhibitor switch study found a reduction in intra-abdominal fat accumulation but no improvement in lipoatrophy.<sup>20</sup> In 2 small studies, lipoatrophy improved after switching or ceasing nucleoside analog therapy. In the first, switching stavudine to zidovudine or abacavir led to increased limb fat on computed tomography (CT), but this study was not randomized.<sup>21</sup> In a randomized study, ceasing stavudine or zidovudine without drug substitution resulted in increased limb fat on dual-energy x-ray absorptiometry (DXA) but also frequently led to increased plasma HIV RNA level (viral load).<sup>22</sup> Given these data, and because abacavir appears less toxic to mitochondria in vitro,<sup>23</sup> we undertook a randomized, multicenter, 24-week study to evaluate the hypothesis that switching from either stavudine or zidovudine to abacavir would improve peripheral lipoatrophy without affecting control of HIV replication. Further

analyses were performed to explore whether any patient subgroup derived more or less benefit from this strategy.

**METHODS**

**Study Sample**

Participants were recruited at 17 HIV hospital outpatient or community-based primary care sites. Study eligibility criteria included documented HIV infection, age older than 18 years, moderate or severe peripheral lipoatrophy<sup>5</sup> in at least 1 region (face, arms, legs, or buttocks) on physical examination, no prior abacavir therapy, viral load below 400 copies/mL for at least the preceding 3 months, and stable well-tolerated antiretroviral therapy including stavudine or zidovudine for at least the preceding 8 weeks. The last 2 criteria were chosen because switching 1 drug of an antiretroviral regimen in a patient without fully suppressed HIV replication would not be ethical because resistance to the new drug would be likely.<sup>24</sup> The NRTIs stavudine and zidovudine were chosen as the control NRTIs because these drugs form part of almost all antiretroviral regimens<sup>24,25</sup> and because the total duration of NRTI therapy is linked to lipoatrophy (often zidovudine is followed by stavudine), as is current NRTI type (particularly current use of stavudine).<sup>15,16</sup> Other entry criteria were absence of an active acquired immunodeficiency syndrome (AIDS)-defining condition in the pre-

ceding 3 months; use of standard-of-care opportunistic infection prophylaxis; plasma venous lactate level of less than 45 mg/dL (5 mmol/L); serum hepatic transaminase levels of less than 5 times the upper limit of normal; negative pregnancy test result in women of childbearing age; no use of chemotherapy, radiotherapy, or immune modulators (except hydroxyurea); and no ongoing alcohol or substance abuse. All patients provided written informed consent after study approval by each site's research ethics committee.

**Definitions**

In the absence of a validated case definition, lipodystrophy was defined subjectively by the presence of peripheral lipoatrophy (face, arms, buttocks, or legs) and/or central fat accumulation (abdomen, dorsocervical fat pad) using a standardized physical examination procedure.<sup>1,4,5</sup> Lipodystrophy intensity (mild, moderate, or severe) has been found to significantly ( $P = .003$ ) correlate with DXA measurement of peripheral fat mass.<sup>4</sup> Virologic failure was defined as viral load above 400 copies/mL on 2 occasions more than 14 days apart in the absence of intercurrent illness or an isolated value above 5000 copies/mL.<sup>20,24,26</sup> Abacavir hypersensitivity was defined according to criteria developed by the manufacturer.<sup>27</sup>

**Interventions**

The study was designed to equally randomize 100 eligible patients. Patients either ceased stavudine or zidovudine and commenced open-label abacavir, 300 mg twice per day, or continued all current NRTI therapy including stavudine or zidovudine (with an option to switch to abacavir at week 24). All patients continued all other concomitant antiretroviral therapy (FIGURE 1).

Randomization was performed centrally at the National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia, after confirmation of eligibility and stratified by factors previously associated with lipoatrophy presence and severity<sup>5,6,14-16</sup>; current use of stavudine (n=85) or zidovudine

(n=26), current use of protease inhibitors (n=59) and/or nonnucleoside reverse transcriptase inhibitors, and presence or absence of lactic acidemia (>18 mg/dL [2 mmol/L]) (n=24).

Cessation of abacavir was mandatory for related grade 3 or 4 adverse events, including hypersensitivity; dose reduction or rechallenge was not permitted. Patients ceasing abacavir could start alternative antiretroviral therapy at investigators' discretion. Grade 1 or 2 adverse events (other than abacavir hypersensitivity) were managed according to treating physicians' assessments. Substitution of antiretroviral drugs other than abacavir was mandatory for recurrent grade 3 or 4 drug-related adverse events and was optional for persistent drug-related grade 1 or 2 adverse events and for virologic failure.

