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Metabolic Abnormalities and Body Composition of HIV-infected South African Children on Ritonavir-Boosted Lopinavir-based or Nevirapine-based Antiretroviral Therapy: A Comparative Study

Stephen Arpadi, MD MS^{a,b}, Stephanie Shiau, MPH^{a,b}, Renate Strehlau, MBChB^d, Leigh Martens, MBChB^d, Faezah Patel, MBChB^d, Ashraf Coovadia, MBChB^d, Elaine Abrams, MD^{b,c}, and Louise Kuhn, PhD^{a,b}

^aColumbia University, Gertrude H. Sergievsky Center, New York, NY

^bColumbia University, Mailman School of Public Health, Department of Epidemiology, New York, NY

^cColumbia University, College of Physicians and Surgeons, Department of Pediatrics, New York, NY

^dUniversity of the Witwatersrand, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, Johannesburg, South Africa

Abstract

Background—Few studies have assessed metabolic and body composition alterations in young perinatally HIV-infected African children on antiretroviral therapy (ART). We compared metabolic profiles and regional fat of children on a combination of ritonavir-boosted lopinavir (lopinavir/ritonavir), lamivudine, and stavudine to those switched to nevirapine, lamivudine, and stavudine.

Methods—This study evaluated metabolic and body composition outcomes in 156 HIV-infected children completing a randomized trial that assessed the continued use of lopinavir/ritonavir-based or switch to NVP-based ART in Johannesburg, South Africa (2005–2010). Fasting total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides were measured. Total and regional body fat (BF) were estimated by anthropometry and bioelectrical impedance analysis (BIA). A clinical assessment for lipodystrophy was conducted. Modified intent-to-treat analyses were conducted.

Results—156 children (mean age 5.1±0.8 years, mean duration of treatment 4.2±0.7 years, mean time since randomization 3.4±0.7 years) were enrolled. 85 were randomized to the lopinavir/ritonavir- and 71 to the nevirapine-group. The lopinavir/ritonavir-group had lower mean HDL (1.3±0.4 vs. 1.5±0.4 mmol/L, p<0.001) and higher mean TC (4.4±1.0 vs. 4.1±0.8 mmol/L, p=0.097), LDL (2.6±0.9 vs. 2.3±0.7 mmol/L, p=0.018), and triglycerides (1.1±0.4 vs. 0.8±0.3 mmol/L, p<0.001). The lopinavir/ritonavir-group had more total BF by mean skinfold sum

(43 ± 11.1 vs. 39 ± 10.1 mm, $p=0.031$) and BF% by BIA (17.0 ± 7.0 vs. $14.1\pm 8.0\%$, $p=0.022$). Thirteen (8.4%) met criteria for lipodystrophy.

Conclusions—Unfavorable alterations in lipid profile and triglycerides, and differences in fat are detectable in young HIV-infected South African children receiving lopinavir/ritonavir-based vs. those switched to nevirapine-based regimens. Interventions to mitigate these alterations are warranted to reduce long-term cardiovascular disease risk.

Keywords

HIV; Antiretroviral Therapies; Body Composition; Lipids

INTRODUCTION

Unfavorable alterations in lipid and glucose metabolism, well established risk factors for cardiovascular disease (CVD), are reported among children and adolescents with perinatally acquired HIV-infection receiving antiretroviral therapy (ART).^{1–8} Significant proportions of ART-treated children have elevated total cholesterol (TC), low density lipoprotein (LDL), triglycerides and abnormal glucose and insulin homeostasis.^{1–8} The etiology of the metabolic derangements is multi-factorial, and specific ART drugs, particularly protease inhibitors (PIs), are an important cause of dyslipidemia and impaired glucose homeostasis.^{1–3,7–10} Exposure to nucleoside (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have also been associated with dyslipidemia.⁷

Abnormal body fat distribution, or lipodystrophy, also occurs in HIV-infected children both alone and in combination with metabolic abnormalities and may also contribute to increased CVD risk.^{2,11–16} A number of drugs, including thymidine analogue NRTIs and PIs, are associated with lipodystrophy.¹⁷ With greatly improved survival due to effective therapies, developing treatment strategies for children that optimize long-term viral suppression and limit long-term adverse effects is an important goal.

Few studies have evaluated lipid profiles and insulin-glucose metabolism or body fat distribution in young children receiving ART in sub-Saharan Africa, where over 90% of HIV-infected children reside.¹⁸ The objectives of this study are to examine the lipid profiles, insulin sensitivity, markers of inflammation, and regional fat distribution of HIV-infected children in South Africa who were initiated on a PI-based regimen prior to age 2 years and randomly assigned to continue on a PI-based regimen or switch to an NNRTI-based regimen. These parameters are also compared in children with and without lipodystrophy.

