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# Safety and Efficacy of Atorvastatin in Human Immunodeficiency Virus-infected Children, Adolescents and Young Adults With Hyperlipidemia

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**Background:** Human immunodeficiency virus (HIV)-infected children receiving antiretroviral therapy (ART) have increased prevalence of hyperlipidemia and risk factors for cardiovascular disease. No studies have investigated the efficacy and safety of statins in this population.

**Methods:** HIV-infected youth 10 to <24 years of age on stable ART with low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL for ≥6 months initiated atorvastatin 10 mg once daily. Atorvastatin was increased to 20 mg if LDL-C efficacy criteria (LDL-C < 110 mg/dL or decreased ≥30% from baseline) were not met at week 4. Primary outcomes were safety and efficacy.

**Results:** Twenty-eight youth initiated atorvastatin; 7 were 10–15 years and 21 were 15–24 years. Mean baseline LDL-C was 161 mg/dL (standard deviation 19 mg/dL). Efficacy criteria were met at week 4 by 17 of 27 (63%) participants. Atorvastatin was increased to 20 mg in 10 participants. Mean LDL-C decreased from baseline by 30% (90% confidence interval: 26%, 35%) at week 4, 28% (90% confidence interval: 23%, 33%) at week 24 and 26% (90% confidence interval: 20%, 33%) at week 48. LDL-C was less than 110 mg/dL in 44% at week 4, 42% at week 12 and 46% at weeks 24 and 48. Total cholesterol, non high-density lipoprotein (non-HDL)-C and apolipoprotein B decreased significantly, but IL-6 and high-sensitivity C-reactive protein did not. Two participants in the younger age group discontinued study for toxicities possibly related to atorvastatin.

**Conclusions:** Atorvastatin lowered total cholesterol, LDL-C, non HDL-C and apolipoprotein B in HIV-infected youth with ART-associated hyperlipidemia. Atorvastatin could be considered for HIV-infected children with hyperlipidemia, but safety monitoring is important particularly in younger children.

**Key Words:** HIV, children, atorvastatin

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Accumulating evidence suggests that adults with human immunodeficiency virus (HIV) infection are at increased risk for early cardiovascular disease.[1–5] Statins have proven efficacy and safety for adults with HIV infection who meet criteria for treatment[6]

Guidelines from the National Heart, Lung and Blood Institute and the American Academy of Pediatrics[7] provide recommendations for the use of statins in children and adolescents with hypercholesterolemia. HIV infection is one of the risk factors to be taken into account when determining the low-density lipoprotein cholesterol (LDL-C) level at which drug therapy should be considered. Elevated cholesterol levels are common in ART-treated HIV-infected children with greatest increases associated with use of protease inhibitors[8–13]; however, there are no clear recommendations for management of ART-associated hyperlipidemia in children and adolescents.

Atorvastatin is US Food and Drug Administration (FDA)-labeled for treatment of heterozygous familial hypercholesterolemia in adolescents and children as young as 10 years,[14–18] but no studies of atorvastatin (or any statin) treatment have been reported in HIV-infected children and adolescents. The purpose of this study was to investigate the safety and efficacy of daily atorvastatin in HIV-infected children, adolescents and young adults with elevated LDL-C.

## MATERIALS AND METHODS

### Participants

Subjects were HIV-infected children, adolescents and young adults 10 to <24 years of age on stable antiretroviral (ARV) regimens for at least 6 months before study entry (hereafter, the term "youth" will be used to indicate the entire age range). Participation required direct LDL-C ≥ 130 mg/dL at study screening and at least twice over the previous 6 months (fasted calculated LDL-C allowed for these measurements), with documented attempts at modifying diet and other risk factors for at least 3 months. Other inclusion criteria included: CD4% ≥ 15%, HIV-1 RNA ≤ 10,000 copies/mL and Tanner stage ≥2. Participants were excluded for laboratory values above grade 2 toxicity criteria [above grade 0 for liver enzymes and

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creatine kinase (CK)], past myopathy or neuromuscular disorder, chronic myositis, hepatitis, diabetes mellitus, use of contraindicated medications, chemotherapy and pregnancy. The protocol was approved by the institutional review board at each participating site, and all guardians and children, as appropriate, gave written consent.

