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Pubertal Onset in HIV-infected Children in the Era of Combination Antiretroviral Treatment

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Abstract

Objective—To evaluate associations of perinatal HIV infection (PHIV), HIV disease severity, and combination antiretroviral treatment with age at pubertal onset.

Design—Analysis of data from two U.S. longitudinal cohort studies [IMPAACT 219C and PHACS AMP], conducted 2000–2012, including PHIV and HIV-exposed uninfected (HEU) youth. Tanner stage assessments of pubertal status (breast and pubic hair in girls; genitalia and pubic hair in boys) were conducted annually.

Methods—We compared the timing of pubertal onset (Tanner stage ≥2) between PHIV and HEU youth using interval-censored models. For PHIV youth, we evaluated associations of HIV disease severity and combination antiretroviral treatment with age at pubertal onset, adjusting for race/ethnicity and birth cohort.

Results—The mean age at pubertal onset was significantly later for the 2086 PHIV youth compared to 453 HEU children (10.3 vs 9.6, 10.5 vs 10.0, 11.3 vs 10.4, and 11.5 vs 10.7 years according to female breast, female pubic hair, male genitalia, and male pubic hair staging, respectively, all $p<0.001$). PHIV youth with HIV-1 RNA viral load >10,000 copies/mL (vs ≤10,000 copies/mL) or CD4% <15% (vs ≥15%) had significantly later pubertal onset (by 4–13 months). Each additional year of combination antiretroviral treatment was associated with a 0.6- to1.2-month earlier mean age at pubertal onset, but this trend did not persist after adjustment for birth cohort.

Conclusions—Pubertal onset occurs significantly later in PHIV than in HEU youth, especially among those with more severe HIV disease. However, in the current era, combination antiretroviral treatment may result in more normal timing of pubertal onset.

Keywords

puberty; antiretroviral therapy; protease inhibitors; pediatrics; CD4; viral load; statistics; interval-censored; Tanner stage; BMI

INTRODUCTION

Puberty is a complex biological process involving physical and hormonal changes in which the body transitions to sexual maturity. Epidemiological studies have established a trend over the past two decades toward earlier pubertal onset, particularly in girls [1–5]. These changes have occurred against a backdrop of increasing prevalence of childhood obesity in parallel with changing dietary patterns and declining physical activity [6]. In addition, environmental exposures may play a role in trends of earlier pubertal onset [1,7].

Perinatally HIV-infected (PHIV) youth have historically demonstrated decreased growth [8–9] and delays in pubertal onset, particularly among those with more advanced HIV disease [10–16]. Metabolic and endocrine abnormalities in PHIV youth may also play a role in deficient growth and delayed pubertal onset [17–24]. Combination antiretroviral (ARV) treatment has been associated with improvement in growth [25–28] which could reduce the risk for pubertal delay. However, few studies have addressed the effect of combination treatment on pubertal onset. Buchacz *et al* observed significantly earlier pubertal onset among boys with prior protease inhibitor (PI) use, but no clear association with PI use among girls [14]. This study was conducted prior to 2000, at a time when mono- or dual-agent therapy as a standard of care was transitioning to more effective combination regimens, including the use of PIs. Two recent studies observed later pubertal onset among HIV-infected youth with lower CD4+ cells, but neither addressed the association with antiretroviral regimens [16,29].

We used data collected from two U.S.-based longitudinal cohort studies, the International Maternal Pediatric and Adolescent Clinical Trials (IMPAACT) 219/219C study (219C) and the Adolescent Master Protocol (AMP) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network, to compare the timing of pubertal onset among PHIV children to that of perinatally HIV-exposed but uninfected (HEU) children. In addition, we evaluated the association of HIV disease severity and ARV treatment with pubertal onset in children with perinatal HIV infection.

METHODS

Description of Protocols and Study Population

This investigation included children born to HIV-infected women who had pubertal staging assessed at age 7 years or older in the 219C or AMP studies. The 219C study was a large prospective study conducted at over 80 U.S. clinical research sites between 1993 and 2007 to evaluate the long-term effects of HIV infection and *in utero* ARV exposure [30–31].

AMP is a smaller ongoing prospective cohort study which opened in March 2007 [32]. Subjects were eligible for AMP (whether in 219C or not) if they were perinatally HIV-infected or HIV-exposed, and 7 to <17 years old. Both studies were approved by the site Institutional Review Boards and written informed consent was obtained from each parent or legal guardian, with assent from children as appropriate.

At each study visit, we obtained medical histories through chart reviews and ascertained health status through physical and laboratory evaluations. HIV disease severity information for HIV-infected youth was collected at scheduled visits (every 3 months for 219C, every 6–12 months for AMP). Race and ethnicity were self-reported at study entry and categorized as white Non-Hispanic, black non-Hispanic, Hispanic, or “other”. We excluded participants of PACTG 219 who did not participate in 219C and youth who were judged to be at later stages of pubertal maturity (Tanner stage 3 to 5) at their first study visit.

Pubertal Staging Measures

Study clinicians trained to evaluate child growth and development assessed pubertal staging annually in 219C and at each study visit in AMP (initially every 6 months and then annually after August 2010) by visual inspection according to criteria of Tanner and Whitehouse [33], ranging from 1 (pre-pubertal) to 5 (sexually mature). Pubertal onset was defined for each Tanner measure as attaining stage 2 or higher, with separate indicators for breast development and pubic hair in girls, and for genitalia and pubic hair in boys.

