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Time course and predictors of glucose homeostasis in HAART-treated HIV-infected children and adolescents: 4 years of follow-up

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ABSTRACT

Background: Disorders of glucose metabolism and their risk factors have been extensively studied in HIV-infected adults. Pediatric data on this topic are limited, controversial and obtained mainly by cross-sectional studies.

Methods: Insulin and glucose during 3 hr oral glucose tolerance test (OGTT) were measured at baseline and yearly for 4 years in 37 HIV-infected children receiving a PI-based HAART containing 3TC/d4T plus IDV or RTV or NFV or a NNRTI-based HAART containing 3TC/TDF/EFV. Age, weight, height, BMI, Tanner pubertal stage, CD4%, viral load and type and duration of HAART were recorded at baseline and yearly for 4 years. Generalized estimating equations were used to study the relationship between the log-transformed area under the curve of OGTT-insulin (I-AUC), time, type of HAART and potential confounders (gender, age at baseline, pubertal stage, z-score of BMI, CD4%). The 3TC/d4T/IDV regimen was arbitrarily chosen as the HAART reference group and the effects of other regimens were modeled against it.

Results: The patients were 4 to 16 yrs-old at baseline. They were 37 up to the 2nd yr, 35 at the 3rd yr and 31 at the 4th yr. During the study, HIV-RNA was undetectable in most patients and the median value of CD4% increased. At baseline, PI-based regimens were administered to 35/37 patients (IDV n=16; RTV n=13; NFV n=6) but their use decreased progressively at the 3rd (2/33) and 4th (2/29) year of follow-up in favor of 3TC/TDF/EFV. The median values of I-AUC increased up to the 2nd year and decreased thereafter. The changes in glucose-AUC were more limited. None of the patients had diabetes mellitus or impaired glucose tolerance at any time of the study. Tanner stage $\geq$ 4 was strongly and positively associated with I-AUC (regression coefficient: 1.32; 95%CI: 0.91 to 1.74; p<0.001). Among HAART regimens, NFV/3TC/d4T (regression coefficient: -0.69; 95%CI : -1.29 to -0.09; p< 0.05) and EFV/3TC/TDF (regression coefficient:-0.93; 95%CI: -1.82 to -0.03; p< 0.05) but not RTV/3TC/d4T (regression coefficient: 0.29; 95%CI: -0.85 to 0.26; p=0.297) were associated with lower insulin levels as compared to IDV/3TC/d4T.

Conclusions: Our 4-yrs follow-up study of HIV-infected children shows that HAART regimens containing NFV/3TC/d4T or EFV/3TC/TDF are associated with higher insulin sensitivity as compared to IDV/3TC/d4T and that puberty is a primary determinant of decreased insulin sensitivity.

BACKGROUND

Disorders of glucose metabolism and their risk factors have been extensively investigated in HIV-infected adults. Pediatric data are limited, controversial and mainly obtained by cross-sectional studies.

AIMS

To describe glucose homeostasis in HAART-treated HIV-infected children and adolescents, using oral glucose tolerance test (OGTT). To investigate possible risk factors, both related and unrelated to antiretroviral therapy, associated with insulin resistance

STUDY DESIGN

4 years longitudinal study of glucose homeostasis in 37 HIV-infected children and adolescents receiving an HAART regimen containing one PI / 3TC / d4T or EFV / 3TC / TDF. The study was approved by the Ethic Committee of L. Sacco Hospital of Milan, Italy.

METHODS

Patients underwent **c**linical, anthropometric assessment and an OGTT, after a 8-hr overnight fast, at baseline and yearly during the 4-year follow-up. Blood samples were collected at 0, 30, 60, 90, 120 and 180 min for measurement of serum insulin and plasma glucose. Impaired glucose tolerance and diabetes mellitus were defined according to the guidelines of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.

TABLE 1. Demographic, anthropometric and clinical data, at baseline and during 4 years of follow-up, in HAART treated HIV-infected children.

	Baseline	1-yr	2-yr	3-yr	4-yr
N	37	37	37	35	31
Gender (M / F)	17/20	17/20	17/20	15/20	14/17
Age (years)	12 (5)	13 (6)	14 (6)	15 (5)	16 (5)
Tanner stage ($\geq$ 4 / $\leq$ 3)	20/17	28/9	29/8	28/7	28/3
Weight (kg)	30 (18)	43 (28)	49 (24)	50 (24)	56 (18)
Z-weight (SDS)	- 0.3 (1.4)	- 0.1 (1.3)	0.1 (1.5)	- 0.1 (1.8)	- 0.1 (1.5)
Height (m)	1.39 (0.32)	1.54 (0.28)	1.57 (0.24)	1.59 (0.23)	1.60 (0.16)
Z-height (SDS)	- 0.3 (1.0)	- 0.3 (1.4)	- 0.3 (1.4)	- 0.4 (1.1)	- 0.5 (1.0)
BMI (kg / m2)	16.7 (3.6)	19.0 (4.2)	19.8 (4.7)	19.6 (4.9)	21.0 (5.0)
Z-BMI (SDS)	- 0.3 (1.6)	0.2 (1.3)	0.3 (1.4)	0.1 (1.5)	0.1 (1.6)
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
CD4+ %	31 (11)	34 (10)	35 (12)	36 (11)	36 (8)
RNA < 50 copies / mL (yes / no)	34 / 3	33 / 4	35 / 2	32 / 3	28/3

Values are median (interquartile range) for continuous variables and number of subjects for categorical variables.

