

Impaired Glucose Tolerance and Other Metabolic Abnormalities in Adolescents and Young Adults with HIV Infection Acquired Perinatally or in Childhood

C Hadigan¹, JB Purdy², C Worrell^{2,4}, H Gebrehiwet³, R Hazra^{2,3,4}

¹ Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases; ² HIV and AIDS Malignancy Branch, ³ Pediatric Oncology Branch, National Cancer Institute; ⁴ Pediatric Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development
National Institutes of Health, Bethesda, MD



Rohan Hazra, MD
6100 Executive Blvd.
Bethesda, MD 20892-7510
301-435-6868
hazrar@mail.nih.gov

ABSTRACT

Background: Metabolic complications of ARV therapy may pose a significant challenge for health maintenance among the emerging population of young adults who acquired HIV in infancy/childhood. The purpose of this study was to characterize the extent of metabolic abnormalities in a cohort of HIV-infected patients who acquired HIV in infancy or childhood.

Methods: This is a cross-sectional study conducted between 2004-07 in which 40 patients (54% male, mean age 17 y, range 11-27 y, 38% Black, 48% white, 8% mixed race and 3% Hispanic) completed oral glucose tolerance testing, fasting insulin and lipid studies. Additionally, anthropometric assessments including whole body DXA scan were performed.

Results: All subjects were ARV experienced with a mean duration of 13.4 (2.6 [std.dev]) years; all had current or past protease inhibitor (PI) and d4T exposure. One subject was not on ARV therapy; 88% were currently on a PI. Half of the subjects had <50 HIV RNA PCR copies/ml, and the mean CD4 T-cell count was 665 (416). Impaired glucose tolerance was present in 20% of subjects; no subject had type 2 diabetes. Mean fasting insulin was 18.0 (13.7) IU/ml, glucose 86 (9) mg/dl and the mean homeostatic model for assessment of insulin resistance (HOMA) was 3.9(3.2). A HOMA value >4.0 is considered insulin resistant in adolescents; 38% of subjects had a HOMA >4.0. Dyslipidemia was common; 50% had triglycerides \geq 150 mg/dl, 53% had HDL cholesterol < 50/40 mg/dl for females and males, respectively, and 24% had total cholesterol \geq 200 mg/dl. The mean BMI was 21.9 (3.6) kg/m²; 15% were overweight with a BMI > 25 kg/m², only one patient had a BMI >30 kg/m². The mean waist-hip ratio (WHR) was 0.92 (0.07); 16% had a WHR > 1.00, and the mean % body fat by DXA was 19.9 (8.7). There was a significant positive correlation between WHR and HOMA ($r=0.39$, $p=0.015$).

Conclusions: Abnormal glucose homeostasis characterized by impaired glucose tolerance and HOMA >4.0 was common among heavily treated adolescents and young adults with HIV infection. Insulin resistance was related to WHR in this non-obese patient group. Dyslipidemia was also common and similar to results from adult HIV+ cohorts. These data demonstrate that long term exposure to ARV therapy may convey substantial metabolic risk including increased risk for subsequent type 2 diabetes and cardiovascular disease. These findings warrant careful monitoring in this population as well as further research.

Introduction

- High rates of hyperlipidemia and hypertriglyceridemia have been reported in data from cohorts of HIV-infected adults and children.^{1,3}
- Lipodystrophy has also been reported in data from cohorts of HIV-infected adults and children.^{4,5}
- In these studies, hyperlipidemia, hypertriglyceridemia, and lipodystrophy were associated with HAART, PI use, stavudine use, and duration of ART.
- Lipodystrophy is commonly defined as subcutaneous fat atrophy and visceral abdominal (and sometimes cervical) fat hypertrophy, and it can be associated with impaired glucose tolerance and steatosis.
- In a study of HIV-infected children (median age 12 years) the prevalence of impaired glucose tolerance was low (< 5%),³ but there are concerns that this abnormality will become more prevalent as HIV-infected children age and progress through puberty.
- We designed this study to assess dyslipidemia, glucose tolerance, and anthropometrics in a cohort of older HIV-infected children and adolescents who acquired HIV perinatally or early in life. Members of this cohort include subjects who participated in the first trials of PIs in children.^{6,7}

Methods

- Subjects were evaluated between 2004 and 2007, in up to 2 studies of long-term complications of HIV performed in the Intramural Program of the NIH.
- Evaluations included oral glucose tolerance testing, fasting insulin and lipid studies, and anthropometric assessments including whole body DXA scan.

