Lipid Profiles in Young HIV-infected Children Initiating and Changing Antiretroviral Therapy

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Abstract

Background—Both HIV infection and antiretroviral therapy are associated with dyslipidemias in adults but there are fewer data on outcomes in young children. Here we examined lipid profile changes in a cohort of young children before and after suppression on an initial ritonavir-boosted lopinavir (LPV/r)-based regimen and after switch to a nevirapine (NVP)-based regimen.

Methods—195 HIV-infected children who initiated LPV/r-based therapy when <24 months of age at one site in Johannesburg, South Africa, and who achieved viral suppression (<400copies/ml sustained for   3 months) were randomised to either continue on the LPV/r-based regimen (n=99) or to switch to a NVP-based regimen (n=96). Non-fasting concentrations of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG) were measured pre-treatment, at randomization when suppressed, and at 9, 20 and 31 months post-randomization.

Results—Median age at treatment initiation was 9 months and the initial regimen was maintained for an average of 9 months before randomization. TC, LDL and HDL increased from pre-treatment to randomization (p<0.0001) and TC/HDL ratio and TG decreased (p<0.0001). After switching to NVP, HDL was significantly higher (p<0.02) and TC/HDL and TG significantly lower (p<0.0001) through 31 months post-switch relative to remaining on the LPV/r-based regimen.

Conclusion—Initiating antiretroviral therapy was associated with changes to a more favorable lipid profile in young children. Switching from a LPV/r-based regimen to a NVP-based regimen accentuated and continued these improvements. Investigation of safe and effective methods for managing dyslipidemias in children of different ages in resource-limited settings is warranted.

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Introduction

Lipid abnormalities are reported in association with HIV infection as well as with its treatment. Dyslipidemias occur in treatment-naive HIV-infected persons, indicating that HIV infection per se may affect fatty acid metabolism.[1] Furthermore, despite clinical and virologic benefits of antiretroviral therapy (ART), therapy itself is associated with metabolic derangements, including dyslipidemias.[2] ART-related dyslipidemias, even in children, are characterised by elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL) and plasma triglyceride (TG) levels and lower high density lipoprotein cholesterol (HDL) levels.[3-10] Protease inhibitor (PI)-containing regimens, particularly those including ritonavir, have been strongly implicated as a cause of dyslipidemias, including hypercholesterolemia and hypertriglyceridemia.[2] Other antiretroviral drug classes have also been implicated.[11]

The limited study of lipid metabolism in infants and young children is of particular concern since they are exposed to ART during developmentally-critical periods and will likely have longer cumulative exposure to ART. Current HIV treatment guidelines recommend routine use of PI-based regimens for first-line treatment of young children because of exposure to nevirapine (NVP) to prevent mother-to-child HIV transmission (PMTCT).[12] Concerns are heightened by accumulating evidence of the importance of childhood metabolic parameters in long-term development of atherosclerosis in adults[13,14] as well as increasing recognition of the role of early exposures in shaping development of these metabolic pathways.[15] Dyslipidemias have been described in 50-70% of children receiving ART.[16-20] But studies of young children and infants are limited, and generally have not followed children prospectively or compared different treatment regimens.

In the context of a trial evaluating re-use of NVP for children exposed to this agent at birth when it was used as prophylaxis,[21] we examined lipid profiles of HIV-infected South African children initiating PI-based ART when less than two years of age. We assessed changes from pre-treatment to the time of viral suppression and then subsequent changes when children were either continued on their primary PI-based regimen or were switched to a NVP-based regimen. The randomized design allowed us to investigate whether switching from a PI-sparing regimen to a NVP-based regimen would result in measurable changes in young children's lipid profiles.

