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High Prevalence of Dyslipidemia and Insulin Resistance in HIV-Infected Pre-Pubertal African Children on Antiretroviral Therapy

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Abstract

BACKGROUND—Data describing the true extent of antiretroviral therapy (ART)-induced dyslipidemia and insulin resistance in perinatally-infected children on ART in Africa is sparse.

METHODS—Fasting total cholesterol, LDL, HDL, triglycerides, insulin and glucose were performed on the first 100, of 190 pediatric ART clinic attendees. Diet assessment was performed by a trained dietician. Lipoatrophy was formally graded by consensus between two expert HIV pediatricians. Durations of previous ART exposures, clinical stage, pre-ART viral load, nadir and current CD4 were recorded. Dual energy X-ray Absorptiometry (DEXA) was performed on a subset of 42 patients selected semi-randomly.

RESULTS—Prevalences of insulin resistance, abnormal total cholesterol, LDL, HDL and triglyceride were 10%, 13%, 12%, 13 % and 9% respectively. Overall, 40% had at least one lipid abnormality or insulin resistance. Adjusted mean LDL cholesterol increased by 0.24mmol/L for each additional year of cumulative lopinavir/r exposure ($p=0.03$) after correcting for age, gender, body mass index, previous stavudine exposure, age at ART initiation, dietary fat and refined carbohydrate, while adjusted mean LDL cholesterol was 0.9mmol/L higher in children exposed to efavirenz within the previous six months ($p=0.02$). Adjusting for age, gender and ethnicity, DEXA revealed that greater trunk fat and lower peripheral subcutaneous fat were associated with elevated triglycerides but not with total cholesterol, LDL, HDL or HOMA. Similarly, the presence of visually obvious lipoatrophy was associated with elevated triglycerides but not with total cholesterol, LDL, HDL, HOMA or lactate.

CONCLUSIONS—Prevalences of insulin resistance and dyslipidemia were high. Cumulative lopinavir is an independent risk factor for dyslipidemia, with efavirenz exposure having only transitory effect.

Keywords

HIV; antiretroviral therapy; Dyslipidemia; Insulin resistance; African children

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The UNAIDS global report 2011 estimated that three million children in Sub-Saharan Africa are HIV-infected ¹. In South Africa alone, almost half a million children under 15 years of age are HIV-infected, and, despite reductions in vertical transmission, new infections continue to occur ². South Africa has the largest antiretroviral treatment (ART) program in the world, with an estimated 157,000 infants and children currently on ART (personal communication, Corry van der Walt and Jaco Stokes, South African National Department of Health, 15 October 2013), with many more being added as the antiretroviral program rolls out. These children face a lifetime of ART exposure, extending into several decades. In addition, the rapid changes related to growth may make them more sensitive than adults to drug-induced changes in metabolism. Dyslipidemia is a common late adverse effect of ART in HIV-infected children in the developed world ³. Dyslipidemia and insulin resistance significantly increase the long-term risk of atherosclerotic vascular disease and may have major public health implications for HIV-infected children in Africa, who must already deal simultaneously with the complexities of social stigma, chronic illness and medication adherence. The public health importance of atherosclerotic vascular disease in this extremely vulnerable population will only increase as ART coverage expands. Despite this importance, very little is known about the prevalence and risk factors for dyslipidemia and insulin resistance in pre-pubertal African children on ART. Previous studies of ART-related dyslipidemia in children have focused mostly on children living outside of Africa, who make up less than 8% of the global burden of pediatric HIV infections ¹.

We investigated the prevalence and predictors of blood lipid abnormalities and insulin resistance in pre-pubertal South African children on ART. Specifically, we examined the correlation of lipid and insulin abnormalities with subcutaneous fat maldistribution (measured by Dual-energy X-ray Absorptiometry [DEXA] and formal grading of visually obvious lipoatrophy), and with ART exposures.

