

Impaired Glucose, Insulin and Other Metabolic Abnormalities in a Cohort of HIV-1 Vertically Infected Latin American Children: The NISDI PLACES Protocol

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ABSTRACT*

Background: Highly Active Antiretroviral Therapy (HAART) has substantially reduced mortality due to HIV, but some of these drugs have been linked with metabolic abnormalities, including insulin resistance, diabetes, and other metabolic complications. The purpose of this study was to characterize the extent of metabolic abnormalities in insulin, glucose, and lipids in a cohort of HIV-infected children in Latin America.

Methods: This is a cross sectional analysis of a long term observational study of a cohort of vertically HIV-infected Latin American children (Brazil, Mexico, and Peru). Participants underwent routine medical history, clinical evaluations and fasting lipids, glucose, and insulin testing. Descriptive statistics were used to describe metabolic abnormalities, including triglycerides >110 (age < 10 y) and >150 mg/dL (age ≥ 10 y) and homeostatic model assessment insulin resistance (HOMA-IR) [(fasting insulin x fasting glucose)/405] greater than 2.5 in children (Tanner stage 1) or greater than 4.0 in adolescents (Tanner stage >1). The association between HAART and metabolic abnormalities was assessed using Fisher's exact test.

Results: Among 483 subjects enrolled by June 2009, 258 were eligible for fasting glucose and insulin testing; 197 (76%) had results available. At time of specimen collection, median age was 7.0 years, HIV RNA and CD4 count were 357 and 860, and 64% were CDC Class B or C; 54% were female. Median (range) duration of ARV therapy at time of specimen collection was 1.8 (0.1-8.4) years; 46% were receiving a PI-containing regimen, 23% an NNRTI-containing regimen, and 31% were not receiving ARVs. Mean BMI Z-score did not differ among ARV groups (p=0.38). Median (range) insulin and glucose levels were 3.0 (<2-18) mcIU/mL and 80 (54-106) mg/dL, and HOMA-IR was 0.53 (0.30-4.31). All glucose levels were normal; 6.1% of the children were insulin resistant, 11% had total cholesterol >200 mg/dL, 22% had HDL <35 mg/dL, 14% had LDL >130 mg/dL, and 34% had abnormally high triglyceride values. Type of ARV therapy received was not associated with fasting insulin, glucose, HOMA-IR, or total cholesterol (p>0.15), but was of borderline significance for HDL and LDL cholesterol and triglycerides (p<0.07).

Conclusions: Insulin resistance and lipid abnormalities were present in this relatively young cohort of HIV-infected children in Latin America. Continued follow up of this cohort and others like it are necessary to characterize the extent of the abnormalities and evolution in settings outside the United States and Europe.

* Updated from original abstract to include data through June 2009.

BACKGROUND

- The effect of HIV and its treatment on the risk for cardiovascular disease in adults has been described extensively (Boccarda, 2008).
- Even as the perinatally-infected population enters the 3rd decade of life in some countries, most of these youth are too young to have experienced actual cardiovascular outcomes.
- However, there are now a number of reports of high rates of traditional risk factors for cardiovascular disease, such as obesity, dyslipidemia, and insulin resistance, in perinatally-infected youth (Hazra, 2010).
- The objective of this study was to describe abnormalities of insulin, glucose, and lipids in a cohort of perinatally-infected Latin American children.

BACKGROUND, CONT.

- This is a substudy of the NICHD International Site Development Initiative [NISDI] Pediatric Latin American Countries Epidemiologic Study [PLACES], an observational cohort study that is currently following 500 perinatally-infected children in Brazil, Mexico, and Peru. The earlier version of this protocol has been described (Hazra, 2009).

METHODS

Study Population

PLACES eligibility criteria include the following:

- Perinatally HIV-infected
- Less than 6 years of age at the time of enrollment to the earlier version of the NISDI pediatric protocol (2002-2007) OR less than 6 years of age at enrollment to PLACES (current version of the NISDI pediatric protocol)

Enrollment to PLACES began in Brazil (12 sites), Mexico (1 site), and Peru (1 site) in June 2008. Target accrual of 500 was reached in July 2009.

Protocol evaluations include medical history, clinical, and laboratory assessments every 6 months. Growth z-scores were determined using WHO standards.