Methods

Study design

We report results of serum lipoprotein and triglyceride measurements from 195 HIV-infected infants and young children enrolled in an ART strategies trial before and after they were suppressed on their primary regimen containing ritonavir-boosted lopinavir (LPV/r).[21] Children initiated treatment between April 2005 and July 2007 at a single secondary-level hospital in Johannesburg, South Africa (Rahima Moosa Mother and Child Hospital). Children were referred from inpatient wards, as well as nearby hospitals and surrounding clinics. Participants lived mainly in the urban neighbourhoods surrounding the health facility and came from poorer socioeconomic backgrounds. All children were exposed to single-dose NVP prophylaxis at birth and were younger than 24 months of age when they initiated PI-based ART. Those who achieved and sustained plasma HIV-1 RNA <400 copies/ml for at least 3 months within the first 12 months of treatment were eligible for randomization to

either continue on the LPV/r-based regimen or to switch to a NVP-based regimen. Here we describe the lipid profiles of the children prior to starting any therapy, at the time of randomization when suppressed, and at 9, 20 and 31 months post-randomization. The study was approved by the Institutional Review Boards of Columbia University (New York, NY) and the University of the Witwatersrand (Johannesburg, South Africa). Signed informed consent was obtained from the child's parent or guardian.

Treatment regimens

As per South African Department of Health guidelines in place at the time,[22] children >6 months were started on ritonavir-boosted lopinavir-230mg/m^2 (LPV/r), lamivudine-4mg/kg (3TC) and stavudine–1mg/kg (d4T) taken 12 hourly. In children <6 months of age, or those receiving concomitant rifampicin-based tuberculosis (TB) treatment, LPV/r was replaced with ritonavir-450mg/m^2 (RTV). Once older than 6 months and at the completion of TB treatment, RTV was replaced with LPV/r. All children were receiving a LPV/r-based regimen at the time of randomization. Dosages were recalculated monthly according to weight. All medications were in liquid formulation.

Randomization divided the cohort into two groups. The control group underwent no regimen change and continued with the LPV/r-containing regimen. The switch group substituted NVP for LPV/r. Both groups continued d4T and 3TC. If children in either group were diagnosed with TB post-randomisation, they commenced anti-tuberculous therapy and their regimen was modified according to South African guidelines. For the switch group this entailed discontinuation of NVP. In the event of viral failure that did not respond to adherence counselling, children in the switch group were returned to the LPV/r-based regimen. None of the children received any lipid lowering agents.

Laboratory analysis

TC, LDL, HDL and TG concentrations were measured at five time points: pre-treatment (Time 0), randomization (Time 0R) and 9, 20 and 31 months post-randomization. Due to the young age of the cohort, children were not fasted prior to the blood draw. One child in each group was still breastfeeding at the time of enrolment into the study. Due to enrolment procedures, pre-treatment blood samples were only available for 151/195 children who had been randomized. Quantitative determination of the serum lipogram was performed using the Roche COBAS®INTEGRA 400 system. Lipogram values were all reported in mmol/l. For ease of interpretation we present key findings also in mg/dl. For these calculations we multiplied lipid values by 39 and triglyceride values by 89. Hypercholesterolemia was defined as TC 5.13 mmol/l (200mg/dl). LDL was classified as borderline high if between 2.82-3.31 mmol/l (110-129 mg/dl) and high if 3.31 (130mg/dl). HDL was considered low if <1.03 mmol/l (<40 mg/dl). Hypertriglyceridemia was defined as TG 1.69mmol//l (150mg/dl).[23] The ratio of TC:HDL was also calculated.

CD4 T-cell counts and percentages were measured pre-treatment and every 3 months during follow-up. For this analysis, we selected the CD4 determinations done pre-treatment, closest to the time of randomization and closest to the follow-up lipogram measurements. CD4 cell counts and percentages were obtained using the Beckman Coulter FlowCARE™ PLG CD4 Reagent system. HIV-1 RNA quantity (viral load) was measured pre-treatment and 3-monthly until randomization, and at 1, 4, 6 months post-randomization and every 3 months thereafter. The standard assay was used for the sample collected pre-treatment (quantification range 400-750 000 copies/ml) and the ultrasensitive assay (quantification range 50-150 000 copies/ml) for samples collected after ART initiation (Roche Amplicor Assay, version 1.5, Branchburg, NJ).

