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Improvement in Lipids after Switch to Boosted Atazanavir or Darunavir in Children/Adolescents with Perinatally Acquired HIV on Older Protease Inhibitors: Results from the Pediatric HIV/AIDS Cohort Study

Jennifer Jao, MD, MPH¹, Wendy Yu, MPH², Kunjal Patel, DSc, MPH³, Tracie L. Miller, MD⁴, Brad Karalius, MPH³, Mitchell E. Geffner, MD⁵, Linda A. DiMeglio, MD, MPH⁶, Ayesha Mirza, MD⁷, Janet S. Chen, MD⁸, Margarita Silio, MD, MPH⁹, Elizabeth J. McFarland, MD¹⁰, Russell B. Van Dyke, MD⁹, Denise Jacobson, PhD², and for the Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol (AMP) Study

¹Icahn School of Medicine at Mount Sinai, Department of Medicine, Department of Obstetrics, Gynecology and Reproductive Medicine, New York, NY, USA

²Harvard T. H. Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, USA

³Harvard T. H. Chan School of Public Health, Department of Epidemiology, Center for Biostatistics in AIDS Research, Boston, MA, USA

⁴University of Miami, Department of Pediatrics, Miami, FL, USA

⁵Keck School of Medicine of USC, The Saban Research Institute of Children's Hospital Los Angeles, Los Angeles, CA, USA

⁶Indiana University School of Medicine, Department of Pediatrics, Indianapolis, IN, USA

⁷University of Florida College of Medicine, Department of Pediatrics, Jacksonville, FL, USA

⁸Drexel University College of Medicine, Department of Pediatrics, Philadelphia, PA, USA

⁹Tulane University School of Medicine, Department of Pediatrics, New Orleans, LA, USA

¹⁰University of Colorado School of Medicine, Department of Pediatrics, Aurora, CO, USA

Abstract

Background—Dyslipidemia is common in perinatally HIV-infected (PHIV) youth receiving Protease Inhibitors (PIs). Few studies have evaluated longitudinal lipid changes in PHIV youth after switch to newer PIs.

Methods—We compared longitudinal changes in fasting lipids [Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein-C (LDL), High-Density Lipoprotein-C (HDL), and

Corresponding author: Jennifer Jao, MD, MPH, Icahn School of Medicine at Mount Sinai, Department of Medicine, One Gustave L. Levy Place, Box 1087, New York, NY 10029, 212-824-7497 (office), 212-824-2317 (fax), jennifer.jao@mssm.edu.

Conflicts of Interests:

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TC/HDL] between PHIV youth enrolled in the PHACS Adolescent Master Protocol (AMP) study who switched to atazanavir/ritonavir (ATV/r)- or darunavir/ritonavir (DRV/r)-based antiretroviral therapy (ART) from an older PI-based ART vs. those remaining on an older PI. Generalized estimating equation models were fit to assess the association of switch to ATV/r- or DRV/r-based ART with the rate of change in lipids, adjusted for potential confounders.

Results—From 2007–2014, 47 PHIV children/adolescents switched to ATV/r or DRV/r, while 120 remained on an older PI [primarily lopinavir/r (72%) and nelfinavir (24%)]. Baseline age ranged from 7–21 years. After adjustment for age, Tanner Stage, race/ethnicity, and HIV RNA level, switch to ATV/r or DRV/r was associated with a more rapid annual rate of decline in the ratio of TC/HDL ($\beta = -0.12$, $p = 0.039$) than remaining on an older PI. On average, TC declined 4.57 mg/dL/year ($p = 0.057$) more in the switch group. A switch to ATV/r or DRV/r was not associated with the rate of HDL, LDL, or TG change.

Conclusions—Switch to ATV/r or DRV/r may result in more rapid reduction in TC and TC/HDL in PHIV youth, potentially impacting long-term cardiovascular disease risk.

