Effect of Specific ART Drugs on Lipid Changes and the Need for Lipid Management in Children With HIV

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Background: We investigated the effects of individual antiretrovirals on lipids in HIV-infected children and the proportion potentially eligible for dietary or pharmacologic intervention.

Methods: St Mary's and Great Ormond Street Hospital's, London, United Kingdom, patients between 1995 and 2007 were included. Associations between lipids (millimoles per liter) and specific antiretroviral therapy were assessed using mixed-effects models adjusted for confounders. Children eligible for lipid-lowering management were assessed according to American Academy of Pediatric criteria [low-density lipoprotein (LDL) > 190 mg/dL or 4.9 mmol/L for children with no known cardiovascular disease risk factors or LDL > 160 mg/dL or 4.1 mmol/L for children with 2 or more cardiovascular disease risk factors].

Results: Four hundred forty-nine children had median 4.5-year follow-up. On average, antiretroviral therapy–naive children had normal lipids except for low high-density lipoprotein cholesterol (HDL) (median 0.8). All cholesterol subsets were elevated for the 4 drugs assessed. Protease inhibitors had greater rises in total cholesterol with the maximal non-HDL rise for lopinavir/ritonavir at 4+ years of exposure, 0.8 (0.57–1.03). The nonnucleoside reverse transcriptase inhibitors also raised non-HDL, but this was associated with additional clinically significant increases in HDL. Nevirapine raised non-HDL by 0.38 (0.09–0.31) at 2–3 years and HDL by 0.34 (0.28–0.41). Efavirenz raised non-HDL by 0.2 (0.09–0.31) and HDL by 0.12 (0.08–0.17) at 1 year. Ten percent had LDL above the 95th percentile, but only 3 met the 4.9 cutoff for pharmacologic intervention.

Conclusions: Intervention strategies (dietary and exercise advice, treatment switching, and pharmacotherapy) are required for persistent hyperlipidemia and should be assessed in randomized control trials.

Key Words: child, HIV, antiretroviral therapy, hypercholesterolemia, treatment switch, statins

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INTRODUCTION

As HIV-infected children are now living into adulthood, there are increasing concerns regarding their long-term cardiovascular health.[1] The etiology of cardiovascular disease (CVD) in this population may be driven by endothelial inflammation[2,3] and traditional risk factors, including dyslipidemia.[4] Treatment with antiretroviral therapy (ART) is associated with hypercholesterolemia, a risk factor for coronary heart disease (Tien 2006). Although both nonnucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitor (PI) classes are implicated,[5,6] the greatest effects are reported with PI use.[6–16,20] The PI of greatest concern is ritonavir especially when used as a booster.[6,17,18] Similar effects are reported in children,[6–16,19] which is particularly concerning, as children will receive treatment for a large proportion of their life.

CVD is rare in young children, and no HIV positive pediatric myocardial infarctions have been reported. However, recent reports suggest that young adults perinatally infected with HIV have high rates of coronary artery abnormalities, suggesting possible early atherosclerosis.[21] Surrogate markers, such as lipids, are often used to assess CVD risk. Although the long-term sequelae of dyslipidemia in HIV-infected children are unknown, their total cholesterol (TC) levels are reported to be similar for children with heterozygous familial hypercholesterolemia, who are at increased risk of premature atherosclerotic disease.[5,13]

Studies report a prevalence of TC above 5.2 mmol/L (95th percentile) in 13%–27% of ART-treated children,[11] many of whom experience a rise in TC from their pretreatment value.[5,13,15] Typically, high-density lipoprotein (HDL), the

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cardioprotective cholesterol, is low in HIV-infected individuals but normalizes after starting highly active antiretroviral therapy that may be beneficial.[5]

The immediate benefits of ART for survival far outweigh the increased risk of CVD in later part of life. However, prevention of premature CVD is an important consideration in the management of HIV-infected children. Little is known of the specific effects of individual drugs, and although there is clear evidence to support an adverse effect of PI on the lipid profile, evidence informing treatment changes is scarce. Two large longitudinal studies have attempted to look at the effects of individual drug and class effects of antiretroviral (ARV); however, both studies have focused on TC levels.[6,16] Pediatric guidelines for the management of hyperlipidemia focus on low-density lipoprotein cholesterol (LDL), and therefore, we proposed to study the association between cholesterol subfractions and commonly used individual ARTs. The aim of this study was to investigate the association of HIV viral load (VL), CD4 count, and individual ARV drugs with changes in the lipid profile of infected children. A secondary aim was to identify the number in need of hyperlipidemia management.

METHODS

Participants

All HIV-1–infected children attending pediatric outpatient clinics at Imperial College Healthcare Trust, St. Mary's Campus (London, United Kingdom), and Great Ormond Street Hospitals (GOSH) (London, United Kingdom) between September 1995 and July 2007, who were younger than 16 years and had at least one recorded TC measurement, were included.