Clinical Monitoring

Clinical evaluations were performed at regular intervals and included anthropometric measurements (height, weight and head circumference), consultation with study physicians, phlebotomy, adherence assessments, including one and two-day recall and reconciliation of returned medications, and dispensing of medications.

Statistical methods

Paired t-tests were used to compare lipid values before and after treatment initiation and McNemar tests to compare changes when classifying lipid abnormalities in categories. Treatment groups were compared as randomized (intent-to-treat). Wilcoxon rank-sum tests were used to compare continuous variables between groups and Chi-squared or Fisher's exact tests for categorical variables. Kaplan-Meier methods were used to describe virologic endpoints. Associations on the continuous scale were examined using Spearman Rank Order correlations or using chi-squared tests if categorical. Weight-for-age Z (WAZ)-scores and height-for-age Z (HAZ)-scores were calculated using WHO software.[24] All p-values are two-tailed and p-values <0.05 were considered statistically significant. Data analysis was performed using SAS software (Cary, NC).

Results

Study population

The median age when treatment was started was 10 months (range 2-24 months) in the whole cohort of 195 HIV-infected children who achieved viral suppression and were randomized, and 47% were female. Prior to starting therapy, 55% had HIV RNA quantity >750,000 copies/ml, the median CD4 percentage was 18.5 and the mean weight-for age Z-score was −2.18. The characteristics of the 151 children with pre-treatment samples available for lipid measurements are shown in Table 1. Those missing pre-treatment samples did not differ significantly from those with available samples in age, sex, CD4 percentage or weight-for-age. Pre-treatment viral load results were missing for most of those missing pre-treatment samples. In those with pre-treatment samples, the median age at treatment initiation was 9.3 months and by the time of randomization, after a mean 9.4 months on PI-based ART, all children had viremia <400 copies/ml (by definition), 70.9% were suppressed <50 copies/ml, the median CD4 percentage had risen to 29.8, and the mean weight-for-age Z-score was −0.54.

Changes in lipids with treatment initiation

There were significant increases in TC, LDL and HDL and significant decreases in TC:HDL ratio and TG from pre-treatment to the time of randomization when viral suppression was attained (p<0.0001) (Table 2). Prior to starting therapy, TC, LDL and HDL were low, with no children with high levels of TC or LDL and 93.1% of children with HDL values considered low. TG above the threshold considered high were observed in 63.3% of children (Table 2). On average 9 months later, after viral suppression had been attained, TC increased by an average of 1.09 mmol/l and LDL by 0.86 mmol/l and 5.6% and 7.0% of children were classified as having high TC and LDL measurements, respectively. Although HDL increased on average 0.44 mmol/l, by the time of suppression, 59.6% were still considered to have low HDL. TG decreased 0.39 mmol/l with 37.7% remaining elevated at randomization. Only results for the 151 children who had samples available pre-treatment are shown. Those missing pre-treatment samples had similar post-treatment levels to those with both time points (data not shown).

There were no significant differences by gender. Lipid changes observed with treatment occurred in both girls and boys. HDL was lower and LDL higher among children older at

the time of treatment initiation but, at the time of suppression, no age associations were observed. As a result, the magnitude of the LDL increase was larger and the change in HDL smaller in children who initiated therapy younger than a year of age. Higher pre-treatment HDL was associated with higher CD4 percentage. Lower LDL and higher TG were associated with higher pre-treatment viral loads. There were no associations at the time of randomization.

