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The Association Between Oral Disease and Type of Antiretroviral Therapy among Perinatally HIV-Infected Youth

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Abstract

Objectives: This study explores the association between combination antiretroviral therapy (cART) and oral health outcomes (dental and periodontal) among perinatally HIV-infected (PHIV) youth.

Methods: We conducted a cross-sectional study of oral health among PHIV youth participating in the Oral Health substudy of Pediatric HIV/AIDS Cohort Study (PHACS). Dentists at research sites were trained/calibrated on how to perform a standardized oral mucosal, dental, and periodontal examination. They assessed the decayed-missing-filled-surfaces and teeth index (DMFS/T). The number of decayed surfaces and teeth (DS/DT), and the number of teeth with bleeding on probing for each participant were derived from the examination. Data for analysis included lifetime measurements of CD4 count and viral load (VL), socio-demographic information, and current/ past history of ART.

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Results: Among 209 PHIV youth, 95% were on ART at the time of enrollment. Among 143 PHIV youth on the same cART for at least one year, we found that the mean DT score of those receiving cART containing an integrase inhibitor (II) was 86% higher than that of those on cART without an II after adjusting for age, lifetime proportion of unsuppressed VL and CD4 nadir. Initiating protease inhibitors (PI) before age 6 years was associated with a significantly lower DMFT score compared to participants who initiated at age 6 and older.

Conclusion: Our study revealed that PHIV youth who received cART containing II had a significantly higher number of untreated active caries than those on cART without II. This may warrant closer dental surveillance of those receiving II.

INTRODUCTION

Combination antiretroviral therapy (cART) has been very successful at preserving immune function and controlling opportunistic infections among individuals infected with the human Immunodeficiency virus (HIV).[1] Oral mucosal diseases associated with advanced immunosuppression such as candidiasis and hairy leukoplakia are significantly less common among patients on cART.[2–11] In a recent study among perinatally HIV-infected (PHIV) youth participating in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), oral mucosal lesions were very rare.[12] This was not surprising since the majority of youth had been on cART for many years. In contrast, this group was found to have a high burden of dental and periodontal disease with 61% having at least one tooth with untreated caries, and over 30% having some form of periodontitis.[12, 13] In comparison to perinatally HIV exposed uninfected (PHEU) youth in AMP, PHIV youth had a greater mean number of untreated decayed teeth whereas no differences were found between groups with respect to periodontal disease. Of note, there were no differences in cumulative history of caries between HIV infected and uninfected groups suggesting a more recent influence on the development of current caries. Although these analyses were comprehensive in their consideration of potential risk factors for dental and periodontal disease, the effect of type of ART exposure was not assessed.

To date, 24 Food and Drug Administration-approved drugs, organized into six distinct classes, are available for treatment of HIV-1 infections: nucleoside-analog reverse transcriptase inhibitors (NRTI), non–nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (FI), integrase inhibitors (II), and co-receptor antagonists.[14] Given the different mechanisms of action of these drugs, their effect on the oral microbiome might vary, which may in turn affect dental and periodontal conditions. Thus the objective of this study was to examine the association between ART and oral health outcomes (dental and periodontal diseases) among PHIV youth participating in the AMP/PHACS Oral Health Substudy, controlling for indicators of HIV disease severity. We did not include oral mucosal disease as an endpoint given its very low prevalence in this study population.[12]

METHODS

Study Design and Population

We conducted a cross-sectional study of oral health among participants in 11 AMP/PHACS sites.[12, 13]. As described previously, PHACS is a prospective cohort study designed to determine the impact of HIV infection and ART among PHIV youth.[15, 16].

The study was approved by Institutional Review Boards (IRB) at clinical sites, and at the Harvard T.H. Chan School of Public Health. Parents or legal guardians provided written informed consent for their child's participation. Youth consented or assented per local IRB guidelines.