PATIENTS AND METHODS

Study Design

This cross-sectional study evaluated HIV-infected children at the final study visit of a randomized clinical trial (NEVEREST 2) that assessed continued ritonavir-boosted lopinavir (lopinavir/ritonavir)-based therapy vs. switching to nevirapine-based therapy, conducted from 2005 to 2010.¹⁹ In NEVEREST 2, children who maintained a viral load (VL) <400 copies/mL for 3 months while on their primary lopinavir/ritonavir-containing regimen

were randomized to one of two groups. Children randomized to the lopinavir/ritonavir-group continued to receive lopinavir/ritonavir (230 mg/m²), lamivudine (4 mg/kg), and stavudine (1 mg/kg) whereas the nevirapine-group children switched to nevirapine (120 mg/m² once per day for the first 2 weeks and thereafter 200 mg/m² every 12 hours), lamivudine, and stavudine, the two regimens recommended for pediatric use in South Africa.²⁰ The study was conducted at the Empilweni Clinical Research Unit at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa and was approved by the Institutional Review Boards of Columbia University and the University of the Witwatersrand. Each child's guardian provided signed informed consent.

Measurements

Weight (kg) was measured using a digital scale and height (cm) was measured using a stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m²). Weight-for-age (WAZ), height-for-age (HAZ), and BMI-for-age z-scores (BAZ) were determined using WHO standards.²¹ Blood pressure was measured using an electronic sphygmomanometer with a pediatric cuff (Angelus, Model number SN-AJ710150) and compared with age and sex reference values.²² A clinical assessment for lipodystrophy was completed by two trained physicians (RS, LM) and children were classified as having lipodystrophy (LD+), possible lipodystrophy (possible LD), and no signs of lipodystrophy (LD-) if 2, 1, or 0 of the following features of lipoatrophy (sunken cheeks, temporal wasting, skinny limbs, wasting of buttocks) or lipohypertrophy (increased abdominal girth, dorsal cervical enlargement, breast enlargement) were present.¹²

Following an overnight fast (8 hours), TC, LDL, high-density lipoprotein (HDL), triglycerides, C-reactive-protein (CRP), and insulin were measured using the Roche COBAS®INTEGRA 400 system and venous blood glucose with a handheld glucometer. VL by quantitative HIV-1 RNA PCR (Cobas Ampliprep Taqman V2, Roche), absolute CD4 count, and CD4 percentages (Beckman Coulter Flow Analyzer) were also determined. TC categories were set as <4.4 mmol/L (<170 mg/dL) for acceptable, 4.4–5.1 mmol/L (170–199 mg/dL) for borderline, and ≥5.2 mmol/L (≥200 mg/dL) for elevated.²³ A cut off value of 0.9 mmol/L (<35 mg/dL) was used for abnormal HDL concentrations.²⁴ LDL categories were set as <2.9 mmol/L (<110 mg/dL) for acceptable, 2.9–3.3 mmol/L (110–129 mg/dL) for borderline, and ≥3.4 mmol/L (≥130 mg/dL) for elevated. Triglycerides >1.69 mmol/L (>150 mg/dL) and CRP >3 mg/L were considered elevated.^{23–25} Impaired fasting glucose was defined as ≥6.11 mmol/L (≥110 mg/dL).²⁶ Homeostasis model assessment of insulin resistance (HOMA-IR) >3.16 was used to determine insulin resistance.²⁷ All impaired fasting glucose measurements were repeated for confirmation.

Anthropometrics, including circumferences and skinfold thicknesses, were measured by two trained physicians (RS, LM) unblinded to treatment using the average of triplicate standardized measurements. Circumferences were measured to the nearest 0.1 cm using a flexible tape measure with a spring tension attachment at the mid-upper arm (MUAC), mid-upper thigh (MTC), mid-waist (MWC), and maximum hip (MHC). Skinfolds, including bicep skinfold (BSF), tricep skinfold (TSF), subscapular skinfold (SSF), suprailiac skinfold (SISF), umbilical skinfold (USF), and mid-thigh skinfold (MTSF), were measured with a

Harpndon caliper (Baty International, England). Cumulative skinfold sum (SFS) was calculated by adding BSF, TSF, SSF, SISF, USF, and MTSF.