All routine nonfasting serum TC, triglyceride (TG), HDL, LDL, and non-HDL measurements recorded on each child during the study period were obtained. Evidence suggests that non-HDL is a better predictor of adult CVD than ratio and has been used in this investigation.[22] Varying numbers of samples at different time points were obtained from each child during the study period, as part of routine clinical practice. There are no HDL cholesterol results from one of the participating hospitals (GOSH) until 1999, and routine measurement started in 2001. Measurements of HIV VL and CD4 T-lymphocyte count, sociodemographic, anthropometric, and data describing complete ARV history were obtained from the Children's HIV Paediatric Study database.[23] Body mass index (BMI) *z* scores were calculated using the Centers for Disease Control and Prevention 2000 reference data (http://www.cdc.gov/growthcharts/zscore.htm). Analyses were performed using SAS Version 9.0 (SAS Institute Inc, Cary, NC).

Ethical approval was obtained from the committees of the Institute of Child Health and GOSH for Children and St Mary's Hospital NHS Trusts.

Statistical Analysis

Association of Lipids With HIV VL and CD4 Count

To explore associations of HIV infection and lipids, we first looked at baseline characteristics of treatment-naive children. Correlations between TC, TG, HDL, LDL, and non-HDL with HIV-1 VL and CD4 count were assessed.

Association of Lipids With Use of Specific ARV Drugs

The 4 most commonly used PIs and NNRTIs during the study period were studied in detail: nevirapine (NVP), efavirenz (EFV), lopinavir/ritonavir (LPV/RTV), and nelfinavir (NFV). We also considered the use of abacavir due to its associated increased risk of myocardial infarction in adults.[24] Pre-ART TC, TG, HDL, LDL, and non-HDL measurements for naive children before starting treatment and the change 1 year later according to the individual drugs were plotted. Differences in baseline lipid measurements according to receipt of regimens containing EFV, NVP, PI, or NNRTI only were calculated using a Kruskal–Wallis test.

Next, we considered all lipid measurements in a longitudinal analysis (ie, all children were included regardless of ARV treatment history). A mixed-effects regression model was used to examine the association between lipid levels and length of exposure to each specific ARV drug.[25] Each lipid subfraction (TC, TG, HDL, LDL, and non-HDL) was considered in a separate model. Random intercept and slope terms were included. The underlying "time" variable used was age and was included in every model. The cumulative length of exposure to each ARV (ie, the total length of time each specific ARV drug was ever taken, regardless of whether the individual was currently on ARV) was assessed, as has been considered previously.[1] Length of exposure to ART associated with lipid levels appeared nonlinear and was therefore fitted as a categorical variable using 1-year increments. Assessing the relationship between age and TC showed that fitting age as a continuous, linear variable was appropriate. Analyses were adjusted for age, sex, ethnicity, and CD4% nadir (fixed-time variables), calendar year, total ARV exposure time, and BMI *z* score (time-updated variables). HIV RNA VL was not included because of its strong correlation with ARV exposure. CD4% nadir was included rather than most recent CD4% as this variable may be on the causal pathway between receipt of ARV drugs and effects on lipid levels. An autoregressive (1) correlation structure was included. As a sensitivity analysis, we repeated the above analyses but considered present (as opposed to cumulative) exposure to specific ARVs.

Children Eligible for Intervention

Finally, we investigated the number of children who would potentially be eligible for pharmacological treatment for hyperlipidemia. The American Academy of Pediatrics Committee on Nutrition (AAP) criteria for intervention and treatment of persistent pediatric hyperlipidemia[26] suggests using LDL> 190 mg/dL or 4.9 mmol/L for children with no known CVD risk factors or LDL >160 mg/dL or 4.1 mmol/L for children with 2 or more CVD risk factors for intervention. For this study, we defined "persistent" as 2 consecutive clinic visit's LDL cholesterol measurements above cutoff. We identified the number of children in our study who would be eligible for treatment using these guidelines (considering all children and those younger than 8 years). We also considered whether these elevated LDL levels persisted, by considering

each child's level 6 months and 1 year after they met the criteria for possible intervention (ie, the second of the 2 elevated LDL levels). The LDL levels measured on each child nearest to 6 months (within a window of 3–9 months) and 12 months (within a window of 9–15 months) after meeting the above criteria were considered. Guidelines for the management of high-risk cardiovascular patients suggest the use of lower cutoffs for children with chronic inflammatory diseases, and we have, accordingly, explored using a cutoff of LDL >130 mg/dL or 3.3 mmol/L in our cohort.[27]

RESULTS

Baseline Characteristics

Four hundred forty-nine children with at least one recorded TC measurement were included. In total, 7040 measurements [median (interquartile range, IQR): 14 (4–26)] per child for TC, 4331 [8 (0–15)] HDL, 3881 [8 (0–14)] LDL, 7065 [14 (4–26)] TG and 4322 [8 (0–14)] non-HDL measurements were available. There were 1997 years of follow-up, with a median of 4.5 years (range 0–11.7 years) available per child. The median (IQR) TC was 3.9 (3.3–4.5) at baseline (first TC measurement available for each child). The median (IQR) time from the first TC measurement to the first TG, HDL, and LDL measurements was 0 week (0–0 weeks; 449 children), 25 weeks (0–90 weeks; 275 children), and 25 weeks (0–87 weeks; 272 children) weeks, respectively.