Variables and Measures

PHACS Database, and Data Collection Overview—Variables and measures collected as part of the oral study and/or obtained from the PHACS/AMP database have been described previously.[12, 13] Sixteen dentists at 11 sites were trained and calibrated on how to perform a standardized oral mucosal, dental, and periodontal examination. The mean (SD; range) concordance level was 97.7% (2.4%; 92% - 100%) for probing depths, 98.3% (2.4%; 92% - 100%) for gingival margin, and 99.2% (1.3%; 96% - 100%) for the presence/absence of clinically detectable caries.[12]

Dental and periodontal endpoints—The decayed-missing-filled-surfaces and teeth index (DMFS/T) was used to assess the prevalence and history of dental caries, and the number of decayed surfaces and teeth (DS/T) was used to assess untreated active caries.[17] The Plaque Index developed by Silness and Löe was measured on all teeth (one buccal and one lingual site per tooth) as an objective measure of oral hygiene.[18] Extensive periodontal parameters were measured on 6 sites per tooth, including the bleeding on probing (BOP).[13] The number of teeth with BOP at more than 1 site was derived. All tooth counts were corrected for missing teeth by multiplying by the ratio of 28 over the number of scored teeth.

Based on the periodontal parameters of attachment loss and probing depth, periodontitis was defined as either absent, mild, moderate, or severe in accordance with the Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC-AAP case definition).[19] Among those with no periodontitis, we used a definition for gingivitis adapted from work by Offenbacher and colleagues where individuals had to have BOP on at least 10% of the sites scored to be considered as having gingivitis.[20] A 5 minute unstimulated whole saliva flow rate was performed.[21, 22]

Exposure to ART—The main variables of interest reflected exposure to ART. For this analysis, cART was defined as any regimen containing at least three drugs from at least two drug classes. Classes considered were NRTI, NNRTI, PI, FI, and II.

Any regimen that stopped before a cutoff of 6 weeks (42 days) after birth was considered prophylaxis and not considered as part of our analyses. Likewise, any regimen that lasted less than 3 days was not considered.

When exploring history of ART, we considered if a participant had ever received cART and any drug within each class of medication as binary variables. Age at first exposure to any ART, cART, and class of medication was explored both as a continuous variable (years), and as a categorized variable: <2 years, 2 to <6 years, 6 years or older.

When exploring the current ART regimen, we defined as "current stable ART regimen" participants on a specific regimen with a start date at least one year prior to the oral health exam, and who had no changes to the regimen during that time. To explore the effect of specific classes of medications included in cART, we grouped the regimens by several categorized variables for the most common classes as follows: cART inclusive of an NNRTI versus cART without NNRTI; cART inclusive of a PI versus cART without PI; and cART inclusive of II versus cART without II.

Clinical indicators of history of, and current, HIV disease severity—HIV disease severity history was considered in the characterization of the study participants and in various analyses using the following clinical Indicators (among all available lifetime measures up to the time of the oral examination): percent of HIV RNA measures detectable (>400 copies/mL), CD4 cell count nadir (dichotomized to<200 or ≥200 cells/mm^3), and history of a clinical AIDS-Defining Illness (as defined in CDC Stage 3).[23]

Current HIV disease severity was considered in the characterization of the study sample and in various analyses using the following binary clinical Indicators measured at or within 90 days of the oral study visit: HIV RNA viral load (≤400 or >400 copies/mL), and CD4 cell count (<350 or ≥350 cells/mm^3).

Statistical Analyses

The study population was characterized descriptively for history of ART exposure, current ART exposure, history of HIV disease severity, and current HIV disease severity. Summary statistics were calculated for continuous measures, and frequencies were calculated for discrete measures.

Summary statistics of the dental and periodontal tooth count endpoints were calculated. Considering the excess zero and over-dispersion relative to Poisson distribution for DT or other tooth counts, zero-inflated negative binomial (ZINB) models [12, 13] were applied to assess the association between each ART exposure measure and dental or periodontal outcomes (SAS proc genmod). We used a Directed Acyclic Graph (DAG) to distinguish between variables which could play potential confounding versus mediating roles.[24, 25] Thus all models were adjusted for age, and historical HIV disease severity using two indicators selected based on their associations with the ART exposures and oral health outcomes, the input of the principal investigators, and their interpretability: the percent of detectable HIV RNA measurements over the participant's lifetime up to the oral health visit and CD4 nadir (< versus ≥ 200 cells/mm^3). An example of DAG drawn in exploring DT as primary outcome is shown in supplemental Figure 1. All variables were only assessed through the negative binomial component of the ZINB models. We used a similar approach, relying on a similar DAG with age and historical HIV disease severity as confounders, to

explore the association between age at first cART exposure and dental or periodontal outcomes. We explored both cART and specific drug classes.