MATERIALS AND METHODS

This was a sub-analysis of cross-sectional data from a longitudinal cohort study of lipoatrophy in children ⁴. The first 100 of 190 eligible (on ART, pre-pubertal) clinic attendees were recruited from a centralized pediatric ART service in Cape Town, South Africa. Participant selection and cohort characterization have been previously described, including a comparison with the clinic patients that were not available for recruitment, which showed no evidence of selection bias ⁴. Total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, glucose and insulin were measured after an overnight fast. Homeostatic Model Assessment (HOMA) insulin resistance index was calculated as fasting glucose (mmol/L) $\times$ insulin (mU/L) / 22.5 ⁵. The following thresholds were considered abnormal: total cholesterol >200mg/dL (>5.18mmol/L) ⁶; LDL cholesterol >130mg/dL (>3.37mmol/L) ⁶⁻⁷; HDL cholesterol <35mg/dL (<0.91mmol/L) ⁷; triglycerides >150mg/dL (>1.7mmol/L) ⁶⁻⁷; fasting glucose >100mg/dL (>5.6mmol/L) ⁸. HOMA values were evaluated against norms presented by de Almeida et al ⁹, which are the most appropriate norms available in current literature for children in a developing country, since norms for African children are not available. Lipoatrophy was formally graded by consensus between two HIV pediatricians who were experienced in identifying lipoatrophy

using a standardized visual grading scale similar to that described by Carr and others¹⁰⁻¹²: Grade 0 – No fat changes; Grade 1 – Possible minor changes, noticeable only on close inspection; Grade 2 – Moderate changes, unequivocally noticeable only to an experienced clinician or a close relative who knows the child well; Grade 3 – Major changes, readily noticeable to an uninformed observer. Visually obvious lipoatrophy was defined as a score of 2 or 3. Face, arms, legs and buttocks were assessed for loss of subcutaneous fat resulting in a lean, muscular appearance of limbs and face, abnormally prominent limb veins, and loss of gluteal fat pad with reduction in buttock size and loss of gluteal contour. Where the assessment of the two investigators did not concur, the change was graded as the lower score to ensure that only those with unequivocal changes were labeled as having lipoatrophy. Durations of previous ART exposures, maximum previous WHO clinical stage, pre-ART nadir and most recent CD4 and HIV RNA viral load were recorded. Formal diet assessment was performed by an experienced dietician using a local standardized 48-hour recall questionnaire (Appendix 1). Using data from this interview, the dietician categorized each recruit as receiving inadequate, appropriate or excessive daily refined carbohydrate intake, daily dietary fat intake and total daily energy intake, based on recommended daily allowances for each¹³.

DEXA was performed on a subset of 42 patients using a Hologic Discovery scanner (Bedford, MA, USA) as per manufacturer's instructions. The machine was calibrated daily and weekly using appropriate manufacturer-supplied phantoms. DEXA was requested for all recruits but was not obtained in many participants because of DEXA scanner breakdowns and prioritized use for patients with clinical indications. There was no difference in gender, CD4 or cumulative time on standard dose stavudine between the 42 subjects who underwent DEXA scanning and the 58 who did not ($p>0.50$ for all). The children who underwent DEXA were marginally younger than those who did not (7.1 versus 8.0 years, $p=0.03$).

Statistical analysis

A Student's t-test was used to compare continuous variables and Pearson's chi-square test for categorical comparisons. Multiple linear regression was used to correlate DEXA measures of body fat with total cholesterol, LDL, HDL, triglycerides and HOMA, adjusting for age, gender and ethnicity. Multiple regression models were constructed to identify which ART drug exposure variables remained predictive of lipid or HOMA abnormalities after adjustment for age, gender, body mass index, dietary intake of fats and refined carbohydrate, age at ART initiation and stavudine exposure. Since stavudine exposure was common in our setting, all models included adjustment for both recent and cumulative stavudine exposure. A separate model was constructed for each biochemical outcome variable (total cholesterol, HDL, LDL, triglycerides, HOMA). For each ART drug, recent drug exposure (defined as current exposure or exposure within the previous six months) and cumulative lifetime exposure were included as separate variables. All statistical analyses were performed using R (version 2.10.0, Bell Laboratories, New Jersey).