### Study Design

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1063 was a phase I/II, single-arm safety and efficacy study of atorvastatin (Lipitor) for the treatment of elevated LDL cholesterol in HIV-infected youth. Enrollment was stratified by age group, with a target of 20 participants 10 to <15 years of age and 20 participants ≥15 to <24 years of age. Enrollment was discontinued prematurely for administrative reasons after 28 participants enrolled. Participants started on atorvastatin at 10 mg once daily. If the participant's direct LDL-C was either reduced to <110 mg/dL or declined by ≥30% from baseline at week 4, the participant continued on the 10 mg daily dose. Otherwise, the participant's dose was increased to 20 mg once daily starting from week 8, provided that the participant did not develop any atorvastatin-related grade ≥ 3 toxicity [or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ grade 2] by week 8. Study duration was 48 weeks.

### Laboratory Assessments

Fasting (minimum 8 hours) sera were obtained at screening, entry and weeks 4, 12, 24 and 48. Sera in serum separator tubes were allowed to clot for 30 minutes at ambient temperature and subsequently centrifuged within 1 hour. Aliquots were preserved at ≤−70°C within 8 hours of collection.

Ultrafrozen sera aliquots were shipped to Quest Diagnostics, Baltimore, MD, for real-time determination of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), directly measured LDL-C and triglycerides which were assayed using commercially available FDA-cleared methods.[19–22] Additional aliquots were stored at less than or equal to −70°C for end of study batch testing of specialty chemistry analytes. Apolipoproteins A1 and B and high sensitivity interleukin-6 (IL-6) were measured at Quest Diagnostics Nichols Institute.[21,23,24] High sensitivity C-reactive protein (hs-CRP was tested with an FDA-cleared, particle enhanced immunonephelometric assay at Quest Diagnostics.[23,25]

### Adherence Assessment

Adherence to ART and atorvastatin for the prior 3 days and for the last month was assessed using a standardized questionnaire at each study visit. Adherence was defined as excellent if the participants reported no missed doses in the previous 3 days.

### Primary Efficacy Endpoint

Baseline LDL-C was defined as the mean of the direct LDL-C values at screening and entry. Subjects were identified as having an efficacious outcome if their LDL-C was <110 mg/dL or if their LDL-C decreased by at least 30% from baseline at a given visit.

### Toxicity Management

Safety labs were measured at each study visit. The study team reviewed all laboratory values ≥ grade 2 for relatedness to atorvastatin, and all adverse events were reviewed by the IMPAACT Study Monitoring Committee. Safety endpoints included any grade ≥3 toxicity; AST and ALT ≥ grade 2; total amylase and direct bilirubin ≥ 2 times the upper limit of normal.

### Statistical Analyses

Baseline values for lipids and inflammatory markers were calculated by taking the mean of screening and entry (week 0) values. Intent-to-treat analysis of efficacy included all participants who started study drug; those without a fasting direct LDL-C at the relevant follow-up week were considered failures. The as-treated analysis of efficacy included those participants who were on study treatment and had direct LDL-C data available at the specified follow-up week. Exact 90% confidence intervals (CIs) for proportions were computed based on the binomial distribution. Mean percent change from baseline and corresponding 90% CIs were computed for normally distributed data, and median percent change from baseline and corresponding 90% CIs were computed for highly skewed data. The use of a 90% level of confidence reflects the intent of the study to produce pilot estimates of safety and efficacy outcomes in this population for descriptive purposes rather than to conduct hypothesis testing. Statistical analysis and graphics were performed using SAS 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Baseline Characteristics of Participants

All 28 participants initiated study treatment within 3 days of enrollment. The median age was 17 years (range, 10–23), 68% of participants were female and 64% were black non Hispanic (Table 1). Median body mass index was 22.7 kg/m$^2$. Median CD4 percent was 36% at screening. Plasma HIV-1 RNA was below the lower limit of quantitation of the local site assay in 71% of participants. ART regimens at study entry contained at least 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) for 32% of participants and at least 1 protease inhibitor (PI) for 79% of participants.

