Correlates of risk of adipose tissue alterations and their modifications over time in HIV-1-infected women treated with antiretroviral therapy

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Objective: To assess the correlates of risk of the different types of lipodystrophy and their modifications over time in a cohort of HIV-positive women receiving antiretroviral therapy (ART).

Methods: A consecutive series of HIV-infected women receiving ART was prospectively enrolled between 1 and 31 March 1998, and followed up for 2 years. Adipose tissue alterations (ATAs) and their variations over time were assessed by means of clinical observation and anthropometric measurements, and logistic regression analysis was used to describe the associated risk factors identified by univariate and multivariate analyses.

Results: One-hundred-and-seventeen of the 212 women (55.2%) developed ATAs during the 24 months of follow-up. Central adiposity was observed in 95 patients and peripheral lipoatrophy in 91, with 21 patients (9.9%) showing pure lipoatrophy, 26 (12.3%) pure fat accumulation and 70 (33%) combined forms. Only six of the 223 regional adipose tissue alterations identified in 74 patients during the first 12 months of the study had disappeared by month 24. Of the 43 patients who developed breast enlargement during the first 12 months, 11 (25.6%) showed a decrease in breast size during the second year of follow-up that was unrelated to changes in therapy or therapeutic success. The development of ATAs during the first 12 months of follow-up independently correlated with protease inhibitor (PI) use (OR 2.81, *P*=0.002) but, by the end of the second year of follow-up, the only factor significantly related to the development of ATAs was the overall duration of ART (OR 1.85, *P*=0.041). The use of PI significantly increased the risk of developing central adiposity during the first 12 months of the study (OR 2.27, *P*=0.002), whereas the only variable significantly influencing the risk at month 24 was HIV-infection due to intravenous drug use, which proved to be protective (OR 0.53, *P*=0.043). During the first 12 months of follow-up, the development of peripheral lipoatrophy was significantly associated with stavudine (OR 2.19, *P*=0.037) and PI use at enrolment (OR 2.27, *P*=0.023). At the end of the study, the variables associated with peripheral lipoatrophy were stavudine use at enrolment (OR 2.82, *P*=0.002), ART exposure for >1000 days at enrolment (OR 2.32, *P*=0.007), a CD4 cell count of >200/µl at enrolment (OR 2.89, *P*=0.002) and an age of >28 years (OR 1.91, *P*=0.036). The only factor significantly associated with an increased risk of breast enlargement during the first 12 months of follow-up was PI use (adjusted OR 2.51; 95% CI: 1.16–5.46, *P*=0.02); however, at month 24, none of the tested variables was associated with a significantly increased risk of this ATA.

Conclusions: ATAs (particularly central adiposity) are frequent in women treated with ART, and the different forms have different correlates of risk. Once they have become clinically evident, they generally tend to remain or worsen, and improve in only a small minority of cases. The considerable variations in adipomasty over time are apparently unrelated to changes in ART.

Introduction

Combined antiretroviral therapy (ART) has radically improved the prognosis of AIDS and prolonged the life expectancy of HIV-infected patients [1,2]. However, unexpected toxic effects emerged in a relatively short time and rapidly raised serious concerns [3–9]. This complex pattern of metabolic and adipose tissue abnormalities represents a significant challenge for the continuation of ART.

A further unexplained phenomenon is the high frequency of adipose tissue alterations (ATAs) in females [10–14], which is not related to the type or duration of drug exposure, or to a gender-related lower adherence to therapy [12,14], and specific investigations have so far failed to identify any specific endocrinological cause [15–17]. In addition to the adipose tissue accumulation or loss in various body

regions observed in men, women frequently show an accumulation of breast fat [15–17], whose temporal modifications cannot be attributed to changes in therapy [18].

Most published studies of correlates of the risk of developing ATAs have involved too few women to be able to provide specific information, and the data from prospective investigations are still very limited.

The aim of this prospective study was to assess the correlates of the risk of developing lipodystrophy and describe the changes in ATAs over time in a cohort of women receiving ART.