Post-randomization changes in lipids

Post-randomization, lipid changes in both groups displayed similar trends to that observed after treatment initiation, namely increases in TC, LDL and HDL and decreases in TC:HDL ratio and TG. However, increases in HDL and decreases in TG were greater in the switch group (Figure 1). The switch group had significantly higher HDL compared to the control group at 9, 20 and 31 months post-randomization (Table 3). The switch group had continued increases in HDL after randomization with slower increases in the control group. By 31 months post-randomization, 19.0% of children in the switch group and 40.3% of children in control group had persistently low HDL (p=0.01) (Table 4). The switch group also had more pronounced declines in TG and in TC:HDL ratio (Table 3). By 31 months post-randomization, 10.5% of children in the switch group and 35.3% of children in control group had persistently high TG (p=0.001) (Table 4). There were no consistent differences between the groups in LDL or TC levels post-randomization. At the time of randomization, there were no significant differences between the groups in HDL, LDL, TC or TC:HDL ratio. There was a borderline difference in TG levels, but the later larger differences between the groups remained significant after adjusting for TG levels at the time of randomization.

There were no significant differences in lipid concentrations by sex within treatment groups at any time point. However, differences between the groups in HDL were more marked among boys and TG declines were stronger among girls. There were no consistent associations between age at starting therapy or at randomization and lipid concentrations.

As we have previously reported, children randomized to the switch group were significantly more likely to meet the virological endpoint used in the trial to consider regimen change (defined as confirmed viremia >1000 copies/ml) than children randomized to the LPV/r group. By 9 months, 17.2% of children in switch group had confirmed viremia >1000 copies/ml compared to 2.2% in the control group. By 20 and 31 months respectively, these proportions were 23.9% and 23.9% in the switch group; and 9.6% and 11.1% in the control group (p=0.009). There were no significant differences in lipids in those who failed virologically overall or within treatment group but numbers of failures were small. The associations between group assignment and HDL, TC:HDL ratio and TG persisted if the analysis was restricted only to those who did not fail therapy.

Discussion

In this randomized clinical trial, young HIV-infected children had low TC, HDL and LDL and high plasma TG prior to starting therapy. Initiation of a PI-based regimen resulted in significant increases in TC, LDL and HDL and decreases in TC:HDL ratio and TG. This pattern corresponds with prior descriptions of viremia-associated dyslipidaemia and changes after therapy.[4,25] However, even when virologically-suppressed, a large proportion of children still had low HDL and high TG. After randomization, only those switched from their LPV/r-based regimen to the NVP-based regimen showed further significant improvements in HDL, TC:HDL ratio and TG levels.

While metabolic abnormalities have been well described among HIV-infected children and youth *on treatment*,[2-9,16,20,25] fewer studies have characterized patterns of dyslipidemia

among young children prior to ART. Among untreated adults, there is an early decrease in HDL followed by decreases in LDL and increases in TG.[26] Chantry et al. reported that, in a cohort of ART-naïve children, 30% had HDL abnormalities compared with 4% among a matched comparison group.[18] Among 103 ART-naïve children in London with mild/moderate HIV disease, median age 7.1 years, lipid levels were normal with the exception of below normal HDL.[20] In the British cohort no association was found between lipids and viral load or CD4+ cell count.[20] In our young cohort, where most children had advanced disease, 93% had low HDL and 63% had elevated TG prior to ART initiation. Lower LDL and higher TG were associated with higher HIV RNA while higher HDL was associated with higher CD4 percentage. The high rate of lipid abnormalities pre-treatment may be related to the young age and advanced state of disease among children in our cohort. We hypothesize that the initial improvements in lipids may be secondary to ART-mediated control of viral replication and restoration of immune function.

Those children randomized to remain on the LPV/r-based regimen continued to have increases in TC, LDL and HDL and declines in TC:HDL ratio and TG. Despite 31 months of treatment, high rates of abnormalities persisted in this group including high TC (16%), LDL (12%), TG (36%) and low HDL (40%). Among children randomized to switch to NVP-based treatment, the pattern of improvement in lipids (HDL increase and TC:HDL and TG decline) was more pronounced. In comparison to those remaining on LPV/r-based therapy, HDL was significantly higher and TC/HDL and TG significantly lower through 31 months among those switched to the NVP-based regimen.

