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Long-Term Evaluation of Glucose Homeostasis in a Cohort of HAART-Treated HIV-Infected Children

A Longitudinal, Observational Cohort Study

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Abstract

Background and objectives: Few and mainly cross-sectional studies of glucose homeostasis are available in HIV-infected children treated with highly active antiretroviral therapy (HAART). The aim of the present study was to describe a 4-year course of glucose homeostasis in a cohort of HAART-treated children and adolescents, using glucose and insulin levels during an oral glucose tolerance test (OGTT) as outcome measures. In addition, we investigated possible risk factors, both related and unrelated to antiretroviral therapy, associated with insulin resistance.

Methods: We assessed glucose metabolism yearly for 4 consecutive years in 37 HIV-infected children receiving a protease inhibitor (PI)-based HAART regimen containing lamivudine/stavudine plus indinavir or ritonavir or nelfinavir or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART regimen containing lamivudine/tenofovir/efavirenz. Generalized estimating equations were used to evaluate the relationship between the $\log_e$-transformed area under the serum concentration-time curve (AUC) of insulin during OGTT and antiretroviral therapy, controlling for time, sex, baseline age, puberty, body mass index and CD4+ T cells percentage.

Results: Ritonavir-unboosted PI-based HAART regimens were administered to most children at baseline; however, their use decreased during follow-up in favour of an NNRTI-based regimen. The nelfinavir/lamivudine/stavudine (regression coefficient = −0.69, $p < 0.05$) and efavirenz/lamivudine/tenofovir (regression coefficient = −0.93, $p < 0.05$) regimens, but not the ritonavir/lamivudine/stavudine

regimen, were negatively associated with log_e-transformed insulin AUC compared with indinavir/lamivudine/stavudine. Puberty was positively associated with log_e-transformed insulin AUC.

Conclusions: This 4-year prospective study of HAART-treated HIV-infected children shows that: (i) the nelfinavir/lamivudine/stavudine and the efavirenz/lamivudine/tenofovir regimens but not the ritonavir/lamivudine/stavudine regimen were associated with higher insulin sensivity, i.e. lower insulin AUC, compared with indinavir/lamivudine/stavudine; (ii) the treatment switched substantially in favour of NNRTI from the third year on and this change was associated with an improvement in insulin sensitivity compared with the previous HAART-based regimens; and (iii) puberty is a primary determinant of insulin sensitivity.

Background

Several studies suggest that antiretroviral regimens containing protease inhibitors (PIs) are associated with insulin resistance and impaired glucose tolerance in HIV-infected adults.[1-3] Longitudinal studies have shown that insulin resistance might precede significant changes in body composition in adult patients initiating regimens that include indinavir[4] or a variety of other PIs.[5]

Further evidence of the effect of these drugs on insulin sensitivity arises from 'switch studies' showing improvement in glucose metabolism after replacement of PIs with abacavir,[6] nevirapine[7] or efavirenz[8] from studies showing a reduction in insulin sensitivity after short-term administration of indinavir in healthy volunteers;[9] and from *in vitro* studies showing a direct action of some PIs on glucose movement through the glucose transporter (GLUT)-4.[10] While the bulk of evidence is consistent with a direct drug effect of PIs in reducing insulin sensitivity, recent studies suggest that nucleoside reverse transcriptase inhibitors (NRTIs) may play a role in these metabolic abnormalities.[11,12]

The mechanism by which NRTIs may alter glucose homeostasis is unclear. In healthy subjects, short-term administration of stavudine reduces insulin sensitivity and causes a 52% reduction in muscle and mitochondrial DNA.[13] NRTI drugs (especially stavudine) have been implicated as a cause of lipoatrophy,[14,15] and lipoatrophy has been associated with insulin resistance.[16] A recent analysis of the D:A:D (Data Collection on Adverse events of Anti-HIV Drugs) cohort showed that use of stavudine and zidovudine is associated with development of diabetes mellitus after adjustment for confounders in HIV-infected adults.[17] Moreover, lipodystrophy did not modify this association, suggesting that these two thymidine analogues could contribute to insulin resistance by means of mitochondrial toxicity.