Extremity fat area (cm²), including upper arm fat area (AFA), percentage of fat in upper arm (%AF), upper leg fat area (LFA), and percentage of fat in upper leg (%LF) were calculated.²⁸ Regional (arm, trunk, leg) fat as proportions of total body fat were calculated as follows: arm [(BSF+TSF)/SFS], trunk [(SSF+SISF+USF)/SFS], and leg [MTSF/SFS]. The following trunk-extremity skinfold ratios were calculated as indicators of central subcutaneous fat as compared to extremity fat: trunk-arm [(SSF+SISF)/(BSF+TSF+SSF+SISF)] and trunk-leg [(SSF+SISF)/(MTSF+SSF+SISF)].²⁹ Total body resistance was measured by single-frequency bioimpedance analysis (BIA) (Quantum II, RJL Systems, Clinton Township, MI) and used in a prediction equation to estimate percent body fat (%BF).³⁰

Statistical Analysis

Modified intent-to-treat analyses of the treatment groups (lopinavir/ritonavir vs. nevirapine) were conducted using the Wilcoxon rank-sum test for non-normally distributed and t-test for normally-distributed continuous variables. Chi-squared or Fisher's exact tests were used for categorical variables. These tests were also used for comparisons across lipodystrophy categories. Multiple linear regression was performed to assess differences in arm, trunk, and leg fat across lipodystrophy groups, adjusting for total fat, sex, and age. All statistical tests were 2-sided and a *p*-value <0.05 was considered statistically significant. Analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 195 children randomized in the NEVEREST 2 clinical trial, 156 completed the final study visit and were included in this analysis (Figure 1). Six(3.1%) children died, 28(14.4%) were lost to follow up, and 5(2.6%) transferred out. At the time of this assessment, subjects were between 3.3 and 7.3 years old, 52% were male, and 85 were previously randomized to the lopinavir/ritonavir-group and 71 to the nevirapine-group (Table 1). There were no differences in total time on ART or time since randomization between the groups. WAZ, HAZ, or BAZ were similar between groups at randomization and at the time of this assessment. At the final study visit, 5(5.9%) in the lopinavir/ritonavir-group and 7(9.9%) in the nevirapine-group had moderate or severe malnutrition i.e. WAZ <-2.²¹ Sixteen(18.8%) lopinavir/ritonavir-group and 13(18.3%) nevirapine-group children had a HAZ <-2. No differences in proportion of children with abnormal systolic (38.8 vs. 26.8%, *p*=0.112) or diastolic (42.3 vs. 35.2%, *p*=0.363) blood pressure were detected. Most children (88%) had a VL<50 copies/mL. There were no virologic differences between the groups. Compared to the lopinavir/ritonavir-group, the nevirapine-group had a higher median CD4 cell count. There were no differences in lipodystrophy classification between lopinavir/ritonavir- and nevirapine-groups.

Several metabolic measurements differed between the treatment groups (Table 2). The mean TC was greater in the lopinavir/ritonavir-group, as was the proportion with elevated TC. Significantly lower mean HDL concentrations and higher mean LDL concentrations were

observed in the lopinavir/ritonavir-group. Additionally, a significantly higher ratio of TC:HDL was observed in the lopinavir/ritonavir-group. The mean triglyceride concentration and proportion with abnormal triglycerides were also greater in the lopinavir/ritonavir-group. Mean CRP and proportion with elevated CRP were lower for the lopinavir/ritonavir-group. There were no differences in recent (i.e. past 1 month) or acute illnesses between the groups.

In addition, multiple abnormalities were more common in the lopinavir/ritonavir group. More children in the lopinavir/ritonavir-group had elevated TC and LDL (13.2 vs. 5.5%, $p=0.054$) and elevated TC and triglycerides (5.9 vs. 0.0%, $p=0.038$) compared to children in the nevirapine-group. Mean glucose and HOMA-IR did not differ between the groups. A repeat impaired fasting glucose was detected in 1(1.2%) child in the lopinavir/ritonavir-group and 1(1.4%) child in the nevirapine-group. None in the lopinavir/ritonavir-group had insulin resistance compared to 3(4.3%) in the nevirapine-group ($p=0.09$).

Complete body composition measurements were available for 139 children (Table 3). Children in the lopinavir/ritonavir-group had a greater amount of body fat than children in the nevirapine-group, as measured by mean SFS. A similar pattern in total BIA-determined %BF was observed. Leg fat area and percentage of fat in upper leg were both significantly greater in the lopinavir/ritonavir-group. In addition, while the arm fat proportion of total fat was not different between the groups, the trunk fat proportion of total fat was lower for the lopinavir/ritonavir-group and the leg fat proportion of total fat was significantly greater for the lopinavir/ritonavir-group. Although there was no difference in trunk-arm skinfold ratios between the groups, the lopinavir/ritonavir-group had a lower trunk-leg skinfold ratio compared to the nevirapine-group.

Thirteen(8.3%) children were classified as LD+ and 18(11.5%) as possible LD. Of the 13 LD+ children, all had signs of lipotrophy and 6 also had signs of lipohypertrophy. There were no differences in age, sex, age at ART initiation, total time on ART, randomization group, WAZ, HAZ, BAZ, or proportion with VL <50 copies/mL between the three lipodystrophy groups.

No differences in TC, HDL, LDL, TC:HDL ratio, CRP, glucose, or HOMA-IR were detected across lipodystrophy groups (data not shown). However, mean triglycerides and proportion with abnormal triglycerides was higher for LD+ than LD- children as well as for possible LD than LD- children.