Several studies have documented lipid abnormalities among children on treatment but most of these studies have been observational and included older children on a variety of different ART regimens. Our study is randomized and focuses only on young children under 2 years of age when initiating ART. In a large multi-site cross-sectional study in the U.S., Aldrovandi et al. found a high prevalence of lipid abnormalities among treated children compared with seronegative controls: among 161 children receiving PI-based ART, 52% had elevated TG, 29% high TC, 19% high LDL and 10% low HDL (< 35 mg/dl.)[8] Each year of ritonavir use was associated with increases in TC, TG and LDL while NVP and efavirenz were associated with increases in HDL.[8] Among 441 children followed in London, Rhoads et al. evaluated changes in lipid levels and associations with individual antiretroviral drugs.[20] All lipids rose over a period of 4.5 years of observation. LPV/r was associated with increases in non-HDL of 0.43 millimoles per year in the first 0-1 year and 0.8 millimoles per year at >4-year exposure compared with a more modest effect of NVP with increases of 0.2-0.39 millimoles per year.

Our findings highlight the subtleties of the metabolic effects of different antiretroviral agents. It is likely that the early impact of ART initiation which leads to correction of HIV-related dyslipidemia (even with a LPV/r-based regimen) is balanced, over time, by the specific drug-related lipid abnormalities associated with this regimen. By comparison, in the switch cohort, the additional improvements in lipid profile can be attributed to the particular characteristics of NVP which have been associated with a more favourable lipid profile and lower long-term cardiovascular risk.[27] Several substitution studies in adults where a PI was switched to NVP resulted in significant improvements in dyslipidemia changes which are likely due to both the discontinuation of the PI as well as the specific drug substitution.[27-30] A pediatric study also observed significant improvements in lipid profile with switch to efavirenz.[31]

Recent developments in antiretroviral therapies offer an increasingly large array of treatment options for adults with HIV infection. Many of the newer agents have better toxicity profiles and, in well-resourced settings, drug regimens can be individualized to improve efficacy,

facilitate adherence and minimize both short and long term side effects. Unfortunately, for children, particularly infants and young children, treatment options remain profoundly limited. LPV/r-based regimens are currently recommended for children who have been exposed to nevirapine used as part of PMTCT.[12] The comparative virologic efficacy of different regimens is important, but other short- and long-term impacts on other disease parameters also need to be studied in order to understand how to optimize use of the available drugs.

The long-term consequence of abnormal lipids in infants and young children with HIV infection is unknown. Several studies have identified early atherosclerotic changes with carotid artery imaging studies among youth with perinatal HIV infection and long term ART exposure.[32,33] With increased availability of ART in high HIV prevalence settings, increasingly large numbers of infants and young children are initiating treatment, with either NVP- or LPV/r-based regimens. The long-term consequences of ART starting early in life and extending through childhood and adolescence are unknown but warrant careful study. Childhood metabolic parameters are associated with atherosclerosis and cardiovascular disease in adulthood. Current guidelines in the US recommend biannual monitoring of fasting lipids in children on ART but such tests are generally not available in resource-constrained settings.[34] Recommendations for management of lipid abnormalities include switching antiretroviral drugs, exercise and dietary interventions and, for older children, use of lipid-lowering agents but are not widely implemented.[19,34] Most commercially-available lipid-lowering medications have not been studied in children with HIV.

There are several limitations of our study. Due to the young age of the cohort, fasting blood samples were not obtained. While most normative lipoprotein reference data are based on fasting samples, sample timing with respect to feedings does not significantly influence results.[35] Our approach is also similar to many of the published pediatric studies and our findings appear comparable. Moreover, since the same protocols were followed for the collection of samples pre- and post-treatment and between the groups, any measurement error introduced is likely to be non-differential resulting in weaker associations. We note that our reference levels are based on data obtained from children in North America as there are no population-specific lipid reference levels for South African children. No information on the children's diet or family history of lipid disorders was recorded but since the study is randomized this is unlikely to have any consequence. Since all children received d4T, the individual impact of this agent could not be discerned.[36]