Fasting insulin, glucose, and lipid panel are obtained once a year in those 5 years of age and older. Specimens for insulin and glucose are stored locally and shipped to a central laboratory (Quest Diagnostics, Baltimore) every 6 months for testing. Lipid panels are performed at local laboratories.

Homeostatic model assessment insulin resistance (HOMA-IR) = (fasting insulin (mcIU/mL)*fasting glucose (mg/dL))/405

Insulin resistance defined as HOMA-IR >2.5 in those with Tanner stage 1 and >4.0 in those with Tanner stage >1.

Impaired fasting glucose (IFG): glucose ≥110 mg/dL

Abnormal Triglycerides: (mg/dL): >110 for age <10 years or >150 for age ≥10 years

RESULTS

Figure 1: Derivation of Study Population

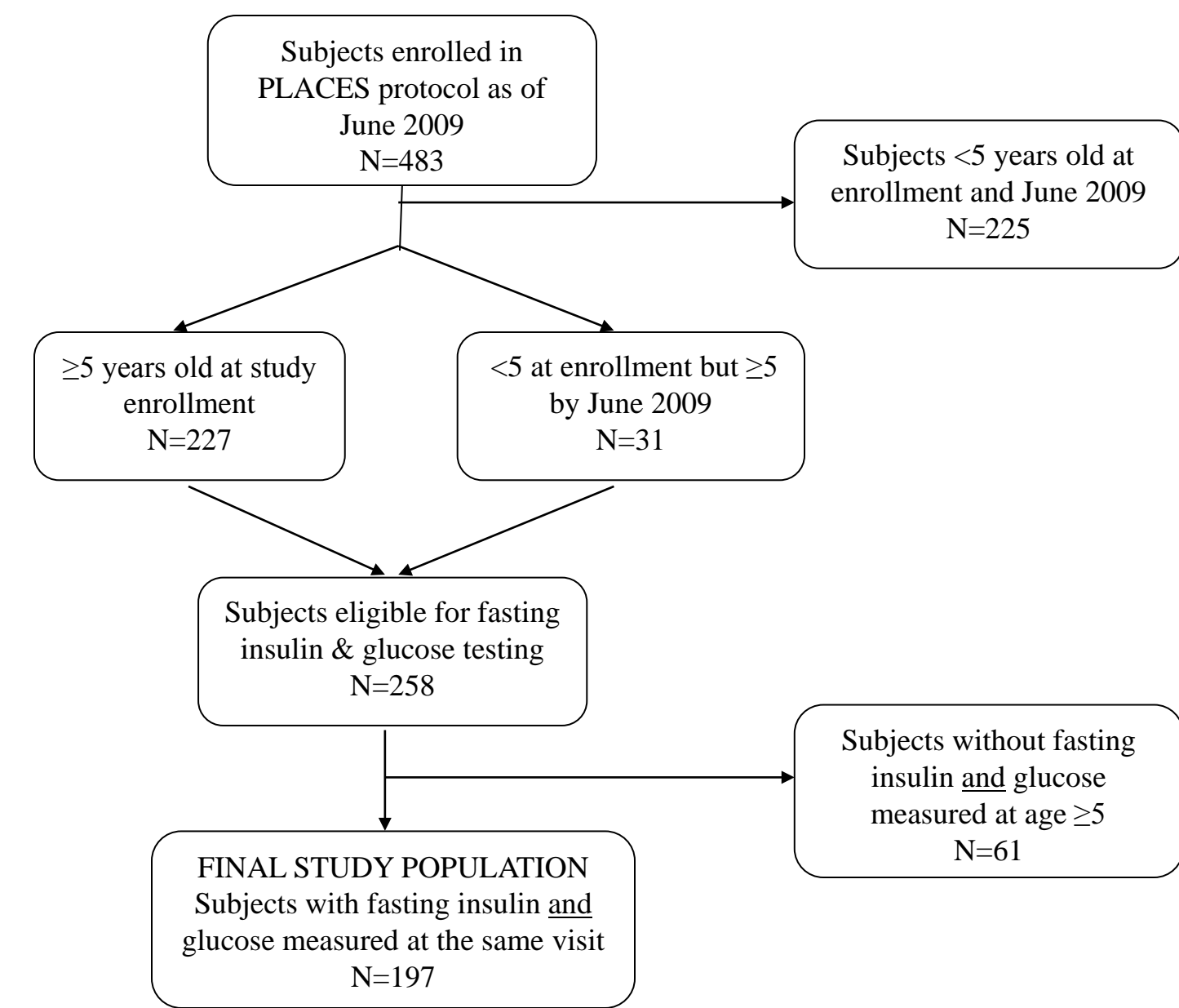


Table 1. Characteristics of the Study Population

Country: N (%)	
Brazil	150 (76.1)
Mexico	41 (20.8)
Peru	6 (3.1)
Median (range) age at specimen collection: (years)	7.0 (5 - 11)
Female gender: N (%)	106 (53.8)
Race: N (%)	
Black	42 (21.3)
Mestizo/Mulato	74 (37.6)
White	81 (41.1)
