Growth and Lipid Profiles in a South African Cohort of HIV+ Children and HIV- Controls

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Abstract

Background: Prior research in sub-Saharan Africa reports elevated lipids in perinatally HIV-infected children receiving ritonavir-boosted lopinavir (LPV/r) compared to non-nucleoside reverse transcriptase inhibitors (NNRTIs); however, interpretation of findings is limited by lack of comparison data from HIV-uninfected children. Here, we compare lipid profiles and body composition between HIV-infected children (stratified by LPV/r vs NNRTIs) and HIV-uninfected controls.

Methods: The Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study (CHANGES) is a longitudinal cohort study of perinatally HIV-infected children and HIV-uninfected controls aged 4-9 years in Johannesburg, South Africa. At enrollment, anthropometrics, viral load, CD4, total cholesterol (TC), HDL, LDL, and triglycerides (TG) were measured. Weight- (WAZ), height- (HAZ), and BMI-for-age (BAZ) z-scores (per WHO) were calculated. US pediatric thresholds for dyslipidemia were used.

Results: 553 HIV-infected children (46% male, median age 6.9 years) and 300 HIV-uninfected controls (54% male, median age 7.0 years) were enrolled. Of the HIV-infected children, 94.8% were on antiretroviral therapy (ART) (65.4% on LPV/r and 29.4% on NNRTIs) and 90.8% had undetectable plasma HIV RNA; median CD4% was 34.4. Compared to HIV-uninfected controls, mean WAZ was lower in HIV-infected children (-0.7 vs -0.3, p<0.01), a greater proportion of HIV-infected children were stunted (HAZ <-2) (18.4 vs 9.3%, p<0.01), and a smaller proportion were overweight (BAZ>1) or obese (BAZ>2) (14.4 vs 21.7%, p=0.01). Whether on LPV/r or NNRTIs, a higher proportion of HIV-infected children had borderline/elevated TC or abnormal TG than HIV-uninfected controls, although a higher proportion of those on LPV/r had borderline/elevated TC, borderline/elevated LDL, or abnormal TG than those on NNRTIs. A greater percentage of children on LPV/r had borderline/elevated LDL than HIV-uninfected controls.

Conclusions: In a South African cohort of HIV-infected children and population-appropriate HIV-uninfected controls, HIV-infected children were of smaller size than controls. Unfavorable alterations in lipid profiles were detected in HIV-infected children on LPV/r as well as those on NNRTIs compared to HIV-uninfected controls. In light of childhood origins of cardiovascular disease and the need for HIV-infected children to remain on lifelong ART, strategies for early life management of lipid alterations may be warranted.

Background

- Dyslipidemia, impaired growth, and abnormalities in body composition have been observed in HIV-infected children from a young age.
- Increased lipid abnormalities have been observed in children taking protease inhibitors (PIs) compared to children on non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Earlier research on dyslipidemia in HIV-infected children in sub-Saharan Africa has been limited by lack of established population norms and appropriate control groups.
- Here we compare the lipid profiles, growth, and body composition of HIV-infected and HIV-uninfected children, stratified by those taking ritonavir-boosted lopinavir (LPV/r) and those taking NNRTIs.

Methods

Study Sample

- This is an analysis of enrollment data from the Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study (CHANGES), a longitudinal study of perinatally HIV-infected children.
- There are two study sites: Empilweni Services and Research Unit (ESRU) and Perinatal HIV Research Unit (PHRU) in Johannesburg, South Africa.
- All HIV-infected children initiated ART before age 3 years.
- A population-appropriate HIV-uninfected control group was recruited from communities served by study sites and the contacts and relatives of participants.

Outcomes

- Weight- (WAZ), height- (HAZ), and BMI-for-age (BAZ) z-scores using WHO growth standards
- Sum of skinfolds as a proxy for total body fat: Sum of bicep, tricep, subscapular, suprailiac, umbilical, mid-thigh skinfolds, in millimeters
- Mid-upper arm circumference (MUAC), in centimeters
- Viral load in copies/mL and CD4%
- Non-fasting total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), in mg/dL

Statistical Analysis

- We used student t-tests, Wilcoxon tests, Fisher exact tests, chi-squared tests, ANOVA, and Tukey-Kramer tests, as appropriate.
- Missing skinfolds were imputed using several methods; however the results of the analyses based on the imputed datasets and the complete case datasets did not differ substantially, so only the results of the complete case analysis were reported.

