

Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study

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Objective: To determine if long-term improvement in HIV lipoatrophy can be attained by substitution of thymidine analogues zidovudine (ZDV) or stavudine (d4T) with abacavir (ABC).

Design: Long-term follow-up (104 weeks) of a randomized, open-label study.

Setting: Seventeen ambulatory HIV clinics in Australia and London.

Subjects: Patients with HIV lipodystrophy were randomized to switch from a thymidine analogue to ABC, while continuing all other antiretroviral therapy (ABC arm) (n = 42) or continue current therapy (ZDV/d4T arm) (n = 43).

Intervention: At week 24, all control patients could switch to ABC. Of the original 111 patients randomized, 85 had long-term follow-up data, with 77 having imaging data available at 104 weeks.

Main outcome measure: The primary endpoint was time-weighted change in limb fat mass, measured by dual-energy X-ray absorptiometry (DEXA).

Results: At week 104, the mean increase in limb fat for the ABC and ZDV/d4T group was 1.26 ± 2.02 kg and 0.49 ± 1.38 kg, respectively. The time-weighted change for limb fat was significantly different between the two arms (0.43 kg; $P = 0.008$). On-treatment analysis demonstrated a trend for increased limb fat in patients in the ABC arm. Visceral fat accumulation, buffalo hump, self-assessed lipodystrophy or the lipodystrophy case definition score (LCDS) did not improve.

Conclusions: In patients with moderate-to-severe lipodystrophy, significant improvements in subcutaneous fat continued over 104 weeks after switching from a thymidine analogue to ABC. Nevertheless, the lipodystrophy syndrome was still evident, indicating additional strategies need evaluating. © 2004 Lippincott Williams & Wilkins

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Keywords: HIV lipodystrophy, lipoatrophy, thymidine analogues, abacavir

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Introduction

The HIV-associated lipodystrophy syndrome affects approximately 50% of HIV-positive patients, particularly those receiving antiretroviral therapy based on nucleoside reverse transcriptase inhibitors and protease inhibitors [1–2]. The selection of an optimal treatment regimen for HIV infection is influenced by increasing evidence that particular antiretroviral drugs may exacerbate lipodystrophy and associated metabolic abnormalities. However, because of cross-resistance among antiretroviral drug classes and other treatment toxicities, it is likely that, in a lifetime, patients will have to take drugs that are associated with the development of the lipodystrophy syndrome.

A number of cohort studies have suggested that long-term exposure to thymidine-based analogues, particularly stavudine (d4T), results in lipodystrophy that is associated with mitochondrial toxicity and lactic acidemia [3–5]. The PIILR extension study examined lipodystrophic patients on a protease inhibitor-sparing antiretroviral regimen for a least 12 months, who then ceased d4T or zidovudine (ZDV) [6]. This study resulted in significant improvements in lipodystrophy but an unacceptable rate of HIV virological rebound [6]. More recently, replacement of d4T or ZDV with abacavir (ABC) in randomized controlled trials has been shown to lead to modest improvements in fat mass over a relatively short period of time [7,8].

The initial MITOX study reported a significant increase of 0.4 kg (11%) in limb fat in the ABC-treated subjects at 24 weeks, as well as significant relative increases in subcutaneous thigh and abdominal fat mass [7]. However, this difference in limb fat was not apparent clinically.

This long-term follow-up study was undertaken to determine if the modest improvements seen at 24 weeks were sustained or enhanced, or even whether lipodystrophy might resolve over a more prolonged period of follow-up.

Methods

Study sample

The study participants' eligibility, randomization and demographic details are described in the original MITOX study [7]. All patients provided written informed consent after study approval by each site's research and ethics committee.

