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ORIGINAL PAPER

Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study

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Abstract
Objective The aim of this study was to assess the changes in body fat distribution and lipid abnormalities in a population of HIV-infected children and adolescents followed in one single centre who had been exposed, or not, to antiretroviral therapy (ART).
Materials and methods Patients aged between 3 and 19 years were evaluated in a cross-sectional study carried out between October and December 2002. Fat redistribution was evaluated independently by the physician and the patient. Fasting blood lipid profile, glucose, insulin and C peptide were measured. Among the 88 patients evaluated, 74 were taking ART.
Results Fat redistribution was present in 20 patients, metabolic alterations alone were found in 22 children and 46 children had neither physical nor metabolic abnormalities. Patients with fat redistribution were found to have been on ART for a significantly longer period of time, with 42% of the children showing fat redistribution having been treated with anitretroviral agents for more than 5 years. These children had also been exposed to a higher number of antiretroviral agents. In contrast, metabolic alterations in the absence of fat redistribution were not related to the duration of ART nor to the number of drugs received. Treatment with stavudine or protease inhibitors was significantly associated with the presence of physical changes.
Conclusion Regular assessment of fat redistribution and metabolic markers should be carried out in children treated with antiretroviral agents and taken into account when adapting therapy during the long-term follow up of these children.

Keywords Children · Fat redistribution · HAART · HIV · Lipodystrophy

Abbreviations

ART	Antiretroviral therapy
BMI	Body mass index
D4T	Stavudine
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PI	Protease inhibitors

Introduction

Alterations in lipid metabolism in HIV-infected adults were first described in 1989 [22] and have become increasingly more prevalent with the widespread use of highly active antiretroviral therapy (HAART) [30]. The result has been that metabolic changes and body fat redistribution have been regrouped into an entity called "HIV-associated lipodystrophy syndrome" [12]. The three main components of this syndrome are abnormal blood lipid profiles, insulin resistance and body fat redistribution. The observed changes in lipid profiles comprise mostly hypercholesterolemia and hypertriglyceridemia [11]. Although HAART has led to an overall reduction of morbidity and mortality in HIV-infected patients, lipid changes have been associated in a few studies with a significantly increase in cardiovascular

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risk in adults [18, 20] and with vascular changes in children [16]. However, a large retrospective study in adults did not reveal any increased mortality associated with cardiovascular diseases [8]. The insulin resistance is associated with an increased risk of developing diabetes in predisposed patients. Both of these metabolic abnormalities could affect the long-term prognosis of HIV-infected patients.

The pathophysiological mechanism of the HIV-associated lipodystrophy syndrome has not yet been completely elucidated. The role of protease inhibitors (PI) in inducing apoptosis of adipocytes and dysregulation of the transcription factors involved in adipogenesis was the first potential mechanism to be described [14, 27]. Subsequent studies demonstrated the contribution of nucleoside reverse transcriptase inhibitors (NRTIs), probably through mitochondrial toxicity [13, 24, 26, 29, 40]. Genetic factors may also play a role [19]. With respect to body fat redistribution, most authors distinguish between lipohypertrophy (central gain in adiposity in the abdomen, posterior neck and breast) and lipoatrophy (loss of adipose tissue in the face or limbs), the mechanisms of which may differ from each other [14, 21, 27, 35, 39]. NRTI and stavudine have specifically been implicated in the lipoatrophy syndrome [29, 32].

The lipodystrophy syndrome has been described in HIV-infected children treated with HAART, but most of the paediatric studies reported to date have involved small samples or were multicentric [1–4, 7, 9, 21, 23, 25, 36, 38, 41]. Unlike the situation in adults [12], the definition of lipodystrophy syndrome has not been validated in children. There is no consensus regarding the monitoring of lipids in children on HAART or the modification of treatment in the presence of lipid alterations. In part this is due to the fact that the lipodystrophy syndrome is more difficult to define in HIV-infected children because of normal body changes with age and the decreased insulin sensitivity that occurs normally during puberty. Hence, based on the result from paediatric studies, the prevalence of lipodystrophy syndrome in HIV-infected children has been estimated to range from 18 to 33% [1, 4, 21, 23, 36].

