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Body fat abnormality in HIV-infected children and adolescents living in Europe: prevalence and risk factors:

Fat abnormality in children

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Abstract

Objectives—To estimate the prevalence of, and identify risk factors for Lipodystrophy Syndrome (LS) and body fat abnormality in a population of HIV-infected children and adolescents.

Design—Cross-sectional observational study.

Methods—HIV-infected subjects aged 2-18 years were recruited from 15 HIV centres in Belgium, Italy and Poland between January 2007 and December 2008. Standardized assessments by the patient's long-term clinician were performed to establish presence of abnormality. Risk factors were explored in logistic regression models for fat abnormality outcomes and LS (abnormality plus dyslipidemia).

Results—Among 426 subjects (70% white), median age was 12.2 (Inter quartile range, IQR: 9.0, 15.0) years and median duration of antiretroviral therapy (ART) was 5.2 (IQR: 2.2, 8.8) years. Prevalence was 57% ($n=235$) for LS and 42% ($n=176$) for fat abnormality; 90 subjects with abnormality were affected in 3 locations. Lipoatrophy occurred in 28% ($n=117$) subjects, and lipohypertrophy in 27% ($n=115$), most commonly in the face and trunk respectively. In multivariable analysis, white ethnicity, BMI, ritonavir/lopinavir and NNRTIs were each associated with increased risk of LS ($p<0.05$). White ethnicity, history of CDC-defined disease and stavudine were associated with risk of lipoatrophy ($p<0.05$). Increased risk of lipohypertrophy was associated with BMI and prior HIV disease.

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Conclusions—Fat abnormality was prevalent in close to half of children and adolescents, who had accumulated long treatment durations. Risk of fat redistribution was associated with specific drugs, including stavudine and ritonavir, and other variables. Our results underline the importance of continued surveillance of children treated with ART.

Keywords

Children; adolescents; lipodystrophy syndrome; fat redistribution; ART

Introduction

Lipodystrophy Syndrome (LS), characterized as body fat abnormality and/or metabolic disturbances, has been associated with antiretroviral therapy (ART) in HIV-infected adults[1-7] and children[8-11]. Less is known about LS in children and adolescents than in adults, as most paediatric studies have been cross-sectional and/or of limited size[11-15]. Furthermore, investigation of LS in children is hampered by the lack of a consensus definition as exists for adults[16].

Investigation of LS in childhood and its relationship with ART is increasingly important given continued high prevalence and incidence of paediatric HIV worldwide[17] and the increasing availability and use of ART[18], resulting in substantially improved AIDS-free survival and reduced morbidity[19-21]. The recommendation that all HIV-infected infants start ART and the fact that therapy is usually life-long[22, 23] will result in children receiving ART for increasingly long durations, being exposed to drugs at critical points in physiological development, and accumulating exposures to multiple regimens; the impact of this on LS pathogenesis is unknown.

The European Paediatric HIV and Lipodystrophy Study Group has established a cohort of HIV-infected children and adolescents to investigate LS. Our objectives here are to characterise the cohort to estimate prevalence of LS, lipoatrophy and lipohypertrophy, and to identify risk factors, in cross-sectional analysis conducted at baseline.

Methods

HIV-infected children and adolescents were recruited between January 2007 and December 2008, in 15 paediatric HIV centres in Belgium (3), Italy (11) and Poland (1). Most sites were concurrently participating in the European Collaborative Study[8] and/or the Italian Register of HIV Infection in Children[24, 25]. All HIV-infected children aged >2 years and adolescents aged 18 years under care were invited to participate, regardless of ART history. Patients treated with anabolizing steroids in the previous six months were excluded. Ethics approval was obtained according to local procedures. At recruitment, a screening questionnaire for each subject was completed by their clinician to collect baseline demographic and clinical characteristics.

Variables and definitions

Subjects were classified by age at enrolment (2-6, 7-11, 12-18 years) and by pubertal stage using the Tanner scale (I: pre-pubertal, II-III: intermediate stages and IV-V: completion of puberty[26]). Degree of immuno-suppression was assessed using CD4 percentages according to the Centers for Disease Control and Prevention (CDC) classification[27, 28]. Nadir and recruitment CD4 cell counts were recorded. Similarly, maximum and recruitment HIV clinical status, according to the CDC classification[29], were collected. Viral load (undetectable defined as HIV-RNA <50 copies/ml) at enrolment was recorded. Complete ART history was collected. Highly active antiretroviral therapy (HAART) was defined as at

least three ART drugs, including 1 nucleoside reverse transcriptase inhibitor (NRTI), with 1 non-nucleoside reverse transcriptase inhibitors (NNRTI) or 1 protease inhibitors (PI). Triple class therapy was defined as ART including at least one PI, one NRTI and one NNRTI.

Outcomes

Body fat abnormality was assessed following clinical examination, and classified as none, mild, moderate or severe. “Mild” abnormality symptoms were defined as those only noticeable when specifically inspected, “moderate” as those readily obvious to the child/carer and physician and “severe” as those obvious to a casual observer. This assessment was made by the child’s principal clinician, who had usually provided long-term care. Specific body locations were inspected. Lipoatrophy was defined as fat loss in 1 of the following sites: face (sunken cheeks/eyes, or prominent zygomatic arch), arms and legs: (skinny with prominent veins, muscularity or bones), and buttocks (loose skin folds, prominent muscles, or loss of contour and fat, or hollowing). Lipohypertrophy was defined as fat gain in 1 of the following sites: trunk (increased abdominal girth), base of neck/back (“buffalo hump”), or breast enlargement. Hypercholesterolemia and fasting hypertriglyceridemia were defined according to age and sex thresholds[30]. The definition of LS incorporated fat abnormality (lipoatrophy and/or lipohypertrophy) with or without metabolic disturbance (hypercholesterolemia and/or fasting hypertriglyceridemia and/or impaired fasting glucose: defined as fasting plasma glucose > 100mg/dL). Outcomes investigated were any fat abnormality, lipohypertrophy, lipoatrophy, combined phenotype of both lipohypertrophy and lipoatrophy, and LS.

Statistical Methods

Associations between body fat abnormality and demographic and clinical characteristics were investigated using χ^2 tests. ART use, both individual and class, were assessed as dichotomous variables (current/non-current; ever/never use at enrolment). Duration of cumulative ART exposure was estimated as the difference between earliest start date and enrolment date. Comparisons of median values of continuous measures (e.g. BMI, serum cholesterol etc.) between groups used Kruskal-Wallis tests.

Risk factors for outcomes were identified using logistic regression models. The final multivariable models were selected using a backwards stepwise approach. All multivariable models retained age and duration of ART at recruitment, and contained a random effect for clinical site as potential confounders *a priori*. Tanner score was not included in the models to prevent over-adjustment for puberty. Variables were systematically removed from the saturated model containing all explanatory variables until those remaining were significant at the 5% level. Discarded variables were then methodically reintroduced to investigate any influence on effect size and statistical significance. All possible variable combinations were investigated in nested models; reintroduced variables were retained and the process was repeated if reintroduction resulted in a change in effect size >10% in other variables, or was itself statistically significant. The final optimal models were those where all variables were significant at 5%. Models were investigated to ensure that missing data had no impact. For each outcome, multivariable models were constructed using specific ART drugs and using ART class. Additional multivariable models were used to estimate the association of current regimen (NRTI monotherapy, PI/NNRTI-based HAART, and triple class ART) with each outcome.

All statistical analyses were conducted using STATA 11.1 (STATA Corp, USA).