Interventions

At baseline, patients were randomly assigned to switch from a thymidine analogue (85% d4T, 15% ZDV) to

ABC, while continuing all other antiretroviral therapy or to continue all current antiretroviral therapy for up to 24 weeks. Patients were followed beyond the randomized phase for up to 128 weeks (mean, 102 weeks, but indicated as week 104). At the completion of week 24, the MITOX study subjects who were randomized to continue their current therapy were permitted to switch to ABC. Therefore, subjects taking part in the long-term follow-up were:

- randomized to take ABC at the commencement of the MITOX study
- switched to ABC at (or after) week 24 or
- elected to continue on a thymidine analogue regimen after week 24.

Assessments

At the completion of the 24-week randomized phase, subjects were assessed at weeks 48, 72 and 104. At each visit, body composition was quantified by dual-energy X-ray absorptiometry (DEXA; Lunar DPXL, Madison, Wisconsin, USA) and single-cut abdominal computed tomography, as described previously [7]. Body composition assessment consisted of limb fat mass, total bone mineral density (BMD), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT). The validated lipodystrophy case definition scoring system (LCDS), derived from 10 demographic, body composition and metabolic parameters, was also used to determine the severity of lipodystrophy in each patient at each visit [9]. The LCDS has a sensitivity of 79% and specificity of 80% [9]. A score of ≥ 0 indicates the presence of lipodystrophy; the higher the score the greater severity of lipodystrophy [10].

Real-time plasma HIV RNA using either the Roche Amplicor Monitor assay version 1.0 (Roche Diagnostics, Branchburg, New Jersey, USA; lower limit of detection 400 copies/ml plasma) or the Chiron b-DNA assay version 3 (Chiron Corp., Emeryville, California, USA; lower limit of detection 50 copies/ml) and T lymphocyte subsets were also collected at all study visits. Fasting lipid and glycaemic parameters (total cholesterol, high density and low density lipoprotein cholesterol, triglycerides, C-peptide, insulin and glucose) and lactate and anion gap were collected at baseline, week 48 and 72.

Subjective measures of lipodystrophy severity were assessed by the patient at weeks 0, 48 and 72. In each body 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 [11]. The presence of buffalo hump was assessed by self-assessed severity of neck lipodystrophy.

Statistics

The primary study endpoint was the mean change in limb fat mass from baseline to week 104, measured by DEXA. Secondary endpoints were change in VAT; self-assessed lipodystrophy severity; lipid, glycaemic, and biochemical measurements; viral load; and CD4 cell count. Change in LCDS and total BMD were analysed in addition to these original endpoints.

Changes in study endpoints from baseline were summarized by nominal study weeks using a time-window approach; the average value was used if there was more than one value in a time window. Time windows were created around the primary scheduled visits and ranged over approximately 4 months, except for week 104, which included data up to week 128.

Primary analysis was by intention to treat on available data. An analysis based on last visit carried forward was not conducted because of the early attrition rate in the study. Changes from baseline to nominal study week and time-weighted average change from baseline were compared between and within treatment groups using two- and one-sample t tests, respectively. All hypothesis tests were two sided, with statistical significance at the 0.05 level. Linear regression was used to determine significance for trends over time. There was no adjustment of *P* values for multiple comparisons. Analyses were performed using SAS statistical software, version 8 (SAS, Cary, North Carolina, USA).

An ‘on-treatment analysis’ was also performed, enabling a comparison of change in limb fat in those who had been on ABC for more than 28 days with those who had not (*n* = 85). Week of switch was used as the baseline for persons who elected to commence ABC at or after week 24. Data were only included while patients remained on ABC; if ABC was discontinued, subsequent data was omitted from the analyses.

Univariate and multivariate linear regression were used to determine predictors of change in limb fat from baseline to week 104. Baseline demographic, biochemical, lipid and glycaemic variables were assessed as predictors. Pretrial and on-trial duration of thymidine analogues, protease inhibitors and ABC were also included. The final predictive model was determined using forward stepwise regression. Variables with a univariate *P* value < 0.1 were assessed in multivariate analysis.

