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Delayed tooth emergence in children infected with HIV

Walter J. Psoter, DDS, PhD¹ [Director of Dental Research],

Department of Dental Medicine, NYU-Lutheran Medical Center, 150 55th Street, Brooklyn, NY 11220, United States of America, wp9@nyu.edu

Evelyn M. Nelson, DDS, MPH [Clinical Assistant Professor],

Cariology and Comprehensive Care, New York University College of Dentistry, 433 1st Ave, NY, NY 10010, USA, en23@nyu.edu

Kevin J. Psoter, PhD [Research Associate],

Department of Pediatrics, The Johns Hopkins University School of Medicine, 5200 Eastern Ave, Mason F. Lord Bldg, Baltimore, MD 21224, USA, kpsoter1@jhu.edu

Bianca A. Dearing, DDS, MPhil [Assistant Research Professor],

Epidemiology and Health Promotion, New York University College of Dentistry, 433 1st Ave, NY, NY 10010, USA, bad272@nyu.edu

Ralph V. Katz, DMD, MPH, PhD [Professor], and

Department of Epidemiology & Health Promotion, New York University College of Dentistry, 433 1st Ave, NY, NY 10010 USA, rvk1@nyu.edu

Frank Catalanotto, DMD [Professor]

Department of Community Dentistry and Behavioral Science, University of Florida College of Dentistry, 1600 SW Archer Rd, Gainesville, FL 32603, USA, fcatalanotto@dental.ufl.edu

Abstract

Objective—There is limited evidence that early deficits in growth might be reflected in tooth emergence in children infected with human immunodeficiency virus (HIV). The purpose of this study was to prospectively evaluate tooth emergence timing between HIV positive and HIV negative children; exposed and unexposed groups, respectively.

Methods—A longitudinal study of HIV positive children and household HIV negative peers, aged 2–15 years was conducted between 1993–1996. Tooth emergence status was determined for teeth comprising the maxillary and the mandibular permanent first molars, central and lateral incisors. A multivariable discrete time proportional hazards model was fitted to the data. Median

¹Corresponding author: Walter J. Psoter, DDS, PhD, Director of Dental Research, NYU-Lutheran Medical Center, 150 55th Street, Brooklyn, NY 11220, United States of America, Telephone: (413) 386-5041, Fax: 718-630-8714, wp9@nyu.edu.

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The study these findings are based on was made possible only because of the children. The nature of the disease, the time (1993–97), known clinical science, and often their social conditions did not make life, let alone study participation easy. We should honor their contribution to society with their participation.

age of emergence for each of the six tooth pairs was calculated using the parameter estimates from the regression model.

Results—A total of 116 participants (62 HIV positive, 54 HIV negative) completed six examinations over the 36-month study period. Statistical differences in tooth emergence timing was observed for five of the six tooth pairs with HIV positive children being less likely to have a corresponding tooth emerged than the HIV negative children. Age differences for each tooth pair ranged from 0.7 to 1.5 years with a median emergence age difference of 1.03 years.

Conclusion—Delayed tooth emergence of the permanent dentition was observed in children with HIV.

Keywords

tooth eruption; tooth emergence; AIDS; HIV; developmental delay; minority; permanent teeth; prospective cohort; proportional hazards; cloglog

INTRODUCTION

Each year approximately 200,000 children are newly infected with human immunodeficiency virus (HIV) worldwide¹ with 187 new cases of <13 year-olds reported by CDC for 2013². The development of and access to therapeutic treatments, in particular antiretroviral therapy, has decreased HIV-associated infant mortality and provided greater potential for extended life. However, postnatal growth retardation, including diminished weight, stature and head circumference, has been reported in infants with HIV.^{3–5} Alterations in growth and development of these children may require adjustments in their health management.

The literature supporting early deficits in growth may be reflected in the development and emergence of teeth in children with HIV. Several cross-sectional studies have reported that the pattern of permanent tooth emergence in HIV positive children appeared delayed when compared to HIV-negative subjects^{6–10}. Importantly, factors thought to be associated with tooth emergence, such as prematurity, failure to thrive, and mode of HIV transmission, were not found to account for the observed emergence delay⁹; disease progression in children with HIV was associated with delayed dental development^{10,11}. While findings are consistent across studies, these studies were limited by their cross-sectional nature, small sample sizes, and limited adjustment for potential confounders other than age, (e.g. sex).