Statistical Methods

The date of the first pubertal staging assessment at age ≥7 years was considered to define the start of longitudinal follow-up for pubertal onset. The last available measures of height and body mass index (BMI, kg/m^2) prior to this index date were obtained, and Centers for Disease Control and Prevention (CDC) 2000 growth standards were used to calculate age- and sex-adjusted Z-scores [34–38]. For HIV-infected youth, latest measures of CD4 T-lymphocyte percent (CD4%), CD4 count, HIV-1 RNA viral load, and CDC clinical classification were identified prior to or at the index date. Nadir CD4% and peak viral load were based on the lowest CD4% and highest viral load measure, respectively, prior to or at the first pubertal assessment. For those with at least two viral load measures before their first pubertal assessment, a cumulative measure of copy-years viremia was calculated as described by Cole et al [39]. Combination antiretroviral treatment was defined as concurrent use of at least three drugs from at least two drug classes, and cumulative ARV history was reflected by years of receipt of combination treatment, PIs, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) prior to the index date. We summarized characteristics of the participants by HIV infection status. The percentage of children with delayed pubertal onset, defined as not attaining Tanner stage 2 by age 12 in girls (by both breast and pubic hair staging) or by age 13 in boys (by both genitalia and pubic hair staging) was assessed by birth cohort and HIV infection status.

Interval-censored approaches under an assumed normal distribution were used to estimate the mean age at pubertal onset separately for each Tanner measure, by HIV infection status, race/ethnicity, and birth cohort (pre-1990, 1990–1992, 1993–1996, 1997 or later). The

interval-censoring approach accounts for whether pubertal onset occurred prior to the first pubertal assessment (left-censored), between study visits (interval-censored), or had not occurred by the last study visit (right-censored); this is the most appropriate statistical approach for evaluating pubertal onset based on longitudinal data [40]. The mean age at pubertal onset was compared between HIV-infected and HEU youth in unadjusted models and with adjustment for race/ethnicity and birth cohort. Further adjustment for BMI and height Z-scores was performed, but since these measures may be on the causal pathway between HIV infection and pubertal onset, results of these sensitivity analyses are presented only in online supplemental tables. Caregiver education level was considered but not found to be associated with timing of pubertal onset. We also qualitatively compared the estimated mean ages at pubertal onset with the general US population as reflected by the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) [4,5,40].

For perinatally HIV-infected youth, interval-censored models were fit to evaluate each HIV disease severity measure and ARV treatment characteristic separately, in unadjusted models and after adjustment for race/ethnicity and birth cohort. ARV regimens were classified as combination treatment with PI, combination treatment without PI, or not on combination treatment (not on ARVs, or on other regimen). Sensitivity analyses were conducted to examine effects of further adjustment for potential intermediates between combination antiretroviral treatment and pubertal onset, including BMI and height Z-scores and CD4% <15%. Duration of prior use of combination treatment and specific drug classes (PIs and NNRTIs) were considered as continuous predictors after evaluation of linearity assumptions. A sensitivity analysis was also conducted to examine consistency of results when restricting the study population to only pre-pubertal youth.

RESULTS

Characteristics of the Study Population

We evaluated 3006 children from 219C or AMP who were born to HIV-infected women and who had pubertal staging at age 7 years or older. We excluded 467 youth who had pubertal onset prior to study entry and were at Tanner stage 3 or higher at their first visit, leaving 2539 in analyses of pubertal onset (1253 girls and 1286 boys). Demographic characteristics are shown in Table 1 by HIV infection status; 56% were Black non-Hispanic and 29% were Hispanic.

The 2086 PHIV youth more often were born in earlier years than the 453 HEU children and had lower mean Z-scores for both BMI and height at the time of their first pubertal assessment. Among HIV-infected youth, 12% had CD4% <15%, and 27% had viral load >10,000 copies/mL proximate to the first pubertal assessment (Table 1). Males more often had low CD4% and high viral load than females (Supplemental Digital Content 1). At the time of the first pubertal assessment, 64% were on combination ARV therapy (55% including a PI and 9% without a PI); the median duration of prior combination treatment among those with any prior use was 3.24 years. Of the 752 children not on combination treatment, 82% received mono- or dual-agent therapy, 6% were on three or more NRTIs, and 12% were not on any ARV treatment.

Age at Pubertal Onset by HIV Status, Race/Ethnicity, and Birth Cohort

HEU girls had pubertal onset at mean ages of 9.6 and 10.0 years according to breast and pubic hair stages respectively, while boys had onset at mean ages of 10.4 and 10.7 years based on genitalia and pubic hair, respectively (Table 2). Consistent with most studies in girls, thelarche (reflected by breast staging) occurred earlier on average than pubarche (reflected by pubic hair growth) [40–43]. Mean ages at pubertal onset by race/ethnicity were similar for HEU youth to those based on NHANES III data for girls [40–43], but were later than NHANES III among both Black non-Hispanic (10.0 vs 9.2–9.5 years) and white non-Hispanic boys (11.6 vs 10.0 years) [3–5,40].