Results

Participants

One hundred and eleven patients were randomized into the original MITOX study. Patient follow-up is summarized in Fig. 1. From the 105 patients that completed the randomized 24 weeks of the trial, 85 patients attended for the week 104 follow-up. Forty

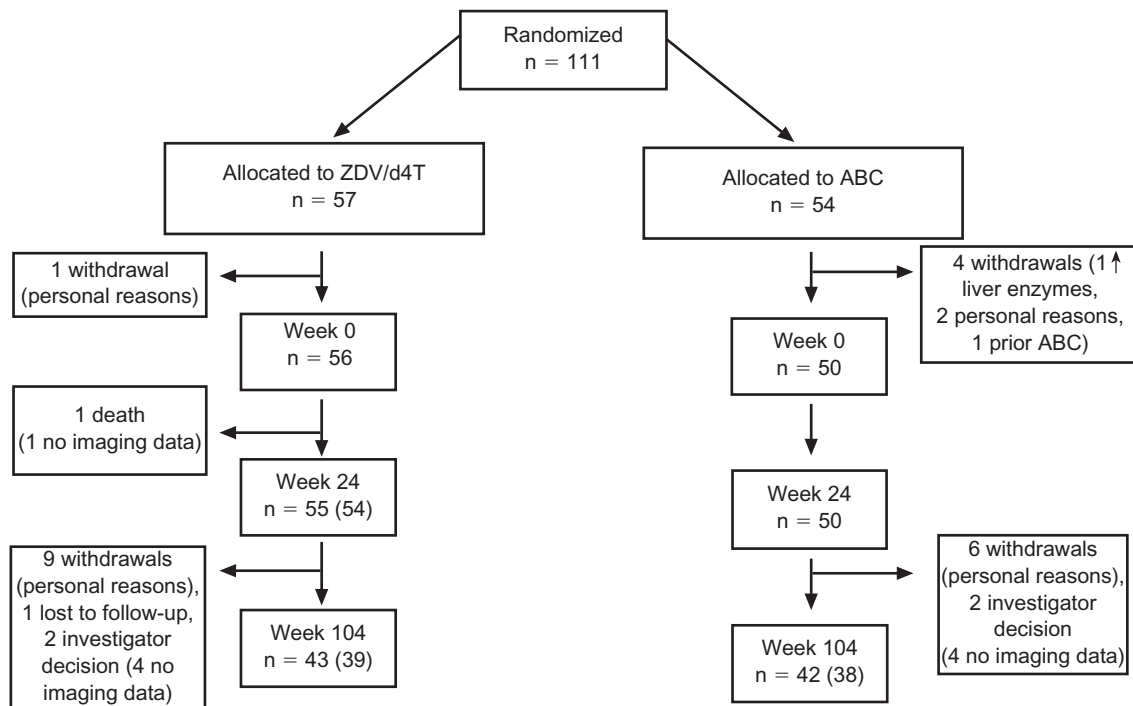


Fig. 1. Patient follow-up. Number of patients given, with number in parentheses being the number with body imaging data. ZDV, zidovudine; d4T, stavudine; ABC, abacavir.

two patients were randomized to commence ABC at week 0; 21 patients elected to switch to ABC after the week 24 visit and 22 elected to remain on their thymidine analogue therapy. The baseline demographics and clinical data of the 85 patients who completed all scheduled visits did not differ in age, duration of infection, proportion with undetectable viral load, CD4 cell count, limb fat mass, VAT, SAT or total BMD from those that did not complete the long-term follow-up (data not shown). Using the LCDS, the 85 patients had a mean score of 11 (± 18) at trial entry, which is equivalent to moderate lipodystrophy.

Lipoatrophy

There was a significant difference between the ZDV/d4T and ABC arms from baseline to last follow-up for limb fat of +0.43 kg, with the ABC arm greater [mean time-weighted change, 95% confidence interval (CI), 0.12–0.75 kg; $P = 0.008$]. The mean increase in limb fat at week 104 in the ABC patients was 1.26 ± 2.02 kg (35%; $P = 0.001$), whereas the ZDV/d4T arm increased by 0.49 ± 1.38 kg (13%; $P = 0.039$) (Fig. 2).