Results

The study population included 426 children and adolescents, with median age 12.2 years (interquartile range, IQR; 9.0, 15.0), and 70% (285/409) of white ethnicity (Table 1). Ninety-eight percent ($n=400$) were vertically infected. Overall, 6% (25/416) were co-infected with hepatitis C virus (HCV). At recruitment, most subjects were either asymptomatic or had mild symptoms (>85% across all age groups), showed no immuno-suppression (>75%) and had undetectable viral load (>58%). However, 23% of subjects aged ≥ 12 years had previously experienced severe immuno-suppression or severe clinical symptoms. Four subjects had missing information about body fat abnormalities.

Twenty-nine participants were not receiving ART at recruitment (Table 1), all ART-naïve, and for a further 33 ART history was missing. Over 90% of the 364 participants on ART at enrolment were receiving HAART. The most common NRTI in current use was lamivudine ($n=247$) and the most common NNRTI was efavirenz ($n=94$). Ninety percent ($n=197$) of the 218 subjects receiving PIs were on ritonavir-boosted regimens. Median duration of ART was 5.2 years (IQR 2.2, 8.8). Median duration was higher in subjects with body fat abnormalities and/or metabolic abnormalities compared with those without: none of these differences reached statistical significance (Supplemental Digital Content Table 1). Median age at treatment initiation was 5.8 years (IQR 2.6, 9.9), with the youngest children starting ART earlier compared with the oldest age group ($p<0.001$) (Table 1).

Prevalence of body fat abnormality and lipodystrophy syndrome

Prevalence of body fat abnormality was 42% (176/422), and of lipohypertrophy and lipoatrophy were 27% ($n=115$) and 28% ($n=117$) respectively (Figure 1). High prevalence of fat abnormality was reported in the following groups: those currently receiving stavudine (30/44; 68%), efavirenz (49/93; 53%), or triple-class ART (9/13; 69%) (as illustrated in Supplemental Digital Content 2), HCV-positive subjects (16/24; 67%) and children with experience of CDC stage C disease (45/87; 52%). Children aged 2-6 years at enrolment had the lowest prevalence of body fat abnormality (7/43; 16%).

Median BMI was 18.6 (IQR 16.4, 21.4) and differed according to presence or absence of body fat abnormalities (19.4 [IQR 17.1, 22.5] vs 17.8 [16.1, 20.2] respectively $p<0.001$) and of ALH (21.3 [18.5, 23.7] vs 17.6 [16.2, 19.9] $p<0.001$). Significant differences in waist-hip ratio were seen amongst 12-18 year olds by presence or absence of LS, fat abnormality, lipohypertrophy in males, and of lipoatrophy in females ($p<0.05$, data not shown). Prevalence of metabolic disturbance in subjects with fat abnormality was 28% (49/174): 24 (14%) had hypercholesterolemia, 30 (17%) had fasting hypertriglyceridemia, and 6 (3%) had impaired fasting glucose (metabolic data unavailable for two subjects).

Figure 2 highlights severity of abnormality by body site among the 176 subjects with fat abnormality: 53% had lipoatrophy in the face, 50% in the arms, 51% in the legs and 40% in the buttocks; while 59% had lipohypertrophy in the trunk, 21% in the neck, and 29% in the breasts. Eighty-seven (74%) of the 117 subjects with lipoatrophy and 53 (46%) of the 115 subjects with lipohypertrophy were affected in ≥ 2 locations. Over 51% ($n=90$) of subjects with fat abnormality showed ≥ 3 signs of abnormality, with 15% ($n=27$) and 28% ($n=50$) having two or one sign(s) respectively. Over half (62%) of those with one sign had mild ($n=25$) or moderate ($n=6$) truncal lipohypertrophy, while 22% ($n=11$) had mild facial lipoatrophy. There were significant differences in patterns of fat abnormality by sex (Supplemental Digital Content Table 3), with more lipohypertrophy in females versus males in the trunk (63/212, 30% versus 38/199, 19%, $p<0.05$) and in the neck (24/212, 11% versus 24/212, 6% $p<0.05$). Overall, there was greater prevalence of lipoatrophy in the arms, legs

and buttocks in the 12-18 year and 7-11 year age group compared with the 2-6 year old age group ($p<0.05$) (Supplemental Digital Content Table 4).

Prevalence of LS was 56.5% (95%CI 51.7, 61.3, 235/416); most LS cases were defined on the basis of fat abnormality with ($n=49$) or without ($n=127$) metabolic disturbance rather than metabolic disturbance alone ($n=59$); 10 children were excluded from this analysis due to missing data on metabolic disturbance or fat abnormality. Among the 108 subjects with metabolic disturbance, 47(45%) had isolated fasting hypertriglyceridemia, 29(28%) had isolated hypercholesterolemia, 4(4%) had impaired fasting glucose only, 22(21%) had combined hypercholesterolemia and fasting hypertriglyceridemia, with 1(1%) having either hypercholesterolemia with fasting hypertriglyceridemia, hypercholesterolemia with impaired fasting glucose, or all three metabolic outcomes; three subjects excluded due to missing data.

Six of the 29 ART-naïve participants had body fat abnormalities, significantly fewer than among those non-naïve (20.7% versus 43.3% (170/393) $p<0.05$). One had mild buttock lipoatrophy, three moderate trunk, or mild neck lipohypertrophy, one had severe trunk, moderate breast and mild neck lipohypertrophy and one had the combined phenotype (moderate lipoatrophy in face, arms, legs, mild buttock lipoatrophy and mild breast lipohypertrophy).

Factors associated with body fat abnormality and lipodystrophy syndrome

In univariable analyses (Table 2), white ethnicity and history of moderate or severe HIV symptoms were associated with increased risk of all outcomes. Older age was associated with all outcomes except LS. Subjects experiencing or with completed puberty were more likely to have fat abnormality than pre-pubescent children, but this association was not seen for LS. Current and ever use of NRTI, and specifically stavudine, was associated with a 2-5 fold increased risk of LS, fat abnormality and lipoatrophy (Table 2, supplemental digital table 5). In contrast, current use of zidovudine was associated with a 40-75% decreased risk of fat abnormality, lipoatrophy and the combined phenotype. Use of efavirenz was associated with significant increased risk of all fat abnormality outcomes, whilst current PI use was associated with a 60% increased LS risk, and ever PI use with a two-fold increased risk of all outcomes.

In multivariable models including specific drugs as explanatory variables (Table 3), white ethnicity was associated with a 3-4 times increased risk of LS, fat abnormality, lipoatrophy and the combined phenotype. Subjects with past CDC stage B/C disease were twice as likely to have fat abnormality, lipoatrophy and lipohypertrophy compared with other subjects. Prior severe immunodeficiency was significantly associated with reduced risk of lipoatrophy. Current stavudine was associated with a five-fold increased risk of fat abnormality (3.5-fold for ever use) and a three-fold increased risk of lipoatrophy (5-fold for ever use) and LS (Table 3; supplemental digital Table 6). Current efavirenz was associated with two-three fold increased risk of both LS and body fat abnormality, and nevirapine with a three-fold increased LS risk. Current lamivudine and zidovudine use were associated with reduced risk of the combined phenotype; although no current drugs were associated with increased risk of this phenotype, ever use of efavirenz, didanosine, lopinavir and indinavir were associated with a 2-4-fold increased risk.

In refitted models including current ART class, current NNRTI use was associated with increased risk of fat abnormality (adjusted odds ratio (AOR) 1.97, 95%CI 1.11-3.50), lipohypertrophy (AOR 2.49, 95%CI 1.08-5.78), combined phenotype (AOR 6.45, 95%CI 1.62-25.71) and LS (AOR 2.78, 95%CI 1.20-5.45), while current PI use was associated with

increased risk of LS (AOR 2.56, 95% CI 1.26-6.11) and combined phenotype (AOR 5.41, 95% CI 1.36-24.48).