Median (range) duration of current ARV at time of specimen collection among those (69.5%) receiving ARVs: (years)	1.8 (0.1 - 8.4)
Median (range) viral load (copies/mL) at specimen collection:	357 (20 - >10M)
Median (range) CD4 count (cells/mm³) at specimen collection:	860 (39 - 3269)
CDC classification: N (%)	
N/A	70 (35.5)
B	58 (29.4)
C	69 (35.0)
Median (range) height for age Z-score:	-0.6 (-4.6 - 1.5)
Median (range) weight for age Z-score:	-0.5 (-4.9 - 2.8)
Median (range) BMI for age Z-score:	-0.2 (-5.2 - 3.8)

Table 2. Metabolic results – continuous measurements

Outcome measure	Median (range)
Fasting insulin (mcIU/mL)	3.0 (<2 - 18)
Fasting glucose (mg/dL)	80 (54 - 106)
HOMA-IR	0.53 (0.30 - 4.31)
Total cholesterol (mg/dL)	155 (74 - 303)
HDL cholesterol (mg/dL)	44 (9 - 80)
LDL cholesterol (mg/dL)	94 (13 - 248)
Triglycerides (mg/dL)	94 (32 - 333)

Figure 2a: Impaired Fasting Glucose (IFG) and Insulin Resistance (IR) – NISDI and PACTG 1010 (Chanry, 2008), PACTG 1045 (Aldrovandi, 2009), and Thai NNRTI cohort (Lee, 2009)