Compared to the HEU youth, PHIV children had significantly later estimated mean ages at onset, representing delays of about 6 to 11 months (Table 2). The mean age at pubertal onset for PHIV as compared to HEU was 10.3 vs 9.6 years, 10.5 vs 10.0, 11.3 vs 10.4, and 11.5 vs 10.7 years according to female breast, female pubic hair, male genitalia, and male pubic hair staging, respectively (all $p<0.001$). Estimated mean ages by race/ethnicity indicated significantly earlier pubertal onset for black non-Hispanic youth (by 9 to 12 months) and for Hispanics (by 3 to 4 months) than for white non-Hispanic youth, consistent with previous studies [3–5, 40–43]. Striking trends for earlier pubertal onset with more recent birth year were observed in both PHIV and HEU youth; however, the mean ages at onset were typically later for PHIV than HEU within each birth cohort (Figure 1). In interval-censored models, this shift was attenuated after adjustment for race/ethnicity and birth cohort, with 4–6 months later onset for PHIV youth on average (Table 3) according to breast, genitalia, and male pubic hair staging measures. Higher Z-scores for pre-pubertal height and BMI were associated with significantly earlier pubertal onset, but further adjustment for these measures had little effect on differences by HIV infection status. In sensitivity analyses excluding subjects at Tanner stage 2 at their first pubertal assessment (10% HEU, 11% PHIV), estimated mean ages at onset were slightly later (~2 months), but differences by HIV infection status were similar to those reported in Table 3.

The percent of PHIV youth with delay in pubertal onset was 4.1% overall, but showed substantial decreases over time (11.2%, 3.1%, 1.7%, and 0.4% for those born before 1990, 1990–1992, 1993–1996, and 1997 or later, respectively; trend test p-value<0.001). In contrast, delay in pubertal onset was rare among HEU youth (2/453, 0.4%).

Association of HIV Disease Severity with Age at Pubertal Onset

Mean ages at pubertal onset were significantly later for youth with more advanced HIV disease status at the first pubertal assessment (Table 3). For both girls and boys, there was a significant association of low CD4 (as reflected by CD4% <15% and CD4 count <200 cells/mm^3) and high viral load (>10,000 cp/mL) with later pubertal onset, both with and without adjustment for race/ethnicity and birth cohort, with the exception of female pubic hair (Table 3). Associations remained significant for most Tanner measures after further adjustment for BMI and height Z-scores (Supplemental Digital Content 2). Measures of past HIV disease severity showed stronger associations with timing of pubertal onset in boys than in girls. Boys with CDC Class C (prior AIDS-defining condition), low nadir CD4%, or higher peak viral load had significantly later pubertal onset than those with milder

classifications. Cumulative viral burden reflected by copy-years viremia was associated with significantly later age at pubertal onset in boys after adjustment for race/ethnicity and birth cohort, but not in girls. No association with peak viral load or CDC class was observed among girls.

Association of Combination Treatment and ARV Drug Classes with Age at Pubertal Onset

In unadjusted models, youth on combination treatment with a PI at the first pubertal assessment had a significantly earlier mean age at pubertal onset (by 2.7–3.7 months) than did youth not on combination treatment, with the exception of male genitalia (Table 3). In contrast, there was no significant difference in age at onset for those on combination regimens without PIs as compared to those youth unexposed to combination regimens for any Tanner measure. Associations for combination treatment with PI were non-significant in females and reversed direction in males when further adjusted for birth cohort. Examination of differences by birth cohort revealed that mean ages at pubertal onset were earlier for those exposed to combination treatment among those born since 1997 for all measures except male genitalia, but later for those exposed to combination treatment among those born prior to 1990 for all four staging measures (Figure 2); however, statistical tests for interaction were not significant.

Duration of prior combination treatment, overall or with a PI, at the time of the first pubertal assessment also showed significant associations with earlier age at pubertal onset based on all four staging measures in unadjusted analyses (Table 3). Mean ages at onset ranged from 0.6 to 1.2 months earlier for each additional year on combination treatment, depending on staging measure. However, after adjustment for race/ethnicity and birth cohort, there was no association of duration of combination treatment (overall or with PI) in girls, and the direction of effect reversed for boys. Similar associations were observed for prior years of use of PIs and NNRTIs (Table 3). Further adjustment for BMI and height Z-scores and for HIV-disease status as reflected by CD4% <15% had little effect on estimated mean ages of pubertal onset (Supplemental Digital Content 2).

DISCUSSION

We confirmed a significant delay in the mean age at pubertal onset for PHIV children compared to uninfected but perinatally HIV-exposed youth, ranging from a 6- to 8-month later mean age at onset in girls and a 10 to 11-month later onset in boys. The later average age at onset corresponded to an increased prevalence of delayed onset for PHIV vs HEU youth, but clinical delay among youth born after 1997 was rare regardless of HIV status. The PHIV youth in our cohort were more often born in earlier years than the HEU youth, notable given the secular trends in timing of pubertal onset [1–5]; however, the later pubertal onset for PHIV youth persisted even after adjustment for race/ethnicity and birth cohort for all measures except pubic hair in girls. PHIV girls and boys with more advanced HIV disease were at greatest risk of delay in pubertal onset, and these associations persisted for most staging measures after adjustment for birth cohort. Boys had stronger associations with past measures of disease severity than did girls, which could be attributable to either poorer initial immunological status or increased sensitivity of hormonal pathways in boys.