RESULTS

Demographic data on the study participants are presented in table 1. Overall, 40% had at least one fasted lipid, insulin or glucose abnormality. Phlebotomy failed in four children. Of the remaining 96 children, 65 were on a lopinavir/r (LPV/r)-based ART regimen and 31 on an efavirenz (EFV)-based regimen. Comparison of these two groups is shown in table 1. Adjusted mean triglycerides were elevated in the LPV group with a trend towards higher total cholesterol and LDL cholesterol (table 2). Local guidelines recommend LPV/r for children initiating ART below 3 years of age and EFV for children initiating ART over 3 years of age. Mixed ethnicity children tended to be older at diagnosis and therefore more commonly received EFV; the reasons for later diagnosis are unclear. Children with advanced WHO clinical disease stage had higher viral loads and tended to be diagnosed earlier and therefore were more likely to receive LPV/r. In line with local guidelines, over 90% had received stavudine. Around half had recently been switched to abacavir due to a change in national recommendations. All had received lamivudine as their third ART agent.

After adjusting for age, gender and ethnicity, analysis of DEXA measures revealed that greater trunk fat and lower peripheral subcutaneous fat were associated with elevated triglycerides but not with total cholesterol, LDL, HDL or HOMA (tables 3a). Similarly, after adjusting for age, gender and ethnicity, the presence of visually obvious lipoatrophy was associated with elevated triglycerides but not with total cholesterol, LDL, HDL, HOMA or lactate (table 3b).

On dietary assessment, 4/96 children were determined by the dietician to have excessive daily dietary fat intake and 11/96 had excessive daily refined carbohydrate intake. Analysis of dietary variables showed no significant correlation with lipid or HOMA values ($p>0.3$ for all) (table 4).

Analysis of disease severity (pre-ART viral load, nadir CD4 count before starting ART, CD4 nearest to study visit, maximum previous WHO clinical stage) demonstrated no significant correlation to any of the lipid or HOMA measures ($p>0.15$ for all) (table 5).

The multivariate regression model for LDL demonstrated a significant correlation with recent EFV exposure ($p=0.02$) and cumulative LPV/r exposure ($p=0.03$) after adjustment for age, gender, body mass index, dietary intake of fats and refined carbohydrate, age at ART initiation and stavudine exposure (table 6). The model for HDL demonstrated a significant correlation with cumulative LPV/r exposure ($p=0.03$) (table 7). The model for total cholesterol demonstrated a near-significant correlation with cumulative LPV/r exposure ($p=0.08$) and recent exposure to EFV ($p=0.09$) (table 8). Similar models for triglycerides and HOMA demonstrated no significant drug exposure correlations (data not shown). Since recent exposure to LPV/r was strongly inversely correlated with recent exposure to EFV, these two input variables could not mathematically coexist in the models. Therefore, all multivariate models were repeated twice, retaining either recent exposure to LPV/r or recent exposure to EFV. These revealed (surprisingly) that recent exposure to EFV (defined as current exposure or exposure within the previous six months) was significantly associated

with lipids whereas recent exposure to LPV/r was not, and thus only the models incorporating recent exposure to EFV are shown.

DISCUSSION

Our study, which focuses exclusively on pre-pubertal African children on ART, presents three important findings: (1) The prevalence of dyslipidemia and insulin resistance is high; (2) The effect of ART drugs on blood lipids and insulin sensitivity appears to accumulate over time; i.e., cumulative lifetime exposure exerts an effect that is independent of current or recent drug exposure; and (3) ART-induced lipoatrophy, while associated with elevated triglycerides, was not associated with cholesterol abnormalities or insulin resistance.