### Application of Study Algorithm and Efficacy Endpoints

Seventeen of the 28 participants (61%) met the efficacy endpoint at week 4 (Fig. 1) and were eligible to remain on the starting dose of 10 mg until they completed the study. Fifteen remained on the starting dose until week 48. One participant received an unintended dose increase to 20 mg from week 8 to week 48. Another participant experienced a toxicity potentially related to atorvastatin at week 6 and was taken off study treatment. The latter participant had a rebound in LDL-C at week 12 and had missing lipid evaluations for the remainder of the study. Ten of the 28 study participants (36%) did not meet the week 4 efficacy endpoint, and all except one of these received the protocol-prescribed dose increase to 20 mg from week 8 until week 48. The participant who was not dose-escalated (and continued on 10 mg until week 48) entered the study with a grade 2 rash that worsened to a grade 3 by week 4, prompting the family to refuse the dose increase. The rash ultimately resolved and was deemed to be unrelated to atorvastatin. Finally, 1 participant had unknown LDL-C at week 4, was nonadherent to study visits and medication and was taken off study treatment at week 9 and off study at week 47. Mean baseline LDL-C was similar between those who met efficacy criteria at week 4 (161 mg/dL, standard deviation 17 mg/dL) and those who required dose escalation (163 mg/dL, standard deviation 24 mg/dL).

Based on an intent-to-treat analysis with all 28 participants who started study medication included in the denominator, 61% (90% CI: 44%, 76%) met efficacy criteria at week 4, 46% (90% CI: 30%, 63%) at week 12, 57% (90% CI: 40%, 73%) at week 24 and 54% (90% CI: 37%, 70%) at week 48. Among those participants who were on study treatment and had LDL-C data available at the specified time point, 63% (90% CI: 45%, 78%) met efficacy criteria at week 4, 50% (90% CI: 33%, 67%) at week 12, 62% (90% CI: 44%, 77%) at week 24 and 58% (90 % CI: 40%, 74%) at week 48.

**TABLE 1.** Baseline Characteristics of HIV-Infected Children, Adolescents and Young Adults With Elevated LDL Cholesterol (N = 28)

| Characteristic | Number, (%) |
|---|---|
| Age at study entry (yr) | |
| Mean (SD) | 17 (4) |
| Min, max | 10, 23 |
| Median | 17 |
| Age group (yr) | |
| ≥10 to <15 | 7 (25%) |
| 15 to <19 | 12 (43%) |
| 19 to <24 | 9 (32%) |
| Sex | |
| Male | 9 (32%) |
| Female | 19 (68%) |
| Race/ethnicity | |
| White non Hispanic | 4 (14%) |
| Black non Hispanic | 18 (64%) |
| Hispanic (regardless of race) | 5 (18%) |
| Asian, Pacific Islander | 1 (4%) |
| BMI (kg/m$^2$) at entry* | |
| Mean (SD) | 25.6 (9.5) |
| Min, max | 14.7, 55.8 |
| Median | 22.7 |
| CD4 percent at screening | |
| 15 to <25 | 2 (7%) |
| ≥25 | 26 (93%) |
| HIV-1 RNA (copies/mL) | |
| ≥LLQ | 8 (29%) |
| <LLQ | 20 (71%) |
| ARV regimen at entry | |
| At least 1 PI† and at least 1 NNRTI | 5 (18%) |
| At least 1 PI and no NNRTI | 17 (61%) |
| At least 1 NNRTI and no PI | 4 (14%) |
| Other ARV regimen | 2 (7%) |

*Screening data were used when entry data were unavailable; BMI was missing for 1 participant at both screening and entry.