We have previously reported on the virologic constraints of re-using nevirapine in nevirapine-exposed children as well as on the benefits of switching for CD4 response and growth.[21] These new results demonstrate the potential value of switching from an initial LPV/r-based regimen to a NVP-based regimen in young HIV-infected children on select metabolic parameters. Those children who were switched had a more favorable lipid profile with higher HDL and lower TC:HDL ratio and TG concentrations. Although the long-term clinical implications of these changes are unknown, our results raise concern about the long-term risk of cardiovascular disease with prolonged use of LPV/r-based therapy initiated in infants and young children. Our study reinforces the need for ongoing monitoring of the lipid profile of treated children, especially those receiving boosted PI. Investigations of safe and effective methods for managing dyslipidemias in children of different ages in resource-limited settings are warranted.

Acknowledgments

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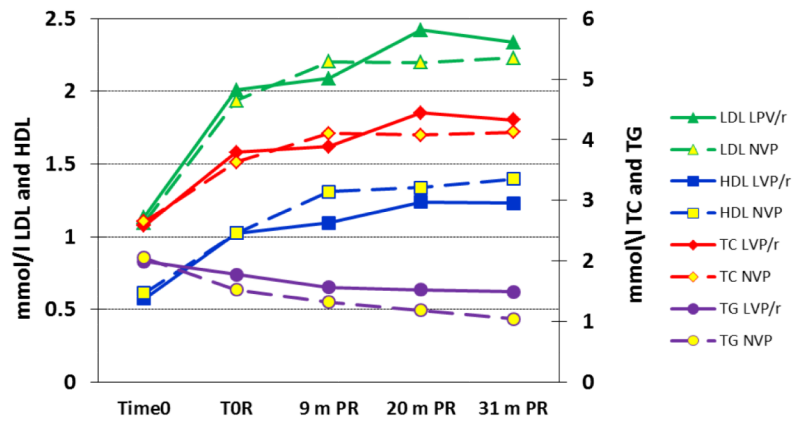
Figure 1.
Mean lipid values among 195 HIV-infected children who achieved viral suppression with ritonavir-boosted lopinavir (LPV/r)-based treatment and then were randomized to either continue on the LPV/r-based regimen (control group) or to switch to a NVP-based regimen (switch group). Mean values are shown prior to starting any treatment (time 0), at the time of randomization when suppressed and at nine (time 0R), 20 and 31 months post-randomization (PR).

Table 1

Characteristics of 151 HIV-infected children with available lipid measurements before starting treatment (pre-treatment) with ritonavir-boosted lopinavir (LPV/r)-based therapy and at the time of randomization after achieving virologic suppression (suppressed) on this regimen.

	Pre-treatment (Time 0)		Suppressed (Time 0R)		p-value*
Sex					
Male	78	(51.7)	78	(51.7)	
Female	73	(48.3)	73	(48.3)	
Age in months					
<6	41	(27.2)	-	-	
6 to 11	58	(38.4)	12	(8.0)	
12 to 17	33	(21.9)	60	(39.7)	
18 to 23	19	(12.6)	39	(25.8)	
24	-	-	40	(26.5)	
Median age in months	9.3		18.5		
Range	2.2-24		9.1-35.5		
CD4 percent					
Median	19.5		29.8		<0.0001
Range	2.6-41.8		7.3-55.7		
CD4 count cells/mm³					
Median	936		1869		<0.0001
Range	10-3762		104-5423		
HIV RNA copies per ml †					
<50	-	-	107	(70.9)	
50-399	-	-	44	(29.1)	
400-99,999	13	(9.0)	-		
100,000-749,999	46	(31.7)	-		
750 000	86	(59.3)	-		
Weight for age Z-score					

	Pre-treatment (Time 0)	Suppressed (Time 0R)	p-value[*]
Mean [std]	−2.07 [1.65]	−0.54 [1.12]	<0.0001
Height for age Z-score			
Mean [std]	−3.17 [1.63]	−3.04 [1.55]	>0.10

[*] Paired t-tests were used to compare appropriate parameters pre- and post-treatment

[†] Pre-treatment measurements missing for 6 children

Table 2

Changes in lipids among 151 HIV-infected children before starting treatment (pre-treatment) with ritonavir-boosted lopinavir (LPV/r)-based therapy and at the time of randomization after achieving virologic suppression (suppressed) on this regimen.

