Body fat changes among antiretroviral-naive patients on PI- and NNRTI-based HAART in the Swiss HIV Cohort Study

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Background: Body fat changes are common in patients with HIV. For patients on protease inhibitor (PI)-based highly active antiretroviral therapy (HAART), these changes have been associated with increasing exposure to therapy in general and to stavudine in particular. Our objective is to show whether such associations are more or less likely for patients on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART.

Methods: We included all antiretroviral-naive patients in the Swiss HIV Cohort Study starting HAART after April 2000 who had had body weight, CD4 cell count and plasma HIV RNA measured between 6 months before and 3 months after starting HAART, and at least one assessment of body fat changes after starting HAART. At visits scheduled every 6 months, fat loss or fat gain is reported by agreement between patient and physician. We estimate the association between reported body fat changes and both time on therapy and time on stavudine, using conditional logistic regression.

Results: Body fat changes were reported for 85 (9%) out of 925 patients at their first assessment; a further 165 had only one assessment. Of the remaining 675 patients, body fat changes were reported for 156 patients at a rate of 13.2 changes per 100 patient-years. Body fat changes are more likely with increasing age [odds ratio (OR) 1.18 (1.00–1.38) per 10 years], with increasing BMI [OR 1.06 (1.01–1.11)] and in those with a lower baseline CD4 cell count [OR 0.91 (0.83–1.01) per 100 cells/μl]. There is only weak evidence that body fat changes are more likely with increasing time on HAART [OR 1.16 (0.93–1.46)]. After adjusting for time on HAART, fat loss is more likely with increasing stavudine use [OR 1.70 (1.34–2.15)]. There is no evidence of an association between reported fat changes and time on NNRTI therapy relative to PI therapy in those patients who used either one therapy or the other [OR 0.98 (0.56–1.63)].

Conclusion: Fat loss is more likely to be reported with increasing exposure to stavudine. We find no evidence of major differences between PI and NNRTI therapy in the risk of reported body fat changes.

Introduction

Abnormal fat distribution and abnormalities in blood lipids, blood glucose and lactate are common in patients with HIV when treated with highly active antiretroviral therapy (HAART) [1]. These changes in body shape and metabolic abnormalities are collectively known as lipodystrophy, although it is not clear whether this is a single syndrome or several [2,3]. Changes in body shape can have a stigmatizing effect [4] and are associated with poor drug adherence [5]. The blood lipid abnormalities are risk factors for cardiovascular disease [6].

Body fat changes were first described in patients receiving protease inhibitors (PIs) and were therefore first associated with this drug class [1]. However, these

changes are also seen in patients receiving nucleoside reverse transcriptase inhibitors (NRTIs) without PIs [7] and these changes may accelerate when PIs and NRTIs are combined [8]. Among NRTIs, stavudine in particular is implicated in fat loss, in both therapy with [8,9] and without a PI [7,10].

Less is known about the association between lipodystropy and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Switching studies have shown a trend towards modest improvements in metabolic abnormalities when the PI component of therapy is replaced by an NNRTI [11]. Cross-sectional studies suggest that body fat changes may be less frequent when NNRTIs are used rather than PIs [12,13].

Nevertheless, lipodystrophy may be partly caused by the HIV infection itself or by recovery following therapy [14–16]; time on therapy may be more important than time on specific drugs or drug classes [9,17], and the risk factors associated with lipodystrophy may depend on the patient population and definition of lipodystrophy used [18].

Many studies on risk factors for lipodystrophy have important design limitations. These include small samples, and cross-sectional or case-control studies where past treatment changes are not part of the analysis. Our data come from a large prospective cohort study where covariates are regularly measured and drug changes are well documented. From this cohort, we selected antiretroviral-naive patients starting HAART with a high percentage of patients on NNRTI-based therapy. The purpose of this study was to consider whether the association between body fat changes and time on HAART differs between PI- and NNRTI-based therapy. Stavudine has been linked with fat loss in other cohort studies but these studies have considered the drug as one of many possible candidates. We concentrated our analysis on stavudine to confirm the association with fat loss at least as far as possible given the limitations of observational data.