Baseline characteristics for all subjects are reported in Table 1. The majority (75%) were black African, and 96% were prenatally infected with HIV. Half were female; the median age at baseline was 6.6 (IQR: 3.3, 9.9) years; and 239 (51%) children were receiving ART, with 118 (26%) on an NNRTI-based regimen, 86 (19%) on a PI-based regimen, and 10 (2%) receiving both PI and NNRTI. A total of 264 (59%) had ever been exposed to ART [median: 1.9 (IQR: 0.4–3.7) years].

One hundred three children started treatment during the study period. Median CD4 nadir at the start of treatment was 250 (IQR: 150, 450) cells per milliliter. Seventy-nine (77%) started on NNRTI-based combinations of which 34 included NVP and 45 EFV. Fewer children were started on a PI regimen 19 (19%), of which 10 (10%) were on LPV/RTV and 9 (9%) were on NFV.

Before starting ART, TC levels in naive children (n = 95) were within the normal range (median: 3.4, IQR: 2.8–3.9).[28] In children for whom data were available (n = 50), HDL-C was below the normal range (median: 0.8, IQR: 0.5–0.9). There were no associations between VL or CD4 count and TC, LDL, HDL, or TG in children unexposed to ART.

ARV-Naive Children Starting ART

One hundred three children started ART for the first time during the study period. Eighty-two had a TC measurement recorded before starting treatment and 1 year later (Figure). There was no significant difference in cholesterol changes from baseline between those children starting on EFV-containing, NVP-containing, PI-containing, and NNRTI-only regimens with respect to TC ($P = 0.50$), TG ($P = 0.25$), LDL ($P = 0.24$), HDL ($P = 0.13$), and non-HDL levels ($P = 0.16$).

Longitudinal Analysis

Table 2 displays the mixed-effects modelling of individual ART effects on TC, TG, HDL, LDL, and non-HDL levels in all children as increase in mmol/L per year of exposure (0–1, 1–2, 2–3, 3–4, and >4 years) compared with no exposure. Data are presented as yearly exposure increases due to the effects not being linear. Sensitivity analyses indicated that the results presented in Table 2 were robust to changes. Unadjusted estimates of the effects of the drugs were similar to the adjusted results presented with the following small exceptions. The impact of NVP on non-HDL and LDL increased moderately in the multivariate analysis, and the effect of EFV on HDL was attenuated (data not shown). However, all results maintained the same significance and trend. Overall, all 4 drugs were significantly associated with increases in all 5 cholesterol subgroups. Abacavir was included in these analyses but was not found to be associated with cholesterol changes (data not shown).

After adjustment for potential confounders, those with 0- to 1-year cumulative exposure to NVP had a median 0.27 higher TC compared to those with no exposure. This increased to 0.57 at 2–3 years before levelling off with time (global $P < 0.0001$). Initial EFV exposure was associated with 0.28 higher TC compared with no exposure, which remained elevated; those with 1- to 2-year and 2- to 3-year cumulative EFV exposure had TC levels 0.28 and 0.29 higher than those with no exposure (global $P < 0.0001$). Those with 0- to 1-year and 1- to 2-year NFV exposure had 0.48 and 0.68 higher TC compared with no NFV exposure ($P < 0.0001$). Cumulative exposure of 0–1 year to LPV/RTV was associated with 0.46 higher TC compared to those with no exposure and continued to increase with prolonged exposure ($P < 0.0001$). Exposure to NVP was associated with lower TG levels, whereas exposure to EFV, NFV, and LPV was associated with higher TG.

NNRTIs were associated with significant increases in HDL (Table 2). Initial exposure to NVP and EFV was associated with an increased HDL (0.20 and 0.12 mmol/L, respectively at 0–1 year). These continued to increase to 0.34 and 0.19, respectively, at 1–2 years, and both remained constant thereafter ($P < 0.0001$). In contrast, the effect of PI on HDL although statistically significant is of little clinical importance.

LDL increased significantly with all 4 medications. The largest increases occurred with NFV, 0.39 at 0- to 1-year up to 0.96 at >4-year exposure ($P < 0.0001$). The lowest impact on LDL was made by EFV that gradually rose from 0.12 at 0–1 year, reaching a maximum of 0.45 at >4 years ($P = 0.02$).

The greatest difference between PIs and NNRTIs is demonstrated by non-HDL. Here, LPV/RTV increases non-HDL by 0.43 millimoles per year in the first 0- to 1-year and by 0.8 millimoles per year at >4-year exposure ($P = 0.007$). NFV has a larger earlier impact, increasing non-HDL by 0.92 mmol/L by 2- to 3-year exposure. This settles to 0.57 increase per year at >4-year exposure ($P < 0.0001$). The NNRTIs have a more modest impact on non-HDL as more of their TC count is HDL. NVP increases by 0.2–0.39 millimoles per year ($P < 0.0001$), and EFV increases between 0.14 and 0.29 per year of exposure ($P = 0.01$).