Disturbances of glucose homeostasis in HIV-infected children have been assessed mainly by cross-sectional studies;[18-20] no randomized controlled trials or 'switch studies' are available. Insulin resistance, impaired glucose tolerance and diabetes mellitus are relatively uncommon in HIV-infected children.[18,21,22] In the study by Jaquet et al.,[21] all 39 children who underwent oral glucose tolerance testing (OGTT), including 31 who were undergoing PI therapy, had normal glucose tolerance. In the largest published series, none of 130 HIV-infected children had diabetes or impaired fasting glucose and only 1 of 32 children who underwent OGTT had impaired glucose tolerance.[22] However, a recent study showed impaired glucose tolerance in 20%

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and insulin resistance in 38% of 40 HIV-infected adolescents undergoing HAART from a mean age of 13.5 years.[23] The majority of published paediatric studies have failed to demonstrate an association between PI use and disturbances of glucose homeostasis.[18-20] PI-treated and PI-naive children had similar values of fasting insulin, pro-insulin, C-peptide, insulin to glucose ratio or insulin resistance as detected by the homeostasis model assessment (HOMA-R).[18-20] However, a recent study of 48 HIV-infected children evaluated by frequent-sampling intravenous glucose tolerance testing (IVGTT) showed lower insulin sensitivity and disposition indexes in PI-treated versus PI-naive children, despite similar levels of fasting insulin, C-peptide and HOMA-R values.[24] Finally, in the only published cohort study, Beregszaszi et al.[22] reported substantial stability in glucose homeostasis after 2 years of follow-up.

The aim of the present study was to describe a 4-year course of glucose homeostasis in a cohort of 37 HAART-treated children and adolescents, using glucose and insulin levels during OGTT as outcome measures. In addition, we investigated possible risk factors, both related and unrelated to antiretroviral therapy, associated with insulin resistance.

Subjects and Methods

Subjects

We performed a longitudinal study of glucose homeostasis in HIV-infected Caucasian children and adolescents receiving a HAART regimen containing one PI/stavudine/lamivudine or efavirenz/tenofovir/lamivudine. All PIs were administered without ritonavir booster. The children were consecutively recruited at the Pediatric Clinic, 'L. Sacco' Hospital, University of Milan, Italy, between January and December 2000. Eligibility criteria were vertical HIV infection and treatment with a stable HAART regimen for at least 6 months. We excluded patients treated with antiretroviral regimens other than HAART and those who had an active AIDS-defining condition in the previous 6 months. Informed consent was obtained from both legal guardians and patients. The study was approved by the Ethics Committee of the 'L. Sacco' Hospital.

Clinical Evaluation

Age, weight, height, body mass index (BMI), pubertal stage, maximum and current clinical HIV disease stage, maximum immunological HIV disease stage, CD4+ T cells percentage, viral load and type, and duration of antiretroviral treatment were recorded at baseline and every year during the 4-year follow-up. Weight was measured to the nearest 0.1 kg with a beam scale (SECA, Hamburg, Germany) and height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Holtain Ltd, Crosswell, UK). BMI was calculated as weight (kg)/height (m^2). Standard deviation (SD) scores of anthropometric measurements were calculated using US Centers for Disease Control and Prevention 2000 reference data.[25] Pubertal status was defined according to Tanner's criteria.[26]

Laboratory Assessment

The percentage of CD4+ T cells and the level of HIV-RNA were measured at baseline and during follow-up as markers of HIV infection. Insulin and glucose from OGTT were measured at baseline and every year during the 4-year follow-up. At 8:00am, after an 8-hour overnight fast and delaying the morning dose of antiretroviral therapy until the end of the test, the patients received 1.75 g/kg bodyweight of glucose (up to 75 g) diluted in 250 mL of water. Blood samples were collected at 0 (fasting), 30, 60, 90, 120 and 180 minutes. The area under the 0–180 minutes serum concentration-time curve (AUC) of insulin and glucose during OGTT was calculated using the trapezoidal rule. Serum insulin was measured using a chemolumines-

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cence immunometric assay (Immunolite 2000, Medical Systems, Genoa, Italy). Plasma glucose was measured using standard laboratory assays. Diabetes was diagnosed as fasting glucose ≥126 mg/dL or 2-hour OGTT glucose ≥200 mg/dL; impaired fasting glucose (IFG) as fasting glucose ≥100 and <126 mg/dL; and impaired glucose tolerance (IGT) as 2-hour OGTT glucose ≥140 and <200 mg/dL.[27]