RESULTS

Socio-demographic, HIV-disease, and oral disease characteristics

Among 335 participants enrolled from 11 sites, 209 were PHIV, 53% of the PHIV youth were female, 63% were non-Hispanic Blacks, 27% were Hispanic, 10% were White/other, 16% were 10 to 13 years, 61% were 14 to 18 years, and 23% were 19 years or older at enrollment.[12] Only 38% lived with a caregiver who was their biological parent, 71% had a caregiver who had graduated high school and for 44% the main caregiver's income was ≤ $20,000 per year.

The median current HIV RNA viral load was 40 copies/mL (1st quartile (Q1): 20; 3rd quartile (Q3): 1760), and 66 (32%) PHIV youth had a current viral load > 400 copies/mL; the median current CD4 cell count was 626 cells/mm^3 (Q1: 441; Q3: 825), and 38 (18%) had a current CD4 cell count < 350 cells/mm^3 (supplemental Table 1). Over their lifetime, 70 (33%) had a CD4 cell count nadir < 200 cells/mm^3, 51 (24%) had a history of an AIDS-defining illness, and the median percentage of lifetime viral load measures which were detectable was 45% (Q1: 20%; Q3: 70%).

As previously described, 61% of PHIV youth had at least one tooth with untreated dental caries, and the mean number of DT among PHIV was 2.2 (SD 3.3).[12] The mean number of DT and DMFT scores were higher in PHIV youth with a CD4 nadir < 200 cells/mm^3 (3.2; SD: 4.6) than among those with a nadir ≥ 200 cells/mm^3 (1.7; SD:2.4).

History of ART and current regimens received by PHIV youth

All PHIV youth had received ART at some point since birth, and 198 (95%) were on ART at the time of the oral health visit. All youth received an NRTI at some point in time, the next most common antiretroviral class ever received by this group was a PI (91%) followed by an NNRTI (67%; Table 1a). The median age when an NRTI was initiated was 0.6 year, and around 3 years for the first PI among those who ever received PI, while the median age at first II was 14.7 years. Nearly three quarter of PHIV youth had been on the same regimen (or no treatment) for the past year, including 143 (93%) on cART. Among the 143 on stable cART, 78% were receiving a regimen containing PI, 30% an NNRTI, and 20% II (Table 1b).

Association between current cART regimen and oral outcomes

Current cART, dental disease and salivary function—Among 143 PHIV youth on the same cART for at least one year, cART with PI or cART with NNRTI were not associated with either DMFS/T or DS/T. However, those who received a cART regimen containing II had a significantly higher number of DT and DS than those receiving cART without II ($p < 0.001$ and $p = 0.002$, respectively), and a higher DMFT score, although this was not statistically significant (Table 2). The mean DT score for youth who received cART with an II was 86% higher than those who received cART without II after adjusting for the lifetime proportion of VL which were suppressed and nadir CD4 (Table 3).

Because a low salivary flow rate is associated with caries, we examined its association with cART. While no difference was found with respect to unstimulated salivary flow rate between those on cART with II and those on cART without, the median flow rate among PHIV youth on the same cART with NNRTI for at least 1 year was 0.5 mL/minute (Q1: 0.3 and Q3: 1 mL/minute) compared to 0.8 mL/minute (Q1: 0.5 and Q3: 1.2 mL/minute) among youth on cART without NNRTI ($p = 0.007$). However, no difference was detected with respect to DMFS/T or DS/T between those receiving a cART with NNRTI compared to those receiving a cART without. Similarly, no difference was detected with respect to DMFS/T or DS/T among those receiving the same cART with PI for at least 1 year compared to those receiving a cART without.

Current cART and periodontal disease—With respect to periodontal disease, there was no difference between those receiving a cART with versus without II, or between those receiving a cART with versus without PI. Mild to moderate periodontitis was diagnosed in 25% of PHIV youth receiving a cART with NNRTI compared to 41% among PHIV youth receiving a cART without NNRTI, and number of teeth with BOP at 2-6 sites were also lower in youth receiving a cART with NNRTI (mean 7.9 versus 10.0, Supplemental Table 2), but this difference was not statistically significant ($p = 0.09$).