Patients and methods

This prospective cohort study consecutively included all of the ART-treated HIV-1-infected women examined at the Outpatient Clinic of Milan University's Institute of Infectious and Tropical Diseases between 1 and 31 March 1998.

The exclusion criteria were: 1) a diagnosis of AIDS dementia complex or AIDS wasting syndrome as defined by CDC criteria; 2) no ART or ART discontinuation, or the irregular collection of antiretroviral drugs from the hospital dispensary in the 3 months preceding enrolment; 3) voluntary changes in caloric intake leading to a significant variation in body weight (≥5 kg or 10% of total body weight) in the 12 months before enrolment or at any time during the course of the study; 4) pregnancy; 5) antineoplastic, steroid or anabolic therapies during the 2 years preceding enrolment or at any time during follow-up; and 6) the presence of an ATA at the time of the enrolment visit.

A record was made of the patient's demographic, laboratory and clinical data at the time of enrolment.

HIV RNA was routinely determined by means of a branched-DNA probe assay, which had a sensitivity of ≥500 copies/ml before May 1998 and a sensitivity of ≥50 copies/ml thereafter.

The patients underwent monthly clinical examinations performed by the same physician, and three-monthly laboratory tests (including CD4 cell counts and plasma HIV RNA measurements).

At the time of enrolment, the presence of ATAs was assessed on the basis of a clinical examination and specific patient reports using a standardized questionnaire.

The criteria for the detection of an ATA in specific body regions during the prospective survey were: 1) a ≥4 cm increase in abdominal circumference measured at the umbilicus between two consecutive measurements; 2) a ≥2 cm reduction in arm circumference measured at the mid-point between the elbow and the shoulder with the arm relaxed at the side of the body; 3) a ≥3 cm reduction in leg circumference measured in the crease just below the buttocks, or any reduction accompanied by increased evidence of superficial veins; 4) a ≥3 cm increase in neck circumference measured at the largest neck circumference with the head upright; and 5) a ≥2 bra-size increase in breast size. All of the measurements were made using the same cloth tape measure.

Direct observation alone was used to assess any reduction in facial subcutaneous fat or buttock adipose tissue, any supraclavicular or interscapular fat accumulation, any fat loss or accumulation in any other body site, and any newly observed circumscribed lipomas.

For the purposes of the analysis, the ATAs were first classified as central adiposity (fat accumulation in the abdomen, breasts, trunk and dorsocervical region, with or without fat loss in other body regions) or peripheral lipoatrophy (fat loss in the legs, arms, face, buttocks, with or without fat accumulation in other body sites). A further analysis was made by dividing the cases into those with pure lipoatrophy (evidence of fat loss in one or more body region, without any simultaneous evidence of fat accumulation in other body sites), pure fat accumulation (fat accumulation in one or more body region, without any evidence of fat loss in other body sites), and combined forms (simultaneous evidence of fat loss and fat accumulation in different body regions).

The correlates of the risk of developing ATAs were assessed after 12 and 24 months of observation taking into account the first type of ATA presented.

The breast fat accumulation (adipomasty) observed during the first 12 months of follow-up was defined as having 'improved' or 'worsened' during the second year on the basis of a decrease or increase of one or more bra-size.

All of the patients receiving ART at enrolment and followed up for at least 3 months were kept in the study regardless of any changes in ART (including its discontinuation).

The variables considered in assessing the risk of developing ATAs were age, previous or present intravenous drug use (IVDU) versus no history of drug abuse, body mass index (BMI), CD4 cell counts, HIV viral load; the use of protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the presence of zidovudine (ZDV) or stavudine (d4T) in the ART combination at enrolment; the duration of exposure to antiretroviral drugs, and any change in therapy after enrolment.

Statistical analysis

The data were analysed using the SPSS 10.0 software package for Windows 98. Intention-to-treat analysis was used to identify the correlates of the risk of developing

ATAs after 12 and 24 months of observation, also taking into account the changes in the clinical pictures of the patients with ATAs.