To explore the association between triple class therapy and body fat abnormality, new models adjusted for age, ART duration and site were tested. Triple class therapy was a significant risk factor for fat abnormality (AOR 4.68, 95% CI 1.07, 20.5), lipohypertrophy (AOR 3.67, 95% CI 1.07-12.65), lipoatrophy (AOR 5.13, 95% CI 1.0-22.0) and the combined phenotype (AOR 4.35, 95% CI 1.11-17.03).

Repeating the model selection procedure with the inclusion of an interaction between age and sex demonstrated a lack of significance for any outcome. Sensitivity analyses were conducted using the outcome of moderate/severe versus no/mild fat redistribution. Similar directions of association were found although not all risk factors reached statistical significance (data not shown).

Discussion

More than half of this cohort of HIV-infected children and adolescents presented with LS (56%) and 42% had body fat abnormality: one in two with moderate or severe abnormalities. Among the subjects with fat abnormality, the proportions with lipohypertrophy-only, lipoatrophy-only and the combined phenotype were roughly equal at approximately one-third each. Factors associated with risk of body fat abnormality included white ethnicity, history of symptomatic HIV disease and use of specific ART.

The prevalence of fat abnormality here was substantially higher than the 18-33% reported in other paediatric studies[8, 10-12, 31-33], reflecting variations in LS definitions and methodology, and underlying population differences. However, restricting the definition to moderate and severe cases resulted in a prevalence of 19%. LS development may be a graded, progressive process and, furthermore, the natural development of adipose tissue in childhood may have a protective effect against LS, which wanes during and after puberty[31]. Thus the comparatively older age of our participants (median 12.2 years compared to the mean of 7.5-11.0 years in the cited studies) may partly explain the greater prevalence we observed.

In our unadjusted analysis, subjects undergoing puberty or with completed puberty had a two to three-fold increased risk of fat abnormality. We excluded Tanner score from our adjusted models as sex and age were included, as we did not want to over-adjust for puberty. In separate analyses where Tanner score was included in our stepwise-modelling, it remained significantly associated with fat abnormality in the final model, giving credence to the role of puberty in LS (data not shown). In analyses adjusting for ever-use of ART, there was a significant 17% and 13% increased risk of lipoatrophy and of the combined phenotype per year of age. The similar associations with age reported in adults are generally of a smaller magnitude: in the Swiss HIV Cohort, there was an 18% increased risk of fat abnormality per decade increase in age at baseline[34]. It is not certain to what extent such changes are the result of 'normal' age-associated fat gain unrelated to HIV in adults[34]. The pattern of body fat abnormalities here, with the trunk the most and the neck the least common location is similar to reports from adult studies[2, 35], but somewhat dissimilar to that reported in children[8] possibly reflecting the older age of our population.

Lipohypertrophy in the trunk reported in a HIV-seronegative individual undergoing post-exposure prophylaxis[36] together with animal studies[37-39], indicate that ART may be central in LS pathogenesis. However, our finding that some ART-naïve children develop fat abnormalities is consistent with a multifactorial process, including possible direct action of HIV itself[40]. We demonstrated an increased risk of LS and/or the combined lipoatrophy/

lipohypertrophy phenotype associated with current and past PI use. PI use has been inconsistently shown to be associated with lipoatrophy in adults[2, 41, 42], with data from cross-sectional paediatric studies similarly conflicting[8, 11, 12, 43]. Postulated mechanisms behind PI use and lipoatrophy include inhibition of proteins involved in lipid metabolism[44-46] and insulin dysregulation[45][47].

NRTI use has been strongly implicated in the pathogenesis of fat abnormalities, particularly lipoatrophy[41], with potential mechanisms including mitochondrial damage in adipocytes[48] and inhibition of adipogenesis[49]. Our findings with respect to stavudine are consistent with previous reports[8, 11, 32, 34, 42, 50-54]; over 10% of our subjects were currently receiving stavudine, despite current guidelines[22].

One third of our subjects had both lipoatrophy and lipohypertrophy. Increasing age and BMI and past use of some specific drugs (from all three classes) were associated with increased risk of this combined phenotype, whilst current lamivudine and zidovudine use were associated with a significantly reduced risk. In subgroup analysis this latter association appeared to be driven by males and children aged >11 years (data not shown). The associations of the combined phenotype with age and past drug exposure suggest that its emergence may be progressive and associated with cumulative ART exposure over time.

Current nevirapine use was associated with increased risk of LS, whilst associations between LS and fat abnormalities were demonstrated with past and/or current use of efavirenz. While the association of NNRTIs with fat abnormality has not been investigated in child/adolescent studies, our results are consistent with adult studies [55-57]. Paediatric reports have described associations between longer treatment duration and increased risk of fat abnormality [11, 24] unlike in our investigation.

Experience of more serious HIV disease was associated with body fat abnormality, lipohypertrophy and lipoatrophy, in accordance with an earlier multi-site European paediatric study[8]. Several studies have identified immuno-suppression as an independent risk factor for lipoatrophy[42, 58] and fat abnormality[59]. Indeed, results from the prospective HIV Outpatients Study demonstrating association between low CD4 counts and lipoatrophy independent of ART, led to the hypothesis that factors associated with more advanced HIV disease predispose individuals to later develop LS[42].

Reports in children and adults[8, 10, 11, 31, 34, 51, 52, 60, 61] demonstrated that females were more likely to have fat abnormality, lipohypertrophy and the combined phenotype than males, possibly due to hormonal or pharmacokinetic differences[62]. We found no association between female sex and increased risk of lipohypertrophy in adjusted analyses, although there was a significant association between sex and lipohypertrophy in the trunk or neck.

Around two-thirds of our cohort was of white ethnicity, associated with three to four times increased risk of lipoatrophy and fat abnormality, consistent with other studies[50, 60, 63]. Underlying genetic differences between ethnic groups may explain these findings, the metabolic syndrome having been shown to occur less frequently in individuals of black compared with white ethnicity in non-HIV infected populations[64].

Several studies have reported a negative impact of body fat changes on self-esteem and psychological profile in HIV-infected adults[65-67], which has been linked to non-adherence to ART[68, 69]. Little is known about the impact in children or adolescents[70], but this is likely to be an issue for adolescents, given that this is a time when self-image is important. Our study did not collect information on self-reported body image, but the fact

that around 7% of children and adolescents had severe and potentially stigmatising fat loss or gain demonstrates the need for further research.

A limitation of our study is its observational nature and the potential for confounding. Some previous studies have relied on self-reported changes potentially leading to over-reporting of body shape changes[66]. Our approach, with fat abnormality assessed according to strictly defined criteria using a scale of severity by the child's established clinician, avoids such misclassification but remains a subjective measure. A minority (28%, 50/176) of body fat abnormality cases were based on abnormality in a single body site; only 31 subjects (7% of all participants) were categorized as having fat abnormality on the basis on trunk lipohypertrophy alone (26 mild and 5 moderate). Furthermore, risk factors identified in our main analyses were confirmed by sensitivity analyses investigating moderate/severe fat abnormality (although not necessarily reaching statistical significance). However, given that the clinician would be aware of the ART status of the patient when making the assessment of fat abnormality, the potential for bias cannot be discounted. Our multi-site design provided us with a large sample size compared with previous paediatric studies, resulting in a diverse study sample and good generalizability. We addressed potential systemic differences in clinical practice by incorporating a random effect for clinical site within our models. Finally, the analyses presented here are based on recruitment data and thus limited by their cross-sectional nature. We are collecting longitudinal data on our cohort and will be able to address issues including incidence and progression or regression of fat abnormality in the future.