Overall, LD+ children had significantly less body fat compared to LD- children as measured by SFS. A similar pattern was observed using BIA-based estimates of total BF%, although this did not achieve statistical significance. As presented in Figure 2, no differences were seen in arm fat; however, LD+ children had a greater trunk fat proportion of total fat and less leg fat as a proportion of total fat compared to LD- children. A similar pattern of differences in arm ($p=0.04$), trunk ($p=0.01$), and leg ($p=0.05$) fat between LD+ and LD- children was detected after adjusting for total fat, sex, and age by means of multiple linear regression. LD+ children also had significantly greater trunk-arm and trunk-leg skinfold ratios compared to LD- children.

DISCUSSION

In this study of young perinatally HIV-infected South African children initiated and suppressed on PI-based ART and then randomized to either remain on the initial PI-based regimen or switch to a NNRTI-based regimen, the group remaining on the lopinavir/ritonavir-based regimen had unfavorable concentrations of lipoproteins and triglycerides compared to those switching to the nevirapine-based regimen. These results confirm and extend our prior, shorter term observations and other published studies.^{1,3,4,31,32} With extended survival and the requirement of lifelong ART, these metabolic alterations may pose long-term risk with respect to CVD, as CVD often results from exposure to risk factors that have their origins in childhood.³³ Serum lipid concentrations, insulin resistance, hypertension, and obesity early in life contribute to the development of atherosclerotic lesions in children and adolescents.^{34,35} In addition, studies among adults contracting HIV indicate that HIV infection *per se* may be associated with greater CVD possibly due to chronic immune activation.³⁶ Also, increased intima-media thickness, an indicator of atherosclerosis, has been reported in studies of HIV-infected children and adolescents receiving ART.³⁷ The constellation of risk factors seen during childhood and adolescence among those with perinatally-acquired HIV suggests that developing strategies for CVD risk reduction during childhood are warranted.

The elevated CRP reported in this study has also been previously reported.³⁷ While CRP might have been expected to cluster with alterations in lipids and triglycerides or regional fat changes depot, our finding of elevated CRP in the NNRTI-group compared to the PI-group is not without precedent nor is the long-term significance known.^{38,39}

In this cohort of children receiving stavudine-backbone ART, continuation on PI-based regimen was associated with greater overall subcutaneous fat, and less central (trunk) fat in relation to leg fat in comparison to children switched to an NNRTI-based regimen. This difference in subcutaneous regional fat was detectable even though the groups had a similar overall WAZ, BMI and proportion of children with lipodystrophy. Since children in our study were randomly assigned to continue on a PI-based regimen or switch to an NNRTI-based regimen, our findings provide less confounded evidence that PI-based regimens are associated with greater amounts of subcutaneous fat compared to NNRTI than available from prior non-randomized studies.^{2,13,40,41} It is not possible to determine which of the patterns of changes in adipose tissue we observed is a departure from normal, since our study did not include a healthy comparison group and appropriate skinfold standards are not available for young South African children. In the present study no relationship was detected between adipose and metabolic measures. Whether the clustering of these features will evolve with additional time and exposure to ARV remains to be determined.

Lipodystrophy is cosmetically stigmatizing and can adversely affect adherence to ART.⁴² Finding a substantial proportion of young children with lipodystrophy has implications for future adherence, especially during adolescence when awareness of physical appearance is heightened. Most studies indicate the prevalence of lipodystrophy increases with age, duration of therapy, and puberty.^{5,15} In addition, stavudine, possibly due to inhibition of mitochondrial DNA polymerase has been implicated in lipoatrophy, and for this and other

reasons, WHO advises phasing out or discontinuing stavudine.^{43,44} Of interest, anthropometry appears to confirm the distinctive regional fat pattern of lipodystrophy observed by clinician assessment. Standardized clinical and anthropometric assessments for early detection of changes in regional fat are a valuable addition to clinical studies.

There are a number of limitations in this study. The metabolic and body composition measurements did not assess visceral adiposity, were obtained at the final visit of this trial, and were not available prior to randomization. For those switched back to nevirapine, observation time was relatively short. In addition, family history of lipid disorders, diet and exercise may be relevant to our findings but were not assessed. In addition, although significant proportions of subjects had abnormal blood pressure, interpretation is difficult as the norms applied were from US children. Furthermore, the measurement of glucose-insulin homeostasis used is relatively insensitive compared to more invasive tests.⁸ Finally, a single CRP measurement may not be reflective of long-term inflammatory status.