Subsequent on-treatment analysis demonstrated that change in limb fat was greater in those patients who were on ABC from baseline compared with those that never took ABC, and that patients who switched to

ABC at week 24 increased limb fat to a greater degree than patients who did not switch (Fig. 3).

There was no significant change in LCDS over time, either within groups (ABC: $P = 0.503$ for trend; ZDV/d4T: $P = 0.604$ for trend), or between groups ($P = 0.117$) (Table 1).

Within-group analysis demonstrated a significant improvement in subjectively assessed lipodystrophy in the ABC group from baseline to 72 weeks ($P = 0.003$ for trend). For those in the ZDV/d4T arm, improvement in subjectively assessed lipodystrophy was not statistically significant ($P = 0.183$ for trend). Differences between the two groups over time were not significant ($P = 0.117$) (Table 1). The subjectively assessed lipodystrophy correlated poorly with change in limb fat as assessed by DEXA (-0.09 ; $P = 0.2$). Self-assessed buffalo hump was present at week 104 in 25% of the ZDV/d4T and 22% of the ABC group ($P = 0.78$).

The change in limb fat mass was assessed by both univariate and multivariate analysis for correlates of risk. A significant univariate association was found between a greater increase in limb fat mass and higher baseline waist circumference ($P = 0.007$), hip circumference ($P = 0.041$), weight ($P = 0.005$), and body mass index (BMI; $P = 0.004$), and shorter duration of thymidine analogue on study ($P = 0.035$) (Table 2). In the multi-