Keywords

Lipids; Longitudinal; Atazanavir; Darunavir; Perinatally HIV-infected; Children

Introduction

Combination antiretroviral therapy (ART) regimens, which often include protease inhibitors (PIs), has markedly advanced the treatment of HIV-infected children and adults. Since the introduction of ART, substantial declines in morbidity (1) and mortality (2) have been achieved in these individuals, though not without potentially significant side effects. Metabolic complications of HIV infection and ART, including dyslipidemia,(3, 4) fat redistribution,(5–7) and insulin resistance(8, 9) (collectively known as the metabolic syndrome), have been documented extensively and may be the result of complex interactions between HIV infection, antiretroviral therapy (ART), age, race, socio-economics, diet, and lifestyle factors.(10) As perinatally HIV-infected (PHIV) children confront the challenge of lifetime ART exposure, these metabolic disturbances are of particular concern since they may place PHIV adolescents and young adults at significantly increased cumulative cardiovascular risk over time.

The prevalence of dyslipidemia in HIV-infected children and adolescents has been reported to be between 11% to as high as 73%, depending on specific study definitions of dyslipidemia, sample size, and study locations worldwide.(11–17) Few studies, however, have assessed longitudinal lipid changes in the pediatric HIV population during this era of newer PIs, such as atazanavir/ritonavir (ATV/r) or darunavir/ritonavir (DRV/r). The objective of our study was to evaluate whether a switch to ATV/r- or DRV/r-based ART from an older PI-based ART was associated with an improved lipid profile over time.

Materials and Methods

Study Population

This study included PHIV youth enrolled in the Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol (AMP), an ongoing prospective cohort study of PHIV youth designed to evaluate the long-term impact of HIV and ART in children, adolescents, and young adults living with PHIV. PHACS AMP began enrollment of children 7–15 years of age in 2007 across 15 U.S. sites, including Puerto Rico. For this analysis, we included PHIV youth who were receiving an ART regimen consisting of an older PI (non-ATV and non-DRV) plus nucleoside reverse transcriptase inhibitors (NRTIs) at study entry with fasting lipids measured at least once. Exclusions included current pregnancy, known diabetes or renal disease, use of ATV or DRV prior to AMP enrollment, switch to a non-PI-based ART regimen, or switch to an ART regimen consisting of 3 classes of antiretrovirals (ARVs) [i.e., NRTI + PI + integrase strand inhibitors (INSTI)]. Institutional review boards (IRBs) at each site approved the protocol, and informed consent was obtained from each youth's parent or legal guardian. Assent was obtained from youth participants per local IRB guidelines.

Primary Exposure of Interest

Switch from an older PI to either boosted ATV or DRV was considered the primary exposure of interest, and this group was compared to those who remained on an older PI ART regimen (non-ATV, non-DRV). Information on specific ARV use over time was collected longitudinally.

Primary Outcomes

Outcomes of interest included the following fasting lipid subfractions: Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein-C (LDL), High-Density Lipoprotein-C (HDL), and TC/HDL. For the group that switched, lipid measures from the visit just prior to switch and then annually thereafter for 3 years were assessed. For the comparison group, lipid measures were assessed starting at the time of first fasting serum sample collection. The “baseline” timepoint was defined as the date of lipid measurement just prior to switch for the former group, and at the time of first lipid measurement for the latter comparison group. Lipid testing was performed in real-time at each clinical site; blood specimens were processed and analyzed using standard techniques. We evaluated rates of change for lipid subfractions over time. Hypercholesterolemia (elevated TC), hypertriglyceridemia, and elevated LDL were defined as levels >95th percentile and low HDL as <5th percentile for age and sex by U.S. standards.(18, 19)

Covariates

Information on potential confounders including age, sex, race/ethnicity, Tanner Stage, anthropometrics, and HIV disease parameters was collected. Body mass index (BMI) and waist circumference were measured in standardized fashion,(20) and BMI z scores (BMIZ) were calculated from CDC 2000 Growth Standards.(21) Blood pressure at baseline was measured and categorized as pre-hypertension if either the systolic or diastolic blood

pressure exceeded the 90th percentile for age, sex, and height according to U.S. National High Blood Pressure Education Program Working Group on Children/Adolescents. (22) HIV CD4 cell count and HIV RNA level at baseline were collected via medical record review.