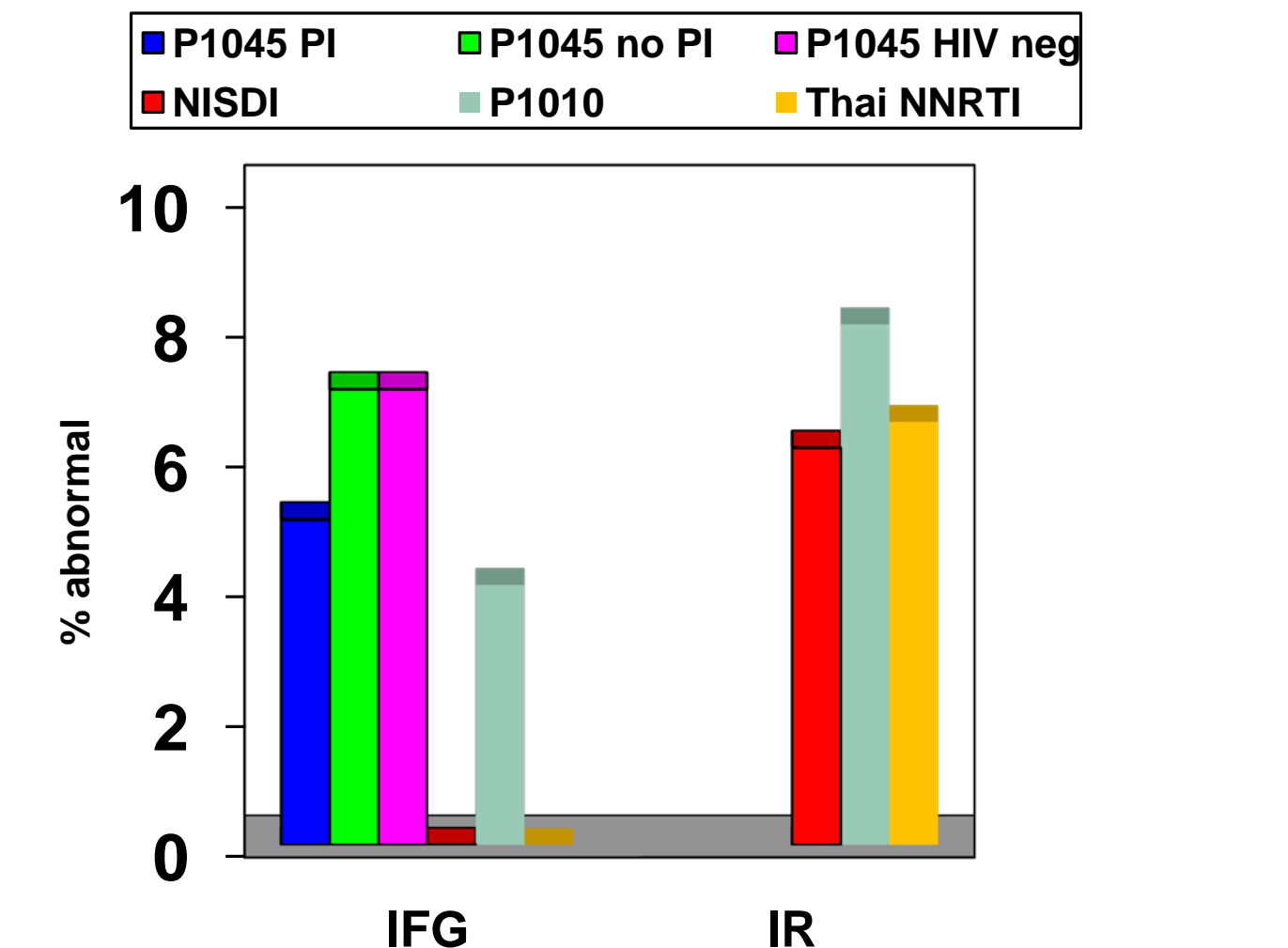


Figure 2b: Lipid results – NISDI and PACTG1045 (Aldrovandi, 2009).

