

Differences in Body Fat Distribution in HIV-infected versus HIV-uninfected Children

Denise L. Jacobson*¹, Kunjal Patel¹, Russell Van Dyke², Rohan Hazra³, Linda A. DiMeglio⁴, Mitchell Geffner⁵, Sue Siminski⁶, Margarita Sillio², Elizabeth McFarland⁷ and Tracie L. Miller⁸ for the Pediatric HIV/AIDS Cohort Study (PHACS)

¹Harvard School of Public Health, Boston, MA, US¹– ²Tulane University, New Orleans, LA , US²– ³Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US³
⁴–Section of Pediatric Endocrinology and Diabetology, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, US⁴– ⁵Saban Research Institute of Childrens Hospital of Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, US⁵
⁶–Frontier Science Research and Technology Foundation, Amherst NY, US⁶ – ⁷Department of Pediatric Infectious Diseases, University of Colorado Denver Health Sciences Center, Denver, CO, US⁷– and ⁸Department of Pediatrics, University of Miami, Miller School of Medicine, Miami, FL, US⁸

Denise Jacobson, PhD, MPH
 Harvard School of Public Health
 651 Huntington Avenue
 FXB Building, Room 609
 Boston, MA 02115

Tel: 617-432-3266
 Fax: 617-432-2843

jacobson@sdac.harvard.edu

ABSTRACT*

Background: Adverse changes in body composition are frequent in HIV disease. We compared body fat distribution in perinatally HIV-infected (HIV-pos) to HIV-exposed, uninfected (HIV-neg) children aged 7-16 years enrolled in the Adolescent Master Protocol (AMP) of the PHACS Study. We also evaluated clinical risk factors for fat redistribution among HIV-pos children.

Methods: Dual energy x-ray absorptiometry (DXA) assessed total body mass (TBM), total body fat (TBF), extremity fat (EXF) and trunk fat (TRF). Fat outcomes were defined as % total fat [(TBF/TBM) *100], % extremity fat [(EXF/TBF)*100], % trunk fat [(TRF/TBF*100)] and trunk-to-extremity fat ratio (TRF:EXF). We fit multiple linear regression models to evaluate differences in fat by HIV status, adjusted for age, Tanner stage, race and sex, and to identify clinical correlates of fat outcomes in HIV-pos children.

Results: DXAs were obtained on 303 HIV-pos and 115 HIV-neg children. HIV-pos were older (12.5 vs 10.7 y), more frequently African American (74% vs 57%) and Tanner ≥ 3 (54% vs. 34%). A similar proportion were male (46% vs. 52%). HIV-pos had a lower BMI-z (median 0.27 vs. 0.95) than HIV-neg children. HIV-pos had median CD4 of 699 cells/mm³ and 44% had viral load < 400 copies/ml. Use of highly active antiretroviral therapy (HAART) was high (87%) (HAART-protease inhibitor (PI) 73%; HAART without PI 14%; non-HAART ARV 6%; No ARV 7%). HIV-pos children had lower % total body fat, lower % extremity fat and a borderline higher % trunk fat than HIV-neg (Table). Trunk-to-extremity fat ratio was 1.09 times higher in HIV-pos than HIV-neg. Among HIV-pos, children who had a lifetime use of PI for ≥ 2 years had higher % trunk fat than those who used PI for < 2 years or not at all (P=0.025). CD4 count and detectable viral load were not associated with fat distribution.

Conclusion: Loss of extremity fat and a trend toward higher truncal adiposity were observed in HIV-infected children compared to HIV-neg and may be related to longer-term use of protease inhibitors. These alterations in body fat may increase the risk of cardiovascular disease outcomes.

* Data presented in abstract based on data available by August 1, 2009

BACKGROUND

Body composition can impact risk of co-morbidities in chronic disease; wasting of lean body mass can impact immune function and predispose individuals to serious infections.

Alternatively, accrual of body fat in the trunk or increased waist-to-hip ratios has been associated with increased cardiovascular risk

Changes in body composition, often described as lipodystrophy, have been described in both adults and children with HIV in the HAART era. These changes may be associated with increased cardiovascular risk.

However, few large, multi-center studies in HIV-infected children have compared body composition and its regionality to demographically similar children. Further, few studies have had enough power to evaluate the associations between specific antiretroviral agents and body composition.