Continuous variable	Pre-treatment (Time 0) Mean [standard deviation]		Suppressed (Time 0R) Mean [standard deviation]		p-value*
	mmol/l	mg/dL	mmol/l	mg/dL	
Total Cholesterol (TC)	2.62 [0.78]	102 [30.3]	3.71 [0.97]	145 [38.0]	<0.0001
Low density lipoprotein (LDL)	1.11 [0.71]	43 [27.7]	1.98 [0.85]	77 [33.3]	<0.0001
High Density lipoprotein (HDL)	0.59 [0.33]	23 [13.0]	1.03 [0.34]	40 [13.3]	<0.0001
Triglycerides (TG)	2.02 [0.86]	180 [76.2]	1.64 [0.87]	146 [77.6]	<0.0001
TC:HDL ratio	6.35 [5.08]		3.90 [1.37]		

Categorical classification	n/N† (%)	n/N (%)	p-value*
Total cholesterol			
Borderline high 170-199 mg/dL	3/144 (2.1)	26/144 (18.1)	
High 200 mg/dL	0	8/144 (5.6)	<0.0001
Low density lipoprotein (LDL)			
Borderline high 110-129 mg/dL	2/144 (1.4)	7/143 (4.9)	
High 130 mg/dL	0	10/143 (7.0)	0.003
High density lipoprotein (HDL)			
Low < 40 mg/dL	134/144 (93.1)	87/146 (59.6)	<0.0001
Triglycerides			
High >150 mg/dl	93/147 (63.3)	55/146 (37.7)	<0.0001

*Paired t-tests were used for continuous variables and McNemar tests for categorical variables

Table 3

Mean lipid values among 195 HIV-infected children suppressed on ritonavir-boosted lopinavir (LPV/r)-based treatment and randomized to either continue on the LPV/r-based regimen (control group) or to switch to a NVP-based regimen (switch group) at the time of randomization (Time 0R) and at 9, 20 and 31 months post-randomization (PR).

	Control group			Switch group			
		Mean [standard deviation]			Mean [standard deviation]		p-value[*]
	N	mmol/l	mg/dL	N	mmol/l	mg/dL	
Total Cholesterol							
Time 0R	93	3.79 (1.08)	148 (42.1)	95	3.63 (0.94)	142 (36.6)	>0.10
9 months PR	93	3.89 (0.97)	152 (37.8)	88	4.10 (0.87)	160 (34.0)	>0.10
20 months PR	79	4.44 (0.86)	173 (33.7)	74	4.08 (0.80)	159 (31.1)	0.007
31 months PR	67	4.32 (0.84)	169 (33.0)	55	4.12 (0.77)	161 (30.1)	0.07
Low Density Lipoprotein							
Time 0R	93	2.01 (0.91)	78 (35.3)	94	1.94 (0.82)	75 (31.8)	>0.10
9 months PR	93	2.09 (0.79)	81 (31.0)	87	2.20 (0.77)	86 (30.1)	>0.10
20 months PR	72	2.42 (0.84)	94 (32.9)	72	2.20 (0.75)	86 (29.2)	>0.10
31 months PR	67	2.34 (0.80)	91 (31.1)	58	2.23 (0.76)	87 (29.7)	>0.10
High Density Lipoprotein							
Time 0R	95	1.03 (0.39)	40 (15.2)	95	1.02 (0.35)	40 (13.7)	>0.10
9 months PR	93	1.09 (0.37)	43 (14.4)	87	1.31 (0.44)	51 (17.1)	0.0006
20 months PR	73	1.24 (0.58)	48 (22.6)	73	1.34 (0.39)	52 (15.2)	0.01
31 months PR	67	1.23 (0.54)	48 (20.9)	58	1.40 (0.48)	54 (18.8)	0.02
TC/HDL ratio							
Time 0R	92	4.14 (1.89)		95	3.83 (1.44)		>0.10
9 months PR	93	3.95 (1.77)		87	3.42 (1.22)		0.03
20 months PR	71	3.98 (1.28)		69	3.24 (0.95)		0.0003
31 months PR	64	3.87 (1.46)		55	3.18 (0.89)		0.0096
Triglycerides							
Time 0R	95	1.78 (0.93)	158 (82.9)	95	1.52 (0.76)	136 (67.9)	0.05