The modality of HIV infection, and baseline treatment with ZDV or d4T, PIs and/or NNRTIs were considered as categorical variables in all of the analyses, as were any changes in ART during follow-up.

Age, CD4 cell counts, HIV viral loads, BMI and the times of exposure to ART were transformed into categorical variables when included as covariates in the multivariate analyses.

Between-group differences in the categorical variables were evaluated using the χ^2 test and Pearson's coefficient or Fisher's exact test. The distributions of the continuous variables in the different groups were tested by means of the Mann-Whitney non-parametric test and the Student t-test.

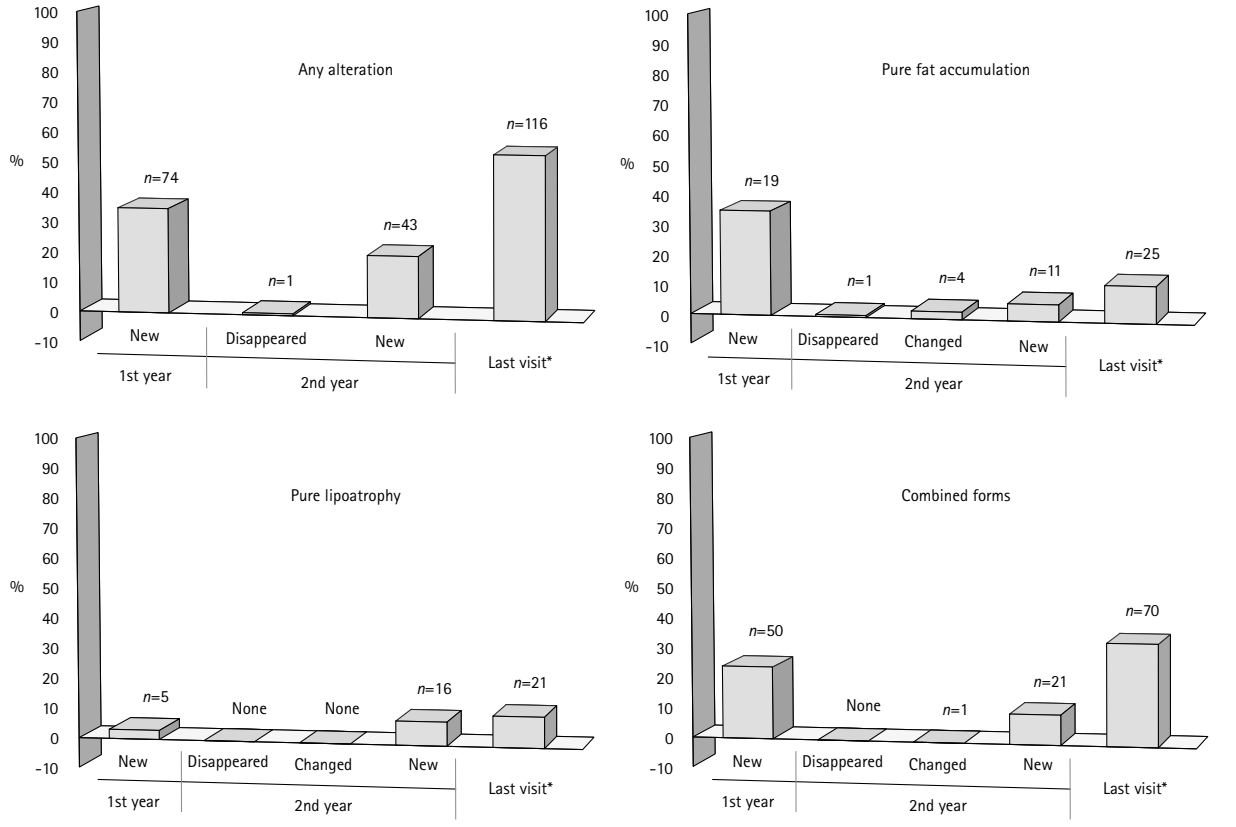
For the multivariate analyses estimating the independent risks of developing ATAs, each type of ATA, and adipomasty after 12 and 24 months, we used a logistic regression model by means of which the adjusted relative risks and 95% confidence intervals were associated with each of the considered covariates.