OBJECTIVES

We sought to evaluate differences in total and regional body fat between HIV-pos and HIV-neg children enrolled in the US-based PHACS Adolescent Master Protocol (AMP) and to evaluate associations with ART and HIV disease severity in HIV-pos children.

METHODS

Study Design

Protocol: The Adolescent Master Protocol (AMP), which is part of the Pediatric HIV/AIDS Cohort Study (PHACS), is a prospective cohort study conducted at 15 US sites designed to define the impact of HIV infection and ART on pre-adolescents and adolescents with perinatal HIV infection (HIV-pos). A group of HIV-uninfected (HIV-neg) but perinatally HIV-exposed children with similar sociodemographic background and age distribution has been enrolled for comparison. Children from 7 years of age until their 16th birthday born to HIV-infected mothers are eligible for enrollment into AMP.
Enrollment: Enrollment began in March 2007. As of December 1, 2009, there were 451 HIV-pos and 227 HIV-neg children enrolled in AMP. *This report includes baseline data on 350 HIV-pos and 158 HIV-neg children who underwent dual energy x-ray absorptiometry (DXA) scans.*

Body Composition Measurements and Outcomes

The first DXA scan on each participant was done at entry in HIV-pos children and at age 12 or the 4th year of PHACS in the HIV-neg children. DXA scans measured **total body mass (TBM)**, **fat mass (TBF) and lean mass (TBL)**. **Regional measures of fat included extremity fat (EXF) and trunk fat (TRF)**. Measurements were **standardized** at the Tufts Body Composition Center.

Body Composition Outcomes were defined as **% total fat** [(TBF/TBM) *100], **% extremity fat** [(EXF/TBF)*100], **% trunk fat** [(TRF/TBF*100)], and **trunk-to-extremity fat ratio** (TRF:EXF).

Clinical and anthropometric data

CDC classification, HIV viral load (copies/mL), CD4 count (cells/mm³), current antiretroviral use, BMI z-score and Tanner staging were collected at the same visit as the DXA scan.

Statistical Methods

Differences between groups were tested by Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables with missings excluded. Multivariate general linear models were fit for each body composition outcome to determine differences between HIV-pos and HIV-neg children, adjusted for age, race, sex and Tanner stage.

Among the 339 HIV-pos children with data on ARV , CD4, viral load and CDC class, we fit general linear regression models to determine which ARV class and individual agents were independently associated with each fat outcome, adjusted for age, race, sex, Tanner stage and CDC class. When current individual agents in a class were associated with an outcome, another term was put in the model for other current agents in the class. When no individual agent in a class was associated with that outcome (P < 0.1), then only the class variable was left in that model. Lifetime use of each ARV class (PI, NRTI and NNRTI) was first evaluated as never, < 2 yr, and ≥ 2 yr . The < 2yr and never groups were collapsed into one category because they did not differ from each other and numbers were small. In these preliminary analyses, lifetime uses of NRTI and NNRTI were not associated with any outcomes and were not included in any models. Data presented in poster based on available data as of December 1, 2009.