Statistical Analysis

With the sample size obtained in our analysis, we had >80% power to detect a difference in the change in lipid outcomes of 20 mg/dL for TC, 15 mg/dL for LDL, 5 mg/dL for HDL and 35 mg/dL for TG. Baseline characteristics between those who switched to ATV/r or DRV/r and those who remained on an older PI were compared using Student's t-test or Wilcoxon rank sum test for continuous and Chi-square or Fisher's exact test for categorical variables, as appropriate. Local weighted scatter-plot smoothing (LOESS) plots were fit to describe longitudinal changes in each mean lipid subfraction over time. Generalized estimating-equation (GEE) linear regression models were fit to assess the association of a switch to ATV/r or DRV/r-based ART with the average annual rate of change in each lipid subfraction, adjusted for potential confounders. Correlation between repeated lipid measures over time on the same participant were accounted for using an autoregressive assumption. Thus, each model had a main effect for treatment group (switch vs. no switch), time since baseline, each confounder variable, and an interaction term for treatment group by time. We employed an interaction term to test for differences in the rate of change of the lipid outcome between those that switched to ATV/DRV compared those who did not switch. Analyses were performed to compare baseline characteristics of those lost to follow-up vs. those not lost to follow-up. Subgroup analyses restricted to those without hypertriglyceridemia at baseline were conducted to evaluate changes in triglycerides. Statistical analyses were performed using SAS® 9.4 (SAS Institute, Cary, NC.)

Results

From 2007–2014, 47 PHIV youth switched to ATV/r (n=27) or DRV/r (n=20) while 120 remained on an older PI. (Table 1) Of the latter, 72% received lopinavir/r, 24% nelfinavir, and 2% fosamprenavir/r. The majority of NRTI backbones at baseline included zidovudine/lamivudine (20%), tenofovir/emtricitabine (20%), abacavir/lamivudine or abacavir/lamivudine/zidovudine (19%), or stavudine/lamivudine (14%). Baseline age ranged from 7–21 years with 73% non-Hispanic black. At baseline, PHIV youth in the switch group were older (median age 14.6 vs. 11.5, $p<0.001$), reported more years of having been on ART (11.9 vs. 8.3 years, $p<0.001$), and less likely to be Tanner Stage 1 (6% vs. 34%, $p<0.001$). At baseline, those in the switch group also had lower TC (158 vs. 177 mg/dL, $p=0.042$) and lower HDL (45 vs. 51 mg/dL, $p=0.021$). There were no differences between groups in race/ethnicity, or in baseline BMI z score, CD4 cell count, HIV RNA level, or rates of hypercholesterolemia, hypertriglyceridemia, elevated LDL, or low HDL. Overall rates of hypercholesterolemia were 12%, hypertriglyceridemia 43%, elevated LDL 14%, and low HDL 4%. The median (range) of follow-up time was 1.9 (0–3) vs. 2.0 (0–3) years, and the median (range) number of visits with lipid assessments was 3 (1–4) and 3 (1–5) in the switch and non-switch groups, respectively. No significant differences in baseline

characteristics were found between those who were lost to follow-up and those who were not lost to follow-up.

Figure 1 shows plots of mean TC, TG, HDL, LDL, and TC/HDL ratio over time by PI treatment groups. After adjusting for baseline age, Tanner Stage, race/ethnicity, and HIV RNA level, switch to ATV/r or DRV/r was associated with a more pronounced rate of decline in the ratio of TC/HDL ($\beta = -0.12$ per year, $p = 0.039$) over time. On average, TC declined 4.57 mg/dL/year ($p = 0.057$) more in the switched group (Table 2). There was no association between a switch to ATV/r or DRV/r and the rate of increase in HDL or decline in LDL or TG. However, in subgroup analyses restricted to youth without hypertriglyceridemia at baseline ($n = 96$), TGs declined on average 7.78 mg/dL/year ($p = 0.051$) more in the switched group, and this relationship persisted even after adjusting for confounders (average decline = 7.15 mg/dL/year more in the switched group, $p = 0.061$).