The aim of this study was to assess the prevalence of the lipodystrophy syndrome in our cohort of HIV-1 infected children and to identify risk factors associated with the development of this syndrome.

Patients and methods

Study design

We performed a cross-sectional study in which clinical and biological markers of the lipodystrophy syndrome in HIV-infected children cared for by the infectious disease unit of the Department of Paediatrics, Centre Hospitalier Universitaire (CHU) Saint Pierre, Brussels were assessed.

Patients

The study population included all HIV-infected patients aged 3 to 19 years who were followed in Hôpital St. Pierre. Recruitment and assessment took place during a single routine appointment between October and December 2002. Exclusion criteria were: AIDS-defining events or severe illness within 1 month of the evaluation, and treatment with glucosteroids or immunomodulators. The study was approved by the local Hospital Ethics Committee, and informed consent was obtained from children's parents or legal guardians.

Data collection

A routine physical examination, including fat redistribution assessment and anthropometrical measurements, was performed by the child's usual physician (MH, AP or JL) together with another physician (LE) who saw the child for the first time and who was blind for the child's antiretroviral therapy (ART). Assessment of fat redistribution included the detection of fat accumulation in the abdominal and thoracic region, of the presence of a buffalo hump and of fat loss in the face, limbs and buttocks. Based on an adult scoring system [14], the fat redistribution was scored separately for limbs, face, buttocks, abdomen, thorax and neck on a scale of 0 to 3, where 0 represents the absence of fat changes, 1 = minor changes (changes detected only by an observer informed of the nature of possible changes), 2 = moderate changes (changes detected without previous information) and 3 = major changes (changes noticeable by other people, such as family or classmates). Anthropometrical measurements, including standard weight and height measurements, brachial perimeter, abdominal and hip circumference, were made by a single investigator (LE) with the same tools.

A specific questionnaire (based on a similar questionnaire used in adults [14]) was completed by the child's parent or legal guardian and/or by the child himself (if older than 16 years), including questions about physical changes; the same scoring system as that described above for the medical evaluation was used. If physical changes were noticed, an unstandardized question on the impact of these changes on the child's normal activities and well being was asked. A question about physical activity/sport was coded as 'Yes' if the patient reported more than 3 h of physical activity per week. In order to avoid examination bias, the investigators were blind to the results of the patient's questionnaires. Adherence to treatment was not investigated in the questionnaire.

The participating children's medical records were reviewed in order to obtain height and weight before treatment, previous immunological status, the ART admin-

istered, and CDC (Centers for Disease Control and Prevention) clinical stage [15]. Fasting venous blood samples (at least 6 h of fasting) were taken for biological measurements, among which: plasma HIV- RNA PCR, lymphocyte population count, glucose, triglycerides and total cholesterol (PPE; Roche, Indianapolis, Ind.), insulin and C- peptide levels (Centaur; Bayer Diagnostics, Elkhart, Ind.). The COBAS Amplicor HIV1 Monitor Test 1,5-PHM (range: 50–1,000,000 copies/ml) (Roche) was used to detect HIV RNA.

Outcome definitions

Fat redistribution was defined clinically by the physical findings of fat accumulation over the abdomen or dorsocervical spine and/or fat wasting (lipoatrophy) in the face, arms or legs (physician score ≥2). Metabolic abnormalities were classified as hyperlipidemia (for values above the 95 percentile for age and gender for cholesterol or triglycerides) [31] or peripheral insulin resistance [abnormal level of insulin or C- peptide with a normal serum glucose level using the local laboratory references [insulin: 5–20 μg/ml, C- peptide: 0.3–5 μg/ml; glucose 70–100 mg/dl)].

On the basis of the presence of physical or metabolic features of the lipodystrophy syndrome, the children were classified in three groups:

- Group A = children with fat redistribution with or without metabolic abnormalities;
- Group B = children with metabolic abnormalities only;
- Group C = children without fat redistribution or metabolic abnormalities.