Our study suggests that body fat abnormality occurs in almost half of HIV-infected children and adolescents, with the same complex range of phenotypes as seen in adults. Moreover, associated risk factors in this population are similar to those seen in adults, with both ART-related and demographic/clinical factors identified. In our cohort of HIV-infected children, most will have accumulated at least a decade of exposure to multiple drugs by the time they become adults. This underscores how important it is to monitor and investigate the long-term implications of life-long HIV and ART use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

CT and AV contributed to study concept and CT, AV, and TG contributed to study design. AV, TG, MM and members of the EPHLS were involved in the acquisition of data. NA performed the data management and statistical analyses, with support from MCB. NA drafted the manuscript, which all authors critically revised for important intellectual content. All authors read and approved the final manuscript.

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References

1. Heath CV, Hogg RS, Chan KJ, Harris M, Montessori V, O'Shaughnessy MV, et al. Lipodystrophy-associated morphological cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS*. 2001; 15:231–239. [PubMed: 11216932]
2. Carr A, Samaras K, Thorsdottir A, Kaufman GR, Chisholm DJ, DA C. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: A cohort study. *The Lancet*. 1999; 353:2093–2099.
3. Saves M, F R, Capeau J, Rozenbaum W, Ragnaud J-M, Peronne C, et al. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. *Clinical Infectious Diseases*. 2002; 34:1396–1405. [PubMed: 11981737]
4. Chene G, Angelini E, Cotte L, Lang J-M, Morlat P, Rancinan C, et al. Role of long-term nucleoside-analogue therapy in lipodystrophy and metabolic disorders in human immunodeficiency virus-infected patients. *Clinical Infectious Diseases*. 2002; 34:649–657. [PubMed: 11810598]
5. Shlay JC, Visnegarwala F, Bartsch G, Wang J, Peng G, El-Sadr WM, et al. Body composition and metabolic changes in antiretroviral-naïve patients randomized to didanosine and stavudine vs. abacavir and lamivudine. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 38:147–155. [PubMed: 15671799]
6. Pujari SN, Dravid A, Naik E, Bhagat S, Tash K, Madler JP, et al. Lipodystrophy and dyslipidemia among patients taking first-line World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 39:199–202. [PubMed: 15905737]
7. George JA, Venter WDF, Van Deventer HE, J CN. A longitudinal study of the changes in body fat and metabolic parameters in a south African population of HIV-positive patients receiving an antiretroviral therapeutic regimen containing stavudine. *AIDS Research and Human Retroviruses*. 2009; 25:771–781. [PubMed: 19619010]
8. European Paediatric Lipodystrophy Group. Antiretroviral therapy fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS*. 2004; 18:1443–1451. [PubMed: 15199321]
9. Beregszaszi MDC, Levine M, Faye A, Deghmoun S, Bellal N, Houang M, Chevenne D, Hankard R, Bresson J-L, Blanche S, Levy-Marchal C. Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 40:161–168. [PubMed: 16186733]
10. Sanchez-Torres AM, Munoz-Muniz R, Madero R, Borque C, Garcia-Miguel MJ, De-Jose-Gomez MI. Prevalence of fat redistribution and metabolic disorders in human immunodeficiency virus-infected children. *European Journal of Pediatrics*. 2005; 164:271–276. [PubMed: 15650834]
11. Ene L, Goetghebuer T, Hainaut M, Peltier A, Toppet V, Levy J. Prevalence of lipodystrophy in HIV-infected children - A cross-sectional study. *European Journal of Pediatrics*. 2007; 166:13–21. [PubMed: 16896646]
12. Amaya RAKC, McMeans A, Schwarzwald H, Kline MW. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *The Pediatric Infectious Disease Journal*. 2002; 21:405–410. [PubMed: 12150177]
13. Bitnun ASE, Babyn P, Holowka S, Stephens D, Read S, King SM. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naïve HIV-infected children. *AIDS*. 2003; 17:1319–1327. [PubMed: 12799553]
14. Parakh A, Prakash-Dubey A, Kumar A, Maheshwari A. Lipodystrophy and metabolic complications of highly active antiretroviral therapy. *Indian Journal of Pediatrics*. 2009; 76:1017–1021. [PubMed: 19907933]
15. Resino S, Micheloud D, Lorente R, Bellon JM, Navarro ML, Munoz-Fernandez MA. Adipokine profiles and lipodystrophy in HIV-infected children during the first 4 years on highly active antiretroviral therapy. *HIV Medicine*. 2011; 12:54–60. [PubMed: 20497248]
16. HIV Lipodystrophy Case Definition Study Group. An objective case definition of lipodystrophy in HIV-infected adults; A case-control study. *The Lancet*. 2003; 361:726–735.

17. UNAIDS. AIDS Epidemic Update. UNAIDS; Geneva: 2010. AIDS epidemic update 2010.
18. WHO. Towards Universal Access; Scaling up priority HIV/AIDS interventions in the health sector. World Health Organization; Geneva: 2009. Edited by HIV/AIDS Department WHO
19. Gortmaker SL, Hughes M, Cervia J, Brady M, Johnson GM, Seage GR, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. 2001; 345:1522–1528. [PubMed: 11794218]
20. Gibb DM, Duong T, Tookey PA, Sharland M, Tudor-Williams G, Novelli V, et al. Decline in mortality AIDS and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *British Medical Journal*. 2003; 327:1019–1023. [PubMed: 14593035]
21. Brahmbhatt HKG, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, Sewankambo N, Kidugavu M, Wawer M, Gray R. Mortality in HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. *Journal of Acquired Immune Deficiency Syndromes*. 2006; 41:504–508. [PubMed: 16652060]
22. PENTA. Paediatric European Network for Treatment of AIDS (PENTA) treatment guidelines. 2009.
23. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Working group on antiretroviral therapy and medical management of HIV-infected children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2009.
24. Italian Multicentre Study. Epidemiology, clinical features, and prognostic factors of paediatric HIV infection. Italian Multicentre Study. *Lancet*. 1988;1043–1045. [PubMed: 2903277] *Infectious Diseases Newsletter*. 1989; 8:14–15.
25. Italian Register for HIV Infection in Children. Epidemiology of HIV infection in children in Italy. The Italian Register for HIV Infection in Children. *Acta pædiatrica*. 1994; 400(Supplement):15–18.
26. Tanner, JM. Growth at adolescence: with a general consideration of the effects of hereditary and enviromental factors upon growth and maturation from birth to maturity. 2nd ed.. Blackwell Scientific; Oxford: 1962.
27. Castro G, Ward JW, Slutker L, Buehler JW, Jaffe HW, RL B. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Reports*. 1993 1992
28. Calwell MBOM, Simonds RJ, Rogers MF. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and Mortality Weekly Report*. 1994:1–10.
29. Schneider E, Whitmore S, Glynn MK, Dominguez K, Mitsch A, MT M. Revised surveillance case definitions for HIV infection among adults, adolescents and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years -United States, 2008. *Morbidity and Mortality Weekly Reports*. 2008:1–8.
30. Jolliffe CJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. *Circulation*. 2006; 114:1056–1062. [PubMed: 16940191]
31. Jaquet D, Levine M, Ortega-Rodriguez E, Faye A, Polak M, Vilmer E, et al. Clinical and metabolic presentation of the lipodystrophic syndrome in HIV-infected children. *AIDS*. 2000; 14:2123–2128. [PubMed: 11061653]
32. Arpadi SMCP, Horlick MN, Wang J, Kotler DP. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4 B-lymphocyte count and CD4 B-lymphocyte percentage at baseline and use of protease inhibitors and stavudine. *Journal of acquired immune deficiency syndromes*. 2001; 27:30–34. [PubMed: 11404517]
33. Bockhorst JLKI, Toye M, Chipkin SR, Stechenberg BW, Fisher DJ, Allen HF. Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. *The Pediatric Infectious Disease Journal*. 2003; 22:463–465. [PubMed: 12797313]
34. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, et al. Lipid profiles for antiretroviral-naïve patients starting PI- and NNRTI-based therapy in the Swiss HIV Cohort Study. *Antiviral Therapy*. 2005; 10:585–591. [PubMed: 16152752]