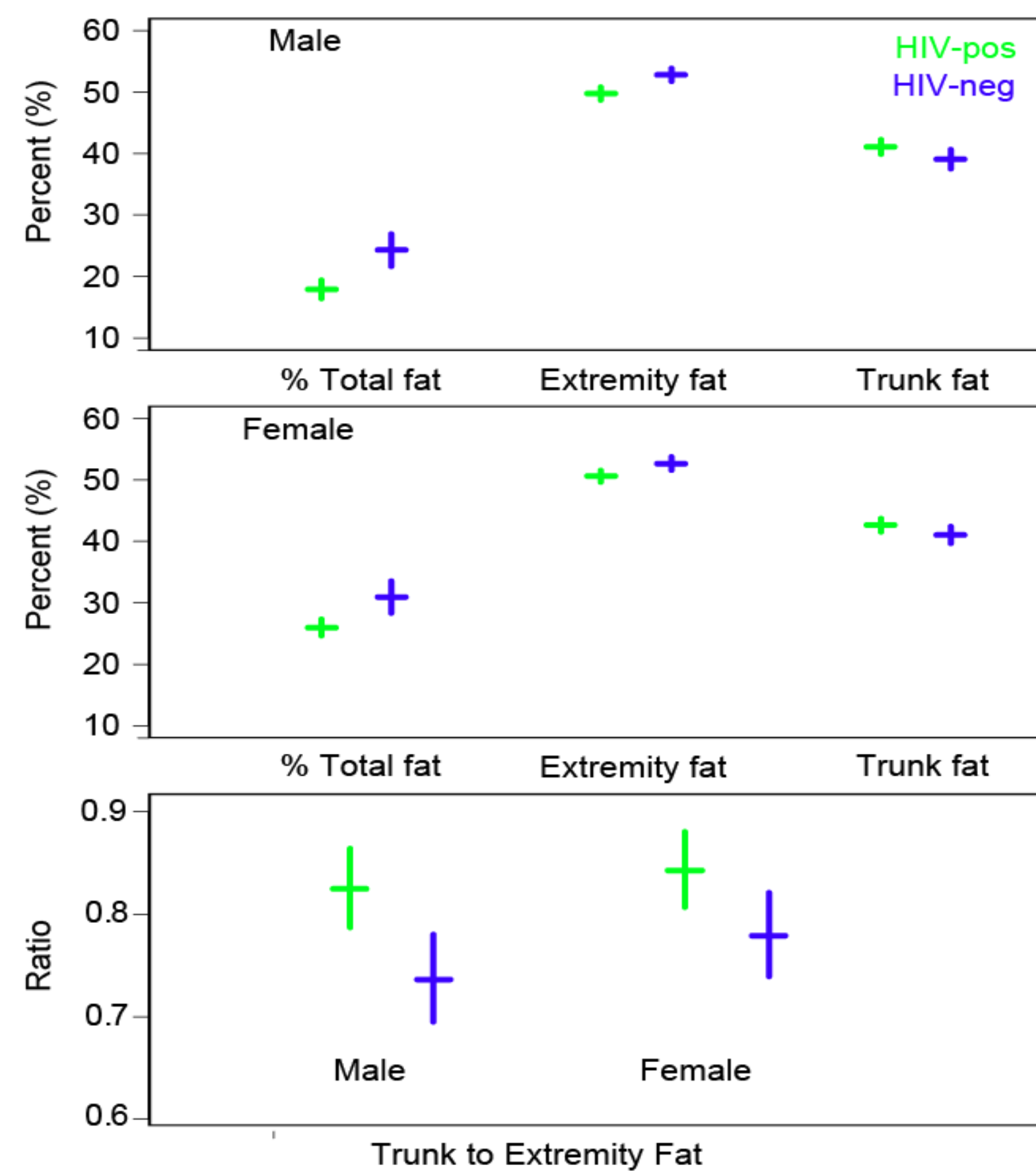
Table 1: Sociodemographic and Nutritional Characteristics by HIV Status

Characteristic		HIV Status		p-value
		HIV-neg (N158)	HIV-pos (N=350)	
Age (yr)	Median (Q1, Q3)	10.6 (8.9, 12.5)	12.5 (10.2, 14.2)	<0.001*
Race/ethnicity	African American White/other Unknown	91 (58) 62 (39) 5 (3)	247 (71) 83 (24) 20 (6)	0.001**
Sex	Male Female	77 (49) 81 (51)	167 (48) 183 (52)	0.83**
BMI Z-score	Median (Q1, Q3)	0.74 (-0.34, 1.75)	0.26 (-0.36, 1.22)	0.003*
Tanner Stage	1 2 3 4 5	56 (35) 50 (32) 18 (11) 17 (11) 17 (11)	91 (26) 73 (21) 59 (17) 72 (21) 55 (16)	< 0.001**

*Kruskal-Wallis Test **Fisher's Exact Test

RESULTS

Figure 1: Differences in Fat Distribution in HIV-positive and HIV-negative Children (mean, 95% CI)



HIV-positive children had significantly lower % total body fat (P< 0.001, and % extremity fat (P< 0.001), and higher trunk-to-extremity fat ratio (P < 0.016) compared to HIV-negative children. These were adjusted for age, sex, race and Tanner stage.