†All PIs were boosted except for 1 participant.

BMI indicates body mass index; LLQ, lower limit of quantification of assay.

## Changes in Lipid Concentrations

Baseline mean direct LDL-C of the 28 participants and decreases by study week are detailed in Table 2 and Figure 2. The percentage of participants with LDL-C less than 110 mg/dL was 44% (90% CI: 28%, 62%) at week 4, 42% (90% CI: 26%, 60%) at week 12 and 46% (90% CI: 29%, 64%) at weeks 24 and 48. LDL-C concentrations after baseline were fairly stable over the 48 weeks of the study for the majority of participants, though some individuals had noticeable variation in their LDL-C concentrations at different study visits.

Table 2 and Figure 2 also show changes in other fasting lipids and apolipoproteins by study week. Mean HDL-C did not change substantially over the course of the study. Mean TC, mean non-HDL-C and mean triglyceride concentrations demonstrated similar patterns of change over time, declining from baseline to week 4 and then remaining relatively constant for the remainder of follow-up.

Mean ApoA1 did not change throughout the study, while mean ApoB and ApoB/A1 declined by 27% (90% CI: 22%, 32%) from baseline to week 12 and were steady for the remainder of study follow-up.

## Safety Events and Drug Toxicity

Two participants (7%; 90% CI: 1%–21%) discontinued study treatment because of toxicities possibly related to atorvastatin by week 48. Both participants were in the younger age group (10 to <15 years old), were receiving zidovudine/lamivudine/lopinavir/ritonavir at study entry and were receiving 10 mg atorvastatin. One participant had a grade 3 creatinine elevation at week 6 with no changes in ARV regimen before week 6; another had grade 4 ALT and AST elevations at the final study visit and also received a diagnosis of drug-induced hepatitis. This participant's ARV regimen had been changed to abacavir/lamivudine/atazanavir at week 24. Both participants had normal values at baseline.

Six other participants experienced nontreatment-related grade 3 events: 1 elevated total bilirubin level at week 8 (attributed to atazanavir), 1 elevated total amylase at week 35 (ibuprofen overdose), 1 elevated CK at week 9 (high levels of physical activity), 1 elevated fasting glucose level at week 3, 1 fever at week 6 (exudative pharyngitis) and 1 nonallergic rash at week 4 (fungal). No other grade 4 events and no deaths occurred.

## Changes in Markers of Inflammation

Descriptive statistics for serum IL-6 and hs-CRP and their percent change over time are shown in Table 3. Median IL-6 was 1.66 pg/mL at baseline and fluctuated over time with no clear trend. Median percent change in IL-6 was also variable, and the corresponding CIs were wide. Median hs-CRP was 1.20 mg/L at baseline and 1.00 mg/L at week 12 before declining to 0.50 mg/mL at week 24 and 0.60 mg/L at week 48; however, the ranges of hs-CRP values at all weeks were relatively large.

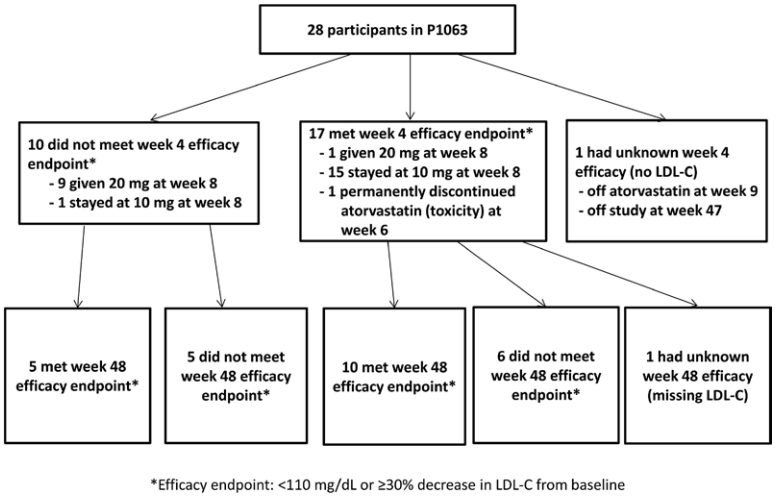


**FIGURE 1.** Study profile.

**TABLE 2.** Lipid and Lipoprotein Concentrations (in mg/dL) Before Atorvastatin Treatment and Changes From Baseline During Atorvastatin Treatment