Association between age of first exposure to cART regimen and oral outcomes

PHIV youth with a later initiation of cART had significantly higher DMFS and DMFT scores, and higher number of teeth with multiple BOP sites, than youth whose exposure initiation was at a younger age (Table 4). The DMFS/T difference was particularly notable among PHIV youth with a later initiation of PI with a median DMFS of 10 [Q1: 4; Q3: 21] in youth ≥ 6 years of age at initiation compared to a median DMFS of 7 [Q1:2; Q3:13] and 4 [Q1: 0; Q3: 8] among those who initiated PI between age 2 to 6 years and before age 2 years, respectively (Kruskal-Wallis test, $p < 0.001$). However, a similar difference was not observed among different age groups of NNRTI initiation, and number of untreated caries (DS/T) did not differ across the various initiation age groups.

The association between age at first exposure to cART and DMFS/T did not persist after adjusting for age at evaluation, lifetime proportion of unsuppressed viral load and low CD4 nadir. However, initiating PI before the age of 2, or between the ages of 2 and <6 years, was associated with a significantly lower DMFT score compared to participants who initiated at age 6 and older (Table 5a).

With respect to periodontal disease, the most notable finding was an association between age at first exposure of cART and BOP. The median number of teeth with at least 2 sites with BOP was significantly higher among youth who started cART older (Table 4). This association was still significant after adjustment (Table 5b). Also of note, the median number of teeth with at least 2 sites exhibiting BOP was significantly higher among youth who were 6 years and older at the time NNRTI initiation (7 [Q1: 2; Q3: 15]), and among those ages 2-6 years at NNRTI initiation (9.5 [Q1: 5; Q3: 16]), compared to those who initiated NNRTI younger than 2 years (4.5 [Q1: 2.5; Q3: 9]; $p = 0.02$ using a Kruskal-Wallis test).

Discussion

In this unique study exploring the effect of various cART regimens on caries and periodontal outcomes among PHIV youth, those who received a cART regimen containing II had a significantly higher number of untreated active caries than those on cART without II, after adjusting for age at oral examination, life history of unsuppressed viral load and low CD4 nadir. Of note, II were initiated, if ever, at a much older age. Considering lifetime exposure to ART, PHIV youth with a later initiation of PI (the majority of them received PI as part of a cART) had significantly higher DMFT/S scores than those initiating PI at an earlier age, after controlling for age at evaluation. With respect to periodontal disease, there was no difference between those receiving cART with versus without II. However, those with a later initiation of cART had significantly higher number of teeth with multiple BOP sites than youth whose initial exposure was at a younger age. The associations between age at first cART exposure and BOP, persisted after adjusting for current age, lifetime proportion of unsuppressed viral load, and low CD4 nadir.

While multiple studies among adults with HIV disease have shown that the prevalence of oral mucosal lesions is significantly lower among adult patients on ART in both the developed and developing world,[2–11] scarce data addressing this topic have been published among HIV-infected children. The few studies reported among children have been conducted mainly in developing countries.[26–31] Among those that included children receiving ART, while the prevalence of oral mucosal lesions was lower among these children than among those not receiving ART, these estimates were overall much higher than those we observed among PHIV youth, who had almost no oral mucosal lesions.[12] This is likely because PHIV youth in AMP/PHACS were prescribed cART early in life, and have remained on it for most of their lives. This is consistent with our finding that the PHIV youth who initiated cART before age 2 had a lower prevalence of gingival inflammation, as suggested by a lower number of teeth with BOP, and those who initiated PI earlier in life had a significantly lower score of DMFS/T, which reflects the history of caries. Another possible explanation is that the group of youth who started cART earlier in life may have had better access to care, including dental care, although 87% of PHIV youth who initiated cART before age 2 years reported having a source of dental care at the time of this study, compared to 74% of the youth who initiated cART after age 2 years (data not shown), and adjusting for this factor did not change the estimate of the association.