While both prior combination antiretroviral treatment with PIs and longer duration of combination treatment appeared to be protective in restoring earlier timing of pubertal onset, these associations did not persist after adjustment for birth cohort. Descriptively, the mean age at pubertal onset was earlier for those on a combination regimen compared to those not on combination regimens for those born in 1997 or later, while the reverse was generally true for those born earlier. We did not observe a significant benefit of combination regimens in models adjusting for birth cohort, possibly due to confounding by indication resulting from only the sickest HIV-infected children receiving combination treatment in the earlier birth cohorts (33% of those in the pre-1990 cohort), while combination treatment was widespread among HIV-infected youth in the later birth cohorts (88% among those born 1997 or later). While there were no statistically significant interaction effects between combination treatment and birth cohort for any of the four staging measures, power for testing interaction may have been limited.

The mean ages at pubertal onset across the four staging measures and by race/ethnicity in our HEU youth from 219C and AMP were generally similar to other studies using NHANES III (1988–1994) data. Among PHIV youth, our estimated mean ages at onset are similar to those reported by Buchacz et al [14] of 10.7 years for girls and 11.8 years for boys (their study population was 52% black non-Hispanic, 33% Hispanic), but substantially earlier than mean ages at onset of 12.1–12.9 years among Caucasian HIV-infected children in an Italian study reported by DeMartino et al [13].

The etiology of delayed puberty in adolescents with HIV infection is not well-understood. It has been ascribed to the general effects of chronic illness mediated through cytokine-induced inhibition of gonadotropin secretion [26, 44,45]. It has also been suggested that HIV infection directly or indirectly affects production or secretion of hormones that regulate or control pubertal initiation and tempo (*e.g.,* leptin produced in adipose tissue) [14]. Delayed pubertal development in HIV-infected children has been attributed in part to reduced adrenal androgen secretion [23,46].

Implications of altered pubertal timing in the general population have received more attention for early maturation, which has been associated with increased incidence of antisocial behaviors and substance use. A general trend of earlier pubertal onset is thus not necessarily desirable, given the potential adverse social and clinical consequences of early puberty noted in the literature [1]. However, while youth in many developed countries are attaining pubertal onset earlier than in previous decades, those with perinatally-acquired HIV still tend to have later onset than US norms based on NHANES. Later maturation may also be associated with risk for psychosocial problems, including lower self-esteem and depression, and may have implications for reproductive health [15,47]. Thus, the implications of our study findings in perinatally infected youth focus at the other end of the spectrum, in the benefits of reducing the risk for delayed pubertal onset along with associated psychosocial and reproductive consequences. Finally, our study findings may have particular relevance for low-resource settings such as sub-Saharan Africa, where rates of vertical HIV transmission remain relatively high and thus the population of youth with perinatally-acquired HIV remains large [48]. Despite wider availability and earlier initiation of ARV treatment in South Africa and other African countries over the past decade, it has

been documented that the majority of children still have severe immunodeficiency before starting treatment, increasing the risk of delayed pubertal onset [49]. Similar studies are warranted to evaluate the impact of early ARV treatment initiation on pubertal onset and maturation in low-resource settings.

We recognize several limitations in our analysis. Our cohort of HEU youth was relatively small and included few white non-Hispanic youth and no uninfected youth born before 1990. Like all studies utilizing Tanner staging measures, there is potential for misclassification, particularly for breast staging which may be confounded by increased body fat deposition [1,40]. Although orchidometers were not used in 219C, they were used in AMP and may provide better accuracy in future evaluations of pubertal progression and sexual maturation. We lacked information on birth weight or other early life exposures because our cohorts were not followed from birth. As an observational study, our analysis was subject to confounding by indication, particularly for evaluating the association of combination treatment with pubertal onset for the earlier birth cohorts; lack of information for most participants on viral load or CD4 prior to combination treatment initiation precluded our ability to evaluate and adjust for such confounding.

Despite these limitations, this is the largest study to date evaluating the timing of pubertal onset, with over 2000 PHIV youth. We found that pubertal onset occurs significantly later in HIV-infected than in uninfected youth, with the greatest delays among those with more advanced HIV disease. Importantly, combination treatment may result in more normal timing of pubertal onset, as suggested for youth born since 1997 who were receiving PI-containing combination regimens. Further evaluation of pubertal onset and sexual maturation in the current era of widespread treatment with combination treatment will be needed to fully understand the impact of ARV treatment on sexual development of youth with HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
AMP	Adolescent Master Protocol
ARV	antiretroviral
BMI	body mass index
CDC	Centers for Disease Control and Prevention
HEU	HIV-exposed uninfected
HIV	human immunodeficiency virus
IMPAACT	International Maternal Pediatric and Adolescent AIDS Clinical Trials
NHANES	National Health and Nutrition Examination Survey
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PHIV	perinatally HIV-infected
PHACS	Pediatric HIV/AIDS Cohort Study
PI	protease inhibitor