35. Thiebaut R, Daucourt V, Mercie P, Ekouevi DK, Malvy D, Morlat P, et al. Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France 1999. *Clinical Infectious Diseases*. 2000; 31:1482–1487. [PubMed: 11096016]
36. Mauss S, Berger F, Carls H, G S. Rapid development of central adiposity after postexposure prophylaxis with antiretroviral drugs: A proof of principle? *AIDS*. 2003; 17:944–945. [PubMed: 12660554]
37. Riddle TM, Kuhel DG, Woollet LA, Fichtenbaum CJ. HIV Protease Inhibitor Induces Fatty Acid and Sterol Biosynthesis in Liver and Adipose Tissues Due to the Accumulation of Activated Sterol Regulatory Element-binding Proteins in the Nucleus. *Journal of Biological Chemistry*. 2001; 276:37514–37519. [PubMed: 11546771]
38. Riddle TM, Schindmeyer NM, Phan C, Fichtenbaum CJ, D Y Hui. The HIV protease inhibitor ritonavir increases lipoprotein production and has no effect on lipoprotein clearance in mice. *Journal of Lipid Research*. 2002; 43:1458–1463. [PubMed: 12235177]
39. Hruz PW, Murata H, Qui H, Mueckler M. Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*. 2002; 51:937–942. [PubMed: 11916910]
40. Safran S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS*. 1999; 13:2493–2505. [PubMed: 10630518]
41. Saint-Marc T, Partisani M, Poizot-Martin I, Rouviere O, Bruno F, Avellaneda R, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS*. 2000; 14:37–49. [PubMed: 10714566]
42. Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, Palella FJ, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS*. 2001; 15:1389–1398. [PubMed: 11504960]
43. Arpadi SM, Cuff PA, Horlick M, Wang J, Kotler DP. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4 B-lymphocyte count and CD4 B-lymphocyte percentage at baseline and use of protease inhibitors and stavudine. *Journal of Acquired Immune Deficiency Syndromes*. 2001; 27:30–34. [PubMed: 11404517]
44. Domingo P, Matias-Guiu X, Pujol RM, Francia E, Lagarda E, Sambeat MA, et al. Subcutaneous adipocyte apoptosis in HIV-1 protease inhibitor-associated lipodystrophy. *AIDS*. 1999; 13:2261–2267. [PubMed: 10563711]
45. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet*. 1998; 351:1881–1883. [PubMed: 9652687]
46. Bastard J-P, C M, Vidal H, Jan V, Auclair M, Vigouroux C, Lubinski J, Lavilee M, Maachi M, Girard P-M, Rozenbaum W, Levan P, Capeau J. Association between altered expression of adipogenic factor SREBP1 in lipotrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. *The Lancet*. 2002; 359:1026–1031.
47. Martinez E, Gatell J. Metabolic abnormalities and use of HIV-1 protease inhibitors. *The Lancet*. 1998; 352:821–822.
48. Nolan D, Hammond E, Martin A, Taylor L, Herrmann S, McKinnon E, et al. Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. *AIDS*. 2003; 17:1329–1338. [PubMed: 12799554]
49. Pace CS, Martin AM, Hammond EL, Mamotte CD, Nolan DA, Mallan SA. Mitochondrial proliferation, DNA depletion and adipocyte differentiation in subcutaneous adipose tissue of HIV-positive HAART recipients. *Antiviral Therapy*. 2003; 8:323–331. [PubMed: 14518702]
50. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS*. 2000; 14:1309–1316. [PubMed: 10930144]
51. Martinez E, Mocroft A, Garcia-Viejo MA, Perez-Cuevas JB, Blanco JL, Mallolas J, et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: A prospective cohort study. *The Lancet*. 2001; 357:592–598.
52. Galli M, Ridolfo AL, Adorni F, Gervasoni C, Ravasio L, Corsico L, et al. Body habitus changes and metabolic alterations in protease inhibitor-naïve HIV-1-infected patients treated with two

- nucleoside reverse transcriptase inhibitors. *Journal of Acquired Immune Deficiency Syndromes*. 2002; 29:21–31. [PubMed: 11782586]
53. Moyle GJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipodatrophy. *AIDS*. 2006; 20:2043–2050. [PubMed: 17053350]
 54. Martin A, Smith DE, Carr A, Ringland C, Amin J, Emery S, et al. Reversibility of lipodatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir; The MITOX Extension Study. *AIDS*. 2004; 18:1029–1036. [PubMed: 15096806]
 55. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in women with HIV infection. *Journal of Acquired Immune Deficiency Syndromes*. 2006; 42:562–571. [PubMed: 16837863]
 56. Shlay JC, Sharma S, Peng G, Gibert CL, C G. The effect of individual antiretroviral drugs on body composition in HIV-infected persons initiating highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*. 2009; 51:298–304. [PubMed: 19412117]
 57. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003; 349:1993–2003. [PubMed: 14627784]
 58. Joly V, Flandre P, Meiffredy V, Leturque N, Harel M, Aboulker J-P, et al. Increased risk of lipodatrophy under stavudine in HIV-1-infected patients; A Results of a substudy from a comparative trial. *AIDS*. 2002; 16:2447–2454. [PubMed: 12461419]
 59. Seminari E, Tinelli C, Minoli L, Sacchi P, Filice G, Zocchetti C, et al. Evaluation of the risk factors associated with lipodystrophy development in a cohort of HIV-positive patients. *Antiviral Therapy*. 2002; 7:175–180. [PubMed: 12487384]
 60. Bogner JRVV, Beckman RA, Michl G, Wille L, Salzberger B, Goebel F-D. Stavudine versus zidovudine and the development of lipodystrophy. *Journal of Acquired Immune Deficiency Syndromes*. 2001; 27:237–244.
 61. Mutimura E, Stewart A, Rheeder P, Crowther NJ. Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*. 2007; 46:451–455. [PubMed: 18077834]
 62. Ofotokun I, Chuck SK, Hitti JE. Antiretroviral pharmacokinetic profile: a review of sex differences. *Gender Medicine*. 2007; 4:106. [PubMed: 17707845]
 63. Lichtenstein KA, Delaney KM, Armon C, Ward DJ, Moorman AC, Wood KC, et al. Incidence of and risk factors for lipodatrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:48–56. [PubMed: 12514413]
 64. Park YW, Zhu S, Palaniappa L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Archives of Internal Medicine*. 2003; 163:427–436. [PubMed: 12588201]
 65. Sanches S. Facial Lipodatrophy Appearances Are Not Deceiving. *The Journal of the Association of Nurses in AIDS Care*. 2009; 20:169–175. [PubMed: 19427594]
 66. Burgoyne R, Collins E, Wagner C, Abbey S, Halman M, Nur M, et al. The relationship between lipodystrophy-associated body changes and measures of quality of life and mental health for HIV-positive adults. *Quality of Life Research*. 2005; 14:981–990. [PubMed: 16041895]
 67. Blanche S, Newell ML, Mayaux MJ, Dunn MJ, Dunn DT, Teglas JP, et al. Morbidity and mortality in European children vertically infected by HIV-1. *Journal of Acquired Immune Deficiency Syndromes Human Retrovirology*. 1997; 14:442–450.
 68. Plankey M, Bacchetti P, Jin C, Grimes B, Hyman C, Cohen M, et al. Self-perception of body fat changes and HAART adherence in the women's interagency HIV study. *AIDS and Behavior*. 2009; 13:53–59. [PubMed: 18688706]
 69. Duran S, Saves M, Spire B, Cailleton V, Sobel A, Carrieri P, et al. Failure to maintain long-term adherence to highly active antiretroviral therapy: the role of lipodystrophy. *AIDS*. 2001; 15:2441–2444. [PubMed: 11740195]