Methods

Patients

The Swiss HIV Cohort Study (SHCS) is a prospective cohort with continuing enrolment of HIV-infected adults. Visits scheduled every 6 months take place at one of seven outpatient clinics or at the office of a collaborating physician. From 1 April 2000, a cardiovascular risk assessment became part of each visit. Fat loss or gain in the face, arms, legs, buttocks, abdomen, breasts or neck is reported by agreement between patient and physician. Weight, hip and waist measurements are also recorded and blood is analysed for glucose, cholesterol, triglyceride and lactate concentrations.

In this study we included all antiretroviral-naive patients in the SHCS starting HAART after April 2000 who had had body weight, CD4 cell count and plasma HIV RNA (viral load) measured between 6 months before and 3 months after starting HAART, and at least one assessment of body fat changes after starting HAART. We define HAART as the combination of at least two NRTIs with one boosted or non-boosted PI or one NNRTI.

Statistical analysis

We considered associations between both time on HAART and time on stavudine and three endpoints: any body fat change, fat loss and fat gain. These associations were estimated using conditional logistic regression [19]. We modelled the probability of reporting a fat change at each visit, given that the change has not been reported previously. This sort of discrete time survival analysis is appropriate because fat changes are not reported between visits. The association between fat changes and time on HAART was estimated after adjusting for other variables that might influence the risk of body fat changes. As time-independent covariates, we used CD4 cell count, viral load and body mass index (BMI) at baseline, age and gender, and intravenous drug use as the likely mode of transmission. Time on HAART or on a specific class or drug was coded as a time-dependent covariate, calculated at each visit as exposure to date in units of 6 months. For each endpoint, four models were fit using the same set of time-independent covariates but with the following time-dependent covariates: time on 1) HAART, 2) PI and NNRTI therapy, 3) HAART and stavudine and 4) HAART, stavudine within PI therapy and stavudine within NNRTI therapy.

We used SAS v8.2 (SAS Institute, Inc., Cary, NC, USA) and report two types of statistics. The evidence for an association between a body fat change and another variable was assessed by a hypothesis test based on the difference in the log likelihood ratio between the full model and a reduced model without that variable. The nature of any association between a body fat change and another variable was assessed by an odds ratio (OR). Wald-based 95% confidence intervals (CI) are given for all ORs.

Sensitivity analysis

To confirm our results, we carried out six additional analyses. Firstly, we estimated the association between fat loss and stavudine using a second method of discrete time survival analysis – a method derived by grouping data from a Cox proportional hazards model into discrete time intervals [19]. This method differs from conditional logistic regression only in that it uses a cumulative log–log link function rather than a logit link function.

Secondly, our models assume regular, equally spaced visits. In reality, visits can be irregular and so we simulated visits every 6 months after starting HAART until the closest date to the date of last actual visit. We estimated the association between fat loss and stavudine under two assumptions: 1) that any fat loss occurs at the simulated visit closest to the actual visit when fat loss was first reported and 2) that any fat loss occurs at the first simulated visit after the last actual visit when no fat loss was reported.

Thirdly, we considered whether stavudine use is confounded by the use of other common antiretroviral drugs. We considered each of the common drugs in turn and estimated the association between fat loss and stavudine, adjusting for both time on HAART and time on the other drug.

Fourthly, we excluded patients with viral load measured after starting HAART and then estimated the association between fat loss and stavudine. These patients are included in the sample so that the sample is representative of the cohort, but viral load can change rapidly after starting HAART.

Fifthly, we allowed for between-physician variability because physician and patient were left to decide what changes were worthy of reporting. We estimated the association between fat loss and stavudine excluding data from physicians with fewer than 10 cardiovascular risk assessments and with 'physician' as a random effect in the model.

Finally we removed from our dataset those patients who had received both PI- and NNRTI-based therapy, and formally tested for differences between the two in those patients who had received only one type of therapy or the other.

Results

Patient characteristics

As of 30 April 2004, 1266 antiretroviral-naive patients in the SHCS had started HAART after April 2000; 1217 (96%) had undergone at least one cardiovascular risk assessment after starting HAART; 925 (73%) had also had body weight, CD4 cell count and viral load measured between 6 months before and 3 months after starting HAART. Body fat changes were reported for 85 (9%) of these 925 patients at their first assessment. For these 85 patients, the median time from starting HAART until the first assessment was 4.4 months (interquartile range 2.8–6.0). A further 165 patients have had just one assessment to date.