### Assessments

Demographic data and details of all prior antiretroviral therapy were recorded at screening. (Screening indicates confirmation of eligibility after signing consent form. All screened patients were eligible. Patients were not referred but were under routine care. Eligibility was confirmed centrally.) After the 2-week screening period, patients were seen at baseline and weeks 4, 12, and 24, including those ceasing therapy but agreeing to follow-up (n=10), and at weeks 2 and 6 in the abacavir group for additional safety assessments. Adverse events, concomitant medication, weight, waist and hip circumference, physical examination, safety assessments involving blood testing (measures of complete blood cell count, electrolytes, liver enzymes, urea, creatinine, creatine kinase, phosphate, and amylase), quality of life (as assessed by patients and physicians using the EuroQol technique, a visual analog scale [0-100] based on perceived overall quality of life on day of assessment),<sup>28</sup> CD4 cell counts, and plasma HIV RNA (lower limit of detection for screening, 400 copies/mL; for analysis, 50 copies/mL batch tested), fasting total and high-density lipoprotein cholesterol, triglyceride, glucose, insulin, and C-peptide measurements were

assessed as described.<sup>1,4,15</sup> Adherence was estimated clinically by counts of remaining pills in each month's supply of study drugs. For collection of venous lactate, patients were advised not to vigorously exercise for 24 hours beforehand and to be well hydrated. Blood was collected after patients rested for at least 5 minutes, without fist clenching or stasis, into a prechilled fluoride-oxalate tube, transported immediately on ice, and processed within 4 hours of collection.

Body composition was quantified at screening and at weeks 12 and 24 by DXA (Lunar DPXL, Madison, Wis) and single-cut CT.<sup>1,2,4,15</sup> The DXA studies were used to measure total and regional body fat and lean tissue, and CT to quantify fat areas at the L4 vertebral level (intra-abdominal and extra-abdominal [ie, subcutaneous]), right mid humerus, and right mid thigh. We did not perform CT of the face because of lack of validated landmarks for this measurement, and we did not assess facial skin folds because of concern about high intraobserver variability (A.C., unpublished data, February 2002). Quality assurance programs were instituted for both scanning techniques prior to study commencement. For DXA data acquisition, the scan was deferred in patients having had recent radionuclide or barium tests until the material was cleared; in addition, jewelry was removed, arms were separated from the body sides, use of sandbags or pillows was avoided, and care was taken to ensure that the whole body was included. The DXA analysis required display of soft tissue and bone for appropriate allocation of soft tissue, use of extended research mode analysis, and detailed Lunar-defined localization of the arm, rib, central, pelvic, lumbar, dorsal, and neck cuts; the regions analyzed were arms, legs, and trunk as previously described.<sup>1,4</sup> Daily quality control and calibration procedures were performed at all sites. A Lunar soft tissue phantom (composite blocks used for calibration) was measured regularly at the central site and the same phantom measurement was taken once at all other sites. All patient and phantom scans were read centrally every month. For CT, each patient un-

derwent imaging using a conventional helical or nonhelical system, with each site using only 1 CT scanner and constant soft-tissue imaging parameters. Patients lay supine with the head straight, shoulders relaxed, and arms raised above the head; patient motion was kept at a minimum. All soft tissue was included in the CT field of view. Using a mid-L4 vertebral scout film as a guide, a single 10-mm axial slice of the abdomen through the point of the marker was performed on a normal setting. Visceral adipose tissue and subcutaneous adipose tissue were traced manually. Both DXA and CT scans were read centrally by technicians unaware of patient assignment.

Subjective measures of lipodystrophy presence and severity in the periphery (lipoatrophy in the face, arms, legs, and buttocks), centrally (fat accumulation in the abdomen and dorsocervical spine region), and overall were assessed using a case record form by a physician every 12 weeks. Each patient was evaluated by the same physician each time. Use of this form and method of assessment have been found to correlate (*P* value for trend=.003) with DXA measurement of peripheral fat mass.<sup>4</sup> All study physicians received prestudy training to ensure physical examination standardization for assessment of lipodystrophy at each site, in particular for rating lipodystrophy severity. The physicians all used the same form (available from the authors on request) for assessing patients and received training regarding use of the form (previously used<sup>4</sup>). Physicians were aware of patient assignment. In each region, a score of 0 for nil, 1 for mild, 2 for moderate, or 3 for severe was assigned, for a maximum possible score of 12 peripherally, 6 centrally, and 18 overall using a previously described scoring system.<sup>4</sup>