Discussion

In the PHACS AMP cohort of PHIV youth, we found that a switch to ATV/r or DRV/r from older PIs resulted in more pronounced declines in TC and TC/HDL over time compared to the values for those who remained on older PIs. Our results are consistent with studies in treatment-naïve HIV-infected adults which have shown improved metabolic parameters with newer PIs.(23–26) Few studies, however, have been published in the pediatric HIV population on longitudinal lipid changes over time with newer PIs such as ATV/r or DRV/r, and most have been limited by small sample sizes.(27–29) Similar to our findings, a case series of HIV-infected children who switched from lopinavir/r to ATV/r or DRV/r reported a significant reduction in TC at 18 months post switch compared to baseline levels, but no changes in TG, HDL or LDL.(29) Children in the DELPHI trial begun on darunavir demonstrated decreases in TG levels 48 weeks post-initiation.(27) The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1020 protocol reported an increase in rates of hypercholesterolemia (TC ≥ 200 mg/dL) from 1% to 5.7% and a decrease in rates of hypertriglyceridemia (TG ≥ 150 mg/dL) from 26% to 14% in treatment-naïve and -experienced children initiating ATV alone or ATV/r in an open-label study at 48 weeks post-initiation.(28)

Associations between ART use and dyslipidemia have been confirmed in several cross-sectional(12, 13, 30, 31) as well as longitudinal(4, 32–35) pediatric HIV cohorts. Longitudinal studies in children with HIV infection have reported associations of dyslipidemia with BMI,(32) Tanner stage,(33) longer duration of ART,(34) HIV RNA levels < 400 copies/mL,(17) and PI use.(4, 32, 33, 35) However, PI use in these studies was limited to older non-ATV and non-DRV PIs. Some studies have evaluated lipid changes after switch or initiation of ART during an era of older PIs.(6, 17, 36) One study in South Africa reported lower mean HDL with higher mean LDL, TG, and TC/HDL ratios in a group of HIV-infected children randomized to lopinavir/ritonavir (PI) vs. those remaining on nevirapine.(6) The Pediatric AIDS Clinical Trials Group (PACTG) 1010 evaluated HIV-infected children initiating PI-based ART or switching to PI plus non-nucleoside reverse transcriptase inhibitor (NNRTI) ART due to virologic failure and found an association between PI + NNRTI-based ART with increased TC/HDL ratios as well as increased TG levels.(17)

Dyslipidemia is known to be associated with cardiovascular disease in adults.(37) Children with dyslipidemia as young as ages 5–10 years are likely to have it as adults, with this correlation between childhood and adulthood dyslipidemia even more pronounced in obese individuals.(38) Current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on cardiovascular risk assessment recommend use of a risk calculator which factors in several variables, including age, race, TC, HDL, systolic blood pressure, treatment for hypertension, diabetes, and smoking.(39) Optimal TC levels are defined as < 170 mg/dL with this same criteria outlined for children and adolescents.(38) In addition, the Pathological Determinants of Atherosclerosis in Youth (PDAY) study demonstrated that each 30 mg/dL increment increase in non-HDL cholesterol (TC minus HDL cholesterol) corresponded to approximately 2 years of vascular aging.(40) In PHIV children on lifelong ART with risk for metabolic complications, a switch to newer PIs such as ATV/r or DRV/r in our study could decrease TC by 30 mg/dL up to five times faster compared to older PIs, potentially decreasing atherosclerotic risk significantly before reaching adulthood. We also observed a more pronounced rate of decline in TC/HDL ratio with switch to ATV/r or DRV/r, likely due to the effect on TC as differences in the rate of change of HDL over time were not noted between groups. The TC/HDL ratio has been shown to have higher discriminatory power in assessing cardiovascular disease risk than either measurement alone.(41) Lastly, the more rapid decline in TGs we found with a switch to ATV/r or DRV/r amongst those with normal TGs at baseline highlights further potential beneficial effects on lipids in PHIV youth receiving newer compared to older PIs.