STATISTICAL ANALYSIS

Generalized estimating equations were used to study the relationship between the log-transformed area under the curve of OGTT-insulin, time, type of HAART and potential confounders (gender, age at baseline, pubertal stage, z-score of BMI, CD4%).

The 3TC/d4T/IDV regimen was arbitrarily chosen as the HAART reference group and the effects of other regimens were modeled against it.

TABLE 2. HAART regimen, at baseline and during 4 years of follow-up

	Baseline	1-yr	2-yr	3-yr	4-yr
RTV/3TC/d4T (yes / no)	13*/24	10/27	6/31	0/35	0/31
IDV/3TC/d4T (yes /no)	16**/21	16/21	9/28	1/34	1/30
NFV/3TC/d4T (yes /no)	6***/31	7/30	5/32	1/34	1/30
EFV/3TC/TDF (yes/no)	2****/35	5/32	18/19	33/2	29/2

Time under drug at baseline visit [median (interquartile range) or number of months] :
* 25 (10) months, ** 34 (1) months, *** 19 (10) months, **** 9 and 8 months.

TABLE 3. Parameters of glucose homeostasis, at baseline and during 4 years of follow-up

	Baseline	1-yr	2-yr	3-yr	4-yr
Fasting insulin (mU / L)	8 (8)	10 (11)	11 (12)	8 (8)	6 (7)
OGTT insulin (AUC / 1000)	4 (8)	8 (15)	9 (8)	6 (6)	6 (5)
Fasting glucose (mg / dL)	79 (11)	82 (8)	85 (12)	86 (7)	83 (12)
OGTT glucose / (AUC / 1000)	18 (4)	18 (3)	18 (4)	18 (3)	17 (3)

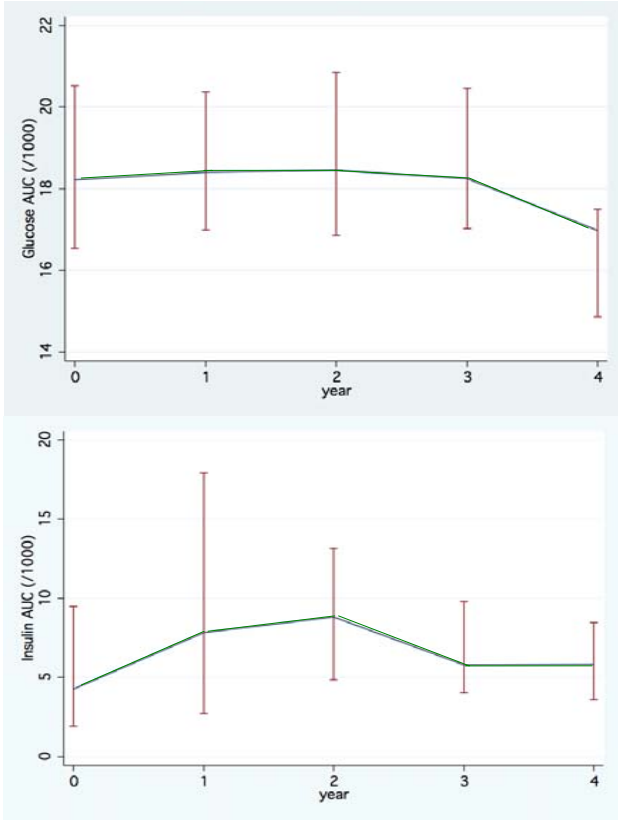
Values are median (interquartile range). AUC = area under the curve

TABLE 4. Predictors of the changes in the log-transformed area under the curve of insulin during an OGTT

	Log_e AUC insulin
RTV/3TC/d4T vs. IDV/3TC/d4T	-0.29 (-0.85 to 0.26)
NFV/3TC/d4T vs. IDV/3TC/d4T	-0.69* (-1.29 to -0.09)
EFV/3TC/TDF vs. IDV/3TC/d4T	-0.93* (-1.82 to -0.03)
Time	0.58** (0.21 to 0.94)
Time ^{2}	-0.13** (-0.20 to -0.05)
Drug*time	0.07 (-0.02 to 0.15)
Male gender	-0.18 (-0.54 to 0.18)
Age at baseline	0.01 (-0.03 to 0.04)
Tanner Stage ≥ 4 *vs.* ≤ 3	1.32*** (0.91 to 1.74)
Z-BMI [SDS]	0.13 (-0.07 to 0.32)
$CD4^+$ %	-0.01 (-0.02 to 0.01)
Constant	7.50*** (6.50 to 8.50)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
Values are regression coefficients (95% confidence intervals)

FIGURE 1. Changes of insulin and glucose AUC (median, interquartile ranges) during OGTT.



CONCLUSION

Our 4-year follow-up study of HIV-infected children and adolescents shows that:

•Fasting insulin and AUC of OGTT-insulin increased up to the 2nd year and decreased thereafter. Fasting glucose and log-transformed AUC of OGTT-glucose slightly changed. No subject developed diabetes mellitus or impaired glucose tolerance.

•HAART regimens containing NFV/3TC/d4T or EFV/3TC/TDF are associated with higher insulin sensitivity as compared to IDV/3TC/d4T.

•Puberty is a primary determinant of insulin sensitivity in these children as in healthy children.