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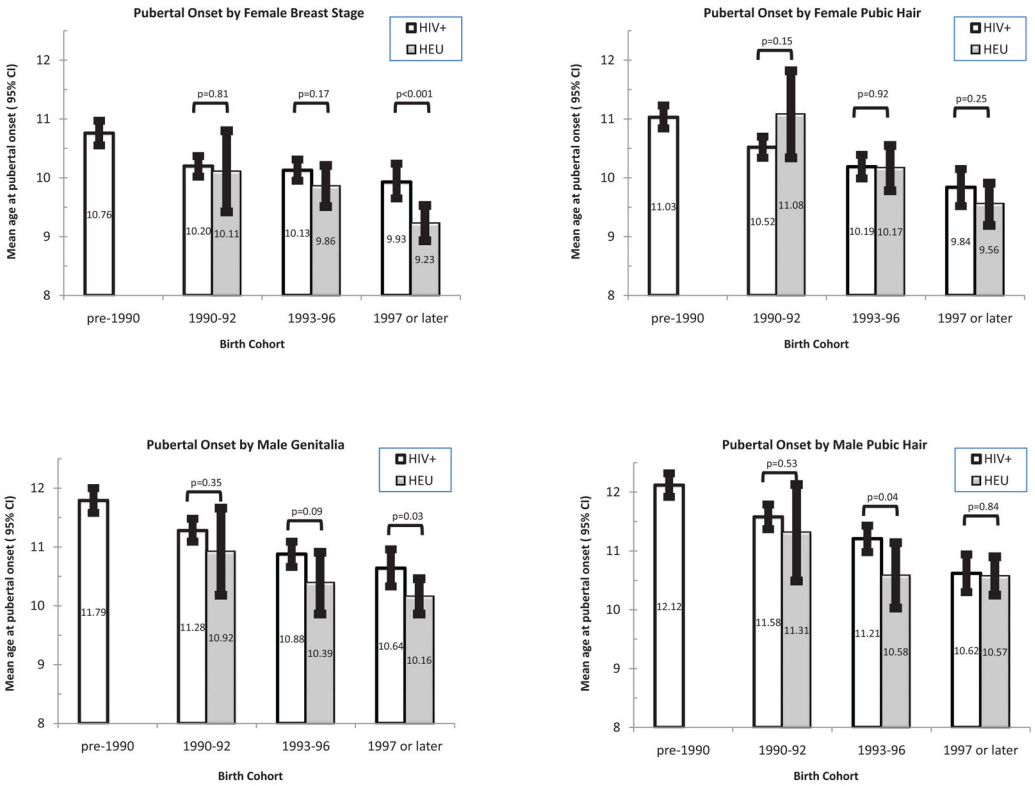

Figure 1.

Mean age at pubertal onset by Tanner measure and birth cohort, for HIV-infected youth (unshaded bars) and HIV-exposed uninfected youth (shaded bars). P-values for statistical significance based on interval-censored models for the effect of HIV infection status fit separately within each birth cohort.

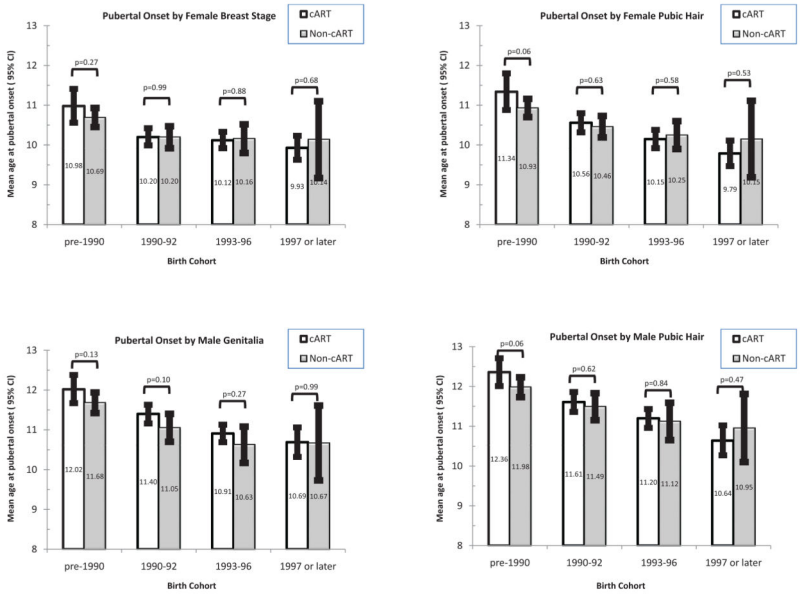

Figure 2.

Mean age at pubertal onset by Tanner measure and birth cohort, for HIV-infected youth on combination antiretroviral treatment (cART, unshaded bars) as compared to those not on cART (non-cART, shaded bars) at the time of the first pubertal assessment. P-values for statistical significance based on interval-censored models for the effect of cART fit separately within each birth cohort.

Table 1

Characteristics of 2539 Youth Evaluated for Pubertal Onset from the IMPAACT 219C and PHACS AMP Studies, and HIV-related Characteristics as of the First Pubertal Assessment* for 2086 Perinatally HIV-infected Children