Results

Between 1 and 31 March 1998, a total of 236 women satisfying the inclusion criteria were consecutively observed at our Outpatient Clinic: the 15 who had been receiving their first ART for less than 3 months and had discontinued it before the first follow-up visit; the seven who missed their follow-up visits during the first 3 months of the study; and the two who become pregnant during the first 3 months of the study were not included in the analysis. The remaining 212 women were followed up regardless of their maintenance on treatment.

ATAs in one or more body region appeared in 74 women (34.9%) during the first year and in 43 (20.3%) during the second year of follow-up. During the study period, a total of 95 women (44.8%) presented central adiposity, and 91 (42.9%) peripheral lipoatrophy, including 21 patients (9.9%) with pure lipoatrophy, 26 (12.3%) with pure fat accumulation and 70 (33%) with combined forms as first manifestations (Figure 1). Most cases of pure fat accumulation and combined forms appeared during the first 12 months of follow-up, whereas pure lipoatrophy was more frequently

Figure 1. Incident adipose tissue alterations during 2 years of follow-up in 212 women receiving ART, and their modifications over time



*Changed and disappeared ATAs are not included.

recorded during the second year. One case of the combined form observed during the first 12 months had changed to pure lipoatrophy by the end of the study; among 19 patients with pure fat accumulation at month 12, four had changed to combined forms and one did not show any significant alteration by the end of the study.

A total of 223 fat tissue alterations were identified in different body regions among the 74 patients who developed an ATA during the first year of the study, only six of which had disappeared by the time of the last follow-up visit.

Figure 2 shows the times of the presentation of adipomasty and its variations over time. In most cases, this alteration appeared in the first year of follow-up, during which 43 women complained of an increase in breast volume equal to at least two bra-sizes; 11 of these patients experienced a decrease of at least one bra-size during the second year. During the first year of observation, adipomasty represented part of a combined form alteration in 33 cases (76.7%); in a further 10 cases, it was the only body fat tissue alteration or was associated with fat accumulation in other body sites. At the end of the follow-up, adipomasty was part of a combined form alteration in 42 cases (60%).

A comparison of the women who developed ATAs or not after 24 months did not reveal any differences in median age, HIV infection risk factors, CD4 cell counts or HIV plasma viraemia at enrolment (Table 1). On the other hand, d4T was more frequently used at enrolment (P=0.038) and the overall duration of the exposure to antiretroviral drugs was significantly longer in the women with ATAs at 24 months than in those without (P=0.006).

The development of ATAs during the first 12 months of follow-up independently correlated with PI use (P=0.002) (Table 2). However, by the end of the second year of follow-up, the only factor significantly related to the development of ATAs was the overall duration of ART (P=0.041). The women infected with HIV as a result of intravenous drug use seemed to be protected against the development of ATAs at a level of borderline statistical significance (P=0.05). None of the risks changed significantly when the BMI data were included in the logistic regression model (data not shown).

The use of PI significantly increased the risk of developing central adiposity during the first 12 months of the study (OR 2.80, P=0.002), but the only variable significantly influencing the risk of developing central adiposity at month 24 was the development of HIV infection as a result of intravenous drug use, which proved to be protective (OR 0.53, P=0.043) (Table 3).