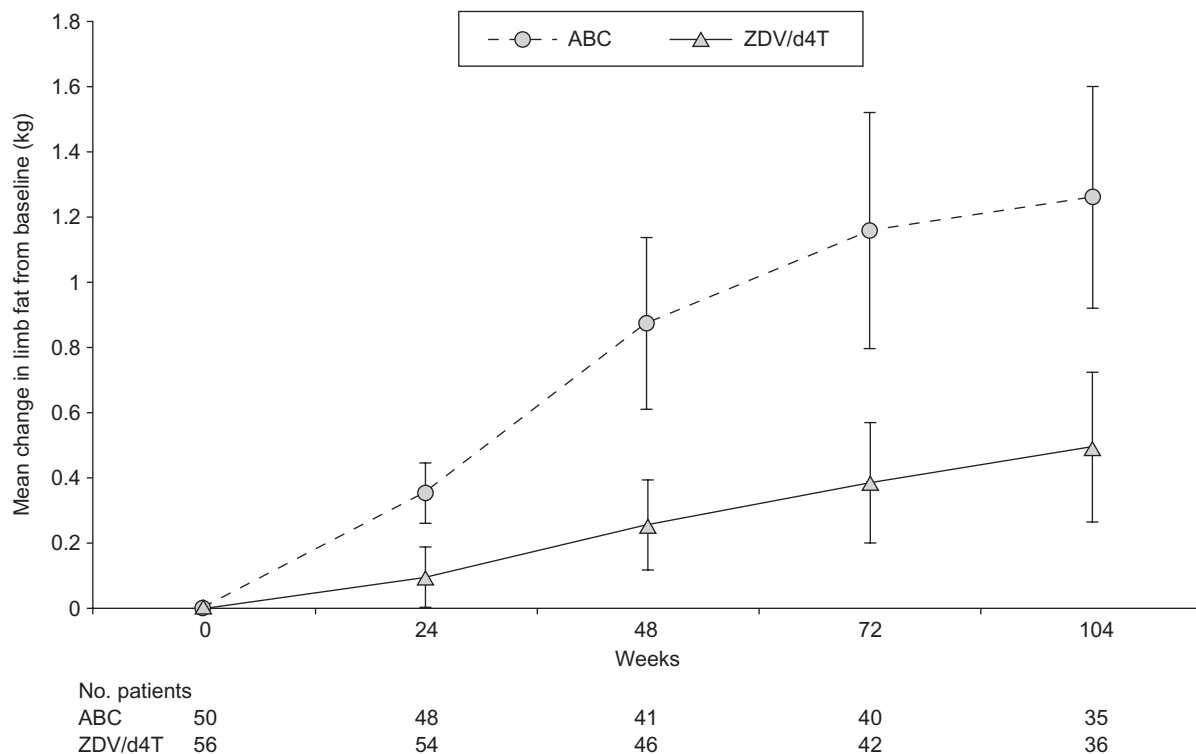


Fig. 2. Mean change in limb fat mass (intention-to-treat analysis). Data presented as mean \pm SEM. ZDV, zidovudine; d4T, stavudine; ABC, abacavir.

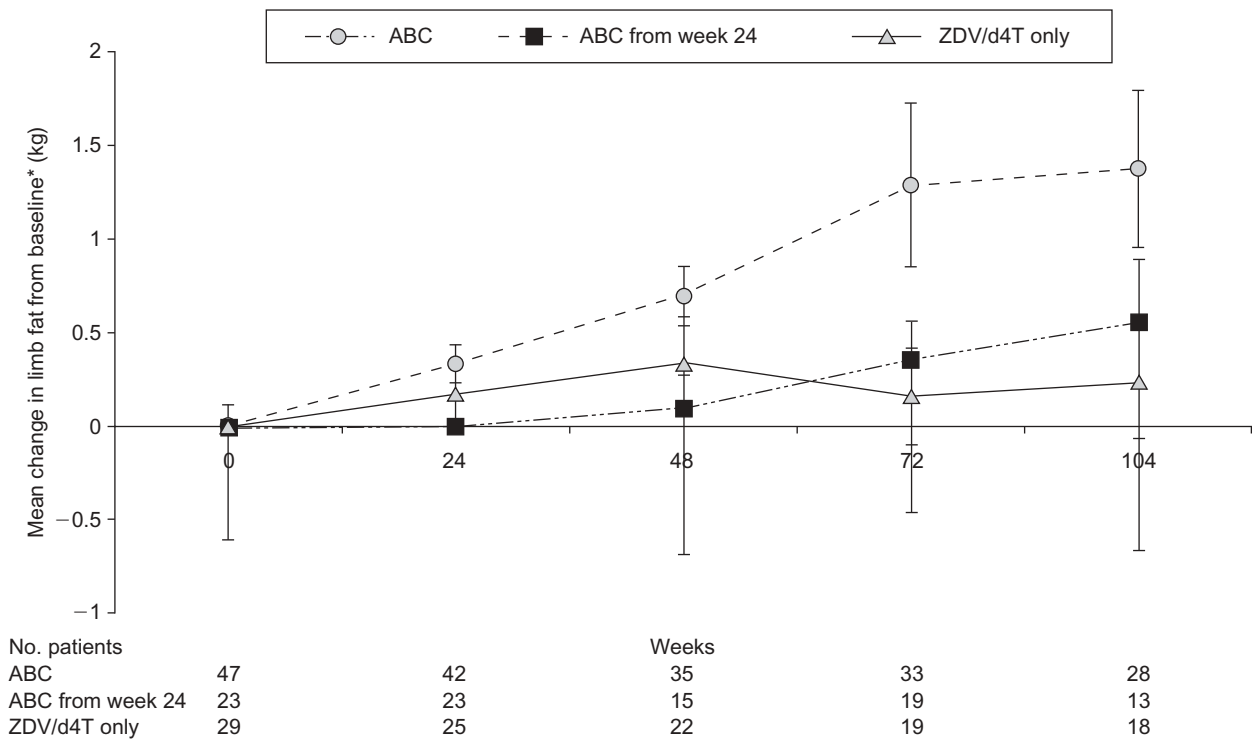


Fig. 3. Mean change in limb fat mass (on-treatment analysis). Data presented as mean ± SEM. ‘Baseline’ refers to data from the week 0 time window for the ZDV/d4T only and the ABC groups, and to data from the week 24 time window for the ABC from week 24 group. ZDV, zidovudine; d4T, stavudine; ABC, abacavir.