### Statistics

The primary study end point was the mean change in limb (arm and leg) fat mass measured by DXA at week 24. Secondary end points were adverse events; anthropometry; total and central fat mass; biochemical, lipid, and glyce-

**Table 1.** Baseline Patient Characteristics\*

Characteristics	Nucleoside Analog Group	
	Stavudine/Zidovudine (n = 56)	Abacavir (n = 50)
Age, y	45 (10)	42 (7)
Sex, male, No. (%)	55 (98)	50 (100)
Duration of HIV infection, y	10.2 (4.5)	8.5 (4.1)
AIDS (category C disease), No. (%)	11 (20)	8 (16)
CD4 cell count, $\mu$ L	570 (292)	587 (258)
HIV RNA <400 copies/mL, No. (%)	54 (96)	46 (92)
HIV RNA <50 copies/mL, No. (%)	53 (95)	42 (84)
Antiretroviral therapy		
No. of agents ever received, median (range)	6 (3-11)	6 (3-11)
Total duration, mo		
	67 (30)	65 (28)
Nucleoside analogs		
No. (%)	56 (100)	50 (100)
Duration, mo	65 (30)	58 (28)
Nonnucleoside analogs		
No. (%)	30 (53)	26 (52)
Duration, mo	25 (15)	34 (2)
Protease inhibitors		
No. (%)	35 (63)	28 (56)
Duration, mo	38 (18)	33 (17)
Current nucleoside analogs		
Stavudine		
No. (%)	46 (82)	44 (88)
Duration, mo	38 (14)	35 (14)
Zidovudine		
No. (%)	10 (18)	6 (12)
Duration, mo	6 (12)	24 (27)
Lamivudine		
No. (%)	46 (82)	40 (80)
Duration, mo	43 (17)	38 (18)
Didanosine		
No. (%)	11 (20)	15 (30)
Duration, mo	34 (12)	33 (13)
Current nonnucleoside analogs		
Nevirapine		
No. (%)	22 (39)	19 (38)
Duration, mo	30 (14)	26 (11)
Efavirenz		
No. (%)	5 (9)	5 (10)
Duration, mo	20 (3)	22 (5)
Delavirdine		
No. (%)	3 (5)	2 (4)
Duration, mo	32 (3)	34 (2)
Current protease inhibitors		
Indinavir		
No. (%)	13 (23)	9 (18)
Duration, mo	39 (16)	27 (19)
Nelfinavir		
No. (%)	4 (7)	8 (16)
Duration, mo	31 (12)	23 (14)
Ritonavir-saquinavir		
No. (%)	5 (9)	5 (10)
Duration, mo	38 (15)	29 (20)
Other		
No. (%)	12 (21)	6 (12)
Duration, mo	14 (16)	23 (17)

(continued)

mic measurements; viral load; CD4 cell count; and quality of life.

The sample size of 100 patients was chosen to have an 80% power to detect a 0.5-kg difference in mean limb fat between the 2 groups and assumed that up to 10% of the abacavir group would cease taking abacavir because of intolerance or virologic failure. These calculations were based on estimates of variability derived from the Protease Inhibitor Induced Lipodystrophy Reversal (PIILR) study.<sup>20</sup>

All analyses were by intention to treat (except they excluded 5 patients withdrawing prior to baseline) and included all follow-up data on all patients receiving stavudine/zidovudine or commencing abacavir at day 0, regardless of any subsequent treatment changes. No interim analysis was performed. In summarizing changes from baseline by nominal study week, a last-value-carried-forward approach was adopted for patients with any missing data for the remainder of the follow-up period (sensitivity analyses on available data only gave qualitatively very similar results and are not presented [A.C., unpublished data, February 2002]). The percentage of patients with detectable HIV RNA ( $\geq 50$  copies/mL) was analyzed using odds ratios (ORs) generated by logistic regression models; 2 patients with no week 24 viral load measurements were assigned a status of virologic failure.<sup>29</sup> Changes from baseline were compared between treatment groups using 2-sample *t* tests. The Spearman correlation was used to assess the correlation between change in limb fat mass and change in subjectively assessed lipodystrophy severity. The  $\chi^2$  test was used to compare the frequency of dorsocervical lipomata at week 24. All hypothesis tests were 2-sided, with statistical significance at the .05 level. There was no adjustment of *P* values for multiple comparisons because these adjustments, with many correlated variables, are overly conservative, both in terms of the type I error rate and reductions in power. Analyses were performed using SAS statistical software, version 8 (SAS Inc, Cary, NC).