70. Dollfus C, Blanche S, Trocme N, Funk-Brentano I, Bonnet F, Levan P. Correction of facial lipoatrophy using autologous fat transplants in HIV-infected adolescents. *HIV Medicine*. 2009; 10:263–268. [PubMed: 19178590]

Figure 1. Frequencies of body fat redistribution ($n = 422$)

*Includes 2 subjects known to have lipohypertrophy but lipoatrophy status was unknown.

**Includes 1 subject known to have lipoatrophy but lipohypertrophy status was unknown.

Figure 2. Presence and distribution of abnormality by body site among the 176 subjects with body fat abnormality

Percentages are given as a proportion of the number of subjects with body fat redistribution.

Missing data: arms; 1, leg; 1, buttocks; 5, neck; 1, breasts; 1

Table 1
Frequency and percentage distribution of baseline socio-demographic and HIV-related characteristics (n=426)

		Age of subject n (%) or median (IQR)		
		2-6 years n=43	7-11 years n=117	12-18 years n=266
<i>Demographic factors</i>				
Age (years)		4.62 (3.80, 5.26)	8.77 (7.68, 9.95)	14.41 (12.57, 16.08)
Gender	Male	21 (50.0)	50 (43.9)	130 (50.2)
	Female	21 (50.0)	64 (56.1)	129 (49.8)
Ethnicity	Black	10 (24.4)	30 (27.3)	67 (26.0)
	White	29 (70.7)	73 (66.3)	183 (70.9)
	Other	2 (4.9)	7 (6.4)	8 (3.1)
Country of residence	Belgium	2 (4.7)	20 (17.1)	62 (23.3)
	Italy	26 (60.5)	76 (65.0)	174 (65.4)
	Poland	15 (34.9)	21 (17.9)	30 (11.3)
<i>HIV clinical factors</i>				
CDC immune stage at recruitment #	Stage 1	27 (62.8)	101 (86.3)	196 (73.7)
	Stage 2	14 (32.6)	14 (12.0)	56 (21.1)
	Stage 3	2 (4.7)	2 (1.7)	14 (5.3)
Nadir CDC immune stage #	Stage 1	14 (32.6)	65 (55.7)	81 (30.5)
	Stage 2	22 (51.2)	40 (34.2)	117 (44.0)
	Stage 3	7 (16.3)	12 (10.3)	68 (25.6)
CDC clinical stage at recruitment ##	N+A	32 (89.0)	94 (93.1)	220 (91.3)
	B	2 (5.6)	6 (5.9)	13 (5.4)
	C	2 (5.6)	1 (1.0)	8 (3.3)
Maximum CDC clinical stage ##	N+A	18 (43.9)	59 (53.2)	93 (37.2)
	B	14 (34.2)	31 (27.9)	98 (39.2)
	C	9 (22.0)	21 (18.9)	59 (23.6)
HIV-RNA at recruitment	50 copies/ml	29 (67.4)	78 (66.7)	139 (52.7)
	>50 copies/ml	14 (32.6)	39 (33.3)	125 (47.4)
Mode of HIV acquisition	Blood products	0 (0)	2 (1.8)	5 (2.0)
	Vertical transmission	43 (100)	111 (98.2)	246 (97.2)
	Other	0 (0)	0 (0)	2 (0.8)
<i>Other factors</i>				
Duration drug use (years)		2.78 (0.84, 4.21)	4.24 (1.99, 7.39)	6.21 (2.52, 9.77)
Age at first ART (years)		1.48 (0.69, 3.13)	3.98 (1.41, 6.77)	7.54 (4.28, 11.49)
Hepatitis C co-infection	No co-infection	39 (95.1)	111 (96.5)	241 (93.0)

		Age of subject <i>n</i> (%) or median (IQR)		
		2-6 years <i>n</i> =43	7-11 years <i>n</i> =117	12-18 years <i>n</i> =266
Tanner score for puberty	Co-infection	2 (5.0)	4 (3.5)	19 (7.3)
	I	37 (97.4)	87 (80.6)	11 (4.8)
	II-III	1 (2.6)	20 (18.5)	64 (28.0)
	IV-V	0 (0)	1 (1.0)	153 (67.1)
BMI (kg/m²)		16.01 (14.38, 17.09)	16.49 (15.07, 18.94)	19.73 (17.69, 22.57)
Current ART at recruitment				
Current use of ART	Yes	34 (89.5)	100 (90.1)	230 (94.3)
	No [†]	4 (10.5)	11 (9.9)	14 (5.7)
NRTI	Yes	34 (89.5)	100 (90.1)	228 (93.4)
	No	4 (10.5)	11 (9.9)	16 (6.6)
Didanosine	Yes	4 (10.5)	13 (11.6)	30 (12.3)
	No	34 (89.5)	98 (88.3)	214 (87.7)
Lamivudine	Yes	27 (71.1)	79 (71.9)	141 (57.8)
	No	11 (28.9)	32 (28.8)	103 (42.2)
Stavudine	Yes	6 (15.8)	13 (11.7)	25 (10.2)
	No	32 (84.2)	98 (88.3)	219 (89.8)
Zidovudine	Yes	16 (42.1)	40 (36.0)	46 (18.9)
	No	22 (57.9)	71 (64.0)	198 (81.1)
NNRTI	Yes	7 (20.6)	46 (46.0)	80 (34.8)
	No	27 (79.4)	54 (54.0)	150 (65.2)
Efavirenz	Yes	5 (13.2)	27 (24.3)	62 (25.4)
	No	33 (86.8)	84 (75.7)	182 (74.6)
Nevirapine	Yes	2 (5.3)	19 (17.1)	18 (7.4)
	No	36 (94.7)	92 (82.9)	226 (92.6)
PI	Yes	24 (63.2)	47 (42.3)	147 (60.2)
	No	14 (36.8)	64 (57.7)	97 (39.8)
Ritonavir/lopinavir	Yes	23 (60.5)	44 (39.6)	130 (53.3)
	No	15 (39.5)	67 (60.4)	114 (46.7)
Type of drug therapy at recruitment				
NRTI monotherapy		3 (8.8)	10 (10.0)	16 (7.0)
NNRTI-based HAART		7 (20.6)	43 (43.0)	67 (29.1)
PI-based HAART		24 (70.6)	44 (44.0)	136 (59.1)
Triple class therapy		0 (0)	3 (3.0)	11 (4.8)