Among the remaining 675 patients, body fat changes were reported for 156 patients at subsequent assessments. From the first to the most recent assessment, these 675 patients have been followed for a median of 20 months and a total of 1181 patient-years, giving an incidence rate of 13.2 reported changes per 100 patient-years. Those with reported body fat changes are on average older than those without reported changes and are, when starting HAART, more likely to have had a CDC group C disease, lower CD4 cell count and higher viral load (Table 1). In general, those with reported fat changes show greater increases in CD4 cell count than those without reported fat changes and those with reported fat gain show greater increases in anthropometric and metabolic markers than those without reported fat gain (Table 2).

Antiretroviral treatment

Of the 675 patients, 288 (43%) used PIs but not NNRTIs, 233 (35%) used NNRTIs but not PIs and 154 (23%) used both. The most common PIs were nelfinavir and lopinavir, used by 235 (53%) and 198 (45%) patients, respectively, out of the 442 using any sort of PI (Figure 1). Most NNRTI use was of efavirenz – this was used by 349 (90%) out of the 387 patients using either of the two NNRTIs. Common NRTIs were lamivudine and zidovudine, used by 659 (98%) and 613 (91%) patients, respectively. Stavudine was used by 144 (21%) patients with a median exposure of 15 months.

Statistical analysis

Fat loss is more likely in older patients [Table 3, OR 1.38 (1.08–1.76) per 10 years, P=0.01] and in those with a lower baseline CD4 count [OR 0.79 (0.65–0.95) per 100 cells/μl, P=0.01]. Fat gain is more likely in females [OR 1.90 (1.27–2.86), P<0.01] and in those with higher baseline BMI [OR 1.12 (1.06–1.17), P<0.01].

Overall, body fat changes are more likely with increasing age [OR 1.18 (1.00–1.38) per 10 years, P=0.04], with increasing BMI [OR 1.06 (1.01–1.11), P=0.02] and in those with a lower baseline CD4 cell count [OR 0.91 (0.83–1.01) per 100 cells/μl, P=0.06]. There is only weak evidence that body fat changes are more likely with increasing time on HAART [OR 1.16 (0.93–1.46), P=0.19]. Estimates for the association between body fat changes and time on therapy are similar for both PI therapy [OR 1.20 (0.98–1.46)] and NNRTI therapy [OR 1.16 (0.93–1.44)].

After adjusting for time on HAART, fat loss is more likely with increasing stavudine use [OR 1.70 (1.34–2.15), P<0.01]. However, estimates for the association between fat loss and use of stavudine are similar for both use within PI therapy [OR 1.54 (1.19–1.98)] and within NNRTI therapy [OR 1.21 (0.87–1.69)].

Sensitivity analysis

Further analysis supports an association between fat loss and stavudine. With the second method of discrete

Table 1. Baseline data for those with and without reported body fat changes* (*n*=925)

	One assessment only (*n*=250)			Two or more assessments (*n*=675)		
	No change (*n*=165)	Fat loss (*n*=25)	Fat gain (*n*=62)	No change (*n*=519)	Fat loss (*n*=62)	Fat gain (*n*=122)
Gender, %						
female	35	12	47	29	24	38
Transmission, %						
heterosexual	39	44	68	46	45	51
homosexual	36	24	16	36	27	29
IV drug	19	28	11	15	23	14
other† or unknown	6	4	5	4	5	7
Clinical stage, %						
A	65	32	68	61	35	53
B	21	28	16	21	32	25
C	13	40	16	19	32	21
Education, %						
more than mandatory	67	56	58	70	71	69
Ethnicity, %						
Caucasian	76	88	65	75	81	73
Age, years, median [IQR]	36 [32–42]	40 [36–46]	39 [33–46]	36 [31–43]	42 [34–47]	38 [32–44]
BMI, median [IQR]	23 [21–25]	19 [18–22]	26 [22–28]	22 [20–24]	22 [19–24]	23 [21–26]
CD4 count, cells/μl, median [IQR]	227 [222–397]	80 [21–211]	201 [136–287]	200 [108–326]	159 [40–220]	154 [66–285]
Log viral load‡, median [IQR]	4.1 [2.6–5.1] (32)	4.9 [3.8–5.5] (6)	4.6 [3.2–5.1] (3)	4.6 [3.1–5.2] (83)	4.8 [3.3–5.3] (7)	4.9 [3.5–5.4] (16)
Duration of infection§, months, median [IQR]	25 [2.0–102] (121)	17 [1.6–153] (23)	4.7 [1.6–29] (48)	11 [1.6–78] (401)	9.4 [1.2–116] (57)	2.5 [1.1–41] (105)
Follow-up¶, months, median [IQR]	2.2 [0.7–5.1]	2.9 [0.0–6.4]	5.0 [3.6–6.0]	18 [11–28]	15 [11–25]	12 [6.3–22]