TABLE 1. Characteristics at Time of First Recorded TC Measurement

	All Children at First TC Measurement, n (%)	Previously Naive Children at the Time of First Starting ART, n (%)
	449 (100)	103 (100)
Demographics		
Age, median (IQR), y	6.6 (3.3–9.9)	7.1 (3.8–9.8)
Baseline date, median (IQR)	March 2002 (July 2000 to January 2004)	May 2003 (September 2001 to October 2004)
Ethnicity, n (%)		
Black African	338 (75.3)	87 (84.5)
White	37 (8.2)	4 (3.9)
Mixed race	53 (11.8)	9 (8.7)
Other	21 (4.7)	3 (2.9)
Sex, n (%)		
Female	224 (49.9)	46 (44.7)
Mode of HIV infection, n (%)		
Vertical	432 (96.2)	100 (97.1)
Age-adjusted/sex-adjusted BMI *z* score, median (IQR)	0.3 (−0.5 to 0.9), n = 401	0.2 (–0.6 to +0.8), n = 86
Age-adjusted/sex-adjusted height *z* score, median (IQR)	−0.6 (−1.5 to 0.2), n = 401	−0.6 (−1.6 +0.2), n = 86
Age-adjusted/sex-adjusted weight *z* score, median (IQR)	−0.2 (−1.0 to 0.6), n = 408	−0.4 (−1.0 to +0.5), n = 89
HIV status, median (IQR)		
CD4 count (cells/mm^3)	610 (370–1050), n = 427	295 (165–492), n = 99
CD4 %	23 (16–30), n = 426	13 (9–19), n = 100
CD4 count nadir (cells/mm^3)	380 (180–680), n = 429	250 (150–450), n = 99
CD4 % nadir	15 (8–22), n = 430	12 (7–16), n = 100
VL (log copies/mL)	3.9 (2.6–4.6), n = 425	5.0 (4.3–5.4), n = 99
Current ARV status		
Type of ART regimen, n (%)		
None	210 (46.8)	—
NNRTI based	118 (26.3)	79 (76.7)
PI based	86 (19.2)	19 (18.5)
NRTIs only	25 (5.0)	5 (4.9)
PI/NNRTI	10 (2.2)	0 (0.0)
Current ARVs at baseline, n (%)		
3TC	162 (36.1)	92 (89.3)
ZDV	104 (23.2)	46 (44.7)
d4T	92 (20.5)	17 (16.5)
ddI	70 (15.6)	9 (8.7)
ABA	75 (16.7)	49 (47.6)
EFV	43 (9.6)	45 (43.7)
NVP	86 (19.2)	34 (33.0)
LPV/r	15 (3.3)	10 (9.7)
NFV	71 (15.8)	9 (8.7)
ARV history		
Total ART exposure, median (IQR), y*	1.9 (0.4–3.7), n = 264	—
Total PI exposure, median (IQR), y*	1.4 (0.4–2.6), n = 117	—
Total NNRTI exposure, median (IQR), y*	0.6 (0.1–1.9), n = 161	—
Ever received at baseline, n (%)		
3TC	202 (45.0)	—
ZDV	117 (39.4)	—
d4T	120 (26.7)	—
ddI	111 (24.7)	—
ABA	89 (19.8)	—
EFV	52 (11.6)	—
NVP	116 (25.8)	—
LPV/r	17 (3.8)	—
NFV	102 (22.7)	—

(*continued on next page*)

TABLE 1. (*continued*) Characteristics at Time of First Recorded TC Measurement

	All Children at First TC Measurement, n (%)	Previously Naive Children at the Time of First Starting ART, n (%)
TC, median (IQR), mmol/L	3.9 (3.3–4.5)	3.4 (2.8–3.9), n = 95
TGs, median (IQR), mmol/L	1.1 (0.8–1.6), n = 444	1.2 (0.8–1.9), n = 95
LDL cholesterol, median (IQR), mmol/L	2.0 (1.3–2.5), n = 104	1.8 (1.3–2.1), n = 49
HDL cholesterol, median (IQR), mmol/L	0.9 (0.7–1.2), n = 108	0.8 (0.5–0.9), n = 50
Non–HDL cholesterol, median (IQR), mmol/L	2.7 (2.3–3.3), n = 107	2.3 (2.1–2.8), n = 50

CD4 count, CD4 percentage, VL, height *z* score, weight *z* score, and BMI *z* score measurements must be within 3 months of baseline, otherwise they are assumed missing.
*Among those with >0-year exposure.
ABA, abacavir; ddC, zalcitabine; ddI, didanosine; d4T, stavudine; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; ZDV, zidovudine; 3TC, lamivudine.