Results

Study Sample (Table 1)

- 553 HIV-infected and 300 HIV-uninfected children were recruited.
- The two groups were similar in terms of median age (6.9 vs 7.0 years, p=0.788) and several markers of socioeconomic status. But the HIV-infected group had a greater percentage of females (53.9% vs 46.0%, *p*=0.028).
- Of the HIV-infected children, 65.4% were on LPV/r-based regimens, 29.4% were on NNRTI-based regimens (Efavirenz or Nevirapine), and 5.3% were not on ART.
- 90.8% of the HIV-infected children had undetectable viral loads (<400 copies/mL).

Table 1: Characteristics of Study Sample

Characteristic	HIV-infected (N=553)	HIV-uninfected (N=300)	*p*-value
Age in years, Median (IQR)	6.9 (5.6, 7.8)	7.0 (5.3, 8.1)	0.788
Female, N (%)	298 (53.9)	138 (46.0)	0.028
Child sometimes has to go to bed hungry, N (%)	64 (11.6)	30 (10.0)	0.332
Caregiver completed high school, N (%)	251 (45.5)	138 (46.0)	0.882
Household has indoor toilet, N (%)	266 (48.2)	157 (52.3)	0.248
Treatment regimen, N (%)			
LPV/r-based	361 (65.4)		
NNRTI-based	162 (29.4)		
Not on ART	29 (5.3)		
Undetectable viral load, N (%) †	501 (90.8)		
CD4%, Median (IQR)	34.4 (30.1, 39.3)		

† <400 copies/mL

Growth by HIV Status (Table 2)

- HIV-infected children had significantly lower mean WAZ (-0.7 vs -0.3, p <0.001), lower mean HAZ (-1.1 vs -0.7, p <0.001), and higher proportion of stunting (18.4 vs 9.3%, p<0.001) compared to HIV-uninfected controls, regardless of whether they were on LPV/r-based or NNRTI-based regimens.
- Overall there was a similar proportion of underweight (6.9 vs 4.3%, p=0.131) and less overweight (14.9 vs 21.7%, p=0.007) among HIV-infected children compared to HIV-uninfected controls.

Table 2: Growth and Body Composition, by HIV Status

Variable	HIV-Infected	HIV-Uninfected	*p*-value
WAZ, Mean (SD)	-0.7 (1.0)	-0.3 (1.0)	<0.001
HAZ, Mean (SD)	-1.1 (1.0)	-0.7 (1.0)	<0.001
BAZ, Mean (SD)	-0.02 (1.0)	0.1 (1.1)	0.046
Underweight, WAZ <-2, N (%)	38 (6.9)	13 (4.3)	0.131
Stunted, HAZ <-2, N (%)	101 (18.4)	28 (9.3)	<0.001
Overweight, BAZ >1, N (%)	79 (14.4)	65 (21.7)	0.007
Sum of Skinfolds, mm, Mean (SD)	38.7 (9.7)	44.0 (12.6)	<0.001
MUAC, cm, Mean (SD)	16.3 (1.7)	17.1 (2.0)	<0.001

Body Composition by HIV Status (Table 2, Figure 1)

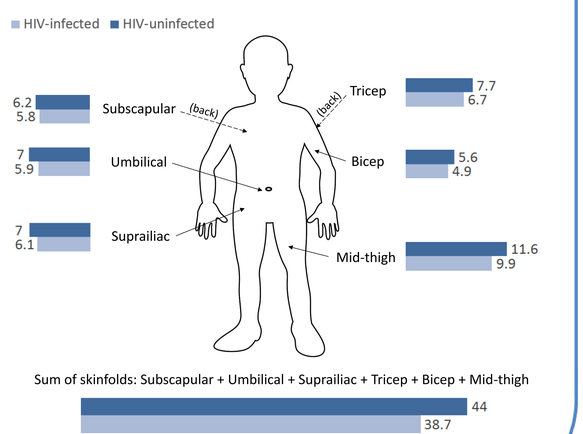
- 61 children (7.2%) lacked a complete set of skinfold measurements They were more likely to be female and were bigger, on average, in terms of WAZ, BAZ, and MUAC.
- The means of all skinfolds, sum of skinfolds, and MUAC were significantly higher in HIV-uninfected controls.
- Sum of skinfolds remained significantly higher in HIV-uninfected controls compared to both HIV-infected groups, after controlling for age, sex, and BMI.