Current U.S. 2017 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection recommend lopinavir/r as part of preferred initial ART regimens for children 14 days to <3 years of age.(42) WHO 2016 Guidelines currently recommend lopinavir/r as the first choice for second-line ART in children with ATV/r recommended only as an alternative second-line ART and DRV/r recommended only in special situations. Amongst adolescents, the first choice for second-line ART remains lopinavir/r or ATV/r with DRV/r only as an alternative second-line ART.(43) In sub-Saharan Africa where the overwhelming majority of HIV-infected youth reside, the mainstay of second-line ART remains lopinavir/r for this population despite its poorer metabolic risk profile. In addition to the global burden of HIV disease in sub-Saharan Africa, the number of deaths there from cardiovascular disease increased 81% between 1990 to 2013,(44) raising concern that metabolic complications from HIV and ART, specifically older PIs such as lopinavir/r, may compound an increasing risk for cardiovascular disease worldwide and in low- and middle-income countries. Switch to an ATV/r or DRV/r-based ART in lieu of lopinavir/r could potentially help modify cardiovascular disease risk early in life in the pediatric HIV population.

Our study was limited by its observational design in that there may be unmeasured confounding of exposure-outcome relationships. However, no randomized control trials exist to date between older PIs and ATV/r or DRV/r in children. Because of the observational design, we were also unable to disentangle any potential effect of NRTI therapy from the switch in PI treatment. However, consistent with evolving pediatric HIV treatment guidelines, participants in both PI treatment groups underwent similar changes in NRTI backbone over time with the vast majority of changes resulting in discontinuation of older

NRTIs and initiation of newer NRTIs. In addition, well over half of participants receiving stavudine had this discontinued throughout the course of longitudinal follow-up.

In conclusion, a switch to newer PIs such as ATV/r or DRV/r presents more favorable declines in TC and TC/HDL over time than older PIs in HIV-infected children and adolescents, potentially impacting long-term cardiovascular disease risk. While decisions to switch to newer PIs are often complex and multifactorial, clinicians may consider this option particularly to balance situations where other cardiometabolic risk factors are prevalent and the long-term metabolic health of the HIV-infected child is of concern.

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Figure 1.

Changes in mean lipid subfractions over time by protease inhibitor (PI) treatment. 1A) Fasting total cholesterol over time by PI treatment. 1B) Fasting triglycerides over time by PI treatment. 1C) Fasting HDL cholesterol over time by PI treatment. 1D) Fasting LDL cholesterol over time by PI treatment. 1E) Ratio of TC/HDL over time by PI treatment. Dashed lines represent the smoothing LOESS plot curve while solid lines represent actual mean values of lipid measures over time. Grey lines represent the group which switched to ATV/r or DRV/r; black lines represent the group remaining on older PIs; ATV/r= atazanavir/

ritonavir; DRV/r= darunavir/ritonavir; HDL=High-Density Lipoprotein-C; LDL=Low-Density Lipoprotein-C; PI=Protease Inhibitor; TC=Total Cholesterol

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Table 1

Baseline Characteristics of Perinatally HIV-infected Youth by Protease Inhibitor Treatment