Statistical Analysis

Continuous variables are reported using median and 25th and 75th percentiles because of skewed distributions. Categorical variables are given as the number of subjects with the characteristic of interest. The longitudinal relationship between insulin, type of antiretroviral therapy and potential confounders was studied using generalized estimating equations (GEEs).[28] GEEs give a population-average or marginal model, i.e. they quantify how much the average response would change across the population for every one-unit increase in a covariate. The outcome variable was the AUC of OGTT insulin, which was transformed using natural logarithms to achieve the normal distribution (Shapiro-Wilk test). The within-subject correlation matrix of GEE was set as unstructured. Time was entered as both time and time squared and a time*drug interaction was used to control for the fact that the treatments changed substantially in favour of efavirenz and tenofovir during the study. The indinavir/lamivudine/stavudine regimen was arbitrarily chosen as the reference group and the effects of the other regimens (ritonavir/lamivudine/stavudine, nelfinavir/lamivudine/stavudine and efavirenz/lamivudine/tenofovir) were modelled against it (yes = 1; no = 0). The other predictors were sex (male = 1; female = 0), age at baseline (continuous), Tanner stage (≥4 = 1; <4 = 0) and percentage of CD4+ T cells (continuous). The cut-point for Tanner staging (late pubertal and adult stages vs other stages) was decided by considering that by the second year of the study, 29 (78%) of the children were at Tanner stage ≥4. This corresponds to modelling the effect of puberty on the outcome of interest. Semi-robust confidence intervals were calculated. Statistical significance was set at a p-value <0.05 and all tests were two-tailed. Statistical analysis was performed using STATA 10.1 (StataCorp, College Station, TX, USA).

Results

The characteristics of the children during the study are given in table I. These data were not used for hypothesis testing because they did not consider within-individual correlation and loss of subjects during follow-up, both of which were taken into account by GEE (see later). The patients numbered 37 in the second year, 35 in the third year and 31 in the fourth year; five patients were discontinued from the study because of their reluctance to undergo a further OGTT, while one patient was lost to follow-up. The patients had a median (25th and 75th percentiles) age of 12 years at baseline. There were slightly more males than females at any timepoint. Seventy-eight percent of patients had reached late puberty or completed puberty by the second year of the study. Compared with US reference data, our patients had medians slightly below or above 0.0 SD scores for z-weight, z-height and z-BMI at any timepoint (the z-score is the difference between the individual value and the population mean, divided by the population SD).

The most common maximum Centers for Disease Control and Prevention (CDC) clinical and immunological stages of disease were class A and class 2, respectively. All patients were asymptomatic for the entire duration of the study (CDC class N). At baseline, 92% of patients had an undetectable viral load and this percentage ranged from 89% to 95% during follow-up; in addition, there was a tendency for the CD4+ T cells percentage to increase during follow-up. At baseline, 35 of 37 patients were receiving a HAART regimen containing lamivudine/

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Table I. Baseline and follow-up measurements of HIV-infected highly active antiretroviral therapy-treated children[a]