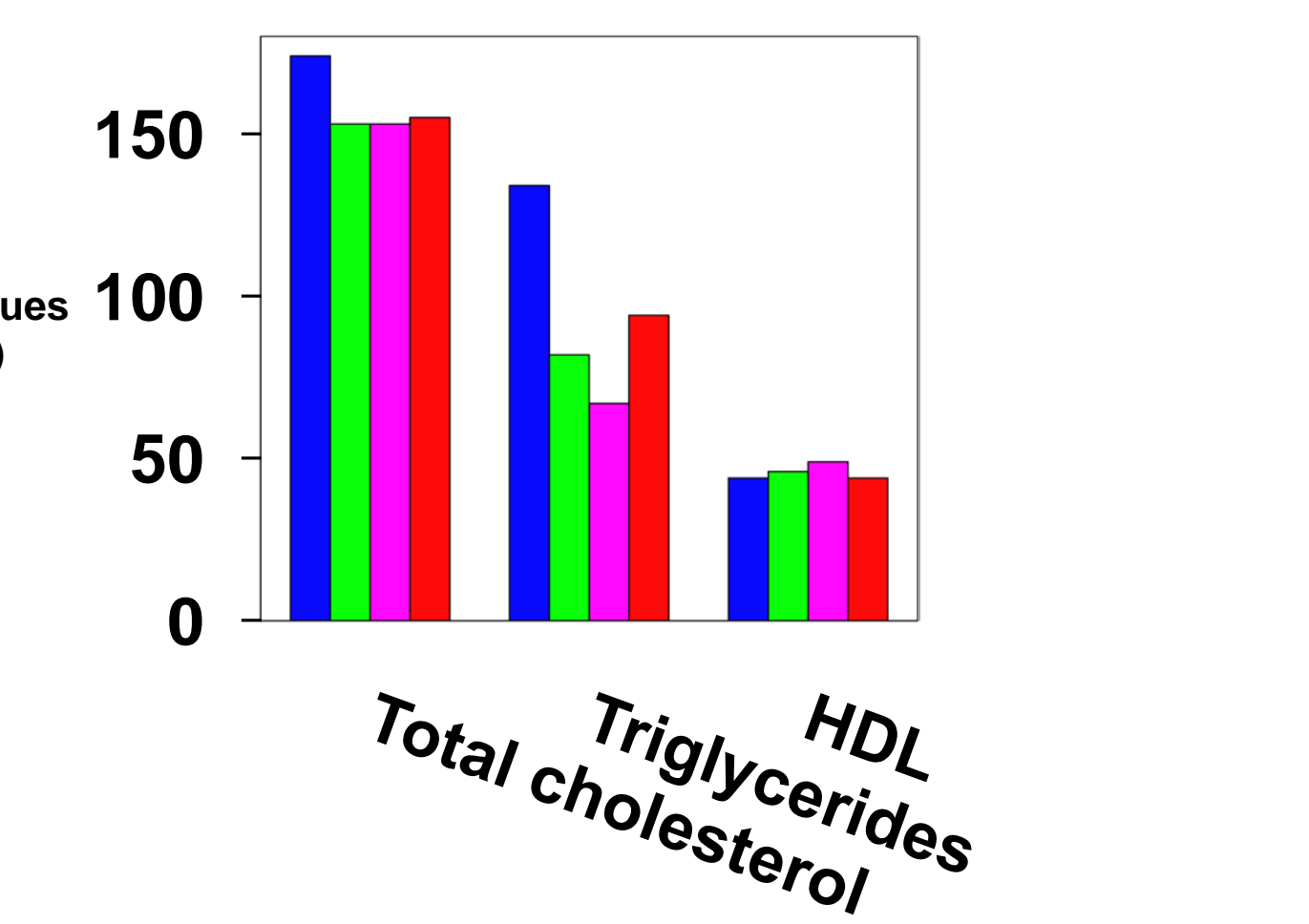


Table 3: Association of ART with metabolic outcomes

Outcome measure	Antiretroviral Therapy			p-value*
	PI-containing regimen N=89	NNRTI-containing regimen (no PI) N=44	No ARVs N=60	
Normal fasting glucose:	89 (100)	44 (100)	60 (100)	1.00
Normal HOMA-IR	84 (94.4)	40 (90.9)	57 (95.0)	0.69
Normal total cholesterol: (≤200 mg/dL)	76 (85.4)	38 (90.5)	45 (95.7)	0.18
Normal HDL cholesterol: (≥35 mg/dL)	67 (80.7)	36 (85.7)	31 (66.0)	0.0696
Normal LDL cholesterol: (≤130 mg/dL)	70 (84.3)	34 (81.0)	45 (95.7)	0.0678
Normal triglycerides:	52 (58.4)	33 (78.6)	33 (70.2)	0.0601

* P-values were obtained using Fisher's Exact test.

SUMMARY AND CONCLUSIONS

Although antiretroviral therapy has been linked with both transient and irreversible hyperglycemia and manifest diabetes mellitus:

- Impaired fasting glucose was not detected in this cohort of perinatally HIV-infected children in Latin America.
- Insulin resistance (as determined by HOMA-IR) was found in 6.1% of children, which is comparable to studies in both the US and Thailand.
- Rates of lipid abnormalities were higher and again comparable to those reported in the US.

Further follow up of this cohort will include evaluating incidence rates for these abnormalities and associated factors.

REFERENCES

Aldrovandi, et al. 2009. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. AIDS 23:661-72.
Boccarda, 2008. Cardiovascular complications and atherosclerotic manifestations in the HIV-infected population: type, incidence and associated risk factors. AIDS 22 (suppl 3):S19-26.
Chanry, et al. 2008. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. Pediatrics 122:e129-38.
Hazra, et al. 2009. NICHD International Site Development Initiative (NISDI): A prospective, observational study of HIV-exposed and HIV-infected children at clinical sites in Latin American and Caribbean countries. Int J Epidemiol 38:1207-14.
Hazra, et al. 2010. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. Annu Rev Med 61:169-85.
Lee, et al. 2009. Low prevalence of insulin resistance among HIV-infected children receiving nonnucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy in Thailand. HIV Medicine 10:72-8.

ACKNOWLEDGMENTS

Supported by NICHD Contract # HHSN267200800001C (NICHD Control # N01-DK-8-0001). We want to thank the study participants, staff at the clinical sites, and the NISDI Executive Committee.