Characteristic	PI Treatment		p-value
	Older PI (n=120)	ATV/r or DRV/r (n=47)	
Age (years)	11.5 (9.8, 13.5)	14.6 (12.3, 16.9)	<0.001
Female	54 (45%)	26 (55%)	0.230
Race/Ethnicity			
Non-Hispanic White	5 (4%)	2 (4%)	0.419
Non-Hispanic Black	90 (75%)	32 (68%)	
Hispanic	24 (20%)	11 (23%)	
Others/More than one race	1 (1%)	2 (4%)	
Caregiver Education			
Less than High School	27 (23%)	16 (34%)	0.140
At least High School	91 (76%)	31 (66%)	
Missing	2 (2%)	0 (0%)	
BMI Z-score	0.15 (1.11)	0.44 (1.09)	0.131
Triceps Skinfold Thickness Z-score	-0.39 (1.33)	-0.12 (1.41)	0.260
Waist Circumference (cm)	65.33 (49.33, 119.33)	74.67 (58.17, 110.00)	<0.001
CD4 Cell Count (cells/mm ³)			
<200	2 (4%)	0 (0%)	0.018
200–350	0 (0%)	6 (5%)	
351–500	10 (21%)	13 (11%)	
>500	35 (74%)	101 (84%)	
Log ₁₀ HIV RNA level	2.34 (0.73)	2.25 (0.99)	0.570
HIV RNA level (copies/mL)			0.073
< 400	67 (56%)	32 (68%)	
400–1000	32 (27%)	5 (11%)	
> 1000	21 (18%)	10 (21%)	
Tanner Stage			<0.001
1	41 (34%)	3 (6%)	
2	25 (21%)	6 (13%)	
3	26 (22%)	8 (17%)	
4	18 (15%)	8 (17%)	
5	10 (8%)	22 (47%)	
Years on ART at Baseline	8.3 (0.00, 12.07)	11.9 (5.14, 17.65)	<0.001
Total Cholesterol (mg/dL)	177 (103, 316)	158 (98, 300)	0.042
Hypercholesterolemia	17 (14%)	3 (6%)	0.195
Triglycerides (mg/dL)	108 (35, 460)	95 (44, 345)	0.651
Hypertriglyceridemia	56 (47%)	15 (32%)	0.117
LDL (mg/dL)	104 (27, 199)	87 (53, 196)	0.106
Elevated LDL	17 (14%)	6 (13%)	1.000

Characteristic	PI Treatment		<i>p</i> -value
	Older PI (n=120)	ATV/r or DRV/r (n=47)	
HDL (mg/dL)	51 (22, 99)	45 (23, 90)	0.021
Low HDL	4 (3%)	2 (4%)	0.674
TC/HDL	3.40 (1.68, 7.90)	3.60 (2.08, 5.40)	0.555

All categorical variables expressed as n (%). All continuous variables expressed as median (InterQuartile Range) except z scores and log10 HIV RNA level which are expressed as mean (SD). P values from Student t-test, Wilcoxon, Chi-Square, or Fisher's Exact Tests as appropriate. ART=antiretroviral therapy; BMI=Body Mass Index; d4T=stavudine; ddI=didanosine; HDL=High-Density Lipoprotein-C; LDL=Low-Density Lipoprotein-C; TC=Total Cholesterol

Crude and Adjusted Effect of Protease Inhibitor Switch to Boosted Atazanavir or Darunavir on Annual Rate of Change in Lipid Outcomes over Time

Table 2

Lipid Outcome	Crude				Adjusted			
	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	p-value
Total Cholesterol (mg/dL) *	-3.77	(-8.45, 0.91)	0.114	-4.57	(-9.29, 0.15)	0.057		
Triglycerides (mg/dL) *	-7.36	(-18.57, 3.85)	0.197	-7.86	(-19.07, 3.34)	0.168		
HDL Cholesterol (mg/dL) *	0.79	(-0.96, 2.53)	0.377	0.56	(-1.22, 2.33)	0.539		
LDL Cholesterol (mg/dL) *	-1.67	(-5.14, 1.80)	0.345	-2.17	(-5.65, 1.31)	0.221		
TC/HDL ^	-0.12	(-0.24, -0.01)	0.040	-0.12	(-0.24, -0.01)	0.039		

* Adjusted for age, Tanner stage, race/ethnicity, and HIV RNA level at baseline.

^ Adjusted for age, Tanner stage, and race/ethnicity at baseline. CI=Confidence Interval; HDL=High-Density Lipoprotein-C; LDL=Low-Density Lipoprotein-C; TC=Total Cholesterol