# EVALUATING ASSOCIATIONS BETWEEN IN UTERO HIV/ART EXPOSURE AND PUBERTAL STATUS

0805

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## BACKGROUND

- Deviations in timing of pubertal onset can impact health.
- Many factors influence timing of pubertal onset, including in utero exposures to medications and infections.
- Few studies have evaluated the influence of in utero HIV/antiretroviral (ARV) exposure on pubertal onset in children who are HIV-exposed uninfected (CHEU).

## OBJECTIVES

**1. To compare the likelihood of having entered puberty by age 9 in CHEU versus children who are HIV-unexposed uninfected (CHUU).**

**2. To explore associations between maternal HIV viral load, CD4 count, and ARV type with likelihood of having entered puberty by age 9 in CHEUs.**

## METHODS

**Population: CHEU** in the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network, and **CHUU** in the Bone Mineral Density in Childhood Study (BMDC) with sexual maturity rating (SMR) assessments at age 9 years (+/-4 months).

**Pubertal onset defined as:** SMR ≥2 separately by sex assigned at birth, for girls (breasts and/or pubic hair) and boys (genitalia and/or pubic hair).

**Analysis:** We fit adjusted log-binomial regression models to estimate the adjusted risk ratio (RR) of each exposure variable with SMR ≥2 at age 9.

**Aim 1:** The exposure is CHEU vs CHUU. We standardized the CHUU to the CHEU by sex and racial distribution.

**Aim 2: Among CHEU only,** separate models were fit for each exposure:

1) protease inhibitor (PI) exposure at ≤30 wk gestation,
2) maternal CD4 ≤200 vs. >200 cells/mm3,
3) HIV viral load (VL) copies/mL,
4) child body mass index (BMI) >95th percentile

## RESULTS

### Characteristics at age 9 years for CHEU and CHUU

| | SMARTT N=215 | BMDCS N=344 | Total N=559 |
|---|---|---|---|
| Age at SMR assessment | | | |
| Media (Q1, Q3) | 9.06 (9.00, 9.16) | 9.00 (8.80, 9.20) | 9.03 (8.90, 9.20) |
| Sex | | | |
| Male | 107 (50%) | 162 (47%) | 269 (48%) |
| Female | 108 (50%) | 182 (53%) | 290 (52%) |
| Race | | | |
| Black | 162 (75%) | 101 (29%) | 263 (47%) |
| Non-Black | 53 (25%) | 243 (71%) | 296 (53%) |
| Ethnicity | | | |
| Hispanic | 57 (27%) | 49 (14%) | 106 (19%) |
| Non-Hispanic | 158 (73%) | 295 (86%) | 453 (81%) |
| Child BMI z-score category | | | |
| ≤ 95th percentile | 149 (69%) | 325 (94%) | 474 (85%) |
| > 95th percentile | 66 (31%) | 19 (6%) | 85 (15%) |

Boys who are HEU were more likely to have reached puberty by age 9 years compared to boys who are HUU.

Higher maternal viremia in pregnancy was associated with greater likelihood of having reached puberty at age 9 years in boys, but not girls.

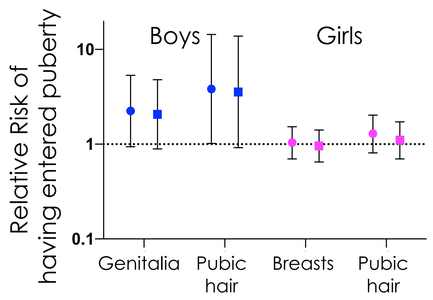
PI exposure was associated with lower likelihood of having reached puberty at age 9 years in boys, but not in girls.