**RESULTS**  
**Participants**

One hundred eleven patients were screened and randomized between June 2000 and January 2001 (Figure 1). Five randomized patients withdrew from the study prior to baseline visits (1 after becoming aware of randomization to abacavir therapy) and were excluded from analyses. Baseline patient characteristics of the remaining 106 patients, who completed all scheduled visits through week 24 (except 1 patient who died), were similar between groups (TABLE 1). The number of patients with lactic acidemia (>18 mg/dL [2 mmol/L]) was 13 (26%) in the abacavir group and 11 (20%) in the stavudine/zidovudine group, but lactic acidemia was asymptomatic in all patients and did not require intervention.

**Treatment Outcomes, Safety, HIV RNA Levels, and Quality of Life**

Overall, 45 (90%) of 50 abacavir patients and 50 (89%) of 56 patients in the stavudine/zidovudine group completed 24 weeks of randomized therapy. Five patients (10%) ceased taking abacavir before week 24 because of hypersensitivity occurring after 1 to 3 weeks of abacavir which resolved a mean of 8 days after abacavir was ceased (TABLE 2). No other adverse event was attributed to abacavir therapy. Of these 5 patients, 2 restarted stavudine and 1, zidovudine. Five patients (9%) in the stavudine/zidovudine group ceased stavudine or zidovudine by week 24 (stavudine in 4 patients; zidovudine in 1 patient). Overall adherence to assigned therapy in the abacavir group was 90% at weeks 12 and 24 and was 93% and 96% in the stavudine/zidovudine group at weeks 12 and 24.

There was no AIDS-defining (Centers for Disease Control and Prevention category C) illness in either group, but 2 patients in the stavudine/zidovudine group had myocardial infarctions; 1 was fatal at week 7 and another (nonfatal) occurred at week 12. Quality of life, as assessed by both patients and their physicians, was similar at baseline between the groups and did not change significantly over 24 weeks (TABLE 3).

**Table 1.** Baseline Patient Characteristics\* (cont)

Characteristics	Nucleoside Analog Group	
	Stavudine/Zidovudine (n = 56)	Abacavir (n = 50)
Body composition		
Limb fat, kg	3.7 (2.4)	3.5 (2.7)
Right mid-humeral subcutaneous fat, cm <sup>2</sup>	11.0 (9.2)	9.4 (6.9)
Right mid-thigh subcutaneous fat, cm <sup>2</sup>	18.2 (17.5)	16.6 (16.3)
Abdominal (L4) subcutaneous fat, cm <sup>2</sup>	99.4 (59.2)	106.0 (79.2)
Intra-abdominal (L4) fat, cm <sup>2</sup>	124.3 (70.0)	120.1 (70.5)
Physician-assessed lipodystrophy, No. (%)		
Peripheral lipodystrophy	56 (100)	50 (100)
Face	50 (88)	47 (94)
Arms	46 (82)	43 (86)
Buttocks	53 (95)	39 (78)
Legs	50 (89)	44 (88)
Central fat accumulation	48 (85)	42 (84)
Abdomen	46 (82)	41 (82)
Dorsocervical fat pad	8 (14)	7 (14)

\*All values are mean (SD) unless otherwise noted. Data exclude 5 randomized patients who did not commence randomized therapy and did not have baseline values. HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

**Table 2.** Treatment Outcomes\*

	Stavudine/Zidovudine		Abacavir†	
	No.	Reason	No.	Reason
Discontinuation				
Abacavir	...	...	5	Hypersensitivity
Stavudine	1	Peripheral neuropathy	...	...
	1	Virologic failure		
	1	Skin reaction		
	1	Patient choice		
Zidovudine	1	Fatal myocardial infarction	...	...
Lamivudine	2	Virologic failure	1	Patient choice
	1	Fatal myocardial infarction		
	1	Skin reaction		
Didanosine	1	Patient choice	0	...
	1	Weight loss		
Adefovir	1	Hypophosphatemia	0	...
Nevirapine	1	Virologic failure	0	...
	1	Fatal myocardial infarction		
	1	Skin reaction		
	1	Weight loss		
Indinavir	0	...	1	Switch to lopinavir
			1	Nephrolithiasis
<b>Total</b>	<b>16 (8 Patients)</b>		<b>8 (6 Patients)</b>	
Recommencement				
Stavudine	...	...	2	...
Zidovudine	...	...	1	...