Lopinavir/ritonavir is highly effective in suppressing HIV and an essential part of treatment for children in resource-limited settings. WHO includes lopinavir/ritonavir as part of first-line treatment for HIV-infected children with prior exposure to NNRTI used for prevention of mother-to-child transmission and for those who experience treatment failure with NNRTIs.⁴³ The long-term impact of the body fat and lipid alterations bears further study, as do efforts to devise safe and effective approaches for prevention and management of these abnormalities. It is also essential to expand access to newer antiviral agents with potentially fewer metabolic effects to children in resource-limited settings.^{43,45}

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What is Already Known on this Topic

Changes in lipid, glucose, and triglyceride metabolism, and regional fat are well described among older children and adolescents with perinatally acquired HIV-infection receiving antiretroviral therapy in high income countries.

There are limited studies of younger HIV-infected children in sub-Saharan Africa, where >90% of HIV-infected children live and where there is increasing availability of ART.

What This Study Adds

Hypercholesterolemia and hypertriglyceridemia were detectable in HIV-infected children who were initiated on antiretroviral therapy before the age of 2 years.

These metabolic markers were significantly higher among patients on lopinavir/ritonavir-based than nevirapine-based ART.

Lipodystrophy is visible in 8.4% of children and was confirmed by simple anthropometry.

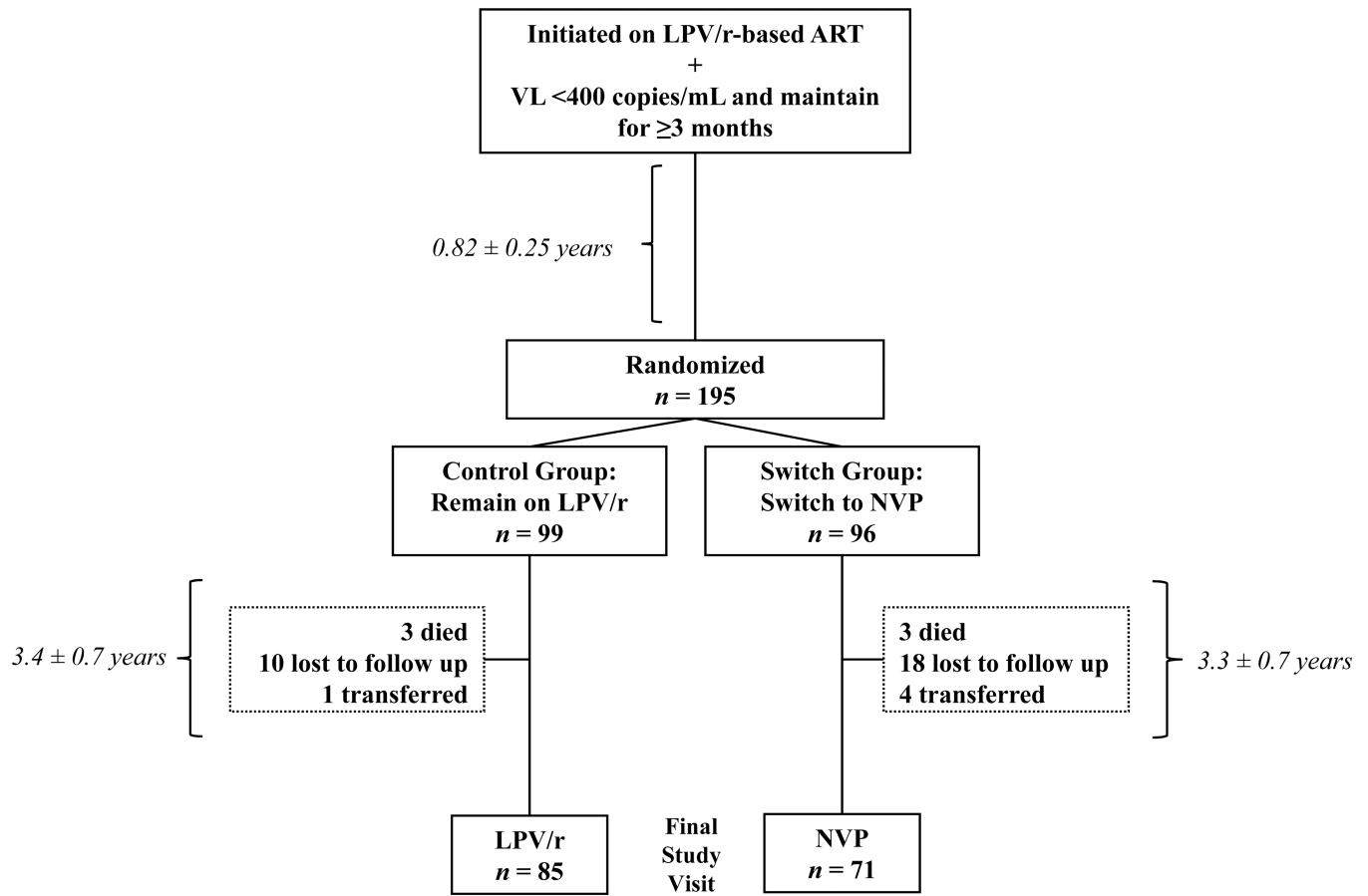
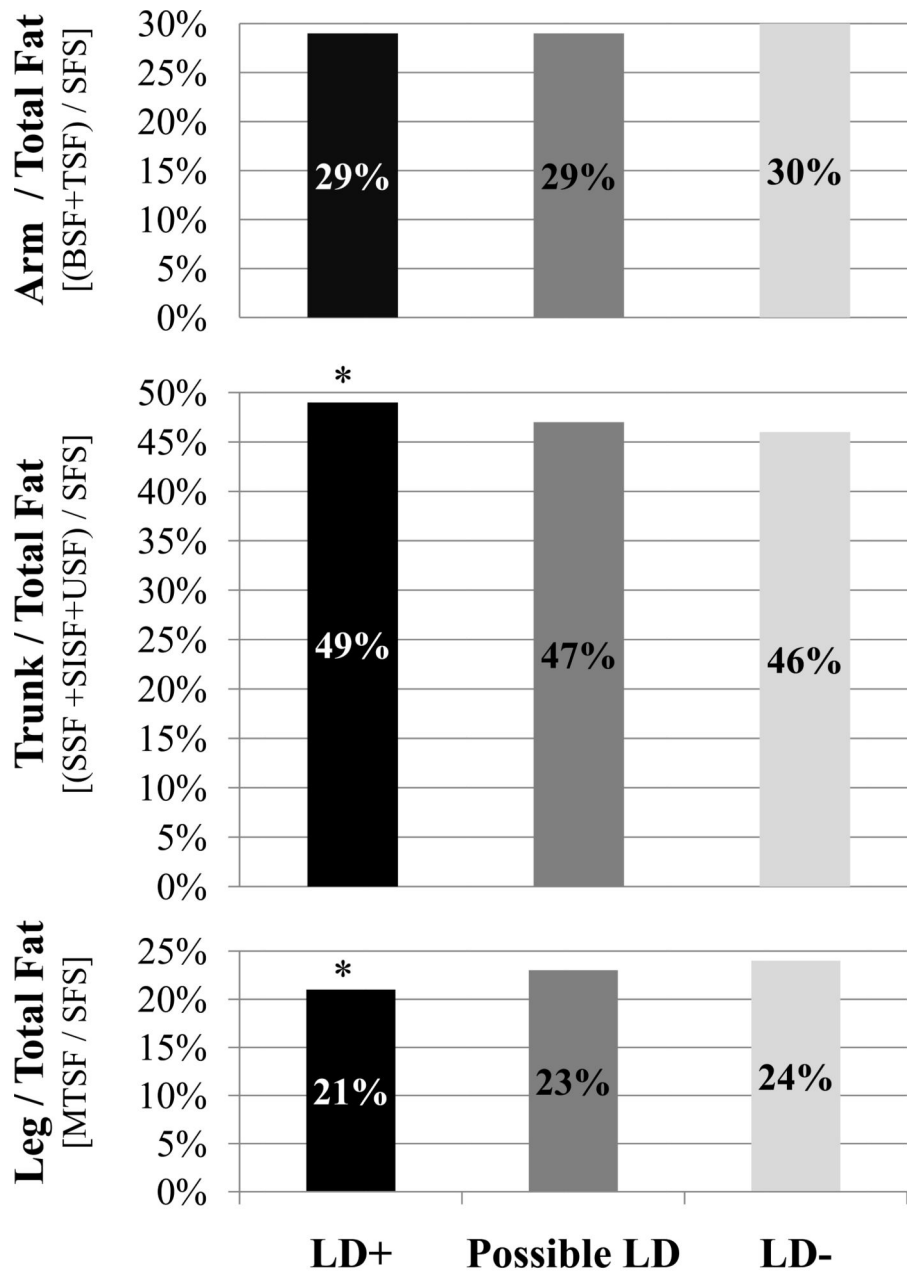