	HIV Infection Status	
Characteristic	**HIV-exposed Uninfected (N=453)**	**Perinatally HIV-infected (N=2086)**
Age at 1st Pubertal Assessment, Median (IQR)	7.60 (7.20, 8.40)	8.00 (7.40, 9.70)
Study Participation		
PHACS AMP & PACTG 219C	101 (22%)	296 (14%)
PACTG 219C only	265 (58%)	1,718 (82%)
PHACS AMP only	87 (19%)	72 (3%)
Sex		
Boys	232 (51%)	1,054 (51%)
Girls	221 (49%)	1,032 (49%)
Birth Cohort		
Before 1990	0 (0%)	500 (24%)
1990–1992	41 (9%)	654 (31%)
1993–1996	150 (33%)	644 (31%)
1997 or later	262 (58%)	288 (14%)
Race/Ethnicity		
White Non-Hispanic	53 (12%)	266 (13%)
Black Non-Hispanic	230 (51%)	1,197 (57%)
Hispanic	162 (36%)	581 (28%)
Other/unknown	8 (2%)	42 (2%)
Body Mass Index (BMI) Z-score; Mean (SD)[a]	0.76 (1.24)	0.28 (1.04)
Height Z-score; Mean (SD)[a]	0.20 (1.08)	−0.64 (1.20)
Primary Caregiver High School Graduate	286 (63%)	1,366 (65%)
HIV-related Characteristics, Perinatally HIV-infected only		
CD4 T-lymphocyte percentage (CD4%)		
Median (IQR)		30 (22, 37)
<15%		257 (12%)
15–25%		462 (23%)
>25%		1,348 (65%)
Not available		19
CD4 T-lymphocyte count (cells/mm^3)		
Median (IQR)		748 (456, 1,032)
0–200		346 (17%)
201–350		233 (11%)
>350		1,487 (72%)
Not available		20
Nadir CD4%; Median (IQR)[b]		20 (12, 28)

	HIV Infection Status	
Characteristic	**HIV-exposed Uninfected (N=453)**	**Perinatally HIV-infected (N=2086)**
HIV-1 Plasma RNA Viral Load		
Median log HIV-1 RNA (IQR)		2.90 (2.60, 4.10)
<400 copies/mL		699 (45%)
401–10,000 copies/mL		434 (28%)
>10,000 copies/mL		417 (27%)
Not available		536
Peak Viral Load (copies/mL); Median (IQR)[b]		28,536 (1,844, 161,881)
Log Copy-years Viremia; Median (IQR)[b]		4.27 (3.38, 4.97)
CDC Class C Condition, N (%)		667 (32%)
ARV treatment at first pubertal assessment, N (%)		
Combination treatment with PI		1,141 (55%)
Combination treatment without PI		193 (9%)
Not on combination treatment		752 (36%)
Duration of prior treatment (years)[c], Median (IQR)		
Years on combination treatment, among prior users		3.24 (1.62, 5.20)
Years on any PI-containing regimen		3.12 (1.66, 4.99)
Years on any NNRTI-containing regimen		1.65 (078, 3.06)

IQR = interquartile range (displayed as 25th to 75th percentile); PHACS = Pediatric HIV/AIDS Cohort Study; AMP = Adolescent Master Protocol; PACTG = Pediatric AIDS Clinical Trials Group; SD = standard deviation; ARV = antiretroviral; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; CDC = Centers for Disease Control and Prevention

[*] All HIV-disease related characteristics are based on measures available prior to or at the first pubertal assessment, at age 7 years or older.

[a] BMI and height Z-scores are sex- and age-adjusted Z-scores based on CDC 2000 growth standards using the latest BMI and height measured as of the first pubertal assessment. Measures of height and BMI were unavailable for 1 HIV-exposed uninfected child and 35 HIV-infected children.

[b] Measures of past HIV disease severity were unavailable for 19 children for nadir CD4%, and for 536 children for peak viral load. Lack of two viral load measures prevented calculation of copy-years viremia for 989 children.

[c] Duration of prior ARV summarized among the subset of youth with any prior use of regimen, and include 1464 with prior combination ARV treatment, 1400 with prior PI use, and 938 with prior NNRTI use; each regimen is considered separately and categories are not mutually exclusive.

Table 2

Estimated Mean Ages in Years (and 95% Confidence Intervals) at Pubertal Onset by HIV Infection status and Race/Ethnicity for Perinatally HIV-exposed Youth from the IMPAACT 219C and PHACS AMP Studies.

	Girls		Boys	
	Breast (N=1222)	**Pubic hair (N=1185)**	**Genitalia (N=1259)**	**Pubic Hair (N=1182)**
	Estimated Mean (95 % CI)	**Estimated Mean (95 % CI)**	**Estimated Mean (95 % CI)**	**Estimated Mean (95 % CI)**
By HIV Infection Status				
HIV-exposed uninfected	9.61 (9.38, 9.84)	9.98 (9.72, 10.23)	10.36 (10.09, 10.63)	10.72 (10.43, 11.01)
HIV-infected	10.28 (10.18, 10.38)**	10.46 (10.34, 10.57)**	11.25 (11.13, 11.36)**	11.54 (11.42, 11.66)**
By Race/Ethnicity				
White Non-Hispanic	10.75 (10.49, 11.01)	11.01 (10.73, 11.29)	11.68 (11.36, 12.00)	12.07 (11.74, 12.40)
Black Non-Hispanic	9.92 (9.80, 10.05)**	10.03 (9.90, 10.16)**	10.90 (10.76, 11.05)**	11.19 (11.04, 11.34)**
Hispanic	10.42 (10.24, 10.60)*	10.80 (10.61, 10.99)	11.29 (11.09, 11.48)*	11.59 (11.38, 11.79)*
Other/Unknown	9.75 (9.13, 10.37)*	10.29 (9.66, 10.91)*	11.15 (10.31, 12.00)	11.64 (10.76, 12.51)
By Race/Ethnicity and HIV Infection Status				
Among HIV-exposed Uninfected	(n=218)	(n=216)	(n=226)	(n=210)
White Non-Hispanic	10.48 (9.81, 11.16)	11.27 (10.44, 12.10)	11.61 (10.68, 12.54)	11.92 (10.89, 12.95)
Black Non-Hispanic	9.15 (8.85, 9.45)**	9.55 (9.20, 9.89)**	10.03 (9.69,10.36)*	10.43 (10.03, 10.82)*
Hispanic	9.95 (9.56, 10.35)	10.15 (9.71, 10.58)*	10.40 (10.00,10.81)*	10.80 (10.33, 11.27)*
Other/Unknown	9.93 (8.75, 11.11)	11.07 (9.60, 12.53)	N/A	N/A
Among Perinatally HIV-infected	(n=1004)	(n=969)	(n=1031)	(n=970)
White Non-Hispanic	10.78 (10,51, 11.06)	10.97 (10.68, 11.27)	11.67 (11.34, 12.00)	12.08 (11.74, 12.42)
Black Non-Hispanic	10.06 (9.93, 10.20)**	10.11 (9.97, 10.25)**	11.04 (10.89, 11.19)**	11.30 (11.14, 11.46)**
Hispanic	10.52 (10.33, 10.71)	10.95 (10.74, 11.15)	11.47 (11.26, 11.68)	11.75 (11.53, 11.97)
Other/Unknown	9.69 (9.00, 10.39)*	10.11 (9.42, 10.79)*	11.07 (10.23, 11.91)	11.57 (10.69, 12.44)