Few previous studies of ART-induced lipoatrophy and dyslipidemia have included African children as >50% of their cohorts¹⁴⁻²⁰. Of these, three included mostly pubertal children and did not report their pre-pubertal data separately¹⁵⁻¹⁷. This is an important distinction since puberty has profound effects on fat metabolism and ART may have distinctly different metabolic effects on pre-pubertal compared to pubertal individuals²¹. Musiime *et al* reported 109 prepubertal African children on ART with prevalence of total cholesterol, LDL, HDL and triglycerides of 10%, 13%, 17% and 6% respectively¹⁹, which are remarkably similar to our findings. However, they did not attempt to correlate these with their skin-fold thickness measurements or specific ART drug exposures. Piloya *et al* reported 364 African children (57% pre-pubertal) with prevalence of abnormal fasting total cholesterol, triglycerides and any lipid abnormality of 6%, 28% and 34% respectively¹⁸. However, they did not report their pre-pubertal data separately, making comparison with our data difficult. In line with our findings, they found no association between visually-assessed lipoatrophy and lipid abnormalities. Bwakura-Dangarembizi *et al* reported 256 African children on ART with prevalence of abnormal fasting total cholesterol and LDL of 25% and 15% respectively (although it was not stated what proportion of those 256 were pre-pubertal)²⁰. Interestingly, they found, as we did, that current EFV exposure was associated with higher LDL cholesterol. In line with our findings, they found no association between body fat maldistribution (measured by skin-fold thickness) and blood lipids. Arpadi *et al* reported 156 pre-pubertal South African children on ART with prevalence of abnormal fasting total cholesterol, LDL, HDL, triglycerides, glucose, and HOMA of 14%, 12%, 6%, 8%, 1%, and 2% respectively¹⁴. These figures are almost identical to our figures, with the exception of HDL (13% in our study) and HOMA (10% in our study). Their study found a distribution of abnormalities between their LPV/r and nevirapine groups that was very similar to our comparison of LPV/r-exposed versus EFV-exposed. The notable exception was the lower prevalence of abnormal HDL (3%) and triglycerides (3%) in their nevirapine group compared to our EFV group (15% and 13%, respectively). Arpadi *et al* also attempted to correlate visible body fat maldistribution (lipoatrophy or lipohypertrophy) with blood lipids and HOMA and, as we did, found no relationship between body fat maldistribution and fasting total cholesterol, HDL, LDL, glucose or HOMA. They did find a difference in triglycerides (both mean value and proportion with abnormally raised triglycerides) between children with and without body fat maldistribution, however, their analysis did not differentiate between lipoatrophy and lipohypertrophy. Although their study did objectively measure abnormal body fat distribution using skin-fold thickness, they did not attempt to

correlate this with blood lipids or HOMA. Our study goes one step further than these studies by comparing both visually obvious lipoatrophy and objective DEXA measures of body fat amount and distribution (particularly limb fat loss, representing lipoatrophy) to blood lipids and HOMA. This analysis should be viewed in light of our previously-published DEXA data on the same cohort of children with and without visually obvious lipoatrophy, whose total extremity fat, limb fat mass/limb lean mass ratios, limb fat mass/limb lean mass ratios and limb fat mass to BMI ratios demonstrated clear and significant differences ⁴.

Risk factors for ART-induced elevations in lipids or HOMA have been investigated previously ³, with stavudine and protease inhibitors being most commonly implicated. However, previous studies have not attempted to separate the effect of current or recent exposure versus cumulative lifetime exposure and our finding that these exert independent effects is novel. The mechanism of association between recent EFV exposure and elevated LDL is unclear, although this is consistent with data from the AIDS Clinical Trials Group A5142 trial, in which EFV was independently associated with elevations in total cholesterol ²².