ART use defined as use at the time of recruitment

Missing data: gender; 11, ethnicity; 17, CDC clinical stage at recruitment; 24, maximum CDC clinical stage; 48, viral load (HIV-RNA) at recruitment; 2, mode of HIV acquisition; 17, duration of drug use; 1, age at first ART; 1, hepatitis co-infection 10, Tanner score for puberty; 14, current use of any/specific ART; 33

stage 1 = no suppression: stage 2 = moderate suppression: stage 3 = severe suppression

N = asymptomatic, A = mild symptomatic: B = moderately severe symptoms: C = severe symptom defining AIDS

† These 29 subjects were ART naive

Table 2
Risk factors for each of the four body fat redistribution outcomes and for lipodystrophy syndrome (univariable analysis)

		Body fat abnormality)	Any lipohypertrophy	Any lipoatrophy	Combined lipohypertrophy and lipoatrophy	Lipodystrophy syndrome
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Demographic factors						
Gender	Male	1	1	1	1	1
	Female	1.24 (0.84, 1.84)	1.76 [*] (1.13, 2.75)	0.87 (0.56, 1.35)	1.31 (0.74, 2.34)	1.10 (0.74, 1.63)
Age (years)	2-6	1	1	1	1	1
	7-11	3.02 [*] (1.22, 7.47)	2.67 (0.95, 7.51)	3.64 [*] (1.02, 12.93)	4.67 (0.58, 37.65)	1.72 (0.85, 3.49)
	12-18	5.10 ^{***} (2.18, 11.94)	3.50 [*] (1.32, 9.27)	7.17 ^{***} (2.15, 23.93)	8.35 [*] (1.11, 62.62)	1.50 (0.78, 2.87)
Ethnicity	Black	1	1	1	1	1
	White	3.29 ^{***} (1.97, 5.48)	2.34 ^{**} (1.33, 4.12)	4.93 ^{***} (2.46, 9.89)	5.30 ^{**} (1.86, 15.10)	3.80 ^{***} (2.36, 6.11)
Country of residence	Other	1.44 (0.46, 4.50)	1.52 (0.44, 5.20)	1.28 (0.26, 6.42)	1.61 (0.17, 15.33)	1.08 (0.37, 3.15)
	Italy	1	1	1	1	1
	Belgium	0.46 ^{**} (0.27, 0.80)	0.61 (0.34, 1.13)	0.42 [*] (0.21, 0.84)	0.55 (0.21, 1.48)	0.44 ^{**} (0.26, 0.73)
	Poland	1.57 (0.91, 2.69)	1.49 (0.85, 2.63)	3.16 ^{***} (1.82, 5.51)	4.66 ^{***} (2.46, 8.84)	2.05 [*] (1.12, 3.74)
Infection factors						
CDC immune stage at recruitment [#]	Stage 1	1	1	1	1	1
	Stage 2	0.51 [*] (0.31, 0.86)	0.66 (0.37, 1.16)	0.44 [*] (0.24, 0.83)	0.52 (0.22, 1.19)	0.47 ^{**} (0.29, 0.77)
	Stage 3	0.66 (0.24, 1.83)	0.52 (0.14, 1.83)	0.68 (0.22, 2.15)	0.36 (0.005, 2.74)	0.50 (0.18, 1.38)
Nadir CDC immune stage [#]	Stage 1	1	1	1	1	1
	Stage 2	0.84 (0.52, 1.24)	1.28 (0.79, 2.08)	0.63 (0.39, 1.03)	1.13 (0.60, 2.12)	0.76 (0.49, 1.18)
	Stage 3	1.21 (0.71, 2.04)	1.10 (0.61, 2.01)	1.15 (0.66, 2.02)	1.01 (0.46, 2.22)	0.95 (0.56, 1.63)
CDC clinical stage at recruitment ^{##}	N+A	1	1	1	1	1
	B	1.32 (0.55, 3.20)	1.11 (0.42, 2.94)	1.73 (0.69, 4.31)	1.74 (0.56, 5.42)	0.98 (0.40, 2.43)
	C	0.55 (0.14, 2.10)	1.04 (0.27, 4.00)	0.62 (0.13, 2.95)	1.64 (0.34, 7.87)	0.54 (0.15, 1.93)
Maximum CDC	N+A	1	1	1	1	1
	B	2.35 ^{***} (1.48, 3.73)	2.09 ^{**} (1.25, 3.49)	2.15 ^{**} (1.28, 3.61)	2.18 [*] (1.10, 4.31)	2.24 ^{***} (1.41, 3.55)
	NGA	2.48 ^{***} (1.45, 4.23)	2.09 [*] (1.17, 3.73)	2.16 [*] (1.20, 3.90)	1.97 (0.90, 4.29)	1.87 [*] (1.10, 3.20)

clinical stage ##	Body fat abnormality)	Any lipohypertrophy	Any lipoatrophy	Combined lipohypertrophy and lipoatrophy	Lipodystrophy syndrome
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
HIV-RNA at recruitment					
RS0 copies/ml	2.35 *** (1.48, 3.73)	2.09 ** (1.25, 3.49)	2.15 ** (1.28, 3.61)	2.18 * (1.10, 4.31)	2.24 *** (1.41, 3.55)
RS0 copies/ml	2.48 *** (0.83, 7.23)	0.82 (0.53, 1.28)	0.93 (0.60, 1.43)	0.95 (0.56, 1.68)	0.87 (0.46, 1.66)
Mode of HIV acquisition					
Blood products	1	1	1	1	1
Vertical transmission	1.75 (0.34, 9.14)	2.24 (0.27, 18.84)	2.31 (0.27, 19.39)	-	1.92 (0.32, 11.65)
Other	-	-	6.00 (0.18, 196.28)	-	-
Other factors					
Hepatitis C co-infection					
Uninfected	1	1	1	1	1
Co-infected	2.96 * (1.24, 7.07)	2.80 * (1.22, 6.44)	1.59 (0.68, 3.74)	1.74 (0.62, 4.88)	1.56 (0.65, 3.74)
Tanner score					
I	1	1	1	1	1
II-III	1.93 * (1.08, 3.42)	1.54 (0.80, 2.95)	2.01 * (1.05, 3.84)	1.68 (0.72, 3.95)	0.68 (0.39, 1.17)
IV-V	2.97 *** (1.81, 4.88)	2.33 *** (1.35, 4.03)	2.53 *** (1.45, 4.43)	2.08 * (1.01, 4.31)	1.16 (0.72, 1.87)
BMI (kg/m²)					
Per unit	1.14 *** (1.08, 1.21)	1.28 *** (1.19, 1.37)	0.97 (0.91, 1.03)	1.08 (1.00, 1.16)	1.04 (0.98, 1.10)
NRTI					
Any NRTI					
Not current	1	1	1	1	1
Current	2.60 * (1.09, 6.21)	1.54 (0.61, 3.89)	3.94 * (1.17, 13.26)	2.26 (0.52, 9.77)	2.28 * (1.04, 5.00)
Didanosine					
Not current	1	1	1	1	1
Current	1.00 (0.54, 1.85)	1.06 (0.53, 2.10)	1.05 (0.54, 2.05)	1.16 (0.49, 2.74)	1.41 (0.74, 2.68)
Lamivudine					
Not current	1	1	1	1	1
Current	0.85 (0.56, 1.28)	0.73 (0.46, 1.15)	0.75 (0.48, 1.17)	0.49 * (0.27, 0.88)	0.88 (0.58, 1.35)
Stavudine					
Not current	1	1	1	1	1
Current	3.31 *** (1.69, 6.47)	1.81 (0.94, 3.48)	2.66 *** (1.40, 5.07)	1.53 (0.67, 3.49)	2.37 * (1.16, 4.84)
Zidovudine					
Not current	1	1	1	1	1
Current	0.60 * (0.38, 0.97)	0.58 (0.33, 1.01)	0.53 * (0.31, 0.92)	0.33 * (0.14, 0.81)	1.11 (0.70, 1.77)
NNRTI					
Any NNRTI					
Not current	1	1	1	1	1