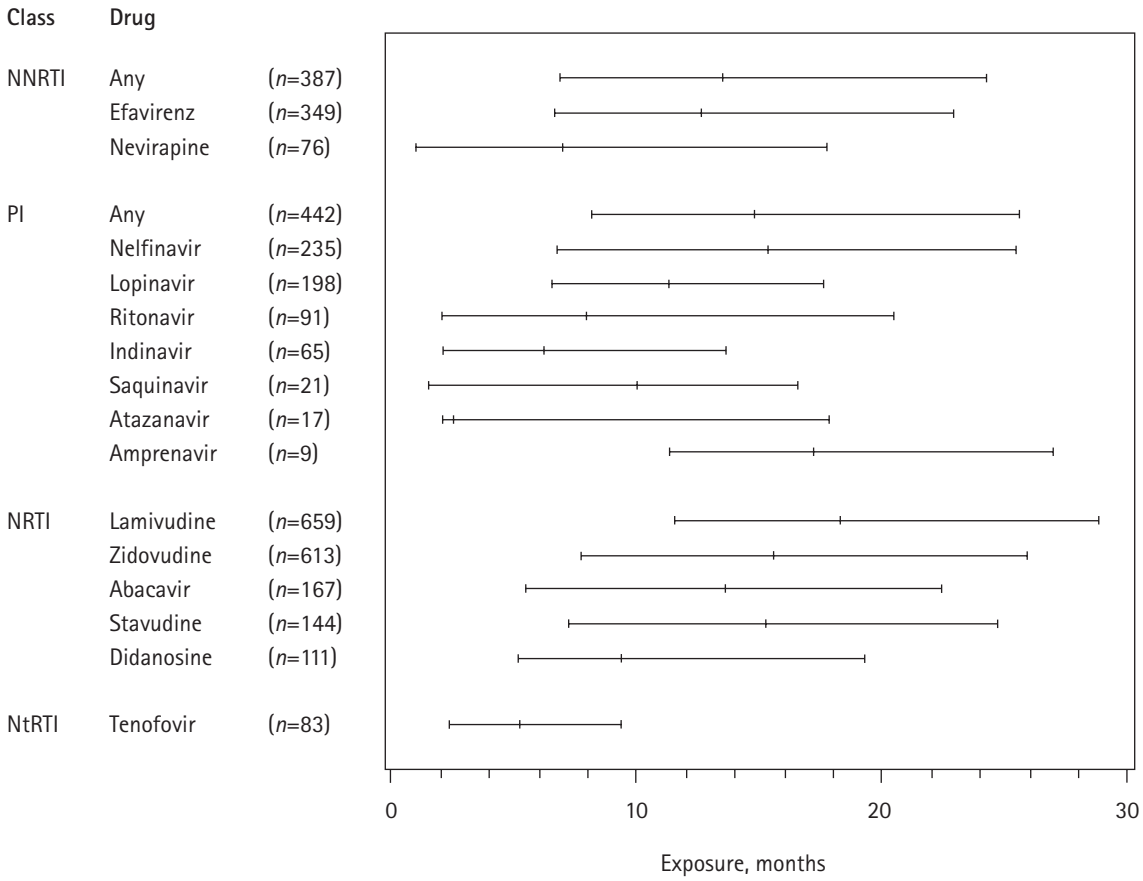
*Both fat loss and fat gain are reported in some patients. †Transmission through blood products or perinatal transmission. ‡Viral load sometimes measured up to 3 months after starting HAART (number shown in round brackets). §From first positive test for HIV until starting HAART – the first positive test date is usually recorded retrospectively, it is therefore less reliable and is not known for all patients (number shown in round brackets). ¶From starting HAART until first reported change or last assessment to date.