The correlations between cholesterol abnormalities and exposure to EFV (recent) and LPV/r (cumulative) presents a practical dilemma to clinicians on the ground since these two drugs are central to the first- and second-line ART regimens recommended by both the World Health Organization ²³ and the South African National Department of Health ²⁴. This dilemma clearly reveals the pressing need to make alternative drug options available, particularly formulations that are palatable and practical for children in Africa.

The prevalences of dyslipidemia and insulin resistance in our cohort were high (40% overall). This may have major public health implications related to long-term risk of atherosclerotic vascular disease, for which HIV-infected individuals are already at increased risk due to persistent immune activation ²⁵. The true proportion with at-risk values may be even higher: Cook et al ²⁶ have suggested centile-related thresholds for lipids that appear to correlate with increased cardiovascular risk in adults (viz. the 88th, 89th and 90th centiles for total cholesterol, LDL and triglycerides in each age and gender group respectively). If these thresholds were applied to our data, the proportion with at-risk values would almost double.

The apparent lack of association between lipoatrophy and either cholesterol abnormalities or insulin resistance is interesting. In existing literature, lipoatrophy and lipohypertrophy have not usually been analyzed separately. Accumulation of intra-abdominal visceral fat (the most metabolically-active form of body fat) as occurs in lipohypertrophy has been clearly linked to dyslipidemias, especially cholesterol abnormalities ¹⁰. Previous data have shown that lipohypertrophy and lipoatrophy occur independently of one another; ^{21, 27-28} therefore, in our opinion, lipoatrophy and lipohypertrophy require separate analysis.

LIMITATIONS

Limitations of this study include the single-center cross-sectional design and limited sample size, which may not have allowed the causes of the observed differences to be conclusively identified.. Analysis of longitudinal follow-up data in this cohort is underway. Another limitation is the lack of local population reference ranges for HOMA and lipids, which may

have led to incorrect interpretation of the lipid and HOMA profiles in our cohort. Although there were proportionally more children of mixed ethnicity in the EFV than the LPV/r group, our multivariate models did not adjust for ethnicity. However, this is unlikely to have skewed our results since the proportions with a biochemical abnormality in the two ethnic groups were not significantly different ($p=0.94$).

CONCLUSIONS

In our cohort of pre-pubertal African children on ART, the prevalences of dyslipidemia and insulin resistance are high. This may have major public health implications related to long-term risk of atherosclerotic vascular disease, for which HIV-infected individuals are already at increased risk due to persistent immune activation. The effect of ART drugs on blood lipids and insulin sensitivity appears to accumulate over time, i.e. cumulative lifetime exposure exerts an effect that is independent of current or recent drug exposure. This presents clinicians on the ground with a dilemma as current alternative pediatric drug options are typically not formulated to withstand sub-Saharan African conditions and are often unaffordably expensive. Alternative ART drug options are urgently needed for children in Africa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of Study Participants: Fasting biochemical parameters in pre-pubertal South African children on lopinavir/r (LPV/r) versus efavirenz (EFV)