Variable	Baseline	Year			
		1	2	3	4
No. of patients	37	37	37	35	31
Sex (M/F)	17/20	17/20	17/20	15/20	14/17
Age (y)	12 (7; 12)	13 (8; 14)	14 (10; 16)	15 (11; 16)	16 (13; 18)
Tanner stage (≥4/<4)	20/17	28/9	29/8	28/7	28/3
Weight (kg)	30 (24; 42)	43 (30; 58)	49 (34; 58)	50 (36; 60)	56 (43; 61)
z-weight (SD score)[b]	−0.3 (−1.2; 0.2)	−0.1 (−0.8; 0.5)	0.1 (−0.9; 0.6)	−0.1 (−1.1; 0.7)	−0.1 (−1.1; 0.4)
Height (m)	1.4 (1.2; 1.5)	1.5 (1.4; 1.6)	1.6 (1.4; 1.7)	1.6 (1.4; 1.7)	1.6 (1.5; 1.7)
z-height (SD score)[b]	−0.3 (−0.8; 0.2)	−0.3 (−1.0; 0.3)	−0.3 (−1.0; 0.3)	−0.4 (−0.7; 0.4)	−0.5 (−0.9; 0.1)
BMI (kg/m^2)	16.7 (14.9; 18.5)	19.0 (17.1; 21.3)	19.8 (17.1; 21.8)	19.6 (17.4; 22.3)	21.0 (17.7; 22.7)
z-BMI (SD score)[b]	−0.3 (−1.1; 0.6)	0.2 (−0.7; 0.6)	0.3 (−0.7; 0.7)	0.1 (−1.1; 0.5)	0.1 (−1.2; 0.4)
Maximum CDC clinical stage (N/A/B/C)	0/14/11/12	0/14/11/12	0/14/11/12	0/13/11/11	0/11/10/10
Current CDC clinical stage (N/A/B/C)	37/0/0/0	37/0/0/0	37/0/0/0	35/0/0/0	31/0/0/0
Maximum CDC immunological stage (1/2/3)	12/15/10	12/15/10	12/15/10	12/15/8	10/15/6
CD4+ T cells (%)	31 (26; 37)	34 (27; 38)	35 (30; 41)	36 (31; 42)	38 (33; 41)
RNA <50 copies/mL (yes/no)	34/3	33/4	35/2	32/3	28/3
Ritonavir/lamivudine/stavudine (yes/no)	13[c]/24	10/27	6/31	0/35	0/31
Indinavir/lamivudine/stavudine (yes/no)	16[d]/21	16/21	9/28	1/34	1/30
Nelfinavir/lamivudine/stavudine (yes/no)	6[e]/31	7/30	5/32	1/34	1/30
Efavirenz/lamivudine/tenofovir (yes/no)	2[f]/35	5/32	18/19	33/2	29/2
Fasting insulin (mU/L)	8 (3; 11)	10 (4; 15)	11 (5; 17)	8 (5; 13)	6 (4; 11)
OGTT insulin (mU/L)					
at 30 min	35 (2; 103)	84 (20; 125)	102 (36; 130)	38 (16; 86)	58 (28; 96)
at 60 min	35 (6; 68)	44 (13; 110)	71 (36; 103)	51 (26; 90)	40 (23; 64)
at 90 min	18 (9; 36)	51 (12; 117)	43 (23; 83)	36 (16; 56)	18 (6; 42)
at 120 min	19 (7; 39)	30 (11; 76)	33 (13; 56)	26 (10; 48)	22 (11; 36)
at 180 min	4 (2; 14)	10 (4; 30)	13 (6; 35)	6 (2; 12)	7 (2; 14)
OGTT insulin (AUC/1000)	4 (2; 10)	8 (3; 18)	9 (5; 13)	6 (4; 10)	6 (4; 8)
Fasting glucose (mg/dL)	79 (75; 86)	82 (77; 85)	85 (80; 92)	86 (83; 90)	83 (77; 89)
OGTT glucose (mg/dL)					
at 30 min	138 (118; 151)	128 (117; 143)	132 (117; 151)	128 (118; 150)	128 (100; 135)
at 60 min	103 (87; 128)	116 (98; 129)	105 (92; 136)	104 (93; 121)	95 (75; 112)
at 90 min	94 (85; 103)	101 (84; 115)	99 (91; 110)	101 (91; 113)	86 (75; 94)
at 120 min	94 (83; 108)	97 (85; 108)	98 (87; 107)	93 (87; 104)	90 (73; 92)
at 180 min	73 (63; 81)	75 (64; 88)	78 (66; 90)	85 (70; 94)	74 (67; 83)
OGTT glucose (AUC/1000)	18 (17; 20)	18 (17; 20)	18 (17; 21)	18 (17; 21)	17 (15; 18)

a Values are medians and 25th and 75th percentiles (in parentheses) for continuous variables and number of subjects for categorical variables.

b Compared with US reference data.[25]

c Time under drug [median (25th; 75th percentile) or number of months] at baseline visit: 25 (22; 32) months.

d Time under drug [median (25th; 75th percentile) or number of months] at baseline visit: 34 (34; 35) months.

e Time under drug [median (25th; 75th percentile) or number of months] at baseline visit: 19 (15; 25) months.

f Time under drug [median (25th; 75th percentile) or number of months] at baseline visit: 9 and 8 months.

AUC = area under the serum concentration-time curve; **BMI** = body mass index; **CDC** = Centers for Disease Control and Prevention; **F** = female; **M** = male; **OGTT** = oral glucose tolerance test; **SD** = standard deviation; **z** = difference between the the individual value and the population mean, divided by the population SD.