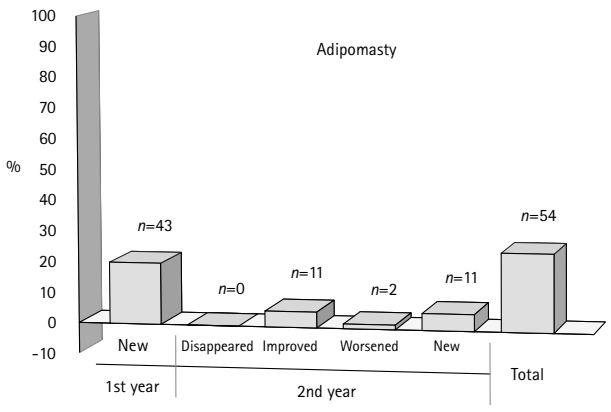
During the first 12 months of follow-up, the development of peripheral lipoatrophy was significantly associated with d4T (OR 2.18, P=0.037) and PI use at enrolment (OR 2.27, P=0.023). At the end of the study, the variables associated with peripheral lipoatrophy were the use of d4T at enrolment (OR 2.82, P=0.002), an ART exposure of >1000 days at enrolment (OR 2.32, P=0.007), a CD4 cell count of >200/µl at enrolment (OR 2.89, P=0.002), and an age of >28 years (OR 1.91, P=0.036) (Table 4).

None of the considered variables were associated with a statistically significant increased risk of presenting pure lipoatrophy during the study, whereas the women treated with d4T at enrolment were significantly 'protected' against pure fat accumulation (OR 0.29, 95% CI: 0.10–0.80, P=0.018). Moreover, combined forms were significantly more frequent in the women receiving d4T (adjusted OR 2.85, 95% CI: 1.45–5.61, P=0.002) and in patients with a longer ART exposure (adjusted OR 2.03, 95% CI: 1.08–3.81, P=0.028).

The only factor significantly associated with an increased risk of breast enlargement during the first 12 months of follow-up was PI use (adjusted OR 2.51; 95% CI: 1.16–5.46, P=0.02); however, at month 24, none of the tested variables were associated with a significantly increased risk of this ATA.

A logistic regression model including drug changes, and the CD4 cell counts and plasma viraemia values recorded after 24 months, showed that none of the considered variables were significantly related to the reduction in adipomasty (data not shown).

Figure 2. Incident adipomasty during 2 years of follow-up in 212 women receiving ART, and its modifications over time



Discussion

The reasons for the high incidence of ATAs in females are still unknown, but studies including a sufficient percentage of women have shown that those receiving their first treatment regimen [12,13] and PI-naive patients [14] are at higher risk of developing ATAs than males.

Table 1. Demographic and laboratory features, and antiretroviral drug exposure in women with and without adipose tissue alterations (ATAs) at the end of the study

	Total		ATA+ (*n*=117)		ATA– (*n*=95)		
	Median	Range	Median	Range	Median	Range	*P*
Age (years)	28	18–56	29	18–56	28	18–55	0.159
CD4 cells/µl							
At enrolment	355	7–1434	350	63–1434	359	7–781	0.965
At last visit	480	1–1641	485	138–1641	467	1–1000	0.238
HIV RNA copies/ml							
At enrolment	<500	<500–641 400	<500	<500–91 060	<500	<500–641 400	0.603
At last visit	400	<50–420 000	150	<50–110 000	480	<50–420 000	0.160
Total ART exposure (days)	975	24–3529	1128	46–3529	698	24–3125	0.006
	n	%	*n*	%	*n*	%	*P*
CD4 cells at enrolment							
<200/µl	33	15.6	15	12.8	18	18.9	
≥200/µl	179	84.4	102	87.2	77	81.1	0.255
HIV RNA at enrolment							
<500 copies/ml	125	59.0	69	59.0	56	58.9	
≥500 copies/ml	87	41.0	48	41.0	39	41.0	0.997
d4T use at enrolment	106	50.0	66	56.4	40	42.1	0.038
NNRTI use at enrolment	6	2.8	2	1.7	4	4.2	0.275
PI use at enrolment	100	47.2	60	51.3	40	42,1	0.183
ART changes during the follow-up	165	77.8	89	76.1	76	80.0	0.493
Risk factor for HIV infection							
Intravenous drug addiction	73	34.4	35	29.9	38	40.0	
Heterosexual contacts	139	65.6	82	70.1	57	60.0	0.124

NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ART, antiretroviral therapy.