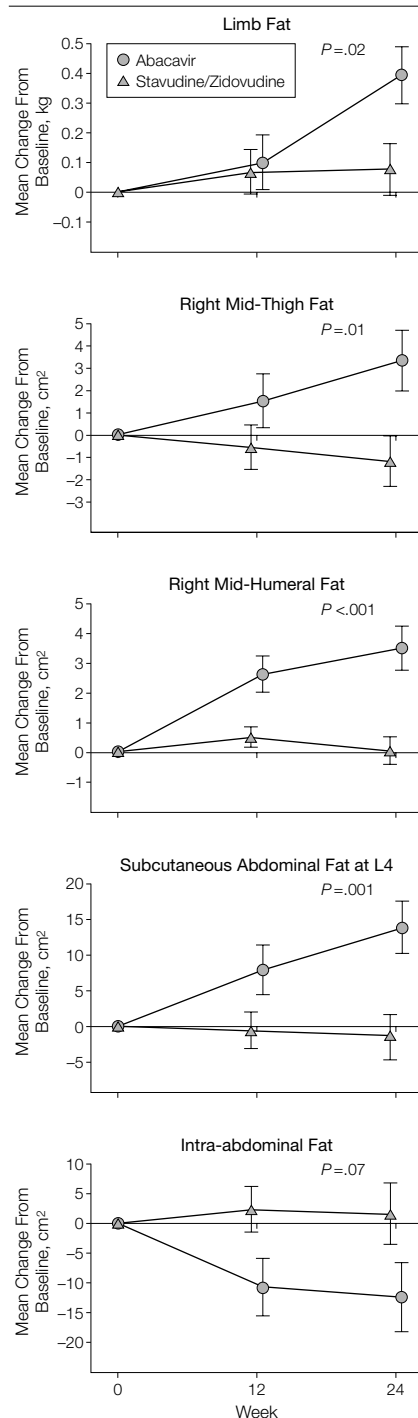
\*Ellipses indicate data not applicable.

†No patient recommenced abacavir after discontinuation because it was not permitted by the study protocol.

The proportions of patients with viral load of at least 50 copies/mL did not differ significantly between the groups (18% and 23%, respectively, in the abacavir and stavudine/zidovudine groups

at week 24; (OR, 1.38; 95% confidence interval [CI], 0.48-3.96; *P* = .26). After adjustment for baseline differences in viral load, there was a nonsignificant trend toward greater control of HIV replica-

**Figure 2.** Changes in Body Composition



P values are for comparisons at week 24 using the 2-sample t test.

tion to below 50 copies/mL in the abacavir group than in the stavudine/zidovudine group at week 24 (OR, 2.66; 95% CI, 0.80-8.85;  $P=.08$ ).

There was no significant change in hematologic or biochemical safety assessments, both between groups at week 24 and between baseline and week 24 within each group (A.C., unpublished data, February 2002), except for a modest relative decline in hemoglobin in the abacavir group (0.3 g/dL; 95% CI, 0.0-0.6 g/dL;  $P=.03$  by 2-sample  $t$  test).

**Body Composition**

All objective measures of peripheral fat mass showed significant increases by week 24 in the abacavir group relative to the stavudine/zidovudine group (FIGURE 2). Limb fat mass on DXA increased by 0.39 kg in the abacavir group vs 0.08 kg in the stavudine/zidovudine group (mean difference, 0.31 kg; 95% CI, 0.06-0.57 kg;  $P=.02$  by 2-sample  $t$  test). This represents an increase of 11% in limb fat mass in the abacavir group over 24 weeks (and 2% in the stavudine/zidovudine group). Subcutaneous right mid-thigh fat area increased by 3.3 cm<sup>2</sup> in the abacavir group vs a decline of 1.2 cm<sup>2</sup> in the stavudine/zidovudine group (mean difference, 4.5 cm<sup>2</sup>; 95% CI, 1.1-7.9 cm<sup>2</sup>;  $P=.01$  by 2-sample  $t$  test). Subcutaneous right mid-humeral fat area increased by 3.5 cm<sup>2</sup> in the abacavir group and did not change in the stavudine/zidovudine group (mean difference, 3.5 cm<sup>2</sup>; 95% CI, 1.8-5.1 cm<sup>2</sup>;  $P<.001$  by 2-sample  $t$  test). Subcutaneous L4 abdominal fat increased by 13.9 cm<sup>2</sup> in the abacavir group and declined by 1.2 cm<sup>2</sup> in the stavudine/zidovudine group (mean difference, 15.1 cm<sup>2</sup>; 95% CI, 6.0-24.2 cm<sup>2</sup>;  $P=.001$ ).