With respect to our finding that among PHIV youth on the same cART for at least one year, those who received cART containing II had significantly higher numbers of DT and DS than those on cART without II: since II are often used as salvage therapy, the group receiving II was possibly sicker closer to the time of the oral examination (since they typically initiated II during adolescence), which could partly explain the higher prevalence of caries in that group, that persisted when explored with a multivariable model. The DMFT/S was not found to be significantly higher in the group receiving II, presumably because it captures long-term history of caries, rather than more recent active disease. Sicker youth may be less likely to seek dental care due to ascendance of medical concerns, decreased energy. This finding may also reflect decreased ability of caregiver to address medication adherence of youth. Older age may be another possible explanation, however, age was not found to be associated with

DT in our initial multivariable model exploring this association. It may also be that II alter the oral microbiome to select more cariogenic bacteria. We are currently exploring this hypothesis through ongoing oral microbiome studies. Salivary hypofunction is also a known risk factor for the development of sudden onset caries, and while we did not find that those on II had lower saliva flow rate than those not receiving II, a difference may not have been detected reliably given the cross sectional nature of our study. Furthermore, both groups had an unstimulated salivary flow rate that was above the 0.1 mL/min threshold and were not considered as having salivary hypofunction.[22]

Our study is unique in that our team of trained/calibrated dentists performed a comprehensive standardized oral examination (including an oral soft tissue examination, caries assessment, and full mouth periodontal evaluation) in a group of PHIV youth with extensive and complete medical history data, including ART, collected at regular time intervals since the onset of the AMP/PHACS project more than a decade ago. The limitation of our study is that it is cross-sectional, which hampers the determination of causality in the associations we uncovered. However, we are in the process of implementing a follow-up visit to our oral AMP/PHACS sub-study, which will allow us to further explore some of our findings as youth transition to adulthood.

Studies have shown that early initiation of cART is associated with better health outcomes in children,[15, 32–34] and the present study suggests that this is also true for oral health outcomes, including dental and gingival health. For instance, we found that PHIV youth who initiated PI earlier in life had significantly lower DMFS/T scores, and those who initiated cART before age 2 had a lower prevalence of gingival inflammation. Furthermore, the finding that PHIV youth who received a cART regimen containing II had a significantly higher number of DT/S than those on cART without II suggest that youth receiving II should undergo closer surveillance of their dental status through preventative visits scheduled perhaps as often as three times per year. Daily topical fluoride home applications and/or regular fluoride varnish applications as part of preventative dental visits should be promoted in this group. Meanwhile, further research into the effect of various cART regimens on the oral microbiome are warranted to better understand the pathogenesis of dental caries among PHIV youth exposed to these regimens almost since birth. Such studies are currently ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

a) History of antiretroviral therapy (ART) received by 209 perinatally HIV-infected (PHIV) youth participating in the Oral Health study in the AMP/PHACS[1]; **b)** Current stable combination antiretroviral therapy (cART)[2] regimen (unchanged for past year prior to study entry)[3] among 153 PHIV youth participating in the Oral Health study in the AMP/PHACS

a) History of ART Regimen (N=209):	Ever received N (%)	Age at first ART exposure Median[4] (Q1, Q3)	Age at first ART exposure Categorized: Age groups (years)	N (%)
cART[2]	205 (98)	2.7 (0.9, 5.2)	< 2	82 (39)
			2 to < 6	85 (41)
			6+	38 (18)
			Not exposed	4 (2)
NRTIs[5]	209 (100)	0.59 (0.2, 2.4)	< 2	145 (69)
			2 to < 6	52 (25)
			6+	12 (6)
PIs[5]	190 (91)	2.7 (1.1, 4.8)	< 2	73 (35)
			2 to < 6	87 (42)
			6+	30 (14)
			Not exposed	19 (9)
NNRTIs[5]	140 (67)	4.6 (2.4, 10.3)	< 2	28 (13)
			2 to < 6	62 (30)
			6+	50 (24)
			Not exposed	69 (33)
IIs[5]	57 (27)	14.7 (12.6, 17.2)	6+	57 (27)
			Not exposed	152 (73)

b) Stable cART(or no cART/ART) for 1 year prior to study entry (N=153)[3]	N (%)
With NNRTIs	43 (28)
No NNRTIs	100 (65)
Non cART or no ART	10 (7)
With PIs	111 (73)
No PIs	32 (21)
Non cART or no ART	10 (7)
With IIs	29 (19)
No IIs	114 (75)
Non cART or no ART	10 (7)

[1] Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS)

[2] cART was defined as any regimen containing at least three drugs from at least two drug classes.