Table 2. Percentage change in markers from first assessment after starting HAART until last assessment to date (*n*=675) – median [IQR] of (final value – initial value) / initial value) × 100

Marker		No change (*n*=519)	Fat loss (*n*=62)	Fat gain (*n*=122)
Anthropometric	Waist circumference	1.4 [–1.5–5.7]	0.0 [–4.7–5.2]	4.0 [–1.1–9.9]
	Waist hip ratio	1.1 [–2.5–4.9]	0.4 [–3.3–7.5]	4.3 [–0.9–8.7]
	BMI	1.6 [–2.7–6.5]	0.0 [–5.5–5.5]	3.8 [–1.3–9.3]
HIV surrogate	CD4 count	45 [5.1–109]	69 [10–219]	68 [29–157]
	Log viral load	–54 [–71 to –21]	–49 [–68 to –17]	–50 [–71 to –28]
Metabolic*	Cholesterol	1.7 [–8.5–14]	–1.2 [–18–10]	2.1 [–11–20]
	Glucose	0.0 [–10–12]	1.8 [–10–10]	2.4 [–8.5–12]
	Lactate	8.3 [–18–47]	6.5 [–27–33]	13 [–14–45]
	Triglycerides	–2.1 [–35–38]	1.3 [–33–43]	16 [–16–55]

*Metabolic parameters were typically not measured in a fasting state.

Figure 1. Exposure (interquartile range and median) to different drugs and drug classes in 675 patients from the SHCS



NtRTI, nucleotide reverse transcriptase inhibitor.

Table 3. Odds ratios [95% CI] for conditional logistic regression models (*n*=675)

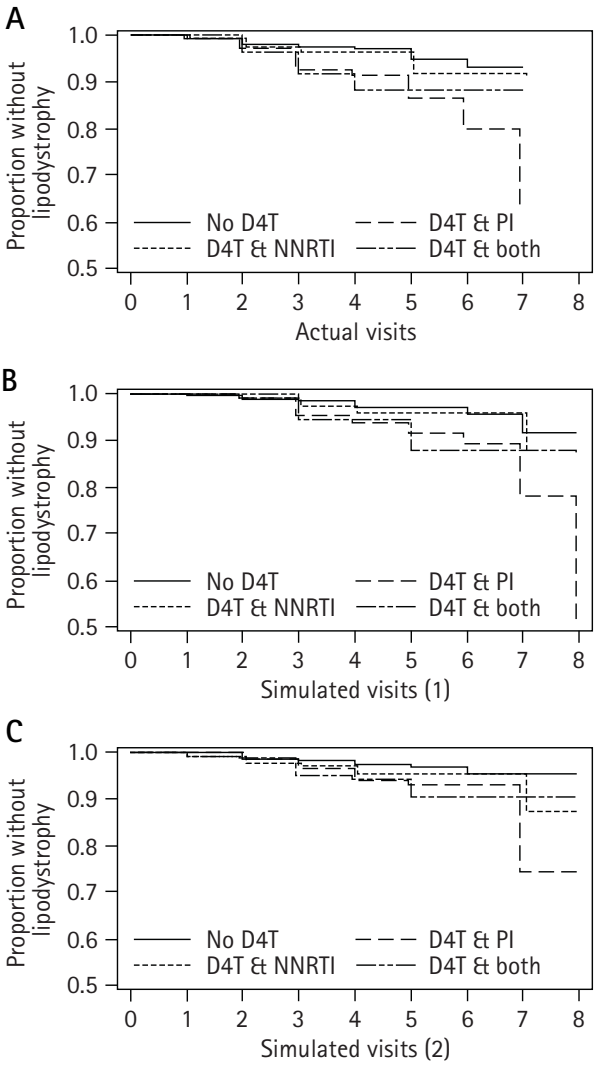
Model	Covariate	Any change	Fat loss	Fat gain
1	Female	1.36 [0.94–1.97]	0.70 [0.38–1.31]	1.90 [1.27–2.86]
	IV drug use	1.34 [0.85–2.10]	1.81 [0.97–3.38]	1.09 [0.63–1.87]
	Age (per 10 years)	1.18 [1.00–1.38]	1.38 [1.08–1.76]	1.10 [0.92–1.31]
	Log RNA	1.05 [0.93–1.20]	0.98 [0.81–1.19]	1.13 [0.97–1.31]
	CD4 (per 100 cells/μl)	0.91 [0.83–1.01]	0.79 [0.65–0.95]	0.93 [0.84–1.04]
	BMI	1.06 [1.01–1.11]	0.93 [0.85–1.01]	1.12 [1.06–1.17]
	t_HAART	1.16 [0.93–1.46]	1.14 [0.80–1.64]	1.20 [0.93–1.55]
2	t_PI	1.20 [0.98–1.49]	1.19 [0.88–1.60]	1.20 [0.94–1.53]
	t_NNRTI	1.16 [0.93–1.44]	1.04 [0.76–1.43]	1.24 [0.97–1.58]
3	t_HAART	1.10 [0.88–1.39]	0.94 [0.65–1.36]	1.16 [0.89–1.51]
	t_D4T	1.25 [1.04–1.50]	1.70 [1.34–2.15]	1.16 [0.93–1.44]
4	t_HAART	1.10 [0.82–1.42]	0.96 [0.66–1.39]	1.15 [0.89–1.50]
	t_D4T_PI	1.30 [1.04–1.61]	1.54 [1.19–1.98]	1.21 [0.94–1.57]
	t_D4T_NNRTI	1.08 [0.82–1.42]	1.21 [0.87–1.69]	1.08 [0.79–1.49]