Overall lipoatrophy severity was not perceived by physicians (assessing patients at screening and weeks 12 and 24) as having improved significantly in the abacavir group relative to the stavudine/zidovudine group; all but 3 patients had lipodystrophy assessed at weeks 12 and 24. Change in limb fat mass at week 24 did not correlate with change in perceived lipoatrophy severity ( $r=-0.06$ ;  $P=.53$  by Spearman correlation). No baseline variable was found to be significantly associated with greater increases in peripheral fat as measured by DXA

(TABLE 4) or CT (A.C., unpublished data, February 2002).

There was no significant change in the abacavir group relative to the stavudine/zidovudine group for total body fat, weight, total lean mass, or waist or hip circumference. Intra-abdominal fat area decreased by 12.5 cm<sup>2</sup> in the abacavir group and increased by 1.5 cm<sup>2</sup> in the stavudine/zidovudine group (mean difference, 14.0 cm<sup>2</sup>; 95% CI, -1.1 to 29.0 cm<sup>2</sup>;  $P=.07$  by 2-sample  $t$  test) (Figure 2E). Intra-abdominal fat did not improve significantly in patients with moderate or severe central fat accumulation at baseline who switched to abacavir (A.C., unpublished data, February 2002). The proportions of patients in the abacavir and stavudine/zidovudine groups with dorsocervical lipomata at baseline were 14% and 13%, respectively, and were 30% and 17%, respectively, at week 24 (for comparison at week 24,  $P=.16$  by  $\chi^2$  test).

**Metabolic Assessments**

There was no significant difference between the 2 groups at week 24 for any metabolic measurement. This was also the case for patients with abnormal baseline values (lactate >18 mg/dL [2 mmol/L], total cholesterol >193 mg/dL [5 mmol/L], high-density lipoprotein cholesterol <39 mg/dL [1 mmol/L], triglycerides >177 mg/dL [2 mmol/L], insulin >10  $\mu$ U/mL, and C peptide >2 ng/mL [A.C., unpublished data, February 2002]).

**COMMENT**

In lipoatrophic, HIV-infected adults with extensive prior antiretroviral therapy, switching an NRTI (either stavudine or zidovudine) to abacavir for 24 weeks was safe and resulted in improvement in objectively defined peripheral lipoatrophy. Suppression of HIV replication improved nonsignificantly with the switch. Metabolic measures associated with lipoatrophy, such as lactic acidemia, insulin resistance, and hyperlipidemia, did not change.

In objective assessments, lipoatrophy improved with switching to abacavir, with consistent and significant ef-

fects seen with 2 imaging methods of several affected regions. However, after 6 months, limb fat mass had only increased by about 11% from baseline. If normal limb fat is about 7 or 8 kg in adult men with normal body mass index,<sup>1</sup> at the rate observed, it might take 5 or more years for limb fat mass to return to normal. This is not surprising since lipoatrophy may take years to develop (patients had a mean 5.5 years of NRTI therapy prior to the study) and antiretroviral toxic effects of slow onset may take as long to resolve or not be fully reversible.<sup>30</sup> Longer follow-up of this population is needed to determine if lipoatrophy can improve clinically or even resolve.

No factor was significantly associated with greater improvement in limb fat mass, although there was a suggestion that it might be greater in those who switched from stavudine rather than from zidovudine (Table 4). This suggests, but certainly does not prove, that stavudine has a greater lipoatrophic effect than zidovudine. Larger populations will need to be studied to identify patients most suitable for the switch strategy used in this study.

It is possible but unlikely that some of the variation in body fat between groups is a product of altered food intake in the abacavir group. However, lean mass did not differ between groups at week 24 and did not change signifi-

cantly in either group over time. Also, no patient ceased either stavudine or zidovudine because of nausea or diarrhea. Last, the dosing schedule was either unchanged (for patients switching from stavudine) or more complex (for those switching from the combined pill containing zidovudine and lamivudine), and abacavir, stavudine, and zidovudine can all be taken with or without food.