Statistical analysis

Statistical analysis was performed using the *Stata 8* statistical package (Stata Corporation, College Station, Tex.). Categorical variables were compared between the three groups using the chi-square test or Fisher's exact test. Continuous variables were compared by using univariate analysis of variance followed by two-by-two comparisons, with Bonferoni corrections. When non-normally distributed, continuous variables were log-transformed. We computed crude odds ratios (ORs) for the associations between type of treatment and the outcome comparing groups A and C, and adjusted ORs by using multiple logistic regression. The association between duration of treatment with differ-

Table 1 General characteristics of HIV-infected children and adolescents based on the presence of fat redistribution (group A), the presence of metabolic abnormalities only (group B) or the absence of clinical or laboratory markers of LPD (group C)

		Group A (*n*=20)	Group B (*n*=22)	Group C (*n*=46)
Age	Mean (years)	12.1	9.7	11.2
	Range	7.5–19.2	3.4–19.0	5.0–18.0
Mean age at initiation of ART (years)[a]		4.0	5.3	7.2
Number of patients ever treated with ART[d]		20 (100)	20 (91)	37 (80)
Mean duration of ART[b,c] (years)		8.0	4.9	4.8
Range		4.5–14.3	0.1–10.5	0.2–11.5
Mean duration of PI[b] therapy (years)		3.0	2.4	2.2
Range		3–5.8	0.1–5.8	0–5.8
Gender[d]	Girls (*n*)	14 (70)	15(68)	23 (50)
	Boys (*n*)	6 (30)	7 (32)	23 (50)
Mean BMI[e]		19.47 (3.10)	18.42 (3.10)	18.35 (2.38)
Weight for age Z- score mean[e]		−0.04 (1.35)	0.42 (0.91)	0.02 (1.40)
Height for age (Z- score mean)[e]		−0.89 (1.42)	−0.11 (0.99)	−0.40 (1.37)
CDC clinical stage[d]	N (*n*)	0	2 (9)	1 (2)
	A (*n*)	3 (15)	6 (27)	13 (28)
	B (*n*)	9 (45)	9 (41)	24 (52)
	C (*n*)	8 (40)	5 (23)	8 (17)
Viral load[d]	≥500 (c/ml) (*n*)	9 (45)	14 (63)	25 (54)
	<500 (c/ml) (*n*)	11 (55)	8 (37)	21 (46)
Mean viral load (in c/ml)[e]		18343 (21611)	14277 (51946)	15258 (37086)
Mean percentage of CD4 at the time of study[b,e]		22.90 (10.60)	31.09 (11.49)	24.37 (8.01)
Mean percentage of CD4 before treatment[c,e]		18.84 (12.19)	19.67 (10.15)	18.44 (13.70)

[a] p=0.01
[b] p<0.005
[c] In patients treated
[d] Percentage is given in parenthesis
[e] Standard deviation (SD) is given in parenthesis

ent drugs and medical score was tested by a non-parametric trend test. Statistical significance was assigned by an alpha level of 0.05. All p values were two-tailed. Anthropometrical measurements (weight and height) adjusted for age Z-score (using standard references from the National Health Service, UK) were used in statistical tests.

Results

Study participants

The study cohort comprised 88 HIV-infected children (52 girls and 36 boys). The mean age of the participants was 11.1 years (range: 3.4–19.0); the majority were black African (n=75) who had acquired HIV by vertical transmission (n=79). Of these 88 children, 74 were currently being on ART. Twenty patients had physical findings of fat redistribution with or without metabolic changes (group A), 22 patients had metabolic but no physical alterations (group B) and 46 had neither physical nor metabolic abnormalities (group C). The general characteristics by groups are shown in Table 1. The viral load (VL) was homogenously distributed between the three groups, but the percentage of CD4+ cells at the time of the study was significantly lower in group A patients than in those of the other two groups. Antiretroviral treatment specified by groups is presented in Table 2.

Fat redistribution

Among the 20 children with fat redistribution, five showed lipoatrophy only, five lipohypertrophy only and ten had mixed features. Eight patients had lipid profiles and insulin in the normal range, and their total lipodystrophy score was significantly lower than the 12 who had also metabolic abnormalities (mean score: 3.63 and 7.83, respectively; p=0.04). Table 3 shows the number of patients in group A with mean scores indicating the moderate or major changes assessed by the patient and by the physician. The physician's score was always higher than that of the patient, but not significantly so. The mean total scores were 4 and 1.5 for the physicians and patients, respectively; however, both scores were significantly correlated (Spearman r=0.70, p=0.003).