Children Meeting Criteria for Possible Pharmacological Intervention

Using AAP guidelines for pharmacological intervention,[26] we identified 17 children during the study period with persistently raised levels above the "borderline" (LDL > 4.1 mmol/L) threshold for children with 2 or more risk factors and 3 children with persistently raised levels above the "intervention" (LDL > 4.9 mmol/L) threshold (Table 3). Of these 3, all were older than 8 years and would potentially be eligible for medical treatment of hypercholesterolemia under these guidelines. For the 17 children above the borderline cutoff, the median (IQR) time between the first and second high values was 98 (72–110) days. Ten (59%) (2.2% of the total population) of the borderline group were older than 8 years. Both groups had BMI *z* scores above average, and most were ART experienced. In the group eligible for intervention, all were ART experienced with a median of 8.1 (2.7–11.9) years of exposure. At 6 months and 1 year after meeting the

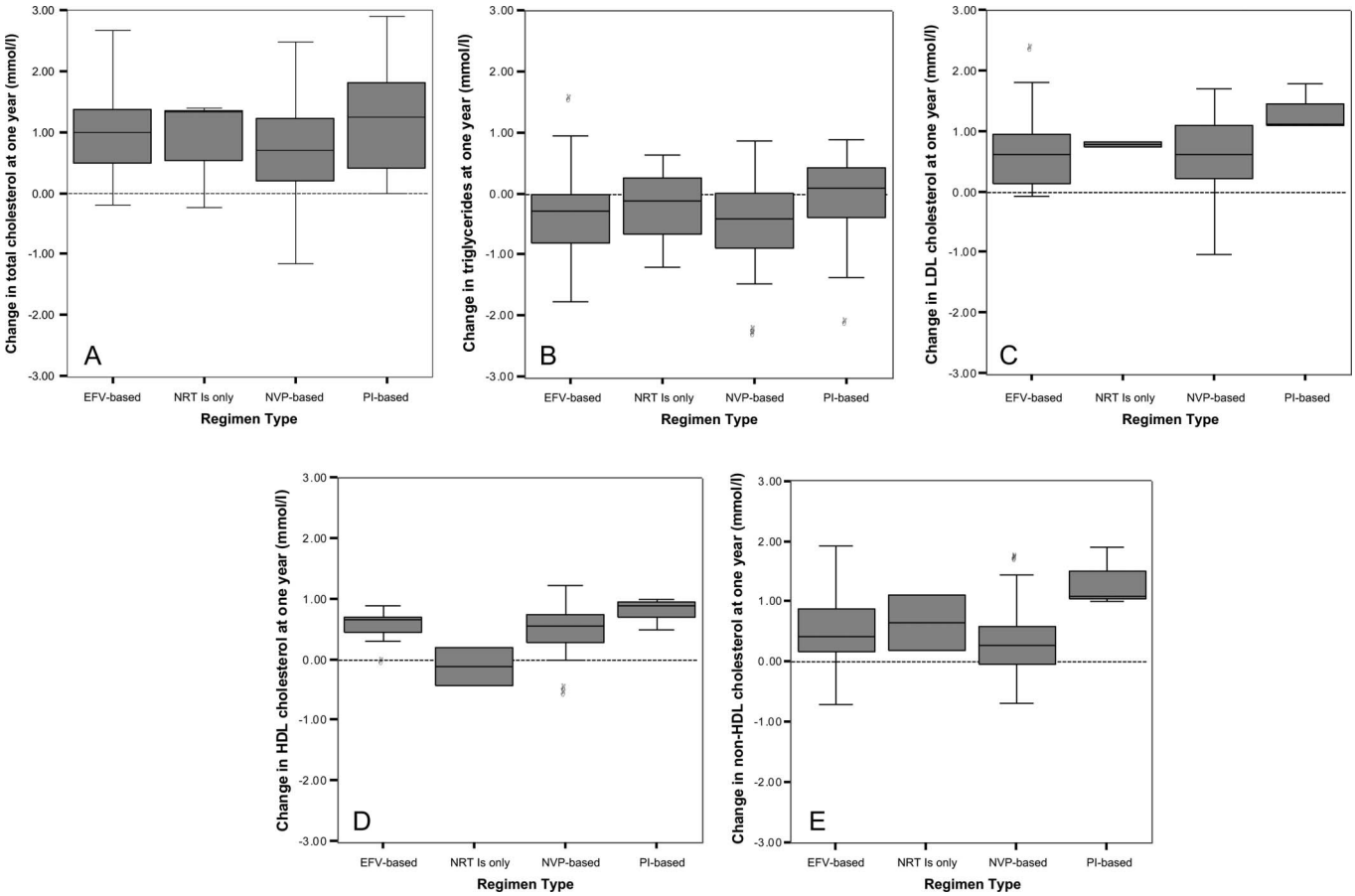

FIGURE. A–E, Changes in lipid markers after 1 year of ART in previously naive children according to regimen type. Note: 16, 36, 27, and 3 eligible children received PI-containing, EFV-containing, NVP-containing, and NRTI-only regimens. NRTI, nucleoside reverse transcriptase inhibitor.