### Pubertal Onset by age 9 years by sex and HEU status

| SMR ≥2 | Boys HEU N=107 | Boys HUU N=162 | Girls HEU N=108 | Girls HUU N=182 |
|---|---|---|---|---|
| Breast or genitalia | 16 (15.0%) | 16 (9.9%) | 38 (35.2%) | 42 (23.1%) |
| Pubic hair | 12 (11.2%) | 6 (3.7%) | 35 (32.4%) | 27 (14.8%) |
| Both | 11 (10.3%) | 4 (2.5%) | 30 (27.8%) | 16 (8.8%) |

### Associations of HEU status with Pubertal Onset by age 9

Showing RR (○) or aRR (□) with 95% CI stratified by sex at birth

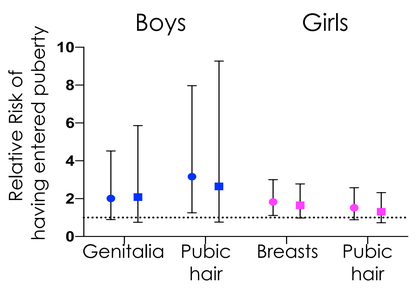



Adjusted for age at Tanner assessment and race

**Among boys, a greater proportion of CHEU had genitalia or pubic hair SMR ≥ 2 compared to CHUU, and this relationship persisted even after adjusting for age and race.**

### Associations between child BMI and Pubertal Onset by age 9 in CHEU

Showing RR (○) or aRR (□) with 95% CI stratified by sex at birth



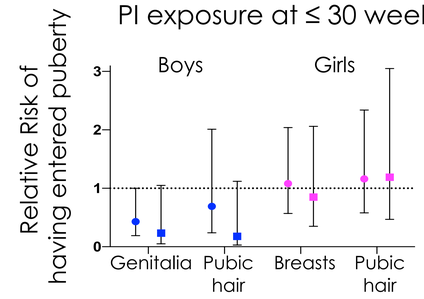

**Child BMI > 95th percentile associated with SMR ≥ 2 for male pubic hair and female breasts in unadjusted analyses**

Adjusted for age at Tanner assessment, race/ethnicity, and household income

### Associations between in utero HIV and ARV exposures and SMR ≥ 2 at age 9 years

Showing RR (○) or aRR (□)with 95% CI stratified by sex at birth

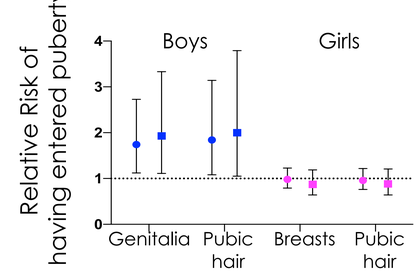
PI exposure at ≤ 30 weeks gestation




**A trend for PI exposure at ≤ 30 weeks gestation with less likely to have entered puberty by age 9 years in boys.**

Adjusted for age at Tanner assessment, race/ethnicity, maternal pre-pregnancy BMI, household income, and earliest CD4 count in pregnancy.

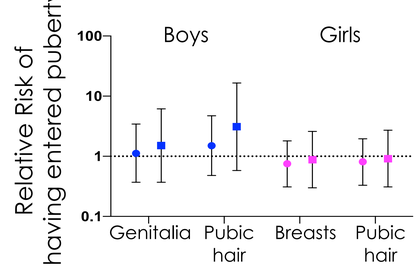
Maternal HIV viral load in pregnancy




**1 log increase in maternal HIV RNA in pregnancy = ~ 2 fold more likely to have entered puberty by age 9 years for boys.**

Adjusted for age at Tanner assessment, race/ethnicity, maternal pre-pregnancy BMI, and household income.

Maternal CD4 count in pregnancy




**No association with maternal CD4 count and having entered puberty by age 9 years in either boys or girls.**

Adjusted for age at Tanner assessment, race/ethnicity, maternal pre-pregnancy BMI, and household income.

## CONCLUSIONS

- Male CHEU were more likely to have started puberty by age 9 years compared to CHUU.
- Higher maternal viremia in pregnancy was associated with higher risk and PI exposure with lower risk of presence of puberty at age 9 years in males but not females.
- Further confirmatory and mechanistic studies are warranted.

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