Table 2: HIV Disease Severity and ART Use in HIV-pos Children at Time of DXA Scan (n=339) ¹

Characteristic		N (%)
CDC Category	N/A	159 (47)
	B	97 (29)
	C	83 (24)
CD4 count (cells/mm ³)	< 200	12 (4)
	200-500	72 (21)
	> 500	255 (75)
HIV-RNA (copies/mL)	< 400	163 (48)
	400-5000	123 (36)
	>5000	53 (16)
HAART	Yes	296 (87)
	No	43 (13)
Regimen type	NRTI+NNRTI+PI	34 (10)
	NRTI+NNRTI	49 (14)
	NRTI+PI	211 (62)
	NNRTI+PI	1 (0)
	Other ARV	21 (6)
	Not on ARV	23 (7)

¹ N=339 includes no missings on variables in the table

RESULTS

Table 3: Factors Associated with Four Fat Outcomes in 339 HIV-pos Children – Multivariate Models

Characteristic ³	% use	% Total Body Fat	% Extremity Fat	% Trunk Fat	Trunk-to-Extremity Fat Ratio
Mean Difference (95% CI), P value					
Male vs. female		-7.6 (-9.7, -5.4) < 0.001	-0.44 (-1.9, 1.0) 0.55	-1.8 (-3.4, -0.23) 0.025	0.96 (0.90, 1.03) 0.26
African American vs. white		-2.4 (-4.9, -0.04) 0.047	1.2 (-0.5, 2.8) 0.17	-0.84 (-2.6, 0.96) 0.36	0.95 (0.88, 1.03) 0.20
Age (per yr)		-0.12 (-0.78, 0.54) 0.72	-0.35 (-0.82, 0.12) 0.14	0.70 (0.2, 1.2) 0.006	1.02 (1.1, 1.05) 0.021
Lifetime PI (yr) ⁴ ≥ 2 vs. < 2 or never		3.5 (-0.08, 7.0) 0.055	-1.07 (-3.2, 1.05) 0.32	2.4 (0.15, 4.6) 0.037	1.07 (0.97, 1.2) 0.17
Current Atazanavir	11%	3.3 (-0.09, 6.6) 0.056			
Current Other PI		-0.68 (-3.4, 2.0) 0.61			
Current Any NRTI use		-0.01 (-4.5, 4.5) 0.99			
Current d4T	27%		-1.8 (-3.4, -0.12) 0.035		1.09 (1.01, 1.2) 0.026
Current ddI	23%			2.1 (0.33, 3.9) 0.020	
Current Abacavir ⁵	26%		-1.8 (-3.5, -0.04) 0.045	2.0 (0.06, 3.8) 0.043	1.09 (1.01, 1.2) 0.032
Current 3TC ⁶	30%				0.93 (0.87, 1.0) 0.065
Current Other NRTI			0.64 (-1.2, 2.5) 0.51	-0.59 (-2.6, 1.4) 0.57	1.02 (0.95, 1.09) 0.57
Current Any NNRTI use		0.04 (-2.6, 2.7) 0.97	-0.30 (-2.0, 1.4) 0.72	-0.97 (-2.8, 0.85) 0.30	0.97 (0.90, 1.05) 0.44

³ See methods for explanation of inclusion of ARV variables in models. All models are adjusted for age, race, sex, Tanner and CDC class.

⁴ Number of children with lifetime PI use: Ever = 289, 1-2 yr = 9, < 1 yr = 7, never = 34). The categories of <2 yr and never use were combined due to small numbers and because there was no trend toward differences between < 2 yr of use versus never use.

⁵ This variable is "any abacavir" use which includes use in a single (14%) or combination formulation .

⁶ This variable is 3TC use in a single formulation. A variable that included 3TC use in either a single or combination formulation (total 53%) was not associated with trunk-to-extremity fat ratio.

SUMMARY AND CONCLUSIONS

HIV-infected children have lower total body and extremity fat, and higher trunk-to-extremity fat ratios than do uninfected children.

Specific antiretroviral agents appear to impact total, extremity and trunk fat differently in HIV-infected children.

Atazanavir, a protease inhibitor, was associated with higher total fat.

Nucleotide Reverse Transcriptase Inhibitors were associated with changes in body fat by region:

- abacavir and d4T were associated with less extremity fat.
- abacavir and ddI were associated with more trunk fat
- abacavir and d4T were associated with greater trunk-to-extremity fat ratios
- 3TC was associated with lower trunk-to-extremity fat ratios.

Children with lifetime use of PI for > 2 years had more total body and trunk fat than those with < 2 years or no use.

Although these positive, cross-sectional findings imply associations, they do not permit determination of the temporal relationship between ARV use and body fat changes. Future analyses will examine duration of individual agents with fat outcomes.

Future prospective studies will incorporate analyses of changes in body composition in HIV-infected children. These studies will allow us to determine how specific ARVs impact body composition.

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