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Table II. Predictors of the changes in the natural logarithm (log_e)-transformed area under the serum concentration-time curve (AUC) of insulin during oral glucose tolerance testing

Variable	Log_e AUC insulin regression coefficient (95% CI)
Ritonavir/lamivudine/stavudine vs indinavir/lamivudine/stavudine	−0.29 (−0.85, 0.26)
Nelfinavir/lamivudine/stavudine vs indinavir/lamivudine/stavudine	−0.69** (−1.29, −0.09)
Efavirenz/lamivudine/tenofovir vs indinavir/lamivudine/stavudine	−0.93** (−1.82, −0.03)
Time (y)	0.58*** (0.21, 0.94)
$Time^2$ (y^2)	−0.13*** (−0.20, −0.05)
Drug*time interaction	0.07 (−0.02, 0.15)
Male sex	−0.18 (−0.54, 0.18)
Age at baseline (y)	0.01 (−0.03, 0.04)
Tanner stage ≥4	1.32† (0.91, 1.74)
z-BMI (SD score)[a]	0.13 (−0.07, 0.32)
CD4+ T cells (%)	−0.01 (−0.02, 0.01)
Constant	7.50† (6.50, 8.50)

a Compared with US reference data.[25]

AUC = area under the serum concentration-time curve; **BMI** = body mass index; **SD** = standard deviation; **z** = difference between the the individual value and the population mean, divided by the population SD. ** $p < 0.05$; *** $p < 0.01$; † $p < 0.001$.

stavudine plus one PI (ritonavir, n = 13; indinavir, n = 16; nelfinavir, n = 6) and only 2 of 37 patients were receiving a HAART regimen containing lamivudine/tenofovir/efavirenz. During follow-up, use of stavudine and PIs decreased in favour of use of tenofovir and efavirenz. At the first, second, third and fourth year of follow-up, the numbers of patients taking a HAART regimen containing lamivudine/stavudine/PI were 33, 20, 2 and 2, respectively, while the number of patients taking a HAART regimen containing lamivudine/tenofovir/efavirenz were 5, 18, 33 and 29, respectively. The change of antiretroviral therapy was undertaken to reduce toxicity and to maintain adherence.

No patient had diabetes at any timepoint. Three unrelated patients had IFG at the baseline (102 mg/dL), second year (104 mg/dL) and fourth-year visit (100 mg/dL); likewise, three unrelated patients had IGT at baseline (140 and 194 mg/dL) and second-year visit (157 mg/dL). AUC insulin values increased up to the second year and decreased thereafter. In comparison, the changes in AUC glucose were more limited (table I). The relationship between log_e-transformed AUC insulin and antiretroviral therapy is shown in table II. The trend of insulin to increase and then to decrease was confirmed by the significance of time ($p < 0.01$) and time squared ($p < 0.01$). The drug*time interaction was not significant, meaning that the effect of the treatments was not time-dependent. Puberty was associated with insulin AUC, while sex, age at baseline, z-BMI and CD4+ T cells percentage were not. The nelfinavir/lamivudine/stavudine ($p < 0.05$) and the efavirenz/lamivudine/tenofovir ($p < 0.05$) regimens, but not the ritonavir/lamivudine/stavudine regimen, were inversely associated with insulin AUC compared with indinavir/lamivudine/stavudine.

Discussion

The present 4-year study is the longest follow-up study of glucose homeostasis performed to date among HIV-infected children. We assessed risk factors, related and unrelated to antiretroviral therapy, associated with insulin resistance. We found that: (i) the nelfinavir/lamivudine/stavudine and the efavirenz/lamivudine/tenofovir regimens but not the ritonavir/lamivudine/stavudine regimen were associated with higher insulin sensivity, i.e. lower insulin AUC, compared with indinavir/lamvudine/stavu-

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dine; (ii) the treatment switched substantially in favour of NNTRI from the third year on and this change was associated with an improvement in insulin sensitivity compared with the previous HAART-based regimen; and (iii) puberty is a primary determinant of insulin sensitivity.

Nevertheless, our study has some limitations. First, our cohort was small (n = 37). However, our loss to follow-up (n = 6) was lower than commonly reported and all losses occurred late in the study (during or after the third year of follow-up). Moreover, we modelled the contribution of all subjects to the outcome using GEEs, which are robust to data missing at random. Secondly, our outcome variable, AUC insulin, is only a surrogate measure of insulin sensitivity. However, it is considered a suitable option in longitudinal studies and may be a useful surrogate marker of insulin-mediated glucose uptake in HIV-infected subjects.[29,30] Thirdly, even if a cohort study cannot provide any definitive clue to a cause-effect relationship, our study is important because glucose metabolism of HIV-infected children has been investigated to date mostly by means of cross-sectional studies. Fourthly, given the role of puberty in determining insulin sensitivity and the great number of subjects in Tanner stage ≥4 in our study, our results may not be generalizable to children who are prepubertal or in early pubertal development.