| | Baseline | Week 4 | Week 12 | Week 24 | Week 48 |
|---|---|---|---|---|---|
| | (N = 28) | (N = 27) | (N = 26) | (N = 26) | (N = 26) |
| LDL cholesterol (mg/dL)* | | | | | |
| Mean (SD) | 161 (19) | 112 (21) | 117 (30) | 116 (27) | 117 (27) |
| Median (min, max) | 162 (133, 207) | 113 (74, 165) | 114 (68, 179) | 110 (84, 173) | 115 (67, 164) |
| Mean % change (90% CI) | | −30.3 (−34.6, −26.1) | −27.3 (−33.3, −21.4) | −28.0 (−32.7, −23.4) | −26.4 (−33.0, −19.7) |
| HDL cholesterol (mg/dL) | | | | | |
| Mean (SD) | 51 (13) | 51 (11) | 52 (15) | 52 (14) | 52 (13) |
| Median (min, max) | 50 (31, 77) | 49 (35, 80) | 50 (25, 88) | 48 (36, 90) | 53 (30, 84) |
| Mean % change (90% CI) | | 1.8 (−2.5, 6.1) | 2.2 (−1.4, 5.8) | 3.0 (−3.1, 9.1) | 4.2 (−3.5, 11.9) |
| Total cholesterol (mg/dL) | | | | | |
| Mean (SD) | 237 (27) | 182 (27) | 186 (34) | 184 (32) | 185 (29) |
| Median (min, max) | 240 (179, 285) | 178 (135, 235) | 187 (113, 249) | 176 (142, 261) | 185 (120, 248) |
| Mean % change (90% CI) | | −23.8 (−26.8, −20.8) | −21.8 (−25.8, −17.9) | −22.5 (−26.0, −19.0) | −21.5 (−26.4, −16.6) |
| Non HDL cholesterol (mg/dL) | | | | | |
| Mean (SD) | 187 (26) | 130 (27) | 133 (29) | 133 (29) | 133 (30) |
| Median (min, max) | 186 (136, 250) | 129 (86, 185) | 132 (79, 181) | 124 (99, 192) | 130 (74, 197) |
| Mean % change (90% CI) | | −30.6 (−34.3, −26.9) | −28.4 (−32.9, −23.9) | −28.9 (−33.0, −24.8) | −28.0 (−34.0, −22.1) |
| Triglycerides (mg/dL) | | | | | |
| Mean (SD) | 160 (89) | 136 (64) | 143 (82) | 130 (50) | 142 (103) |
| Median (min, max) | 124 (61, 387) | 121 (38, 272) | 126 (32, 390) | 121 (57, 250) | 111 (44, 566) |
| Mean % change (90% CI) | | −9.5 (−20.4, 1.4) | −12.2 (−19.3, −5.1) | −11.3 (−22.8, 0.3) | −12.6 (−22.5, −2.7) |
| | Baseline | | Week 12 | Week 24 | Week 48 |
| | (N = 27) | | (N = 24) | (N = 23) | (N = 24) |
| Apolipoprotein A1 (mg/dL) | | | | | |
| Mean (SD) | 140 (22) | N/A | 142 (28) | 143 (22) | 142 (22) |
| Median (min, max) | 142 (91, 195) | | 139 (79, 198) | 141 (101, 206) | 146 (104, 172) |
| Mean % change (90% CI) | | | 0.8 (−3.2, 4.8) | 2.4 (−2.6, 7.5) | 0.3 (−4.8, 5.4) |
| Apolipoprotein B (mg/dL) | | | | | |
| Mean (SD) | 127 (20) | N/A | 92 (19) | 94 (19) | 95 (23) |
| Median (min, max) | 128 (88, 176) | | 95 (58, 127) | 87 (68, 131) | 90 (58, 135) |
| Mean % change (90% CI) | | | −27.2 (−32.1, −22.4) | −25.1 (−29.6, −20.7) | −23.8 (−30.5, −17.2) |
| Apolipoprotein B/A1 ratio | | | | | |
| Mean (SD) | 0.93 (0.22) | N/A | 0.66 (0.15) | 0.67 (0.17) | 0.69 (0.21) |
| Median (min, max) | 0.92 (0.61, 1.56) | | 0.70 (0.34, 0.90) | 0.67 (0.43, 1.05) | 0.65 (0.42, 1.29) |
| Mean % change (90% CI) | | | −27.3 (−32.3, −22.3) | −25.6 (−31.5, −19.7) | −23.5 (−30.1, −16.9) |