TABLE 2. Adjusted Mean Estimated (95% Confidence Interval) Changes in Lipid Levels According to Length of Exposure to Specific ARVs

	Nevirapine	EFV	NFV	LPV
TC (years of exposure)				
0	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
0–1	0.27 (0.17 to 0.37)	0.28 (0.20 to 0.37)	0.48 (0.35 to 0.60)	0.46 (0.38 to 0.54)
1–2	0.53 (0.41 to 0.66)	0.28 (0.18 to 0.39)	0.68 (0.54 to 0.83)	0.49 (0.38 to 0.59)
2–3	0.57 (0.43 to 0.72)	0.29 (0.16 to 0.42)	0.87 (0.71 to 1.03)	0.58 (0.45 to 0.72)
3–4	0.48 (0.32 to 0.64)	0.31 (0.15 to 0.47)	0.79 (0.61 to 0.98)	0.76 (0.58 to 0.93)
4+	0.52 (0.32 to 0.71)	0.33 (0.13 to 0.54)	0.60 (0.39 to 0.82)	0.93 (0.72 to 1.15)
Global *P* value	<0.0001	<0.0001	<0.0001	<0.0001
TGs (years of exposure)				
0	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
0–1	0.03 (−0.07 to 0.13)	0.15 (0.06 to 0.24)	0.13 (0.01 to 0.25)	0.36 (0.26 to 0.45)
1–2	−0.08 (−0.21 to 0.05)	0.03 (−0.08 to 0.14)	0.25 (0.12 to 0.39)	0.38 (0.26 to 0.49)
2–3	−0.20 (−0.35 to −0.06)	0.29 (0.15 to 0.43)	0.11 (−0.04 to 0.25)	0.59 (0.44 to 0.74)
3–4	−0.12 (−0.28 to 0.05)	0.18 (0.00 to 0.35)	0.20 (0.03 to 0.37)	0.52 (0.32 to 0.71)
4+	0.05 (−0.14 to 0.24)	0.24 (0.03 to 0.46)	0.21 (0.01 to 0.41)	0.45 (0.21 to 0.68)
Global *P* value	0.004	0.0001	0.01	<0.0001
HDL cholesterol (years of exposure)				
0	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
0–1	0.20 (0.15 to 0.25)	0.12 (0.08 to 0.17)	0.08 (0.01 to 0.15)	0.01 (−0.03 to 0.05)
1–2	0.34 (0.28 to 0.41)	0.19 (0.12 to 0.25)	0.04 (−0.04 to 0.12)	0.03 (−0.03 to 0.08)
2–3	0.37 (0.30 to 0.44)	0.15 (0.08 to 0.23)	0.14 (0.05 to 0.23)	0.05 (−0.02 to 0.11)
3–4	0.33 (0.25 to 0.41)	0.12 (0.03 to 0.21)	0.12 (0.03 to 0.22)	0.08 (0.00 to 0.17)
4+	0.29 (0.19 to 0.39)	0.11 (0.00 to 0.22)	0.11 (0.00 to 0.22)	0.25 (0.14 to 0.35)
Global *P* value	<0.0001	<0.0001	0.01	<0.0001
LDL cholesterol (years of exposure)				
0	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
0–1	0.27 (0.16 to 0.39)	0.12 (0.01 to 0.23)	0.39 (0.23 to 0.54)	0.27 (0.18 to 0.36)
1–2	0.46 (0.32 to 0.60)	0.16 (0.02 to 0.30)	0.65 (0.47 to 0.83)	0.29 (0.17 to 0.41)
2–3	0.47 (0.31 to 0.63)	0.15 (−0.02 to 0.32)	0.96 (0.76 to 1.15)	0.29 (0.14 to 0.45)
3–4	0.34 (0.15 to 0.52)	0.22 (0.01 to 0.42)	0.70 (0.48 to 0.91)	0.49 (0.30 to 0.69)
4+	0.33 (0.11 to 0.56)	0.45 (0.19 to 0.70)	0.50 (0.25 to 0.75)	0.48 (0.24 to 0.71)
Global *P* value	<0.0001	0.02	<0.0001	<0.0001
Non–HDL cholesterol (years of exposure)				
0	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
0–1	0.20 (0.09 to 0.32)	0.20 (0.09 to 0.31)	0.38 (0.22 to 0.54)	0.43 (0.33 to 0.52)
1–2	0.38 (0.24 to 0.52)	0.14 (0.00 to 0.28)	0.77 (0.58 to 0.95)	0.43 (0.31 to 0.56
2–3	0.31 (0.15 to 0.47)	0.14 (−0.02 to 0.31)	0.92 (0.72 to 1.12)	0.39 (0.24 to 0.54)
3–4	0.21 (0.03 to 0.39)	0.15 (−0.06 to 0.35)	0.73 (0.51 to 0.94)	0.72 (0.53 to 0.91)
4+	0.39 (0.17 to 0.61)	0.29 (0.04 to 0.55)	0.57 (0.32 to 0.83)	0.80 (0.57 to 1.03)
Global *P* value	<0.0001	0.01	<0.0001	0.007

All analyses are mutually adjusted for specific ARVs and for age, sex, ethnicity, CD4 nadir, total cumulative ARV exposure, abacavir use, and BMI *z* score. Results from mixed-effects model with random intercept and slope with autoregressive (1) correlation matrix.

criteria, the median LDL level was 4.8 (4.2–5.4) and 4.2 (3.5–5.8), respectively. One child remained eligible for treatment at 1 year. None had an ARV treatment switch. The borderline group at 6 months and 1 year had LDL levels of 4.1 (3.1–4.7) and 4.3 (3.5–4.5), respectively. At 1 year, there were 4 missing values and 8 of 13 remained above the cutoff.