	Children on LPV/r n=65	Children on EFV n=31	Univariate <i>P</i> (two-tailed)
Age (months), median (IQR)	64 (50 – 85)	98 (77 – 113)	<0.0001
Gender: Male / Female	52% / 48%	48% / 52%	0.72
Ethnicity: Black / Mixed ethnicity	66% / 34%	35% / 65%	0.005
Body mass index, median (IQR)	15.1 (14.4 – 16.0)	15.5 (14.6 – 17.0)	0.02
Nadir CD4 (cells/μl), median (IQR)	767 (431 – 1223)	664 (350 – 1089)	0.07
Nadir CD4%, median (IQR)	17% (12 – 25%)	17% (13% – 23%)	0.94
CD4 at assessment (cells/μl) , median (IQR)	1228 (852 – 1602)	962 (736 – 1233)	0.007
CD4% at assessment, median (IQR)	33% (26 – 39%)	34% (29 – 39%)	0.75
Previous maximum WHO clinical stage: 1 / 2 / 3 / 4	14% / 11% / 44% / 31%	32% / 10% / 45% / 13%	0.10
Log ₁₀ HIV RNA viral load before ART, median (IQR)	6.0 (5.7 – 6.5)	5.0 (4.6 – 5.6)	0.0004
Age at ART initiation (months), median (IQR)	13 (7 – 23)	45 (37 – 65)	<0.0001
Undetectable HIV viral load at assessment	58 (89%)	28 (90%)	0.87
Daily over-consumption of dietary fat	2 (3%)	2 (6%)	0.44
Daily over-consumption of dietary refined carbohydrate	5 (8%)	6 (19%)	0.09
DEXA total body fat (%), median (IQR)	25% (13 – 38%)	27% (11 – 43%)	0.47
DEXA trunk fat (%), median (IQR)	22% (11 – 33%)	24% (9 – 38%)	0.29
DEXA trunk to total body fat mass ratio, median (IQR)	0.4 (0.2 – 0.5)	0.4 (0.3 – 0.5)	0.12
DEXA trunk to limb fat mass ratio, median (IQR)	0.8 (0.5 – 1.2)	0.8 (0.5 – 1.2)	0.61
Visually obvious lipoatrophy	19 (29%)	14 (45%)	0.12
Cumulative antiretroviral exposure (months), median (IQR)	53 (39 – 72)	33 (17 – 61)	0.007
Cumulative stavudine exposure (months), median (IQR)	41 (27 – 53)	27 (15 – 43)	0.05
Recently [§] exposed to stavudine	41 (63%)	18 (58%)	0.63
Total cholesterol (mmol/L), median (IQR)	4.3 (3.4 – 4.8)	3.8 (3.1 – 4.4)	0.10
Abnormal total cholesterol (>5.2mmol/L)	11 (17%)	1 (3%)	0.06
LDL cholesterol (mmol/L), median (IQR)	2.5 (1.9 – 3.0)	2.3 (1.6 – 2.7)	0.14
Abnormal LDL (>3.4mmol/L)	10 (15%)	1 (3%)	0.08
HDL cholesterol (mmol/L), median (IQR)	1.2 (1 – 1.4)	1.1 (1 – 1.4)	0.36
Abnormal HDL (<0.9mmol/L)	7 (11%)	5 (15%)	0.92
Triglycerides (mmol/L), median (IQR)	0.9 (0.8 – 1.2)	0.7 (0.5 – 0.9)	0.13
Abnormal triglycerides (>1.7mmol/L)	8 (12%)	4 (13%)	0.93
Fasting glucose (mmol/L), median (IQR)	4.3 (4 – 4.6)	4.5 (4.2 – 4.7)	0.21
Abnormal fasting glucose (>5.5mmol/L)	1 (1.5%)	1 (3%)	0.59
HOMA index, median (IQR)	0.8 (0.5 – 1.2)	0.8 (0.6 – 1.2)	0.77
Abnormal HOMA [*]	5 (8%)	5 (16%)	0.21
Any lipid or glucose abnormally	26 (40%)	12 (39%)	0.90

IQR = Interquartile range; SD = Standard deviation; LDL = low-density lipoprotein; HDL = high-density lipoprotein; HOMA = homeostatic model assessment insulin resistance index.

[§] Defined as current exposure or exposure within the previous six months.

^{*} Age- and gender-related norms taken from de Almeida et al 2008 ⁹

Table 2

Mean (95% confidence interval) elevations in fasting biochemical parameters in lopinavir group compared to efavirenz group after adjustment for age, gender and ethnicity.