Figure 1. Flow diagram of study participants in NEVEREST 2 (2005–2010) in Johannesburg, South Africa detailing the number of subjects excluded from the analysis, the reason for their exclusion, and distribution of included subjects by randomization group. Time intervals are provided in mean ± standard deviation.



* $p < 0.05$ for LD + vs. LD- by chi-squared test

Figure 2. Regional fat (as % of total) by skinfolds of children with lipodystrophy (LD+), possible LD, or no LD (LD-), as determined by clinician assessment. Children were classified as LD+, possible LD, and LD- if >2 , 1, or 0 of features of lipoatrophy (i.e. sunken cheeks, temporal wasting, skinny limbs, wasting of buttocks) or lipohypertrophy (i.e. increased abdominal girth, dorsal cervical enlargement, or breast enlargement) were present.

Table 1

Characteristics at the time of assessment of 156 perinatally HIV-infected South African children previously suppressed on ritonavir-boosted lopinavir (LPV/r)-based treatment and randomized to either maintain the LPV/r-based regimen or switch to a nevirapine (NVP)-based regimen

characteristic		Randomization group			P-value ^a
		Combined (n=156)	LPV/r (n=85)	NVP (n=71)	
Males	n(%)	81 (51.9)	41 (48.2)	40 (56.3)	0.313
Age, years	Mean±SD	5.1±0.8	5.2±0.8	5.0±0.8	0.095
Total Time on ART, years	Mean±SD	4.2±0.7	4.2±0.7	4.1±0.7	0.338
Time Since Randomization, years	Mean±SD	3.4±0.7	3.4±0.7	3.3±0.7	0.469
Weight, kg	Mean±SD	17.1±2.9	17.2±3.0	16.8±2.8	0.379
Weight-for-Age z-score	Mean±SD	-0.67±1.0	-0.67±0.9	-0.66±1.0	0.912
Height, cm	Mean±SD	105.3±7.2	105.7±7.0	104.9±7.4	0.537
Height-for-age z-score	Mean±SD	-0.98±1.1	-1.02±1.0	-0.93±1.2	0.575
BMI, kg/m ²	Mean±SD	15.3±1.5	15.4±1.6	15.2±1.4	0.529
BMI-for-age z-score	Mean±SD	-0.1±1.0	-0.09±1.0	-0.11±1.1	0.884
Blood Pressure, mmHg	Mean±SD	98.5 ± 13.9	99.6 ± 13.7	97.0 ± 14.1	0.294
Systolic	Mean±SD	62.6 ± 11.6	63.2 ± 12.3	61.8 ± 10.6	0.464
Diastolic					
Viral Load, copies/mL	n (%)	137 (87.8)	72 (84.7)	65 (91.6)	0.450
<50		12 (7.7)	8 (9.4)	4 (5.6)	
50-999		7 (4.5)	5 (5.9)	2 (2.8)	
1000					
CD4 percent, %	Median (IQR)	36.7 (32.7-41.3)	35.9 (31.2-40.6)	37.2 (33.0-41.5)	0.185
CD4 count, cells/mm ³	Median (IQR)	1451 (1048, 1749)	1356 (962, 1620)	1480 (1174,1773)	0.047
LD Classification	n (%)	13 (8.3)	6 (7.1)	7 (9.9)	0.505
LD Possible LD		18 (11.5)	8 (9.4)	10 (14.1)	
No LD		125 (80.1)	71 (83.5)	54 (76.1)	

Abbreviations: SD, standard deviation; IQR, inter-quartile range

^a LPV/r- and NVP-groups were compared using the Wilcoxon rank sum test and t-test for continuous variables and chi-squared or Fisher's exact test for categorical variables

Table 2

Metabolic and other laboratory assessments of 156 perinatally HIV-infected South African children suppressed on ritonavir-boosted lopinavir (LPV/r)-based treatment and randomized to either maintain the LPV/r-based regimen or switch to a nevirapine (NVP)-based regimen

Measure	Randomization Group			p-value ^d
	combined (n=156)	LPV/r (n=85)	NVP (n=71)	
Total Cholesterol , mmol/L(mg/dL)	Mean±SD 4.3±0.9 (166±36)	4.4±1.0 (171±39)	4.1±0.8 (161±31)	0.097
Acceptable: <4.4 (<170)	97 (62.2)	45 (52.9)	52 (73.2)	0.030
Borderline: 4.4–5.1 (170–199)	37 (23.7)	24 (28.2)	13 (18.3)	
Elevated: 5. (200)	22 (14.1)	16 (18.8)	6 (8.5)	
HDL , mmol/L(mg/dL)	Mean±SD 1.4±0.4 (54±15)	1.3±0.4 (51±14)	1.5±0.4 (59±16)	<0.001
Abnormal: <0.9 (<35)	9 (5.8)	7 (8.2)	2 (2.8)	0.183
Normal: 0.9 35)	147 (94.2)	78 (91.8)	69 (97.2)	
LDL , mmol/L(mg/dL)	Mean±SD 2.4±0.8 (94±32)	2.6±0.9 (100±34)	2.3±0.7 (88±27)	0.018
Acceptable: <2.9 (<110)	112 (71.8)	56 (65.9)	56 (78.9)	0.156
Borderline: 2.9–3.3 (110–129)	26 (16.7)	16 (18.8)	10 (14.1)	
Elevated: 3.4 130)	18 (11.5)	13 (15.3)	5 (7.0)	
Total Cholesterol : HDL Ratio	Mean±SD 3.3±1.0	3.6±1.1	2.9±0.9	<0.001
Triglycerides , mmol/L(mg/dL)	Mean±SD 0.9±0.4 (84±36)	1.1±0.4 (94±39)	0.8±0.3 (72±29)	<0.001
Normal: 1.69 (150)	143 (91.7)	74 (87.1)	69 (97.2)	0.038
Abnormal: >1.69 (>150)	13 (8.3)	11 (12.9)	2 (2.8)	
C-Reactive Protein , mg/L	Mean±SD 6.3±15.3	3.5±6.1	9.6±21.4	0.023
Normal: 3	115 (73.7)	69 (81.2)	46 (64.8)	0.021
Elevated: >3	41 (26.3)	16 (18.8)	25 (35.2)	
Glucose , mmol/L(mg/dL)	Mean±SD 5.3±0.5 (96±8.2)	5.4±0.4 (97±7.4)	5.3±0.5 (96±9.1)	0.566