Statistical comparisons with reference group (listed first within group) indicated by ** denoting p<0.001 and *denoting p<0.05. CI=confidence interval

Table 3

Estimated Shifts (months) in Mean Ages at Pubertal Onset by HIV infection status in Perinatally HIV-exposed Youth from the IMPAACT 219C and PHACS AMP Studies and by HIV Disease Severity and ARV Treatment Measures as of First Pubertal Assessment among Perinatally HIV-infected Youth

	Unadjusted*		Adjusted for Race/Ethnicity and Birth Cohort**		Unadjusted*		Adjusted for Race/Ethnicity and Birth Cohort**	
Characteristic	**Mean Shift (95% CI)**	**p-value**	**Mean Shift (95% CI)**	**p-value**	**Mean Shift (95% CI)**	**p-value**	**Mean Shift (95% CI)**	**p-value**
(a) Estimated Shifts (months) in Mean Ages at Pubertal Onset in Girls								
	Breast Development				**Pubic Hair**			
Among all Girls, by HIV Infection status								
			(N=1222)				(N=1185)	
HIV-infected vs uninfected	8.09 (5.05, 11.13)	<0.001	5.55 (2.38, 8.72)	<0.001	5.75 (2.42, 9.07)	<0.001	1.48 (−1.87, 4.83)	0.39
Among HIV-infected Girls: by HIV Disease Severity and Antiretroviral Treatment								
			(N=1004)				(N=969)	
CD4% <15%	7.17 (3.11, 11.23)	<0.001	4.78 (0.71, 8.85)	0.021	10.91 (6.53, 15.30)	<0.001	7.67 (3.40, 11.94)	<0.001
CD4 count < 200 cells/mm^3	7.93 (4.48, 11.38)	<0.001	5.66 (2.18, 9.14)	0.001	9.68 (5.96, 13.39)	<0.001	6.28 (2.64, 9.92)	<0.001
Nadir CD4% <15%	1.58 (−1.19, 4.34)	0.26	0.07 (−2.62, 2.77)	0.96	5.54 (2.57, 8.51)	<0.001	2.97 (0.14, 5.80)	0.040
viral load >10,000 copies/mL	5.64 (2.30, 8.98)	<0.001	3.54 (0.15, 6.92)	0.041	3.94 0.10, 7.77)	0.045	0.61 (−3.13, 4.35)	0.75
Peak viral load >100,000 copies/mL	0.51 (−2.62, 3.65)	0.75	0.99 (−2.04, 4.01)	0.52	−1.34 (−4.86, 2.18)	0.45	−0.34 (−3.60, 2.93)	0.84
Log_{10} Copy-years Viremia	1.60 (−0.06, 3.26)	0.059	1.33 (−0.23, 2.89)	0.094	1.52 (−0.35, 3.40)	0.11	1.00 (−0.72, 2.71)	0.25
CDC Class C	1.50 (−1.15, 4.14)	0.27	1.96 (−0.57, 4.50)	0.13	0.84 (−2.00, 3.68)	0.56	1.18 (−1.45, 3.81)	0.38
ARV regimen as of first pubertal assessment								
Combination with PI	−2.67 (−5.25, −0.08)	0.044	0.40 (−2.36, 3.16)	0.78	−3.68 (−6.45, −0.91)	0.009	0.65 (−2.21, 3.51)	0.65
Combination without PI	−1.76 (−6.46, 2.93)	0.46	0.79 (−3.86, 5.43)	0.74	−2.64 (−7.62, 2.33)	0.30	2.05 (−2.74, 6.85)	0.40
Not on combination regimen	(ref)	---	(ref)	---	(ref)	---	(ref)	---
Each additional year of ART use by regimen or drug class (not mutually exclusive)								
Combination regimen	−0.60 (−1.09, −0.12)	0.015	0.17 (−0.50, 0.84)	0.62	−1.15 (−1.67, −0.64)	<0.001	0.14 (−0.57, 0.85)	0.71
Combination regimen with PI	−0.65 (−1.17, −0.14)	0.012	0.04 (−0.60, 0.67)	0.91	−1.22 (−1.76, −0.67)	<0.001	−0.08 (−0.75, 0.59)	0.83