Of the 20 children from group A, three complained that fat distribution abnormalities impaired their well-being. The patients with physical changes were significantly less active than to patients without (p=0.003).

Metabolic abnormalities

Metabolic abnormalities were observed in 34 children. Among the 20 patients with fat redistribution (group A), 12 had also metabolic abnormalities. In group B, 16 patients had hyperlipidemia only, two had hyperlipidemia and insulin resistance and four had insulin resistance only. Biological measurements specified by groups are shown in Table 4. The mean triglyceride levels and the proportion of patients with elevated triglycerides were higher in group A than in group B, but not significantly. In contrast, the mean cholesterol level and the proportion of children with elevated cholesterol were slightly higher in group B than

Table 2 Rate of exposure to antiretroviral drugs based on the presence of fat redistribution (group A), the presence of metabolic abnormalities only (group B) or the absence of clinical or laboratory markers of lipodystrophy (group C)

Antiretroviral drugs[a]	Group A [patients ever exposed (n=20)]	Group B [patients ever exposed (n=20)]	Group C [patients ever exposed (n=37)]
NRTI			
ZDV	20	19	28
ddI	20	13	18
d4T	16	10	9
3TC	19	20	33
ABC	10	3	19
ddC	2	0	3
NNRTI			
NVP	10	13	17
EFV	3	0	3
PI			
NFV	9	9	11
RTV	12	6	8
IDV	2	2	3
APV	5	0	2
LPV	7	5	5
SQV	7	2	7

[a]NRTI, Nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; ZDV, zidovudine; ddI, didanosine; d4T, stavudine; 3TC, lamivudine; ABC, abacavir; ddC, zalcitabine; NVP, nevirapine; EFV, efavirenz; NFV, nelfinavir; RTV, ritonavir; IDV, indinavir; APV, amprenavir; LPV, lopinavir; SQV.,saquinavir

Table 3 Patient's and physician's evaluation[a] of fat changes in patients with clinically detected fat redistribution (group A)

	Patient score ≥2 (n=16)	Physician score ≥2 (n=20)
Abdomen and trunk	7	12
Face	3	11
Arms	2	6
Legs	2	6
Buttocks	4	5

[a]The differences between both assessments were not significant (tested by the MacNemar test)

Table 4 Biological measurements in HIV-infected children and adolescents based on the presence of fat redistribution (group A), the presence of metabolic abnormalities only (group B) or the absence of clinical or laboratory markers of low-density lipoprotein (LPD) (group C)

	Group A (*n*=20)	Group B (*n*=22)	Group C (*n*=46)	*p* value[a]
Triglycerides (mg/dl)	109.95	78.16	61.99	0.09
Geometric mean (range)	(53.16–227.4)	(46.03–133.05)	(44.56–86.49)	
Hypertriglyceridemia (*n*)	7	6	0	0.51
Mean cholesterol level (mg/dl)[b]	186.68 (42.85)	197.86 (39.21)	150.76 (26.70)	0.39
Cholesterol elevated (*n*)	9	13	0	0.45
Mean glucose level[b]	82.81 (8.10)	83.27 (8.58)	83.33 (7.71)	NS
Insulin (μg/ml)	10.47	9.01	6.92	0.67
Geometric mean (range)	(4.80–22.87)	(2.95–27.57)	(4.29–11.17)	
Insulin elevated (*n*)	2	6	0	0.29
C- peptide (μg/ml)	1.33	1.49	1.06	0.62
Geometric mean (range)	(0.88–2.02)	(0.82–2.68)	(0.87–1.28)	
C- peptide elevated (*n*)	0	0	0	

[a]When A is compared to B
[b]Standard deviation is given in parenthesis

in group A. Eight children had evidence of insulin resistance, the majority of whom were in group B. All C-peptide and fasting glucose values were within normal ranges.

Anthropometrical features

There were no significant differences in height for age, weight for age or BMI between the three groups (Table 1), or in brachial perimeter, abdominal and hip circumference (data not shown).

Antiretroviral therapy

Of the 88 children enrolled in the study, 14 were not taking ART at the time of the study (11 never had been treated and three had stopped their treatment). All children in group A were treated with ART.