Measure	Randomization Group				p-value ^d
	combined (n=156)	LPV/r (n=85)	NVP (n=71)		
Normal: <6.11 (<110)	154 (98.7)	84 (98.8)	70 (98.6)		0.898
Impaired: ≥6.11 (≥110)	2 (1.3)	1 (1.2)	1 (1.4)		
HOMA-IR					
	Mean±SD	1.04±0.6	1.08±0.8		0.716
Normal: 3.16	152 (98.1)	85 (100.0)	67 (95.7)		0.090
Insulin Resistance: >3.16	3 (1.9)	0 (0.0)	3 (4.3)		

Abbreviations: SD, standard deviation; IQR, inter-quartile range

^d LPV/r- and NVP-groups were compared using the Wilcoxon rank sum test and t-test for continuous variables and chi-squared or Fisher's exact test for categorical variables

Table 3

Body composition measures of 156 perinatally HIV -infected South African children suppressed on ritonavir-boosted lopinavir (LPV/r)-based treatment and randomized to either maintain the LPV/r-based regimen or switch to a nevirapine (NVP)-based regimen (Mean±SD)

Measure	Randomization Group			P-value α	
	combined (n=156)	LPV/r (n=85)	NVP (n=71)		
MUAC – Mid Upper Arm Circumference, cm	15.5±2.1	15.8±2.2	15.2±1.9	0.073	
MTC – Mid Thigh Circumference, cm	29.7±3.4	30.1±3.8	29.3±2.9	0.143	
MWC – Mid Waist Circumference, cm	51.1±3.7	51.4±4.0	50.8±3.5	0.325	
MHC – Maximum Hip Circumference, cm	53.9±6.0	54.2±7.3	53.6±4.0	0.556	
MWC – MHC Ratio	1.02±1.0	1.08±1.3	0.95±0.1	0.373	
BSF – Bicep Skinfold, mm	5.29±1.7	5.67±1.8	4.84±1.5	0.002	
TSF – Tricep Skinfold, mm	7.06±1.7	7.24±1.8	6.86±1.7	0.180	
SSF – Subscapular Skinfold, mm	6.24±1.7	6.47±1.7	5.97±1.6	0.069	
SISF – Suprailiac Skinfold, mm	6.40±2.6	6.58±2.8	6.18±2.2	0.329	
USF – Umbilical Skinfold, mm	6.71±4.5	7.01±5.4	6.31±2.9	0.320	
MTSF – Mid Thigh Skinfold, mm	9.80±3.2	10.4±3.3	9.1±3.0	0.018	
SFS – Skinfold Sum, mm	41.3±10.8	43.0±11.1	39.0±10.1	0.031	
%BF = %Body Fat by BIA	15.7±8.0	17.0±7.0	14.1±8.0	0.022	
Extremity Fat Area					
Arm	AFA - Arm Fat Area, cm ²	5.5±1.9	5.8±2.1	5.2±1.7	0.078
	%AF - % of Fat in Arm	29.0±8.3	29.1±8.3	28.9±8.3	0.837
Leg	LFA - Leg Fat Area, cm ²	14.8±5.8	15.7±6.0	13.6±5.3	0.023
	%LF - % of Fat in Leg	20.7±6.4	21.8±6.7	19.4±5.7	0.023
Regional Fat Proportions of Total Body Fat					
Arm	[(BSF+TSF) / SFS]	0.30±0.04	0.30±0.05	0.30±0.04	0.734
Trunk	[(SSF+SISF+USF) / SFS]	0.46±0.06	0.45±0.06	0.47±0.05	0.114
Leg	[MTSF / SFS]	0.24±0.04	0.24±0.04	0.23±0.03	0.046
Trunk-Extremity Skinfold Ratios					
Trunk-Arm	[(SSF+SISF) / (BSF+TSF+SSF+SISF)]	0.50±0.06	0.50±0.06	0.51±0.05	0.256

Measure	Randomization Group			P-value ^a
	combined (n=156)	LPV/r (n=85)	NVP (n=71)	
Trunk-Leg [(SSF + SISF) / (MTSF + SSF + SISF)]	0.56±0.06	0.55±0.07	0.57±0.05	0.034

Abbreviations: SD, standard deviation

^a LPV/r- and NVP-groups were compared using t-tests