All models use the same six time-independent covariates; estimates for these covariates are shown only for the first model with time on HAART as the seventh covariate. In subsequent models, time on HAART is replaced by other time dependent covariates. t_D4T_NNRTI, time on stavudine within NNRTI-based therapy (per 6 months).

time survival analysis, fat loss is again more likely with increasing stavudine use [OR 1.67 (1.33–2.12)] after adjusting for time on HAART. With simulated visits, fat loss is more likely with increasing stavudine use – either assuming fat loss occurs at the closest simulated visit to the actual visit when fat loss was reported [OR 1.69 (1.34–2.12)] or assuming fat loss occurs at the first simulated visit after the last actual visit when no fat loss was reported [OR 1.80 (1.38–2.35)]. Results from these simulated datasets suggest our estimates are robust to irregular visits and missing visits where patients return for a visit only when they experience difficulties. Kaplan–Meier curves suggest that, if anything, support for using stavudine in NNRTI therapy rather than in PI therapy is weaker in these simulated data than in the original data (Figure 2). Stavudine use seems to be confounded only with the use of zidovudine (Table 4): adjusting for time on zidovudine reduces the estimate of the association between fat loss and stavudine [OR 1.52 (0.99–2.35), *P*=0.04]. For the endpoint fat loss, 114 patients used stavudine and of these, 104 (73%) also used zidovudine, although none used both drugs at the same time. If we exclude the 104 patients with viral load measured after starting HAART, the OR for time on stavudine is 1.83 (1.40–2.39). If we exclude data for those physicians who carried out fewer than 10 cardiovascular risk assessments, the OR for time on stavudine is 1.66 (1.28–2.15). If we then add 'physician' as a random effect, there is evidence of between-physician variability (variance estimate 1.04, standard error 0.48) but the OR for time on stavudine is similar [OR 1.79 (1.34–2.40)].

Reported body fat changes seem as probable in patients using either PI or NNRTI therapy. Removing all patients who have taken both therapies allows for a formal test of differences between therapies. When the endpoint is any body fat change, this removes 125 patients and 31 reported changes. Adjusting for time on HAART, there is no evidence for an association between any fat change and time on NNRTI therapy relative to time on PI therapy [OR 0.98 (0.56–1.63), *P*=0.87].When the endpoint is fat loss, this removes 132 patients and 11 reported changes. Adjusting for time on both HAART and stavudine, there is no evidence for an association between fat loss and stavudine use within NNRTI therapy relative to within PI therapy [OR 1.06 (0.60–1.89), *P*=0.84].