[3] Among 209 participants, 153 had a stable regimen (143 on cART, 10 not on cART/ART) in the past year prior to study entry

[4] Median and 1st and 3rd quantiles (Q1, Q3) among those ever received.

[5] NRTIs: Nucleoside-analog reverse transcriptase inhibitors; PIs: Protease inhibitors; NNRTIs: Non–nucleoside reverse transcriptase inhibitors; IIs: Integrase inhibitors (Note: only 10 (5%) ever received a fusion inhibitor in their regimen, and 144 (69%) ever received Didanosine (DDI))

Table 2.

Exposure to integrase inhibitors (II) as part of combination antiretroviral therapy (cART)[1] regimen by oral health outcomes among 143 perinatally HIV-infected youth participating in the Oral Health study in the AMP/PHACS[2] and having received the same cART for the past year prior to oral health study entry

	cART no II N=114	cART with II N=29	Total	*P*-value
DMFS[3] score				
- Mean (SD)	7.0 (6.8)	12.2 (14.6)	8.1 (9.2)	0.14[4]
- Median (Q1, Q3)	5.5 (1, 11)	5 (3, 19)	5 (2, 12)	
DMFT[3] score				
- Mean (SD)	4.7 (4.1)	6.9 (5.5)	5.1 (4.5)	0.07[4]
- Median (Q1, Q3)	4 (1, 7)	5 (3, 12)	4 (1, 8)	
DS[3]				
- Mean (SD)	1.9 (3.3)	5.6 (10.8)	2.7 (5.8)	0.002[4]
- Median (Q1, Q3)	1 (0, 2)	2 (1, 5)	1 (0, 3)	
DT[3]				
- Mean (SD)	1.6 (2.5)	3.6 (4.2)	2.0 (3.0)	<0.001[4]
- Median (Q1, Q3)	1 (0, 2)	2 (1, 5)	1 (0, 3)	
Unstimulated whole saliva flow rate (mL/mn)				
- Mean (SD)	0.8 (0.5)	0.8 (0.5)	0.8 (0.5)	0.90[4]
- Median (Q1, Q3)	0.6 (0.4, 1.0)	0.8 (0.4, 1.0)	0.7 (0.4, 1.0)	
Periodontal disease				
N (%)				
- None	22 (19)	7(24)	29 (20)	0.66[5]
- Gingivitis	49 (43)	10 (34)	59 (41)	
- Mild Periodontitis	18 (16)	7 (24)	25 (17)	
- Moderate Periodontitis	22 (19)	5 (17)	27 (19)	
- Missing	3 (3)	0	3 (2)	

[1] cART was defined as any regimen containing at least three drugs from at least two drug classes.

[2] Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS)

[3] DMFS/T: decayed-missing-filled-surface/teeth score; DS: number of decayed surfaces; DT: number of teeth with caries

[4] Wilcoxon Rank Sum Test

[5] Chi-Square Test

Table 3.

Zero-Inflated Negative Binomial (ZINB) multivariable model exploring the association between stable combination antiretroviral therapy (cART)[1] with II and number decayed teeth (DT), controlling for age, HIV RNA viral load, and CD4 cell count nadir, among 143 perinatally HIV-infected youth participating in the Oral Health study in the AMP/PHACS[2] and having received the same cART regimen for the past year prior to study entry

		Adj. Mean Ratio Estimate	95%CI	*P*-value
cART with II versus no II		1.86	1.05 – 3.30	0.03
Age at time of oral exam (years)	14-<17 vs < 14	1.45	0.68 – 3.10	0.34
	17-<19 vs < 14	1.49	0.71 – 3.12	0.29
	19+ vs < 14	1.41	0.65 – 3.08	0.39
% unsuppressed HIV Viral load[3]		1.01[4]	1.00 – 1.02	0.15
CD4 nadir < 200 cells/mm		1.77	1.09 – 2.86	0.02

[1] cART was defined as any regimen containing at least three drugs from at least two drug classes.