	Unadjusted*		Adjusted for Race/Ethnicity and Birth Cohort**		Unadjusted*		Adjusted for Race/Ethnicity and Birth Cohort**	
Characteristic	**Mean Shift (95% CI)**	**p-value**	**Mean Shift (95% CI)**	**p-value**	**Mean Shift (95% CI)**	**p-value**	**Mean Shift (95% CI)**	**p-value**
Any PI-containing regimen	−0.58 (−1.09, −0.07)	0.025	0.18 (−0.44, 0.81)	0.57	−1.19 (−1.74, −0.65)	<0.001	−0.05 (−0.71, 0.61)	0.89
NNRTI-containing regimen	−0.72 (−1.51, 0.06)	0.069	−0.15 (−0.96, 0.66)	0.72	−1.46 (−2.28, −0.65)	<0.001	−0.39 (−1.22, 0.44)	0.36
3(b) Estimated Shifts (months) in Mean Ages at Pubertal Onset in Boys								
	Genitalia				**Pubic Hair**			
Among all Boys, by HIV Infection status								
			(N=1259)				(N=1182)	
HIV-infected vs uninfected	10.61 (7.08, 14.14)	<0.001	6.02 (2.15, 9.90)	0.002	9.78 (6.03, 13.54)	<0.001	3.92 (−0.14, 7.98)	0.058
Among HIV-infected Boys: by HIV Disease Severity and Antiretroviral Treatment								
			(N=1031)				(N=970)	
CD4% <15%	12.20 (8.41, 15.99)	<0.001	8.95 (5.06, 12.84)	<0.001	12.78 (8.95, 16.62)	<0.001	9.04 (5.16, 12.92)	<0.001
CD4 count < 200 cells/mm^3	10.23 (6.78,13.68)	<0.001	6.98 (3.40,10.56)	<0.001	11.85 (8.37,15.33)	<0.001	8.36 (4.79, 11.94)	<0.001
Nadir CD4% < 15%	8.13 (5.21, 11.06)	<0.001	5.74 (2.85, 8.64)	<0.001	8.70 (5.70, 11.70)	<0.001	5.94 (3.01, 8.88)	<0.001
Viral load >10,000 copies/mL	9.36 (5.88, 12.83)	<0.001	5.07 (1.52, 8.62)	0.005	10.18 (6.60, 13.75)	<0.001	5.50 (1.90, 9.10)	0.003
Peak viral load >100,000 copies/mL	4.60 (1.13, 8.06)	0.009	4.47 (1.18, 7.76)	0.008	3.53 (−0.04, 7.10)	0.053	4.15 (0.83, 7.48)	0.014
Log_{10} Copy-years Viremia	3.23 (1.27, 5.19)	0.001	2.04 (0.24, 3.85)	0.026	4.47 (2.43, 6.51)	<0.001	3.09 (1.23, 4.95)	0.001
CDC Class C	5.30 (2.27, 8.33)	<0.001	5.39 (2.51, 8.27)	<0.001	3.59 (0.43, 6.74)	0.026	3.20 (0.25, 6.15)	0.034
ARV regimen as of first pubertal assessment								
Combination with PI	−0.97 (−3.98, 2.04)	0.53	3.98 (0.88, 7.08)	0.012	−3.17 (−6.25, −0.09)	0.044	1.75 (−1.38, 4.89)	0.27
Combination without PI	0.05 (−5.24, 5.35)	0.98	3.46 (−1.53, 8.46)	0.17	1.82 (−3.53, 7.17)	0.51	4.90 (−0.08, 9.88)	0.054
Not on combination regimen	(ref)	---	(ref)	---	(ref)	---	(ref)	---
Each additional year of ARV treatment by regimen or drug class (not mutually exclusive)								
Combination regimen	−0.62 (−1.19, −0.04)	0.035	0.98 (0.27, 1.70)	0.007	−0.89 (−1.48, −0.31)	0.003	0.90 (0.18, 1.63)	0.014
Combination regimen with PI	−0.61 (−1.22, −0.01)	0.046	0.92 (0.20, 1.64)	0.012	−0.99 (−1.60, −0.37)	0.002	0.71 (−0.03, 1.44)	0.059
Any PI-containing regimen	−0.57 (−1.16, 0.03)	0.062	0.96 (0.26, 1.66)	0.007	−0.92 (−1.53, −0.31)	0.003	0.75 (0.04, 1.46)	0.039
NNRTI-containing regimen	−1.30 (−2.20, −0.40)	0.005	−0.24 (−1.16, 0.68)	0.61	−1.63 (−2.56, −0.71)	<0.001	−0.39 (−1.32, 0.54)	0.41

CI = confidence interval; IQR = interquartile range; ARV = antiretroviral; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; CDC = Centers for Disease Control and Prevention

* All estimated shifts in mean age at pubertal onset are based on interval-censored models; and reflect the estimated shift in mean age at pubertal onset for those with versus without a characteristic, or for each 1-unit change in continuous measures.

** Interval-censored models for covariate of interest adjusted for Race/Ethnicity (classified as White non-Hispanic, Black non-Hispanic, Hispanic, or other/unknown race) and birth cohort (classified as pre-1990, 1990-1992, 1993-1996, and 1997 or later.