	Adjusted mean elevation	Adjusted <i>P</i>
Total Cholesterol (mmol/L)	+0.45 (−0.04 to +0.95)	0.07
LDL (mmol/L)	+0.39 (−0.03 to +0.80)	0.07
HDL (mmol/L)	+0.11 (−0.03 to +0.26)	0.12
Triglycerides (mmol/L)	+0.24 (+0.01 to +0.46)	0.04
Glucose (mmol/L)	−0.13 (−0.38 to +0.12)	0.32
HOMA (mmol.MU)	+0.14 (−0.36 to +0.65)	0.57

Table 3a

Multivariate p-values for linear correlation between fasting biochemical parameters and DEXA measures of trunk fat and peripheral subcutaneous limb fat, adjusted for age, gender and ethnicity. Correlation coefficients (in brackets) are given only for significant or near-significant p-values.

	Total cholesterol	LDL	HDL	Triglycerides	HOMA
Total body fat %	0.39 ---	0.67 ---	0.94 ---	0.05 (r = -0.02) ---	0.45 ---
Trunk fat %	0.25 ---	0.35 ---	0.88 ---	0.33 ---	0.82 ---
Trunk to total fat mass ratio	0.59 ---	0.34 ---	0.82 ---	0.39 ---	0.37 ---
Trunk to limb fat mass ratio	0.33 ---	0.15 ---	0.10 (r = -0.3) ---	0.02 (r = 0.6) ---	0.52 ---
Limb fat mass to BMI ratio	0.83 ---	0.87 ---	0.44 ---	0.02 (r = -2.0) ---	0.72 ---
Limb fat mass to total weight ratio	0.38 ---	0.68 ---	0.69 ---	0.02 (r = -2.8) ---	0.73 ---
Limb fat mass to limb lean mass ratio	0.18 ---	0.60 ---	0.52 ---	0.03 (r = -0.4) ---	0.39 ---
Limb fat mass to total lean mass ratio	0.22 ---	0.60 ---	0.86 ---	0.02 (r = -1.5) ---	0.68 ---
Total extremity fat (kg)	0.53 ---	0.78 ---	0.54 ---	0.01 (r = -0.1) ---	0.40 ---

DEXA = Dual energy X-ray absorptiometry

Table 3b

Fasting biochemical parameters in patients with and without visually obvious lipoatrophy. P-values are adjusted for age, gender and ethnicity. Regression coefficients (in brackets) are given only for significant or near-significant p-values.

	Lipoatrophy n=33			No Lipoatrophy n=61			Multivariate <i>P</i> (two-tailed)
	μ	SD	Proportion abnormal	μ	SD	Proportion abnormal	
HOMA (mmol.MU) *	0.82	0.55		0.88	1.16		0.96
			14%			12%	0.69
Total Cholesterol (mmo/L)	3.69	1.06		3.89	1.05		0.68
			12%			13%	0.85
HDL (mmol/L)	1.03	0.27		1.12	0.30		0.09 ($\beta = -0.1$)
			16%			19%	0.87
LDL (mmol/L)	2.09	0.92		2.29	0.85		0.36
			16%			10%	0.23
Triglycerides (mmol/L)	0.99	0.46		0.86	0.46		0.02 ($\beta = 0.25$)
			12%			5%	0.13
Lactate (mmol/L)	1.38	0.66		1.51	0.84		0.72

* Wilcoxon rank sum test for non-parametric variables was used to calculate p-value for continuous HOMA data.

Table 4

Correlation between fasting biochemical parameters and daily dietary fat and refined carbohydrate consumption

	Daily Fat Intake		Daily Refined Carbohydrate Intake	
	Correlation Coefficient	Univariate <i>P</i>	Correlation Coefficient	Univariate <i>P</i>
HOMA	−0.11	0.33	−0.09	0.39
Total cholesterol	−0.05	0.63	−0.02	0.84
HDL	0.11	0.31	0.08	0.43
LDL	−0.09	0.38	−0.04	0.70
Triglycerides	0.01	0.92	0.05	0.61

Table 5

No correlation between fasting biochemical parameters and markers of HIV disease severity