Figure 2. Kaplan–Meier curves for fat loss in 675 patients from the SHCS



Patients are classified as never using stavudine (D4T) or using stavudine within PI therapy, within NNRTI therapy, or within both. The percentage of patients without lipodystrophy is shown assuming actual visits are regular **(A)** and assuming 6-monthly simulated visits. Simulated visits assume fat loss occurred either at the nearest simulated visit to the actual visit where fat loss was reported **(B)** or at the first simulated visit after the last actual visit when no fat loss was reported **(C)**.

Discussion

Factors not related to antiretroviral therapy, time on therapy and therapy with specific drugs all seem to contribute, to at least some degree, to the lipodystrophy syndrome [20]. The severity of HIV infection may lead to lipodystrophy, either through fat loss associated with wasting in the later stages of the disease or through fat gain associated with recovery following therapy. Fat loss was reported for 25 patients at their first cardiovascular risk assessment after only a short period of therapy (median 2.9 months, Table 1). When starting HAART, these 25 patients had very low CD4 cell counts, high viral load and were much more likely to be in CDC group C compared with other patients. Fat change in general and fat loss in particular, is more

Table 4. Odds ratios [95% CI] for the association between stavudine and fat loss, adjusted for time on HAART and for time on one other drug

Adjusted for time on HAART and time on: Class	Drug	% of all patients on drug (*n*=675)	Odds ratio for stavudine
PI	Nelfinavir	35	1.68 [1.32–2.14]
	Lopinavir	29	1.69 [1.34–2.14]
	Ritonavir	13	1.74 [1.36–2.22]
	Indinavir	10	1.70 [1.33–2.16]
NNRTI	Efavirenz	52	1.69 [1.33–2.15]
	Nevirapine	11	1.70 [1.34–2.16]
NRTI	Lamivudine	98	1.67 [1.30–2.14]
	Zidovudine	91	1.52 [0.99–2.35]
	Abacavir	25	1.68 [1.32–2.14]
	Didanosine	16	1.71 [1.34–2.18]

likely in patients with a lower baseline CD4 cell count. Others have noted that patients with lipodystrophy [16] and lipoatrophy [12] have a lower CD4 cell count. Body fat changes are likely to be more noticeable in patients with advanced disease and in patients who show a greater improvement in general health after starting therapy. However, fat change is also more likely with increasing age and BMI, and this may partly reflect age-associated fat gain unrelated to HIV infection [21].

All the major classes of antiretrovirals have been associated with metabolic abnormalities [17], therefore an association between lipodystrophy and time on therapy is expected. Lipodystrophy has been linked to NRTI-induced mitochondrial toxicity [22]; however mitochondrial toxicity can occur prior to therapy [23] and may be greater in patients with advanced disease and immediately after the start of therapy [24]. In the Martinez study [9], time on HAART was strongly associated with both fat loss and fat gain in patients on PI-based therapy. We found only weak evidence of an increased risk of body fat changes with increasing time on HAART. Their cohort study, which focused solely on lipodystrophy, seems to have used a more rigorous assessment of body fat changes and was carried out in a single hospital, factors that might all lead to different results. We report a higher rate of body fat changes than in their study (13.2 vs 11.7 per 100 patient-years). The prevalence of lipodystrophy and even the risk factors associated with lipodystropy will depend on the definition used [2,18]. Our patients were on either PI or NNRTI therapy: we do not have sufficient knowledge to completely rule out differences between therapies, but large differences between the two seem unlikely. This is consistent with switching studies where only modest improvements in metabolic abnormalities have been reported after replacing the PI component of therapy with an NNRTI [11].