There was a trend toward improved intra-abdominal fat area, but it did not reach statistical significance. The study was not powered to address this end point, however, and about 20% of patients did not have abnormal abdominal fat accumulation identified by their treating physician at study entry. An ex-

**Table 3.** Changes in Secondary End Points\*

Outcome Measures	Baseline		Week 24 Change From Baseline		Between-Group Difference	
	Stavudine/Zidovudine	Abacavir	Stavudine/Zidovudine	Abacavir	Mean (95% CI)	P Value
<b>Body composition</b>						
Weight, kg	74 (11)	77 (13)	0.7 (2.7)	0.5 (2.9)	0.2 (-0.9 to 1.3)	.71
Body mass index, kg/m <sup>2</sup>	23.7 (3.0)	24.3 (3.2)	0.2 (0.9)	0.2 (0.9)	0.1 (-0.3 to 0.4)	.67
Total fat, kg	12.8 (6.3)	12.6 (7.5)	0.4 (2.0)	1.1 (1.9)	-0.7 (-1.5 to 0.1)	.07
Total fat, %	17.7 (6.7)	16.4 (6.9)	0.5 (2.4)	1.2 (2.1)	-0.7 (-1.6 to 0.2)	.13
Total lean mass, kg	57.1 (7.3)	60.0 (6.3)	-0.2 (1.8)	-0.4 (2.0)	0.2 (-0.6 to 0.9)	.67
Hip circumference, cm	90 (9)	92 (8)	0.8 (7.8)	0.3 (3.1)	0.5 (-1.9 to 2.8)	.69
Trunk fat, kg	22.3 (7.2)	21.5 (8.7)	0.8 (3.4)	1.4 (2.7)	-0.6 (-1.8 to 0.6)	.31
Waist circumference, cm	88 (9)	88 (11)	0.3 (4.0)	0.5 (3.4)	-0.2 (-1.7 to 1.2)	.77
<b>HIV disease</b>						
CD4 cell count, $\mu$ L	570 (292)	587 (258)	51 (245)	-4 (216)	55 (-36 to 146)	.24
HIV RNA, log copies/mL	1.75 (0.21)	1.84 (0.35)	0.15 (0.59)	-0.03 (0.27)	0.18 (0 to 0.36)	.04
<b>Physician-assessed lipodystrophy severity, median (range)†</b>						
Peripheral, median (range, 0-12)	6.5	7	-0.9	-1.2	0.4 (-0.5 to 1.2)	.45
Central, median (range, 0-6)	2	2	-0.1	-0.1	0.0 (-0.5 to 0.5)	.99
<b>Quality of life‡</b>						
Patient assessment	81 (14)	84 (13)	1 (16)	1 (11)	0 (-5 to 5)	.93
Physician assessment	85 (15)	87 (13)	-1 (11)	-2 (9)	1 (-3 to 5)	.48
<b>Mitochondrial</b>						
Lactate, mmol/L	1.7 (0.8)	1.7 (0.9)	0.1 (0.8)	-0.2 (0.9)	0.3 (-0.1 to 0.6)	.13
ALT, U/L	38 (20)	38 (19)	2 (21)	3 (35)	-1 (-12 to 11)	.93
<b>Glycemic</b>						
Glucose, mmol/L	5.0 (0.7)	4.8 (0.7)	0.0 (0.1)	0.2 (0.8)	-0.2 (-6.4 to 3.5)	.56
Insulin, $\mu$ U/mL	12.1 (12)	11.1 (11)	5.7 (21)	0.6 (15)	5.1 (-2.2 to 12.4)	.16
C-peptide, ng/mL	3.5 (2.1)	2.8 (1.5)	0.6 (2.5)	0.4 (2.1)	0.2 (-0.7 to 1.2)	.60
<b>Lipids, mmol/L</b>						
Total cholesterol	5.7 (1.4)	5.6 (1.3)	-0.1 (1.0)	0.2 (1.0)	-0.3 (-0.7 to 0.1)	.09
LDL-C	3.4 (1.1)	3.4 (0.9)	-0.1 (0.7)	0 (0.8)	-0.1 (-0.4 to 0.2)	.59
HDL-C	1.2 (0.3)	1.1 (0.3)	0 (0.3)	0.1 (0.3)	-0.1 (-0.2 to 0)	.05
Triglycerides	2.7 (2.8)	2.9 (2.3)	0 (2.2)	0 (2.2)	0 (-0.8 to 0.9)	.96

\*All values are mean (SD) unless otherwise noted. Comparisons were made using the 2-sample *t* test. CI indicates confidence interval; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol (estimated by Friedewald equation); and HDL-C, high-density lipoprotein cholesterol. Ellipses indicate data not applicable. To convert lactate to mg/dL, divide by 0.111. To convert glucose to mg/dL, divide by 0.0555. To convert total cholesterol, LDL-C, and HDL-C to mg/dL, divide by 0.0259. To convert triglycerides to mg/dL, divide by 0.0113.