Forty-seven (10.5%) children were above the 95th percentile for LDL 3.33 mmol/L (130 mg/dL), a suggested intervention cutoff for children with inflammatory conditions,[27] and 25 of the 47 children (53.2%) were older than 8 years. At 1 year, despite conservative management, LDL level remained >3.33 mmol/L in 18 (58.1%) cases. The time between the first and second high values was 91 (63–119) days. All children had dietary and exercise advice, but none received lipid-lowering medication during the study.

DISCUSSION

It is difficult to separate the impact of HIV infection from ART on serum lipid concentrations. Research from the pre-ART era showed LDL and TG to increase as HIV progressed to AIDS.[29] Our study of children starting ART before the onset of

TABLE 3. Characteristics of Hyperlipidemic Children at Time of Eligibility for Medical Intervention or Borderline High With Eligibility for Evaluation*

	Eligible for Medical Intervention, n (%) Persistent LDL > 4.9 mmol/L (190 mg/dL)	Eligible for Evaluation, n (%)* Persistent LDL > 4.1 mmol/L (160 mg/dL)
	3 (100)	17 (100)
Lipid levels at time of eligibility, median (IQR)		
TC	7.9 (7.5–8.1)	6.9 (6.4–7.4)
TGs	2.6 (2.2–2.7)	1.8 (1.3–2.3)
LDL cholesterol	5.3 (5.1–5.8)	4.5 (4.3–4.9)
HDL cholesterol	1.2 (1.2–1.6)	1.4 (1.1–1.6)
Demographics		
Aged > 8 y		
Yes	3 (100.0)	10 (58.8)
Age, median (IQR), y	8.9 (8.7–14.4)	8.4 (4.8–10.5)
Sex		
Female	0 (0.0)	10 (58.8)
Ethnicity		
Black African	1 (33.3)	8 (47.1)
White	1 (33.3)	4 (23.5)
Other	1 (33.3)	5 (29.4)
BMI *z* score, median (IQR)	+0.7 (−1.7 to +2.0)	+0.0 (−0.5 to +1.5)
HIV characteristics, median (IQR)		
CD4 %	26 (25–43)	32 (22–41)
VL (copies/mL)	50 (50–400)	350 (50–3550)
ARV history		
Any ART		
Ever received	3 (100.0)	16 (94.1)
Cumulative exposure, y	8.1 (2.7–11.9)	2.9 (2.2–5.1)
NVP		
Ever received, n(%)	2 (66.7)	7 (41.2)
Cumulative exposure, y*	1.2–1.3	1.3 (0.9–1.5)
EFV		
Ever received, n (%)	1 (33.3)	5 (29.4)
Cumulative exposure, y*	2.8	1.7 (0.9–2.2)
NFV		
Ever received, n (%)	1 (33.3)	11 (64.7)
Cumulative exposure, y*	1.3	1.9 (0.9–2.6)
LPV		
Ever received, n (%)	2 (66.7)	6 (35.3)
Cumulative exposure, y*	0.7–0.9	2.5 (0.6–2.9)
ABC		
Ever received, n (%)	1 (33.3)	8 (47.1)
Cumulative exposure, y*	0.9	1.3 (0.8–2.5)
Made change to ART regimen in the following year	0 (0.0)	6 (35.3)
Subsequent TC measurements, median (IQR)		
6 mo later	7.0 (6.5–8.0)	6.3 (5.3–6.8)
1 y later	6.1 (5.8–8.3)	6.0 (5.9–6.6)
Subsequent LDL measurements		
6 mo later	4.8 (4.2–5.4)	4.1 (3.1–4.7)
1 y later	4.2 (3.5–5.8)	4.3 (3.5–4.5)

*Among those with at least one-day exposure; time of eligibility for medical intervention was taken as the date of the second of 2 consecutive high LDL measurements.

AIDS found no association between TC, LDL, TG or non-HDL, and VL or CD4 count. However, pre-ART protective HDL is low, with a median (IQR) of 0.8 (0.5–0.9) mmol/L.