Children in group A had been exposed to a significantly larger number of antiretroviral drugs, including both NRTI and PI, than those in groups B and C (Table 5). The total duration of exposure to ART and to NRTI (all antiretroviral regimen in the cohort included NRTI) was also significantly longer in group A than in the other groups (8.0, 4.9 and 4.8 years in groups A, B and C respectively, $p<0.005$) (Table 1). Fat redistribution was present in 20 of the 48 children treated for 5 years or more, with a significant trend towards a correlation between severity score with duration of ART ($p=0.03$). In contrast, there was no significant difference in the duration of treatment with PI between the three groups. Metabolic abnormalities were seen in two of the 14 untreated girls (one with hypertriglyceridemia and one with insulin resistance). In patients treated with ART, metabolic abnormalities were evenly distributed irregardless of the duration of treatment.

Table 6 shows the association between exposure to different drugs and lipodystrophy (comparing children from group A and treated children from group C), with and without adjustment for gender, age, duration of ART, CD4 count and disease stage. In the univariate analysis, NRTI as a group, ZDV, ddI and d4T were associated with fat redistribution. In the multivariate analysis, d4T was the only NRTI for which a significant association was found. There was also a significant association between treatment with any PI and fat redistribution, but only a borderline association between RTV, LPV or AMP and fat redistribution after adjustment for confounders.

Discussion

This assessment of lipodystrophy includes the largest number of infected children from a single centre assessed to date. As lipid alterations have been described in

Table 5 Mean number of ART drugs used based on the presence of fat redistribution (group A), the presence of metabolic abnormalities only (group B) or the absence of clinical or laboratory markers of LPD (group C)

	A	B	C	*p* value[a]
NRTI	4.6	3.2	3.1	0.01
NNRTI	0.7	0.7	0.5	0.38
PI	2.6	1.7	1.2	0.003
TOTAL	7.8	5.6	4.9	0.0007

[a]Tested by ANOVA

Table 6 Univariate and multivariate analysis of association between exposure to AR drugs and fat redistribution (group A and C, analysis restricted to children treated with ART, *n*=57)

Antiretroviral drug[a]	Fat redistribution Crude OR	*p* value	Fat redistribution Adjusted OR[b]	*p* value
ZDV use				
No				
Yes	∝	0.014[d]		
3TC use				
No	1		1	
Yes	2.30	0.47	2.15	0.76
ddI use				
No				
Yes	∝	<0.0001[d]		
d4T use				
No	1		1	
Yes	12.44	<0.0001	14.12	0.004
ddC use				
No	1		1	
Yes	1.46	0.65	0.53	0.53
ABC use				
No	1		1	
Yes	0.95	0.92	1.20	0.79
PI use				
No	1			
Yes	4.82	0.026	7.79	0.01
RTV use				
No	1			
Yes	5.44	0.005	3.57	0.07
LPV use no	1			
Yes	3.45	0.065	6.22	0.06
NFV use				
No	1			
Yes	1.93	0.25	3.79	0.11
SQV use				
No	1			
Yes	2.31	0.18	1.48	0.64
AMP use				
No	1			
Yes[c]	5.83	0.048	7.05	0.09

[a] See Table 2 for definitions of antiretroviral drugs
[b] Adjusted for gender, age, CDC stage, CD4 counts and duration of treatment
[c] *n*=7
[d] Fisher's exact test

untreated HIV-infected adults [22], we included all of the HIV-infected children followed in our centre, treated or not, in order to have a complete picture of the lipodystrophy syndrome. Our study was cross-sectional and included all patients being followed in the outpatient clinic. Selection bias is therefore unlikely to have occurred. Fat redistribution was present in 20 of the 88 patients, which is consistent with results from other studies, which have reported a prevalence of between 18 and 33% [1, 4, 21, 23, 36]. In addition, 22/88 children had metabolic changes without detectable fat redistribution on clinical examination; which is substantially lower than the 52% figure reported by Taylor et al. in a cohort of children treated with PI-containing HAART [37]. In total, 42 of the 88 HIV-infected children and 40 of the 74 children receiving ART presented with fat redistribution and/or with metabolic changes at the time of this evaluation. As previously described [21, 24, 27], the proportion of girls showing these changes was higher than those that did not (group C).