*Primary efficacy measure.
N/A indicates samples not available.

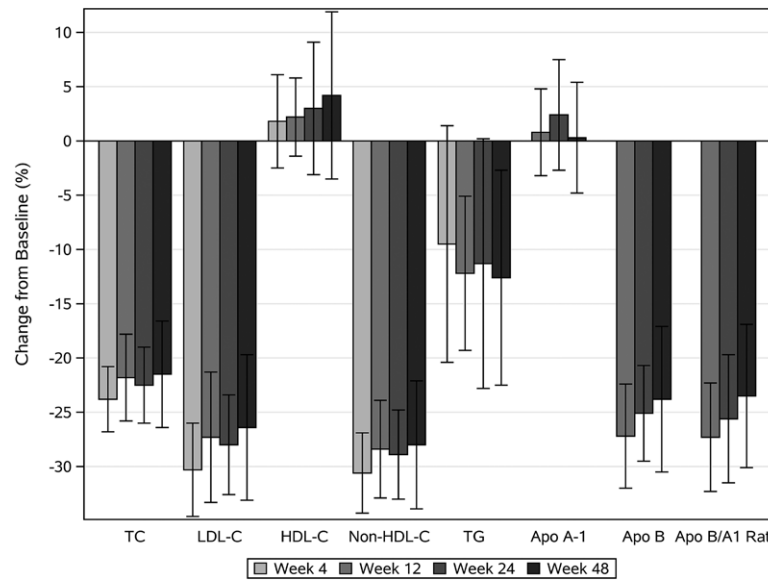


**FIGURE 2.** Mean percent change in lipid and lipoprotein concentrations from baseline during atorvastatin treatment. Error bars show 90% CIs.

**TABLE 3.** Absolute Inflammatory Marker Concentrations Before Atorvastatin Treatment and Changes During Atorvastatin Treatment

| | Baseline | Week 12 | Week 24 | Week 48 |
|---|---|---|---|---|
| IL-6 (pg/mL) | | | | |
| N | 27 | 24 | 23 | 24 |
| Mean (SD) | 1.83 (1.53) | 2.27 (1.71) | 1.53 (1.09) | 2.63 (4.92) |
| Median (min, max) | 1.66 (0.47, 7.94) | 1.94 (0.51, 6.97) | 1.36 (0.42, 4.41) | 1.15 (0.56, 24.56) |
| Mean % change (90% CI) | | 62.1 (11.6, 112.6) | −1.3 (−22, 19.4) | 40.2 (−6, 86.4) |
| Median % change (90% CI) | | −1 (−32, 110) | −19 (−32, −5) | −11.5 (−34, 46) |
| hs-CRP (mg/L) | | | | |
| N | 27 | 25 | 23 | 24 |
| Mean (SD) | 4.32 (5.97) | 4.14 (6.18) | 1.91 (3.92) | 1.88 (4.05) |
| Median (Min, Max) | 1.20 (0.20, 22.00) | 1.00 (0.20, 20.50) | 0.50 (0.20, 18.90) | 0.60 (0.20, 19.30) |
| Mean % change (90% CI) | | 132.2 (23.5, 240.9) | −9.8 (−43.3, 23.7) | 20.4 (−33.8, 74.6) |
| Median % change (90% CI) | | 0 (−35, 44) | −20 (−67, 0) | 0 (−78, 17) |