For children on ART, TC levels were higher among those exposed to either NVP or LPV/RTV. Concentrations rose faster and remained elevated longer than for the NNRTIs. Cross-sectional studies have reported elevations in TC between 1 and 1.6 mmol/L in children on PIs compared with those not on PIs,[7–9,11] which are greater than those reported here. However, we looked at rates of change rather than maximum increases;

therefore, these results are not directly comparable. The increase in TC associated with NFV seems to be driven by non-HDL (primarily made up of LDL), whereas increased LPV/RTV exposure was associated with increases in HDL and non-HDL (both TG and LDL effected). Additionally, whereas lipid levels continued to increase after up to 4-year cumulative LPV/RTV exposure, the initial increases observed with NFV exposure seemed to decline with cumulative (>3 years) drug exposure. The association between PIs and lipid increases, particularly with LPV/RTV, is in line with results observed in adult populations and other pediatric studies.[6,17,18]

For both NNRTIs, an initial TC rise was observed with initial exposure, before levels began to stabilize or decrease. Almost half of this TC increase seems to be driven by HDL increases. Increased exposure to NVP was associated with larger HDL increases in this study. However, the impact of EFV on non-HDL was smaller. Combined with HDL increases seen, overall EVF may be the more cardioprotective NNRTI. This potentially beneficial HDL increase associated with NNRTIs has been seen in other pediatric[5] and adult populations.[30–32]

As CVD is rare in children in the absence of familial hypercholesterolemia or congenital heart disease, it is difficult to know at which level interventions are appropriate. Research in pediatric cardiovascular health suggests that inflammatory disorders such as systemic lupus erythematosus represent a moderate level of risk for heart disease, but when combined with hyperlipidemia, this risk increases to a high level (ie, clinical evidence of CVD under 30 years old).[27] Risk factors for atherosclerosis have been reported as early as the first decade of life.[22] When considering the AAP guidelines for pharmacological intervention in pediatric hyperlipidemia, we found 2.2% of our cohort would meet borderline criteria (ie, would require intervention if 2 or more CVD risk factors are present). A smaller proportion (0.7%) would require pharmacological intervention in the absence of risk factors. However, following recommendations for management of dyslipidemia in inflammatory disorders,[27] just over 10% had LDL >95 percentile, of which 60% remained elevated 1 year later. A possible explanation for lipid levels falling below the cutoff at a year is increase in age[6]; however, we found no association between cholesterol and age.

The patterns of blood lipids seen in this cohort suggest that once children are stabilized on a regimen for 1–2 years, if their LDL is <95th percentile (3.3 mmol/L), then the frequency of monitoring cholesterol could be reduced to yearly. Children on regimens containing boosted PIs may require more frequent monitoring.

Proposed interventions for management of HIV-associated dyslipidemia include lifestyle interventions, treatment switching, and pharmacological management.[33] Dietary interventions include advice for a cardioprotective diet, for example, from the American Heart Association.[34] Physical activity may also be useful for improving dyslipidemia.[35] DHIVA (Dietitians working in HIV/AIDS, a specialist group of the British Dietetic Association) has developed and is currently piloting a treatment algorithm based on American Heart Association/AAP guidelines (http://www.chiva.org.uk/health/guidelines/dyslipidaemia).

Interventions, when conservative management of hyperlipidemia fails, should include treatment switching methods where possible and then pharmacological interventions. Results of PENPACT 1 show no difference between PIs and NNRTIs[36] in treatment efficacy, and switches from PI to NNRTI have demonstrated improvements in TC:HDL ratios in adults[37–39] and in children naive to NNRTIs.[40–42] Which NNRTI would be favorable remains unclear. EFV produces lower rises in non–HDL cholesterol. However, NVP seems to produce greater increases in HDL cholesterol despite increases in non-HDL. In the event that medical intervention is needed, pravastatin does not interact with ART[33,43,44]and has been shown to be safe in children with familial hypercholesterolemia.[45] The risk of noncompliance with ART with the additional pill burden and possible side effects of headache or abdominal discomfort with statins should also be considered.

Limitations to this study include possible channelling bias due to the treating clinician's choice of ART and knowledge of cardiovascular risk. Lipid levels may be confounded with changes that would be expected with increasing age; however, age was a variable in multivariate analysis. The age of this study population was young, mean of 6.6 years at baseline; older study populations are needed. We used nonfasting samples that may overestimate the rate of hyperlipidemia. However, a recent report of postprandial LDL levels over time does not show significant variation either by direct analysis or when calculated by Friedewald equation.[46] Last, we have no information regarding lipodystrophy, pubertal status, other cardiovascular risk factors, dietary intake, or conservative management interventions. However, children with raised cholesterol levels or elevated BMI are referred to the dietitian.

CONCLUSIONS

We have found evidence of an association between specific ARV drugs, in particular the PIs with LPV/RTV showing greater detrimental lipid changes than NFV in a pediatric population. NNRTIs were associated with an increase in cholesterols, but this is in part due to a rise in protective HDL. Only 0.7% of the children considered met the AAP guidelines for pharmacological intervention during an average follow-up period of nearly 5 years. However, using lower cutoff guidelines accounting for the increased risk of inflammation associated with HIV infection, up to 10% may require intervention. Measuring surrogate CVD markers such as lipids over time is required, but monitoring frequency could be adjusted based on the individual child's risk. Clinical trials are required to develop and test intervention strategies to protect against CVD in children born with HIV, growing into adult life.

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