Even if lipodystrophy is mostly due to factors unrelated to therapy, it is still reasonable to look for drugs or drug combinations associated with a higher or lower incidence because almost all patients eventually require antiretroviral therapy. Even if lipodystrophy is inevitable with time on therapy – given that all drugs interfere with metabolism in one way or another – it is still reasonable to look for drugs or drug combinations associated with a higher or lower incidence. In this study, we find good evidence that fat loss is more likely with increasing stavudine use. An association between body fat changes and stavudine use has been reported in a cross-sectional study of this cohort [25] and an association between fat loss and stavudine has been reported in the Martinez cohort study [9]. We report a stronger association than in the Martinez study [OR 1.70 (1.34–2.15) vs hazard ratio 1.16 (1.02–1.31) per 6 months use]. While stavudine might cause less mitochondrial toxicity at a lower dose [26], this may also reduce its efficacy as the stavudine metabolite has a relatively low specificity for HIV reverse transcriptase [24].

The principal limitations of this study are the subjective reporting of body fat changes and the confounding inherent in any observational study. While patient-reported lipodystrophy can agree closely with subsequent clinical examination [27], clinical examination may be insensitive to significant body fat changes [28]. Yet over-reporting is also possible because subjective reporting reflects perceptions of both patient and physician – reported fat gain is more likely in women and their greater sensitivity to fat gain is one explanation [9]. If physicians were particularly sensitive to fat change in patients on stavudine this would lead to a reporting bias. However, the SHCS is not specifically focused on lipodystrophy so this should limit this bias; additionally, fat gain is not associated with stavudine use and such an association would be consistent with a reporting bias. Subjective reporting is probably the best option for this study because lipodystrophy is still easier to recognize than define [29], given the necessary complexity of proposed case definitions [3,30] and because patient perceptions are important, given the association between perceived fat changes and poor drug adherence [5]. Without information on body composition, neither anthropometric [12] nor metabolic [30] parameters appear to give an adequate definition of lipodystrophy. Table 2 shows that there is little change in simple anthropometric parameters for those reporting fat loss. In the SHCS, metabolic parameters are usually not measured in a fasting state. Setting high thresholds for metabolic parameters, to be sure of lipodystrophy, would lead to few lipodystrophy events and survival analyses with little power. It should be more informative to model the mean of these parameters over time, therefore a longitudinal study of this sort is planned.

Confounding is an issue in any observational study. Our data allowed adjustment for many known confounding variables, but the risk of confounding from unknown or unmeasured variables remains. Unlike the Martinez study, we checked for and identified confounding between the use of stavudine and zidovudine. While is it difficult to separate the effects of these two NRTIs in this study, there have been randomized trials [31,32] where stavudine and zidovudine use was mutually exclusive and in these, stavudine was more likely to lead to fat loss than zidovudine. However, time on zidovudine may also contribute to fat loss and indeed zidovudine can convert to the stavudine metabolite [33].

The strengths of this study are high external and internal validity. Reported body fat changes reflect patient perceptions and our data come from a large cohort, estimated to include between 42% and 66% of individuals in Switzerland with HIV [34]. The SHCS is not a single-issue cohort but is ongoing with frequent assessment and well-documented drug changes. From this cohort, we selected antiretroviral-naive patients starting HAART, with a similar number of patients on either PI- or NNRTI-based therapy. Our analysis used discrete time survival models, appropriate when an endpoint is not reported between visits. We considered the sensitivity of our results to irregular visits, to confounding between drugs and to patients who switch between PI- and NNRTI-based therapy. We confirm that fat loss is more likely to be reported with increasing exposure to stavudine. We find no evidence of major differences between PI and NNRTI therapy in the risk of reported body fat changes.

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Appendix

The members of the Swiss HIV Cohort Study are M Battegay, E Bernasconi, J Böni, H Bucher, Ph Bürgisser, S Cattacin, R Dubs, M Egger, L Elzi, P Erb, K Fantelli, M Fischer, M Flepp, A Fontana, P Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, Lausanne), H Furrer (Chairman of the Clinical and Laboratory Committee), M Gorgievski, H Günthard, B Hirschel, L Kaiser, C Kind, Th Klimkait, B Ledergerber, U Lauper, M Opravil, F Paccaud, G Pantaleo, L Perrin, J-C Piffaretti, M Rickenbach (Head of Data Centre), C Rudin (Chairman of the Mother & Child Substudy), P Schmid, J Schüpbach, R Speck, P Tarr, A Telenti, A Trkola, P Vernazza (Chairman of the Scientific Board), R Weber and S Yerly.

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