[2] Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS)

[3] > 400 copies/mL (% among lifetime number of VL assays)

[4] Per one percent increase in HIV RNA unsuppressed viral load

Table 4.

Age of first exposure to combination antiretroviral therapy (cART)[1] by dental and periodontal outcomes[2] among 205 perinatally HIV-infected youth youth ever exposed to cART participating in the Oral Health study in the AMP/PHACS[3]

	< 2 yrs N = 82	2 to 5 yrs N = 85	6+ yrs N = 38	*P*-value[4]
DMFS score				
- Mean (SD)	5.5 (6.2)	9.5 (11.5)	13.8 (17.2)	0.001
- Median (Q1, Q3)	4 (0; 9)	6 (2; 13)	8.5 (4; 19)	
DMFT score				
- Mean (SD)	3.9 (4.0)	5.6 (5.0)	7.5 (5.8)	< 0.001
- Median (Q1, Q3)	3 (0; 6)	4 (2; 8)	6 (4; 11)	
DS				
- Mean (SD)	2.3 (3.7)	3.3 (7.8)	4.4 (8.2)	0.27
- Median (Q1, Q3)	1 (0; 3)	1 (0; 3)	1.5 (0; 5)	
DT				
- Mean (SD)	1.9 (2.7)	2.2 (3.7)	3.0 (4.0)	0.20
- Median (Q1, Q3)	1 (0; 3)	1 (0; 2)	1.5 (0, 5)	
Teeth with 2-6 BOP sites				
- Mean (SD)	7.4 (7.2)	9.9 (7.0)	11.3 (8.6)	0.01
- Median (Q1, Q3)	5 (2; 11)	8 (4.5; 15)	11.5 (3; 18)	

[1] cART was defined as any regimen containing at least three drugs from at least two drug classes.

[2] DMFS/T: decayed-missing-filled-surface/teeth score; DS: number of decayed surfaces; DT: number of teeth with caries; BOP: bleeding on probing

[3] Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS); Note: 4 participants were not exposed to cART

[4] Kruskal-Wallis Test

Table 5.

Zero-Inflated Negative Binomial (ZINB) multivariable model exploring the association between (a) age at first protease inhibitor (PI) and decayed-missing-filled-teeth (DMFT) score (n=204), and (b) age at first combination antiretroviral therapy (cART)[1] and number of teeth with bleeding on probing (BOP), 2-6 sites (n=200); both models controlling for age at oral health study entry, HIV viral load and CD4 cell count nadir, among perinatally HIV-infected youth participating in the Oral Health study in the AMP/PHACS[2]

(a) DMFT		**Adj. Ratio Estimate**	**95%CI**	***P*-value**
Age (years) at First PI	< 2 vs 6+	0.58	0.40 – 0.85	0.006
	2-<6 vs 6+	0.69	0.50 – 0.95	0.03
Age (years) at time of oral exam	14-<17 vs < 14	0.98	0.66 – 1.47	0.94
	17-<19 vs < 14	1.14	0.73 – 1.78	0.56
	19+ vs < 14	1.21	0.76 – 1.94	0.43
% RNA > 400 copies/mL[3]		1.004[4]	1.000 – 1.008	0.06
CD4 nadir < 200 cells/mm		1.10	0.86 – 1.41	0.45
(b) Teeth with 2-6 BOP sites		**Adj. Ratio Estimate**	**95%CI**	***P*-value**
Age (years) at First cART	< 2 vs 6+	0.51	0.35 - 0.75	<0.001
	2-<6 vs 6+	0.79	0.58 – 1.09	0.15
Age (years) at time of oral exam	14-<17 vs < 14	0.87	0.61 – 1.24	0.44
	17-<19 vs < 14	0.67	0.44 – 1.01	0.06
	19+ vs < 14	0.66	0.42 – 1.04	0.07
% RNA > 400 copies/mL[3]		1.00[4]	1.00 – 1.01	0.79
CD4 nadir < 200 cells/mm		1.01	0.78 – 1.29	0.97

[1] cART was defined as any regimen containing at least three drugs from at least two drug classes.

[2] Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS)

[3] > 400 copies/mL (% among lifetime number of VL assays)

[4] Per one percent increase in HIV RNA unsuppressed viral load