## Virologic Changes

The percentage of participants with HIV-1 RNA viral load (VL) below the lower limit of quantitation was 71% at week 0, 69% at week 12, 62% at week 24 and 69% at week 48. Of those with undetectable VL at baseline and follow-up data available, 80% had undetectable VL at week 48 and 55% had undetectable VL at all study weeks. Of those with detectable virus at baseline, median plasma HIV-1 RNA concentration was low (2.5 $\log_{10}$ copies/mL) and unchanging over time.

## DISCUSSION

The HIV-infected youth participating in P1063 experienced a significant decline in plasma lipid concentrations after initiating atorvastatin. The overall decline in LDL-C and TC was somewhat less than that seen in children with familial hypercholesterolemia[15,16] but similar to that in children with Kawasaki disease,[18] type 1 diabetes[26] and systemic lupus.[17] LDL-C and TC decreased by a mean of 39% and 31%, respectively, between baseline and 26 weeks in the 140 children randomized to atorvastatin in a placebo-controlled trial in children and adolescents with familial or severe hypercholesterolemia.[15] The larger decrease may have been due in part to the study design which required dose escalation if LDL-C < 130 mg/dL was not achieved at 4 weeks on 10 mg of atorvastatin. In contrast, participants in P1063 did not dose escalate if their LDL-C decreased by ≥30% regardless of actual concentration achieved. Similarly, studies in adults have found somewhat lower responses to statins in HIV-infected versus uninfected adults.[27–29]

Some individuals demonstrated considerable variability in LDL-C concentrations during the study, suggesting that adherence to atorvastatin may not have been as consistent as was indicated through self-report. Alternatively, dietary intake may have been variable. One participant, who changed from a boosted-PI to an unboosted-PI at week 24, had lower LDL-C at week 48. Two additional participants had ARV changes during the study period which did not appear to affect their LDL-C.

In addition to LDL-C, ApoB, non-HDL-C and ApoB/ApoA-1 ratio decreased significantly from baseline to week 48. ApoB, a measure of total atherogenic particle number, and non HDL-C, which includes very low density lipoprotein cholesterol as well as LDL-C, are additional measures of cardiovascular disease risk.[30–33] Several studies have shown ApoB concentrations to be a better predictor of cardiovascular disease risk than LDL-C concentrations in HIV-uninfected adults treated with statins.[34–36]

The association between childhood risk factors including LDL-C[37,38]and adult cardiovascular disease has been demonstrated through longitudinal epidemiologic studies.[37–39] Similarly, evidence is accumulating for increased cardiovascular risk in HIV-infected children and adolescents, including elevated cholesterol concentrations particularly in those on PI-based ART[8,9,12,13] and increased Pathobiologic Determinants of Atherosclerosis in Youth scores.[40] Increased carotid artery intima-media thickness has been demonstrated in some pediatric HIV-infected cohorts[41–43] but not others.[44] The finding of increased risk of development of coronary heart disease in young HIV-infected adults between the ages of 18–24 years[45] highlights the potential risk for early cardiovascular disease even in children with perinatal HIV infection.