Table 1. Change in body composition and laboratory parameters from baseline to week 72 or 104.

Parameter ^a	ZDV/d4T	Abacavir	P value
VAT (cm ²)	-13 ± 40	-7 ± 33	0.49
SAT (cm ²)	27 ± 72	34 ± 42	0.62
LCDS ^b	14 ± 16	8 ± 19	0.72
Patient lipodystrophy severity score ^b	-0.5 ± 3.15	-1.58 ± 3.07	0.11
BMD (g/cm ²)	-0.011 ± 0.02	0.014 ± 0.12	0.25
CD4 lymphocyte count (× 10 ⁶ cells/l)	110 ± 218	59 ± 274	0.35
Viral load (log copies/ml)	0.26 ± 0.75	0.38 ± 0.80	0.57
Total cholesterol (mmol/l) ^b	-0.08 ± 0.95	0.01 ± 1.31	0.70
HDL cholesterol (mmol/l) ^b	0.02 ± 0.32	0.07 ± 0.59	0.62
LDL cholesterol (mmol/l) ^b	-0.19 ± 0.77	-0.06 ± 0.94	0.53
Triglycerides (mmol/l) ^b	-0.03 ± 2.10	-0.05 ± 2.53	0.97
Lactate (mmol/l) ^b	-0.03 ± 0.81	-0.08 ± 0.74	0.76
ALT (U/l) ^b	0.24 ± 21.77	3.57 ± 29.31	0.53
C-peptide (µg/l) ^b	0.13 ± 2.10	0.61 ± 2.54	0.34
Insulin (mU/l) ^b	-0.01 ± 9.46	0.65 ± 17.89	0.83
Glucose (mmol/l) ^b	0.18 ± 0.84	0.19 ± 0.87	0.96
Anion gap (mmol/l) ^b	-0.77 ± 8.91	1.44 ± 7.91	0.20

ZDV, zidovudine; d4T, stavudine; VAT, abdominal visceral adipose tissue; SAT, L4 abdominal subcutaneous adipose tissue; LCDS, lipodystrophy case definition score; BMD, bone mineral density; HDL, high density lipoprotein; LDL, low density lipoprotein; ALT, alanine aminotransferase.

^aData presented as mean ± SD.

^bMeasured at week 72.

variate analysis, baseline BMI was significantly and independently associated with change in limb fat: the higher the BMI at baseline the greater the limb fat mass gain at week 104 (*P* = 0.004). There was a trend that longer duration of thymidine analogues on study was independently associated with a lower increase in limb

fat; however, this was not significant (*P* = 0.055) (Table 2).

Visceral adipose tissue

There was no significant difference between the ABC and ZDV/d4T arms from baseline to last follow-up for

Table 2. Predictors of limb fat change from baseline to week 104.

Baseline variables ^a	Univariate analysis ^b		Multivariate analysis	
	Coefficient	P value	Coefficient	P value
Duration of HIV (years)	-0.09	0.066	-0.077	0.104
Randomized group	0.767	0.065	0.638	0.117
Waist circumference (cm)	0.06	0.007	0.022	0.536
Hip circumference (cm)	0.048	0.041	0.018	0.496
Weight (kg)	0.049	0.005	0.022	0.524
BMI	0.189	0.004	0.189	0.004
VAT (cm ²)	0.005	0.084	0.000	0.892
Duration ZDV/d4T prior to trial (years)	-0.012	0.091	-0.008	0.295
Duration ZDV/d4T during trial (years)	-0.045	0.035	-0.04	0.055
Duration ABC during trial (years)	0.038	0.051	0.032	0.100

ZDV, zidovudine; d4T, stavudine; BMI, body mass index; VAT, abdominal visceral adipose tissue.