Growth and Body Composition by ART regimen

- Children on LPV/r were similar to children on NNRTIs in terms of mean WAZ (-0.7 vs -0.8, p=0.827) and mean BAZ (-0.1 vs 0.1, p=0.234). However, the mean HAZ of the LPV/r group was significantly higher than the NNRTI group (-1.0 vs -1.3, p=0.007).
- There was no significant difference between mean subscapular skinfold for children on NNRTIs compared to HIV-uninfected controls. Compared to the NNRTI group, tricep skinfold was lower and mid-thigh skinfold was higher in the LPV/r group.
- MUAC and sum of skinfolds did not differ by regimen.

Figure 1: Skinfold Measurements in Millimeters, by HIV Status

All skinfold measurements were significantly smaller in HIV-infected children



Lipids (Figure 2)

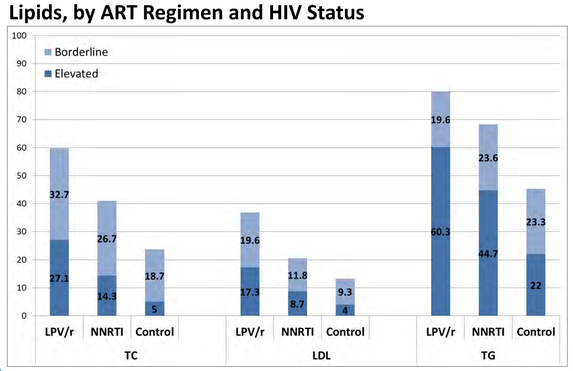
- A higher proportion of HIV-infected children had elevated TC (21.9 vs 5.0%, *p*<0.01), LDL (13.8 vs 4.0%, *p*<0.001), or TG than HIV-uninfected controls (55 vs 22%, *p*<0.001). HIV-infected children also had higher mean TC (175.5 vs 151.5 mg/dL, *p*<0.001), LDL (96.9 vs 83.8 mg/dL, *p*<0.001), and TG (115.5 vs 81.6 mg/dL, *p*<0.001).
- After stratifying by ART regimen, there was a gradient in the proportions of children with elevated TC, TG, and LDL (See Figure 2). The HIV-uninfected controls had the smallest proportions, while the LPV/r group had the highest, and the NNRTI group was in the middle. All comparisons between the groups were significant.
- There was a similar gradient for mean TC and TG. There was no significant difference in mean LDL between the HIV-uninfected controls and the children on NNRTIs.
- There was no difference in the proportions of children who had abnormal HDL (<40 mg/dL) by HIV status (14.0 vs 16.3%, *p*=0.661)
- HIV-infected children had higher mean HDL (55.5 vs 51.3 mg/dL, *p*<0.001), regardless of ART regimen.

Table 3: Pediatric Dyslipidemia Guidelines

Lipid (mg/dL)	Acceptable	Borderline	Elevated
TC	<170	170-199	≥200
LDL	<110	110-129	≥130
TG*	<75	75-99	≥100

*For children ages 0-9. Source: NHBLI 2011 Guidelines[1]

Figure 2: Percent of Children with Borderline or Elevated Lipids, by ART Regimen and HIV Status



Conclusions

- In this cohort of predominantly virally suppressed HIV-infected children who initiated ART early in life, we observed a large proportion with disturbed growth, especially stunting, when compared to a group of HIV-uninfected controls of similar socio-economic background.
- HIV-infected children had less favorable lipid profiles than HIV-uninfected controls. Children on NNRTI-based regimens had more favorable lipid profiles than children on LPV/r-based regimens; nevertheless their lipid profiles were still abnormal.
- Interventions to reduce dyslipidemia among HIV-infected children may reduce their risk of developing heart disease later in life. One way to reduce dyslipidemia may be avoiding prolonged use of PI-based regimens.
- Additional research on strategies for optimizing lipid profiles of HIV-infected children in low resource settings is warranted.

References

1. National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011,128 Suppl 5:S213-256.

Acknowledgements

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