Results

TABLE 1. General Characteristics (N=40)

Age – years (mean +/- SD)	17.4 +/- 3.7
Female sex – no. (%)	18 (45%)
Race or ethnic group – no. (%)	
White	19 (48%)
Black	15 (38%)
Hispanic	1 (3%)
Other	5 (13%)

TABLE 2. HIV Disease Characteristics

Perinatally-acquired HIV – no. (%)	35 (87.5%)
Transfusion-acquired HIV – no. (%)	5 (12.5%)
HIV-1 RNA – copies/ml (mean+/-SD)	46,500 +/- 151,000
< 50 copies/ml – no. (%)	20 (50%)
CD4+ lymphocyte count – cells/mm ³ (mean+/-SD)	666 +/- 416
Cumulative antiretroviral therapy exposure - years	13.4 +/- 2.6
Current exposure to protease inhibitors – no. (%)	35 (87.5%)
Current or past exposure to protease inhibitors – no. (%)	40 (100%)
Current exposure to stavudine – no. (%)	17 (42.5%)
Current or past exposure to stavudine – no. (%)	40 (100%)

TABLE 3. BMI, Waist to Hip Ratio, Body Fat, Lipid Levels, and Triglycerides

Body-mass index* (mean +/- SD)	21.9 +/- 3.6
> 30 – no. (%)	1 (3%)
Waist to hip ratio (mean +/- SD)	0.92 +/- .07
Body fat – percent (mean +/- SD)	19.9 +/- 8.7
Serum total cholesterol – mg per deciliter (mean+/- SD)	173 +/- 42
Serum HDL cholesterol – mg per deciliter (mean+/- SD)	44 +/- 11
Serum LDL cholesterol – mg per deciliter (mean+/- SD)	103 +/- 28
Serum triglycerides - mg per deciliter (mean+/- SD)	235 +/- 256
Use of lipid/triglyceride lowering agents – no. (%)	2 (5%)

* Weight in kilograms divided by the square of the height in meters

FIGURE 2. Prevalence of Hyperlipidemia in PACTG 1045³ (median age of 12 years) compared to findings in the NIH Pediatric Cohort:

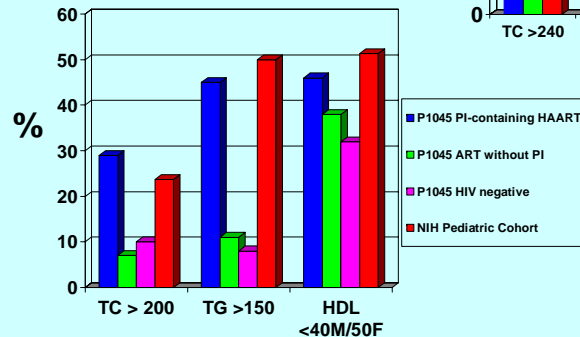


FIGURE 1. Prevalence of Hyperlipidemia in D.A.D. Study¹ (HIV-infected adults) compared to findings

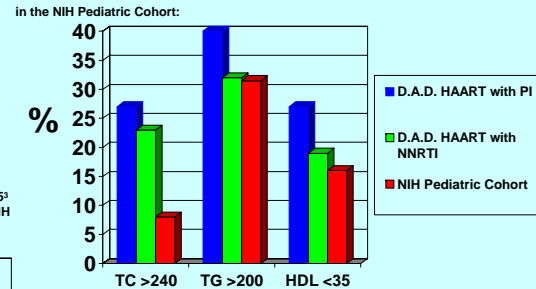


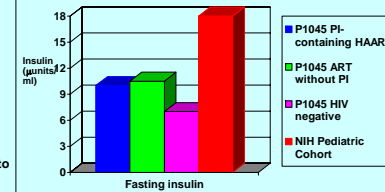
TABLE 4. Glucose and insulin

Fasting glucose – mg per deciliter (mean+/- SD)	86.2 +/- 9.5
Fasting insulin – units/milliliter (mean+/- SD)	18.0 +/- 13.7
HOMA-IR* - fasting insulin x fasting glucose/22.5 (mean +/- SD)	3.9 +/- 3.2
2-hour glucose** – mg per deciliter (mean+/- SD)	109 +/- 33
2-hour insulin*** – units/milliliter (mean+/- SD)	97 +/- 123

* Homeostatic model assessment insulin resistance

** After oral glucose challenge

FIGURE 3. Prevalence of impaired glucose metabolism in PACTG 1045³ compared to findings in the NIH Pediatric Cohort. Prevalence of impaired glucose tolerance was <5% in all 3 P1045 groups but 20% in the NIH Pediatric Cohort.



Conclusions

- Hyperlipidemia is common in our HIV-infected pediatric cohort with rates similar to those seen in studies of HIV-infected adults and to those seen in a younger pediatric cohort enrolled in P1045.
- Insulin resistance is also common and was seen in 38%, as measured by the HOMA-IR.
- Impaired glucose tolerance is also common and was seen in 20%, as measured by the 2-hour glucose concentration after oral glucose challenge.
- These abnormalities are seen despite this cohort being non-obese.
- The rates of impaired glucose homeostasis were higher than those seen in P1045.
- The older age of our cohort compared to the age of subjects enrolled in P1045 suggests that these abnormalities in glucose homeostasis may become more common as HIV-infected children age into adulthood.
- Long term exposure to ARV therapy may convey substantial metabolic risk including increased risk for subsequent type 2 diabetes and cardiovascular disease.
- These findings warrant careful monitoring in this population as well as further research.

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