†As assessed using a previously described scoring system<sup>4</sup> (see Methods).

‡As assessed by the EuroQol method (0-100 visual analog scale).

**Table 4.** Change in Limb Fat Mass at Week 24 in Relation to Baseline Variables

Baseline Variables	Stavudine/Zidovudine		Abacavir		P Value†	
	No. of Patients*	Change in Limb Fat Mass, mean, kg	No. of Patients	Change in Limb Fat Mass, mean, kg	Between Groups	For Interaction
Nucleoside analog type‡						
Stavudine	46	0.05	44	0.46	.002	.07
Zidovudine	8	0.27	6	-0.08	.51	
Lactate level, mmol/L‡§						
≤2	43	0.06	37	0.46	.01	.46
>2	11	0.16	13	0.22	.50	
Protease inhibitor use‡						
Yes	24	0.17	27	0.49	.15	.69
No	30	0.00	23	0.28	.04	
Total nucleoside analog duration, mo						
≤54	30	0.11	25	0.51	.03	.54
>54	24	0.04	25	0.28	.15	
Limb fat mass, kg						
<2.855	24	0.03	28	0.24	.04	.59
≥2.855	30	0.11	22	0.59	.05	

\*Baseline limb fat data were unavailable for 2 patients in the stavudine/zidovudine group.  
 †Comparisons were made using the 2-sample *t* test. The interaction *P* value tests whether the magnitude of the treatment effect between continuing stavudine or zidovudine and switching to abacavir is statistically significantly different between the 2 strata.  
 ‡Patients were stratified based on these variables.  
 §To convert lactate to mg/dL, divide by 0.1110.  
 ||Median values are given instead of mean values.

ploratory analysis of patients with moderate or severe intra-abdominal fat accumulation at baseline found no evidence of benefit in this subgroup (A.C., unpublished data, February 2002).

A nonsignificant trend was noted for an increased likelihood of developing dorsocervical fat accumulation in the abacavir group. This might reflect increased fat accumulation in patients recovering from lipoatrophy or, less likely, that abacavir causes lipomatosis. This finding should be interpreted cautiously given the limited power of the study to evaluate this abnormality.

It has been hypothesized that lipodystrophy may be a consequence of effective suppression of HIV replication.<sup>31</sup> The improvement of lipoatrophy (as assessed by objective methods) in tandem with stable or even slightly (although nonsignificantly) better HIV suppression suggests, however, that lipoatrophy is not due to effective HIV suppression. A similar lack of association was also observed previously in patients switching from a protease inhibitor to a complex non-protease inhibitor antiretroviral regimen in whom intra-abdominal fat accumulation improved but HIV viremia did not change.<sup>20</sup>

Switching to abacavir was safe, and no unexpected adverse events were reported or linked to abacavir use. Also, in these patients having extensive prior antiretroviral therapy, control of HIV replication and CD4 cell count preservation were not compromised.

No metabolic measure improved significantly, but the study was not designed to show a significant benefit of switching for these measures.

There are limitations to our study. Only 2 women and no children were studied, and only 7 of 106 patients were nonwhite. The study also was not powered to assess the effect of switching from stavudine or zidovudine therapy. The lipodystrophy severity assessment, the results of which correlated significantly with DXA fat mass in 2 cross-sectional prevalence surveys,<sup>4,15</sup> was open to patient bias in a previous open-label prospective study<sup>20</sup> and may not have been reliable in the present study; it is almost certainly less reliable than the objective assessment.

In summary, HIV lipoatrophy can improve significantly after switching from stavudine or zidovudine to abacavir without affecting control of HIV replication, although clinically, this benefit on li-

poatrophy was not apparent after 24 weeks. This suggests this switching strategy may be a useful approach over a longer period for a condition that is distressing, potentially stigmatizing, and associated with poorer adherence to antiretroviral therapy. Whether this strategy can lead to clinically apparent improvement or even complete reversal of lipoatrophy may require several more years of follow-up (we are continuing to follow up the study groups described herein), and will depend on no other long-term safety or efficacy issues arising. Other strategies under investigation include intermittent antiretroviral therapy and concurrent therapy with thiazolidinediones, antidiabetic drugs that promote growth and differentiation of peripheral adipocytes and that have been effective in congenital lipoatrophy states.<sup>32</sup>

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*Study concept and design:* Carr, Smith, Hoy, Hudson, Cooper.  
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*Analysis and interpretation of data:* Carr, Smith, Martin, Amin, Freund, Law, Cooper.  
*Drafting of the manuscript:* Carr, Smith, Martin.  
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