^aOther virological, immunological, glycaemic, body fat and antiretroviral treatment parameters are not shown.

^bData presented have univariate $P < 0.1$.

VAT (mean time-weighted change, -5 cm^2 ; 95% CI, -15 to 5). The mean decrease in VAT in patients at week 104 in the ABC group was 7 cm^2 ($P = 0.223$), whereas the ZDV/d4T group decreased by 13 cm^2 ($P = 0.052$) (Table 1).

Bone mineral density

There was no significant difference between the ABC and ZDV/d4T arms in mean time-weighted change from baseline to last follow-up for BMD (0.005 g/cm^2 ; 95% CI, -0.012 to 0.002 ; $P = 0.19$). A small but significant decrease in BMD was noted over the 104 weeks for the ZDV/d4T arm (0.011 g/cm^2 ; 95% CI, -0.019 to -0.003 ; $P = 0.008$), but no change was seen in the ABC arm ($P = 0.51$) (Table 1).

Surrogate and laboratory markers

There were no differences between the groups for mean change in CD4 cell count, viral load, log viral load, lipid or glycaemic parameters (Table 1). Viral control was maintained in both groups of patients throughout the 2-year follow-up.

Adverse events

In the extension phase of MITOX, there were 10 reported serious adverse events. There were four ABC hypersensitivities reported in patients that switched to ABC at week 24, and six hospitalizations that were considered unrelated to study drugs.

Discussion

This study evaluated the long-term effect of switching a thymidine analogue-based regimen to an ABC-based regimen with the aim of reversing lipodystrophy. Overall, patients randomized to ABC had greater recovery of limb fat mass compared with those remaining on thymidine analogues. However, there was no

difference in VAT, buffalo hump, self-assessed lipodystrophy, LCDS or the associated lipid and glycaemic parameters. This demonstrates that lipoatrophy can be abrogated using this switching strategy, but the overall features of the lipodystrophy syndrome may not. The study findings further support a causal role for thymidine analogues in the pathogenesis of the lipodystrophy syndrome.

In short-term studies, there is an increase in limb fat in patients who switch from regimens containing d4T [3,4,6]. The original MITOX trial followed patients for 24 weeks and showed a small but significant increase in limb fat of 0.39 kg [7]. Recently, Moyle *et al.* [8] demonstrated an increase of 0.57 kg in arm fat over a 48 week study in patients who switched from d4T to ABC, compared with a reduction in those who switched to ZDV. Similarly, John *et al.* [12] reported an increase of 0.007 kg/month in leg fat in patients who switched from d4T and a protease inhibitor to ABC plus ZDV over 48 weeks. These studies reported modest increases in limb fat once d4T was ceased over relatively short periods of time. In our longer-term (104 week) study, we found a significant increase in limb fat of 1.26 kg (or 36%) in patients who switched to ABC, demonstrating that a partial reversal of lipoatrophy can be achieved and appears to continue progressively over time.

Improvements in lipoatrophy were seen in the absence of change in VAT. Similar findings are reported by John *et al.* [12] and Moyle *et al.* (2003) [8]; together, these data support the hypothesis that thymidine analogues are associated with SAT loss, but less so with the other features of the lipodystrophy syndrome.

Change in BMD was similar in both the ZDV/d4T and ABC arms. There was a statistically significant decline within the thymidine analogue arm; however, this reduction was clinically very small. Treatment with

d4T has previously been shown to be associated with lower BMD [13]. Fat mass is also positively associated with BMD [14], which is consistent with our findings, as the thymidine analogue group had less body fat mass and lower BMD.

Despite a 36% increase in limb fat mass in those patients randomized to the ABC arm, compared with a 13% increase in the ZDV/d4T arm, patient self-assessed lipoatrophy severity was not different between the two randomized groups. There was, however, a significant improvement in self-assessed body image within the ABC group, but not the ZDV/d4T group. This might be explained by 49% of the ZDV/d4T arm electing to change to ABC after week 24 and that a proportion of the switch arm found an improvement in their body appearance. Therefore, the clinically relevant finding that greater limb fat recovery is seen in patients who switch to ABC compared with those remaining on ZDV/d4T may not be observable by patients because of the bias of the open-label study design. This finding highlights the need to use objective measures for assessing body shape changes in unblinded clinical trials of lipodystrophy.