While no studies directly demonstrate a decrease in mortality related to cardiovascular disease in HIV-infected adults treated with statins, there is evidence that statins decrease subclinical cardiovascular disease: including decreased carotid artery intima-media thickness,[46] improved endothelial function,[47] decreases in markers of vascular inflammation[48,49] and decreased noncalcified coronary artery plaque volume.[50] Statin therapy reduces risk for cardiovascular disease by effectively decreasing both cholesterol concentrations and chronic inflammation. While the immune mechanisms resulting in increased atherosclerosis are complex, hs-CRP has been shown to be a relevant surrogate marker for immune activation and is a significant independent risk factor for myocardial infarction and peripheral vascular disease.[51–53] Statins lower hs-CRP concentrations in adults, and the clinical efficacy in reducing cardiovascular disease is independently related to the ability of statins to reduce both blood lipid concentrations and hs-CRP.[54–57] Both elevated hs-CRP and HIV infection were found to be independent risk factors for risk of acute myocardial infarction in adults,[58] and increased hs-CRP concentrations have been associated with increased carotid artery intima-media thickness in HIV-infected adults[59] and children.[60] Statin use resulted in decreased hs-CRP in HIV-infected adults in some studies[61,62] but not others.[63] Though both hs-CRP and IL-6 concentrations appeared to decrease in this study after initiation of atorvastatin, the variability was high for both analytes. As IL-6 and hs-CRP are acute phase reactants and participants were not required to be free of minor symptoms such as upper respiratory tract infections, the concentrations may have been affected by the clinical status of the participant at the time of the study visits. Therefore this study suggests, but cannot confirm, a decrease in inflammatory markers after initiation of atorvastatin treatment in HIV-infected youth.

Many of the statins currently in use are metabolized by cytochrome P450 3A4 enzymes; therefore the risk for drug interactions with PIs is significant. Simvastatin and lovastatin are contraindicated with PIs because of significantly increased statin levels.[64,65] Atorvastatin concentrations are affected less by concomitant PI administration[65] and atorvastatin has been used safely in HIV-infected adults.[6,66] Atorvastatin should not be coadministered with tipranavir, and the dose should not exceed 20 mg

when co-administered with darunavir, fosamprenavir/ritonavir or saquinavir/ritonavir.[65,67] In contrast, administration of atorvastatin does not affect PI drug concentrations.[64,65] Currently atorvastatin is FDA-labeled for use in children down to age 10 years with heterozygous familial hyperlipidemias.[68]

A systematic review of the literature on the safety and tolerability of atorvastatin found a low incidence of elevated liver enzymes, CK and myalgias, with no clear dose-dependency.[69] Serious muscle-related side effects have been rare across clinical studies. While myalgia occurred in close to 5% of participants, the rate of persistent increase in CK (>10× upper limit of normal) ranged from 0.1% to 0.4%, with few cases of rhabdomyolysis.[69–71] Drug-induced rhabdomyolysis after the concomitant use of boosted PI, macrolide antibiotic therapy (lopinavir/ritonavir together with clarithromycin) and atorvastatin has been reported.[72] There have been reports of increased risk for type 2 diabetes mellitus in adults treated with statins. The increased risk across all statins is low[73] and largely associated with high-dose statin therapy.[74] No adolescents or children were included in these studies.

A meta-analysis of statin use in children showed an overall favorable safety profile similar to that in adults, with increased risk of adverse events mainly with higher doses and co-administration of interacting drugs metabolized by the cytochrome P450 system. Five studies reported on elevations of AST, ALT and CK, with no substantial elevations in 2 studies for AST and 3 studies for ALT and CK.[75] However, because of the limited sample size and short study duration, the authors drew no definite conclusions on liver- and muscle-related adverse effects and recommended monitoring muscle and liver safety markers in pediatric patients. Treatment-related hepatic (1 possibly related) and muscle (0) toxicity were uncommon in our study despite use of PIs in 79% of participants at study entry, consistent with the reported safety of statins in adults with HIV.[6] Renal toxicity has not been reported for atorvastatin, and only 1 report of creatinine increase with concomitant uric acid serum level elevation is in the literature.[76]

## CONCLUSION

Management options for TC and/or LDL-C elevations in HIV-infected children include life-style and dietary changes, or switching to ARVs less likely to elevate lipid concentrations.[77–81] If lipid concentrations do not improve with these interventions or for individuals in whom such interventions are not feasible, our data suggest that treatment with atorvastatin appears to be safe and effective for HIV-infected youth on ART.

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