	Nadir CD4 before ART initiation		CD4 nearest to study visit		HIV RNA viral load before ART initiation		Previous maximum WHO clinical stage	
	Correlation Coefficient	P-value	Correlation Coefficient	P-value	Correlation Coefficient	P-value	Correlation Coefficient	P-value
HOMA	-0.09	0.63	0.07	0.50	-0.07	0.67	-0.04	0.75
Total cholesterol	0.08	0.58	0.11	0.29	0.02	0.88	-0.08	0.45
HDL	0.12	0.44	0.14	0.16	0.16	0.30	-0.03	0.72
LDL	0.20	0.19	0.06	0.50	0.09	0.53	-0.06	0.49
Triglycerides	-0.07	0.63	-0.01	0.96	-0.11	0.50	0.02	0.86

Table 6

Multivariate Regression model of the predictors of fasting LDL cholesterol.

N for model = 89 R² for model = 0.21	Regression coefficient	95% confidence interval		p-value
Age at assessment (years)	-0.18	-0.43	0.07	0.15
Gender (male versus female)	-0.10	-0.46	0.26	0.58
Body mass index	-0.07	-0.19	0.04	0.22
Excessive daily dietary refined carbohydrate intake	0.03	-0.52	0.57	0.92
Excessive daily dietary fat intake	0.72	-0.05	1.49	0.07
Recent efavirenz exposure [§]	0.90	0.16	1.64	0.02
Recent stavudine exposure [§]	-0.40	-0.92	0.13	0.14
Cumulative efavirenz exposure (months)	0.00	-0.02	0.02	0.86
Cumulative lopinivir/r exposure (months)	0.02	0.00	0.04	0.03
Cumulative stavudine exposure (months)	0.01	0.00	0.02	0.10
Age at ART initiation (months)	0.01	-0.01	0.03	0.25

[§] Defined as current exposure or exposure within the previous six months

Table 7

Multivariate Regression model of the predictors of fasting HDL cholesterol

N for model = 89 R² for model = 0.22	Regression coefficient	95% confidence interval		p-value
Age at assessment (years)	-0.02	-0.10	0.06	0.62
Gender (male versus female)	0.04	-0.08	0.17	0.48
Body mass index	0.02	-0.02	0.06	0.32
Excessive daily dietary refined carbohydrate intake	-0.12	-0.30	0.06	0.19
Excessive daily dietary fat intake	-0.08	-0.34	0.17	0.52
Recent efavirenz exposure [§]	0.05	-0.19	0.30	0.67
Recent stavudine exposure [§]	0.03	-0.15	0.21	0.74
Cumulative efavirenz exposure (months)	0.00	0.00	0.01	0.18
Cumulative lopinivir/r exposure (months)	0.01	0.00	0.01	0.03
Cumulative stavudine exposure (months)	0.00	0.00	0.01	0.53
Age at ART initiation (months)	0.00	0.00	0.01	0.33

[§] Defined as current exposure or exposure within the previous six months

Table 8

Multivariate Regression model of the predictors of fasting total cholesterol

N for model = 92 R² for model = 0.18	Regression coefficient	95% confidence interval		p-value
Age at assessment (years)	−0.23	−0.53	0.07	0.13
Gender (male versus female)	−0.02	−0.46	0.42	0.94
Body mass index	−0.05	−0.19	0.09	0.50
Non- excessive daily dietary refined carbohydrate intake	−0.19	−0.86	0.47	0.57
Non- excessive daily dietary fat intake	0.59	−0.35	1.53	0.22
Recent efavirenz exposure [§]	0.77	−0.13	1.68	0.09
Recent stavudine exposure [§]	−0.46	−1.10	0.18	0.16
Cumulative efavirenz exposure (months)	0.00	−0.03	0.03	0.99
Cumulative lopinivir/r exposure (months)	0.02	0.00	0.05	0.08
Cumulative stavudine exposure (months)	0.02	0.00	0.03	0.02
Age at ART initiation (months)	0.02	−0.01	0.04	0.23

[§] Defined as current exposure or exposure within the previous six months