As in other studies [21, 36, 37], we considered fat redistribution to be present on the basis of physical evaluation made by two physicians. Fat redistribution as assessed by physicians has been reported to agree well with objective measurements such as dual X- ray absorptiometry (DEXA), abdominal computerized tomography and magnetic resonance imaging [10, 14]. We compared the

assessment of physical changes by the patient and by the physician and found a significant correlation between both scores. However, as has also been described in adults [5, 14], we observed that patients or their parents were more likely to underestimate mild or moderate physical changes; this is the first report of this tendency to underestimate in children. These findings indicate that physicians have to actively look for clinical signs of fat redistribution during routine evaluation, rather than to wait for patients' or parents' complaints.

The two pure phenotypes – lipoatrophy and lipohypertrophy– were equally represented in our study population, but the mixed syndrome group was the commonest. The small size of the population did not allow us to study them separately but we think that this mixed syndrome could be the end- point of the progressive development of fat redistribution, as has been suggested by other authors [21, 23].

While anthropometrical measurements may provide reliable information in adults with respect to the assessment of lipodystrophy [5, 28, 39, 42], these parameters are less reliable at reflecting fat redistribution in children because of the normal changes in body composition with age [3, 28, 42]. In our study, there were no differences in anthropometrical measurements between the groups.

Although some patients may have had periods of non-adherence to therapy, clinical, psychological and laboratory follow up suggest that the time since the initiation of therapy is a good estimate of the overall exposure to antiretroviral therapy. Although the retrospective design of this study does not allow us to firmly determine the causality, we observed that a history of being heavily experienced to antiretroviral agents (NRTI and PI), as evaluated by the duration of ART and by the total number of drugs received, was associated with body fat redistribution. Of the 48 children treated for more than 5 years, 20 had body fat redistribution compared to none of the 40 children treated for less than 5 years, or untreated. Among the NRTIs, d4T was significantly associated with prevalence of fat redistribution, thereby confirming observations in other studies [21, 24, 32]. NNRTIs seem to have a minimal relationship with the presence of fat redistribution.

Several studies in children [6, 17, 23, 27] and in adults [14, 30, 35, 40] have suggested that abnormalities of the lipid profile represent a subclinical alteration of adipose tissue that precedes the development of fat redistribution. In this study, we evaluated separately children with metabolic abnormalities without physical changes (group B). In patients treated with ART, we did not observe a correlation between duration of treatment or total number of drugs received and prevalence of metabolic abnormalities, whereas a correlation existed with fat redistribution. We found that children with metabolic abnormalities only had higher cholesterol values or hypercholesterolemia more frequently than patients with fat redistribution. Unfortunately, the baseline fasting cholesterol and triglyceride values were not available for most of the children, and we do not know if the metabolic alterations were present at the time ART was started. We are planning to follow up this group of patients in order to assess whether these metabolic abnormalities constitute an intermediate step in the development of the lipodystrophy syndrome in children or whether they represent a distinct entity.

Unlike other studies [37], only 12 of the 20 patients with fat redistribution (group A) had metabolic abnormalities. The observation that the eight patients without metabolic changes had a significantly lower score of lipodystrophy suggests that the initial stages of fat redistribution could occur without alterations in the blood lipid profile. As described in adults with lipodystrophy, high triglyceride values rather than high cholesterol values were associated with fat redistribution [28, 30, 36]. Insulin resistance was found in eight of the 88 children in this study, and C-peptide values were in normal range in all the patients. This contradicts the findings of another study where C-peptide was predictive for the development of lipodystrophy.[14]

In agreement with other studies [3, 14, 27], we found a significant association between CD4% and clinical stage at the time of evaluation and the presence of fat redistribution.

In adults, premature arteriosclerosis and coronary disease are major concerns in HIV-infected individuals treated with HAART [8, 18, 20]. The risk for developing cardiovascular diseases and diabetes has been evaluated for obese children [33, 34], but it is unknown in HIV-infected children with lipodystrophy. Patients infected with HIV have a much better prognosis since the advent of HAART. However, adverse effects such as the lipodystrophy syndrome may potentially affect the long-term prognosis, particularly in children where the treatment is initiated early and will be life-long. Moreover, the development of physical changes is likely to affect the adherence to ART. Longer term follow up is necessary to evaluate the consequences of metabolic and fat redistribution on the morbidity of infected children treated with HAART.

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