| | | Control group | | | Switch group | | | |
| | | Mean [standard deviation] | | | | Mean [standard deviation] | | |
	N	mmol/l	mg/dL	N	mmol/l	mg/dL	p-value[*]
9 months PR	93	1.56 (0.73)	139 (64.6)	87	1.32 (0.65)	118 (58.1)	0.03
20 months PR	70	1.52 (0.71)	136 (63.2)	73	1.18 (0.65)	105 (58.2)	0.0009
31 months PR	68	1.49 (0.71)	133 (63.2)	57	1.04 (0.59)	93 (52.7)	<0.0001

[*] Groups are compared using Wilcoxon rank-sum tests

Table 4

Proportions of children with lipid abnormalities 9, 20 and 31 months after randomization to either remain on ritonavir-boosted lopinavir (control group) or switch to NVP-based therapy (switch group)

	Control group	Switch group	
	n/N (%)	n/N (%)	*p* value[*]
9 months post-randomization			
Total cholesterol			
Borderline high 170-199 mg/dL	14/93 (15.1)	20/88 (22.7)	
High 200 mg/dL	13/93 (14.0)	11/88 (12.5)	>0.10
Low density lipoprotein			
Borderline high 110-129 mg/dL	8/93 (8.6)	8/87 (9.2)	
High 130 mg/dL	8/93 (8.6)	9/87 (10.3)	>0.10
High density lipoprotein			
Low < 40 mg/dL	43/93 (46.2)	22/87 (25.3)	0.004
Triglycerides			
High >150 mg/dl	35/93 (37.6)	25/87 (28.7)	>0.10
20 months post-randomization			
Total cholesterol			
Borderline high 170-199 mg/dL	27/79 (34.2)	18/74 (24.3)	
High 200 mg/dL	16/79 (20.3)	8/74 (10.8)	0.05
Low density lipoprotein			
Borderline high 110-129 mg/dL	15/72 (20.8)	9/72 (12.5)	
High 130 mg/dL	7/72 (9.7)	4/72 (5.6)	>0.10
High density lipoprotein			
Low < 40 mg/dL	29/73 (39.7)	17/73 (23.3)	0.03
Triglycerides			
High >150 mg/dl	22/70 (31.4)	16/73 (21.9)	>0.10
31 months post-randomization			
Total cholesterol			
Borderline high 170-199 mg/dL	28/67 (41.8)	12/55 (21.8)	
High 200 mg/dL	11/67 (16.4)	7/55 (12.7)	0.03
Low density lipoprotein			
Borderline high 110-129 mg/dL	8/67 (11.9)	10/58 (17.2)	
High 130 mg/dL	8/67 (11.9)	5/58 (8.6)	>0.10
High density lipoprotein			

	Control group	Switch group	
	n/N (%)	n/N (%)	p value*
Low < 40 mg/dL	27/67 (40.3)	11/58 (19.0)	0.01
Triglycerides High >150 mg/dl	24/68 (35.3)	6/57 (10.5)	0.001

*Groups are compared using chi-square tests