In this prospective study, 55.2% of the ART-treated women without ATAs at the time of enrolment developed them within 2 years, thus confirming the frequent occurrence of this phenomenon in females. However, it is interesting to note that there were significant variations in the timing of the appearance of the different alterations during the follow-up: in particular, 'pure' lipoatrophy was more frequently a late observation, as has already been described in patients on first-line antiretroviral treatment [13].

Overall antiretroviral exposure was significantly longer, and d4T was more frequently used, in the patients who developed ATAs than in those who did not. The role of d4T in causing ATAs has been widely discussed, and the results of a number of studies suggest that it increases the risk of lipoatrophy [12,13,19–21]. In our exclusively female cohort, the use of d4T was associated with a significant increase in the risk of developing peripheral but not 'pure' peripheral lipoatrophy, and seemed to be 'protective' against pure fat accumulation, although it was significantly associated with an increased risk of developing combined forms. A possible key to the interpretation of these data has recently been offered by the large-scale FRAM study of male subjects [22], which showed that lipoatrophy was not significantly associated with central fat accumulation despite the frequent concomitant appearance of these two types of ATA.

Previous studies have shown that women are at significantly higher risk of developing central adiposity [12,13], whereas peripheral lipoatrophy is equally or more frequent in men [13,23,24]. These findings may predict the high incidence of combined forms in our cohort and, although various pathogenetic mechanisms

Table 2. Adjusted risk of developing adipose tissue alterations (logistic regression). All of the variables are considered at enrolment except for ART changes during the study period

	12th month (observed cases =74)			24th month (observed cases =117†)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >28 years	1.21	0.66–2.25	0.534	1.55	0.87–2.76	0.139
Intravenous drug addiction*	0.64	0.34–1.23	0.180	0.54	0.30–1.00	0.050
CD4 ≥200 cell/μl	1.41	0.59–3.33	0.440	1.94	0.85–4.41	0.113
HIV RNA >500 copies/ml	0.88	0.46–1.70	0.708	0.83	0.45–1.53	0.554
ART duration >1000 days	1.35	0.73–2.51	0.343	1.85	1.02–3.35	0.041
ART including d4T	1.18	0.61–2.27	0.626	1.67	0.90–3.11	0.103
ART including PI	2.81	1.47–5.36	0.002	1.44	0.78–2.66	0.238
ART changes	0.60	0.30–1.17	0.131	0.96	0.47–1.95	0.903

ART, antiretroviral therapy; PI, protease inhibitor.
*Versus heterosexual transmission; † including a case in which ATA disappeared during the second year of follow-up.

can be hypothesized for central fat accumulation and peripheral lipoatrophy, the association of combined forms with the use of d4T may explain their lipoatrophy component.

On the contrary, the apparently protective role of d4T against pure fat accumulation cannot be easily explained and further studies are needed to verify whether d4T actually plays a role in limiting this alteration. Curiously, this was the only correlate of the risk of pure fat accumulation identified in our study, whereas other more obvious candidates (such as BMI) proved to have no effect. Pure lipoatrophy is the least frequently observed ATA in women, and it would be interesting to investigate whether its development is restricted to a particular subpopulation of patients. None of the variables we tested (including the use of d4T) were significantly associated with this alteration, but a longer follow-up would make it possible to assess the role of longer d4T exposure.

Our study revealed a close correlation between peripheral lipoatrophy and the overall duration of ART and an older age, thus underlining the prominent role of a long exposure to antiretroviral drugs in its development.

Peripheral lipoatrophy was also more frequent in patients with CD4 cell counts of >200/μl at enrolment. It has been reported that the degree of immunorecovery is a correlate of the risk for the onset of lipodystrophy [12,25]. We considered CD4 cell counts at enrolment when most of the patients had already been exposed to ART for a considerable period of time and had shown a generally good response to the drugs. In particular, among the patients with a CD4 cell count of >200 at enrolment, 38% had a pre-treatment nadir count of <150/μl (data not shown). Interestingly, the increase in CD4 cell counts after enrolment was the same in the patients who did or did not develop ATAs.