The LCDS did not differ between the two study arms. This score is a measure of the presence and severity of a compilation of lipoatrophy, central fat gain and metabolic abnormalities. Although we found significant improvement in limb fat mass, there was no improvement in VAT, high density lipoprotein cholesterol or anion gap (important components of the case definition), which may explain why the score did not improve.

Previously the HOPS study [1] reported that CD4 cell count was strongly associated with the development of lipoatrophy, but no antiretroviral agent or class of agent was correlated with lipoatrophy. Others have shown that fat wasting is associated with age, BMI and duration of antiretroviral treatment [15]. However, this study determined that only baseline BMI was strongly associated with limb fat mass change. The percentage limb fat change was not analysed in this study because, at baseline, the two randomized groups had a similar BMI. The finding of a trend for duration of thymidine analogue usage is associated with reduced limb fat is not novel. Previous cross-sectional and longitudinal studies have demonstrated that the reduction of peripheral fat is greatest in patients receiving d4T, compared with ZDV, and that this effect is independent of protease inhibitor usage [3,4]. Use of ABC was not independently correlated with limb fat gain in the multivariate analysis. This is most likely related to the study design, as ABC administration precluded concurrent thymidine analogue usage.

In vitro studies of antiretroviral agents suggest that

nucleoside analogues may cause mitochondrial toxicity to varying degrees [16]. However, there are limited published data confirming a direct effect of nucleoside analogues on adipocytes, and these preliminary data are hard to interpret. *In vivo* studies have suggested thymidine analogues, especially d4T, are important in the lipoatrophy component of the lipodystrophy syndrome [4,17,18]. While thymidine analogues appear to play a major role in the development of lipoatrophy, it has previously been unclear whether this condition is reversible in patients remaining on virologically suppressive therapy.

In conclusion, lipoatrophy is partially reversed in the long term, without loss of virological control, by switching thymidine analogues for ABC. However, other components of the lipodystrophy syndrome remained unaffected by this strategy. Prevention of the lipodystrophy syndrome or evaluation of non-antiretroviral agents are areas for future strategic studies.

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Appendix

MITOX Study Group

In Australia: Robert Fielden (St Vincent's Hospital, Sydney); John Chuah, Robyn James, Fiona Clark (Gold Coast Sexual Health Clinic, Miami); Anne Mijch, Claire McCormack (Alfred Hospital, Melbourne); David Baker, Hugh McLeod, Janet Kidd, Robert McFarlane, Robyn Vale (407 Doctors, Sydney); Mark Kelly, Harry Michelmore, Jega Sarangapany (Albion Street Centre, Sydney); Jeff Hudson (Burwood Rd Practice, Sydney) Norman Roth, Helen Wood (Prahran Market Clinic, Melbourne); Robert Finlayson, Neil Bodsworth, David Wheatley, Wilma Goodyear (Taylor Square Private Clinic, Sydney); Marilyn McMurchie (Darlinghurst, Sydney); Ian Chenoweth (Middle Park Clinic, Melbourne); David Austin, Mark Bloch, Tony Frater, Rohan Holland (Holdsworth House General Practice, Sydney); Jonathon Anderson, Julie Patching (Carlton Clinic, Melbourne); Gary Rogers, Michael Curry (Care and Prevention Programme, Adelaide); Nick Medland, Helen Wood, (Centre Clinic, Melbourne); Tuck Meng Soo, Philip Habel (Interchange General Practice, Canberra); Robyn Munro, Terry Sharkey (National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney). In the UK: Mike Youle, Zoe Cuthbertson (Royal Free Hospital, London).