		Body fat abnormality)		Any lipohypertrophy		Combined lipohypertrophy and lipotrophy		Lipodystrophy syndrome	
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Efavirenz	Current	1.34 (0.87, 2.07)	1	1.37 (0.85, 2.19)	1.40 (0.88, 2.21)	1.69 (0.93, 3.08)	1.10 (0.71, 1.71)	1	
	Not current							1	
Nevirapine	Current	1.71 [*] (1.07, 2.74)		1.68 [*] (1.02, 2.77)	1.82 [*] (1.11, 2.98)	2.27 ^{**} (1.23, 4.20)			1.31 (0.81, 2.13)
	Not current		1					1	
	Current	0.87 (0.44, 1.72)		0.81 (0.37, 1.78)	0.87 (0.41, 1.85)	0.75 (0.25, 2.19)	0.94 (0.48, 1.87)		
PI									
Any PI	Not current		1		1			1	
	Current	1.12 (0.75, 1.68)		1.18 (0.75, 1.85)	1.22 (0.78, 1.91)	1.45 (0.79, 2.66)	1.62 [*] (1.08, 2.44)		
Ritonavir/lopinavir	Not current		1		1			1	
	Current	1.21 (0.81, 1.81)		1.22 (0.78, 1.91)	1.33 (0.86, 2.07)	1.55 (0.85, 2.80)	1.93 ^{**} (1.28, 2.90)		
Type of drug therapy									
PI-based HAART	PI-based HAART		1		1			1	
	NRTI monotherapy	0.84 (0.38, 1.87)		0.56 (0.20, 1.54)	0.79 (0.32, 1.95)	0.23 (0.03, 1.79)	0.43 [*] (0.20, 0.96)		
	NNRTI-based HAART	1.20 (0.76, 1.89)		1.12 (0.67, 1.85)	1.16 (0.71, 1.91)	1.13 (0.58, 2.17)	0.85 (0.53, 1.35)		
	Triple class therapy	3.09 (0.92, 10.35)		3.14 [*] (1.01, 9.75)	3.97 [*] (1.25, 12.65)	5.62 ^{**} (1.76, 17.98)	3.39 (0.73, 15.70) [*]		

stage 1 = no suppression; stage 2 = moderate suppression; stage 3 = severe suppression;

N = asymptomatic; A = mMiy symptomatic; B = moderately severe symptoms; C = severe symptoms; ART use defined as use at the time of recruitment; † Includes booster doses;

‡ Includes booster doses;

* 0.05 $p > 0.01$

** 0.01 $p > 0.001$;

*** $p < 0.001$

Table 3
Adjusted risk factors for each of the four body fat redistribution outcomes and for lipodystrophy syndrome (models including current antiretroviral drugs)

		Body fat abnormality		Any lipohypertrophy		Any lipodystrophy		Combined lipohypertrophy and lipodystrophy		Lipodystrophy syndrome	
		n	AOR (95% CI)	n	AOR (95% CI)	n	AOR (95% CI)	n	AOR (95% CI)	n	AOR (95% CI)
Age		n=302		n=337		n=303		n=317		n=313	
per year	302	1.08 (0.99, 1.18)	337	0.93 (0.85, 1.02)	303	1.20*** (1.09, 1.32)	317	1.04 (0.91, 1.19)	313	0.96 (0.88, 1.04)	
Duration of ART		n=302		n=337		n=303		n=317		n=313	
per year	302	1.03 (0.96, 1.12)	337	0.99 (0.91, 1.07)	303	1.03 (0.95, 1.11)	317	1.01 (0.91, 1.12)	313	1.01 (0.94, 1.08)	
Ethnicity		n=302		n=337		n=303		n=317		n=313	
Black	73	1 (0.46, 8.27)	337	1.46*** (1.30, 1.53)	72	1 82	1 79	1 79	1 79	1 79	
White	215	3.32** (1.49, 7.41)	337	1.46*** (1.30, 1.53)	217	4.01** (1.55, 10.38)	220	4.15* (0.99, 17.45)	219	3.53*** (1.93, 6.44)	
Other	14	1.95 (0.46, 8.27)	337	1.46*** (1.30, 1.53)	14	1.35 (0.22, 8.34)	15	0.90 (0.07, 11.70)	15	0.77 (0.23, 2.64)	
BMI (kg/m ²)		n=302		n=337		n=303		n=317		n=313	
per unit	302	1.17** (1.06, 1.28)	337	1.46*** (1.30, 1.53)				1.20** (1.06, 1.36)	313	1.10* (1.01, 1.20)	
Maximum CDC clinical status ##		n=302		n=337		n=303		n=317		n=313	
N+A	121	1.87* (0.99, 3.52)	139	2.08* (1.07, 4.05)	120	1 120	1 120				
B	110	1.87* (0.99, 3.52)	121	2.08* (1.07, 4.05)	111	1.95* (0.99, 3.85)	111				
C	71	2.34** (1.18, 4.65)	77	2.24* (1.07, 4.69)	72	1.58 (0.73, 3.45)	72				
Nadir immune status #		n=302		n=337		n=303		n=317		n=313	
1	111	1.46*** (1.30, 1.53)	111	1 111	1 111	1 111	1 111				
2	122	0.42* (0.21, 0.83)	122	0.42* (0.21, 0.83)	122	0.72 (0.33, 1.58)	122				
3	70	0.72 (0.33, 1.58)	70	0.72 (0.33, 1.58)	70		70				
Stavudine		n=302		n=337		n=303		n=317		n=313	
Not current	266	1 (2.15, 3.56)	268	1 268	1 268	1 268	1 268			1 275	
Current	36	5.40*** (2.15, 3.56)	35	2.69* (1.12, 6.47)	35	2.57* (1.05, 6.31)	35			2.57* (1.05, 6.31)	

	Body fat abnormality		Any lipohypertrophy		Any lipotrophy		Combined lipohypertrophy and lipotrophy		Lipodystrophy syndrome	
	n	AOR (95% CI)	n	AOR (95% CI)	n	AOR (95% CI)	n	AOR (95% CI)	n	AOR (95% CI)
Didanosine	Not current	261	1							
	Current	41	0.42*							
Lamivudine	Not current						98	1		
	Current						218	0.46* (0.21, 0.99)		
Zidovudine	Not current						222	1		
	Current						95	0.33* (0.12, 0.91)		
Ritonavir/ lopinavir	Not current								143	1
	Current								170	3.10*** (1.56, 8.52)
Efavirenz	Not current	226	1						235	1
	Current	76	1.93* (1.03, 3.62)						78	3.17** (1.47, 6.85)
Nevirapine	Not current								281	1
	Current								32	3.17* (1.18, 8.52)

Table columns indicate separate multivariable models; shaded cells indicate that the relevant explanatory variable was not included in that particular final fitted model. For example, the final model for ALA included age, duration of drug use, ethnicity, maximum CDC clinical stage, nadir immune status and stavudine.

stage 1 = no suppression; stage 2 = moderate suppression; stage 3 = severe suppression;

N = asymptomatic, A = mildly symptomatic; B = moderately severe symptoms; C = severe symptoms;

† Includes booster doses;

* 0.05 $p > 0.01$;

** 0.01 $p > 0.001$;

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