Most paediatric studies utilizing fasting indices of insulin sensitivity have failed to demonstrate an association between PI use and insulin resistance.[18-20] However, an association of this type was present in a cross-sectional study in which insulin resistance was evaluated using frequent-sampling IVGTT.[24] Our cohort study showed differences in glucose homeostasis within PI-based antiretroviral regimens that included stavudine. The AUC insulin associated with the ritonavir/lamivudine/stavudine regimen was similar to that for the indinavir/lamivudine/stavudine regimen. This finding is in agreement with evidence that indinavir and ritonavir inhibit GLUT-4 *in vitro* to the same extent.[10] On the other hand, the AUC insulin associated with the nelfinavir/lamivudine/stavudine regimen was lower than that of the indinavir/lamivudine/stavudine regimen. This finding is in accordance with the lower insulin sensitivity of patients treated with indinavir compared with nelfinavir.[3]

In the only published paediatric cohort study, Beregszaszi et al.[22] reported substantial stability of glucose homeostasis over 2 years of follow-up in HIV-infected children receiving antiretroviral therapy. This observation raises the question of whether glucose abnormalities might improve in HAART-treated children. Our study suggests indeed that a change to an efavirenz/lamivudine/tenofovir regimen may improve insulin sensitivity. This treatment was associated with higher insulin sensitivity compared with the indinavir/lamivudine/stavudine regimen. Our finding is in agreement with the improvement in insulin sensitivity observed in 20 HIV-infected adults after substitution of efavirenz for PIs.[8] Our finding is also supported by the results obtained in 1147 antiretroviral-naive adult patients enrolled in the ACTG (AIDS Clinical Trials Group) study A5095.[31] During the first 24 weeks of that study, a modest and comparable increase in glucose and insulin resistance was observed in patients receiving triple nucleoside therapy (zidovudine/lamivudine/abacavir), patients receiving efavirenz (zidovudine/lamivudine/efavirenz) and patients receiving quadruple therapy (zidovudine/lamivudine/abacavir/efavirenz). The similar changes observed in the groups suggest that the alteration in glucose homeostasis is related to the direct effect of the nucleoside backbone rather than to efavirenz.

A large study of HIV-infected men showed an association between cumulative NRTI exposure and fasting hyperinsulinaemia.[11] In addition, when the specific NRTI drugs were studied, stavudine and lamivudine were independently associated with in-

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sulin resistance. Another study of HIV-infected women found that the incidence of diabetes tended to increase with greater cumulative exposure to NRTIs and, among NRTIs, the increase was especially associated with lamivudine.[12] The mechanism by which NRTIs cause disorders of glucose metabolism is unclear. NRTIs, especially stavudine, have been implicated as a cause of lipoatrophy,[14,15] which in turn has been linked to insulin resistance in HIV-infected patients.[16] On the other hand, recent data indicate that stavudine and other NRTIs may contribute to insulin resistance and diabetes independently of lipodystrophy.[13,17]

In our study, PIs and stavudine were replaced with efavirenz and tenofovir at the same time. Due to this concomitant change, our data cannot clarify if the improvement in insulin sensitivity observed with efavirenz/lamivudine/tenofovir regimen was related to the substitution of one or both drugs.

Puberty is associated with a significant decrease in insulin sensitivity in healthy adolescents of both sexes as a result of transient interactions between sexual hormones and glucose metabolism.[32] The effect of puberty on glucose metabolism has been linked to higher body fat, lower physical activity and family history of diabetes.[33] Therefore, puberty onset has been included among the indications for screening for diabetes.[34] Our data confirm that puberty affects insulin, even in the absence of IGT or diabetes. The absence of a control group of healthy children does not allow us to disentangle the effect of puberty from that of the underlying disease, but it is clinically important to note that puberty was a determinant of insulin changes in HIV children followed up for 4 years.

Conclusion

In HIV-infected HAART-treated children, a switch strategy to efavirenz/lamivudine/tenofovir might improve insulin sensitivity compared with stavudine/lamivudine/PI-containing regimens. In addition, AUC insulin increases during puberty so that screening for diabetes should be reinforced at this age. The extent to which insulin resistance contributes to diabetes and cardiovascular disease in HIV-infected children and adolescents remains to be determined.

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