Adipomasty is one of the most striking aspects of lipodystrophy syndrome in women and a relatively early manifestation. However, unlike a recent small-scale study that found relatively stable breast alterations [26], we found that a rapid and considerable increase in breast volume is followed by an evaluable decrease in about 25% of cases. It is interesting to note that neither the indicators of ART failure (such as high viraemia levels or low CD4 cell counts at the end of the study) nor the number of drug changes

Table 3. Risk of presenting central adiposity at month 12 and 24 of follow-up. Patients with combined forms are included in the analysis

	12th month (observed cases =69)			24th month (observed cases =95)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >28 years	1.01	0.54–1.87	0.981	1.19	0.67–2.11	0.545
Intravenous drug addiction	0.69	0.36–1.33	0.270	0.53	0.29–1.00	0.043
CD4 ≥200 cell/μl	1.18	0.50–2.76	0.706	1.26	0.56–2.83	0.574
HIV RNA >500 copies/ml	1.14	0.59–2.20	0.692	0.91	0.50–1.66	0.751
ART duration >1000 days	1.16	0.62–2.18	0.634	1.63	0.91–2.93	0.090
ART including d4T	1.10	0.57–2.14	0.772	1.50	0.81–2.75	0.200
ART including PI	2.80	1.45–5.38	0.002	1.43	0.79–2.61	0.240
ART changes	0.58	0.29–1.14	0.114	0.90	0.45–1.81	0.769

ART, antiretroviral therapy, PI; protease inhibitor.
*Versus heterosexual transmission.

Table 4. Risk of presenting peripheral lipoatrophy in one or more body region at month 12 and 24 of follow-up. Patients with combined forms are included in the analysis

	12th month (observed cases =55)			24th month (observed cases =91)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >28 years	1.76	0.88–3.50	0.109	1.91	1.04–3.51	0.036
Intravenous drug addiction	0.51	0.24–1.06	0.072	0.55	0.29–1.05	0.070
CD4 ≥200 cell/µl	2.47	0.88–6.97	0.087	2.89	1.17–7.14	0.002
HIV RNA >500 copies/ml	0.72	0.35–1.47	0.364	0.64	0.34–1.21	0.170
ART duration >1000 days	1.53	0.77–3.03	0.220	2.32	1.26–4.26	0.007
ART including d4T	2.18	1.05–4.55	0.037	2.82	1.47–5.41	0.002
ART including PI	2.27	1.12–4.58	0.023	0.93	0.49–1.74	0.816
ART changes	0.81	0.38–1.71	0.582	1.37	0.66–2.85	0.392

ART, antiretroviral therapy; PI, protease inhibitor.
*Versus heterosexual transmission.

or interruptions during the study period significantly correlated with the reduction in breast volume.

During the follow-up, four patients who first presented with central adiposity developed a combined ATA. A longer follow-up is needed to establish whether the development of peripheral lipoatrophy is a frequent outcome in patients previously presenting with central adiposity alone.

However, the complete regression of 'lipodystrophy' was observed in only one woman (who showed a transient increase in abdominal adiposity), and only 2.6% of the alterations identified in different body regions during the first year of the study were no longer apparent in the same patients after 24 months. Therefore, it seems that after becoming clinically evident, ATAs generally tend to remain or worsen, and tend to improve in only a small minority of cases.

Regardless of the maintenance of active drug injecting, intravenous drug use as the modality of HIV contact has been associated with behavioural and cultural issues limiting therapy adherence that seem to decrease the risk of ATAs [13]. Our results confirm this finding insofar as the IVDUs tended to be 'protected' against any ATA and to be at a significantly lower risk of developing peripheral lipoatrophy.

In conclusion, our data show that lipodystrophy is a frequent adverse event in women. The appearence of body fat alterations are mainly related to the duration of exposure to ART and present a peculiar pattern: peripheral lipoatrophy generally needs longer exposure to ART than central adiposity, which is the most frequent manifestation in women. ATAs are generally stable over time but adipomasty may change significantly relatively quickly.

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