A contrasting finding was that of Fernandes and colleagues¹² who reported no difference in alveolar emergence of the first and second permanent molar or tooth calcification between children with HIV and the comparison group using panoramic radiographic evaluation. However, this report should be considered in the context of pre-emergent tooth mineralization biology rather than clinical tooth tissue-emergence.

This paper reports the findings for tooth emergence timing over a three-year period between children with HIV and healthy household peers for six selected permanent tooth pairs in a study that was funded by National Institutes of Health/National Institute of Dental and

Craniofacial Research NIH-NIDCR within the Northeastern Minority Oral Health Center, an NIDCR Regional Minority Oral Health Center.

METHODS

Study Population

Children vertically infected with HIV, aged 2 to 15 years and who were under pediatric medical care at the Children's Hospital AIDS Program (CHAP) in Newark, New Jersey, now referred to as the Francois-Xavier Bagnoud Center at The University of Medicine and Dentistry of New Jersey, were eligible to participate in a three-year prospective oral health study. HIV negative household peers of the enrolled HIV infected children if any, were invited to serve as comparison participants. Sixty-seven HIV- household peers agreed to participate.

Identification and enrollment of study participants took place over a one-year period from June 1993 through May 1994; all scheduled study examinations were completed by May 1997. This study was designed to utilize data from all available HIV infected children under treatment at the CHAP clinic, and, as such, this sample represents a near complete population of HIV positive cases at this one treatment center at study initiation. Additionally, this study was planned to be the first longitudinal study to compare oral health status and outcomes in children with HIV to a corresponding household peer unexposed group of HIV negative children. The Institutional Review Boards of all participating institutions approved this study and informed consent was obtained for all participating subjects.

Positive HIV status was confirmed at the CHAP Clinic by the participant's attending physicians. Unexposed participants were selected using the following criteria: 1) residing in the same household as the HIV-infected case (i.e. they were household peers) and 2) HIV negative as determined by the CHAP medical team.

Outcome

Tooth emergence status was determined for each tooth in the six contra-lateral permanent tooth pairings comprising the maxillary and the mandibular permanent first molars, central incisors and lateral incisors. These twelve teeth were selected because they represent the first permanent teeth to normally emerge and therefore maximize the ability to evaluate tooth emergence in young children. Tooth emergence was defined as any part of the tooth penetrating the oral mucosa at the time of examination for either tooth of a contra-lateral tooth pair. Three calibrated dental examiners performed the clinical assessment of DMFS and dmfs using the Radike criteria from which emergence status was determined.¹³ That is, the diagnostic criteria for DMFS/dmfs were those of Radike, which scores the "M" in DMFS, as "missing", when it is determined to be missing due to dental caries or periodontal disease. Thus, if not present in the mouth, and not scored as missing due to caries, then the tooth is considered unerupted. An overall 90% agreement between clinical examiners performing these assessments was achieved prior to the initiation of the study.

Follow-up examinations were planned for 6-month intervals from the initial baseline examination over the first two years of the study (five consecutive exams) while the sixth

and final examination was performed at the end of the 36-month study period. Thus, the exact date of tooth emergence was unknown for each child, rather tooth emergence was only observed to have occurred within the time interval between clinical examinations.

Statistical Analysis

Student *t* test with unequal variances and Fisher's exact tests were used to compare demographic characteristics of HIV infected and healthy household peers for continuous and categorical variables, respectively. Only those children who completed all six clinical examinations were included in the final analysis (n=116).

A population-averaged model was fitted to the longitudinal data. Multivariable analyses modeled emergence status (yes/no) for each of the six tooth pairs using a generalized linear model with a complementary log-log link function. The dependent variable, tooth emergence status, was a repeated measure at all time points corresponding to the clinical examination schedule. To account for this within-subject correlation, generalized estimating equations (GEE) were used to estimate robust standard errors while assuming an unstructured working correlation between examinations¹⁴. The complementary log-log link was utilized and, in this case, is equivalent to modeling a discrete time proportional hazards model with interval censored outcomes. Briefly this model can be written as $\log(-\log[P_{it}]) = \alpha_t + \mathbf{X}_{it}^T \beta$, where α_t is a set of constants for each time period, $\mathbf{X}_{it}^T \beta$ is the design matrix for the *i*th individual at time *t*, (*t*=0,...,5) and P_{it} is probability of tooth emergence occurring within a given time interval. The predictor effects are equivalent to a proportional hazards model and, as such, parameter estimates are interpretable as hazard ratios (HR)^{15,16}. All analyses were adjusted for age at baseline and the reference group was taken as the household HIV negative peer group. Results of regression models are presented as HRs and corresponding 95% confidence intervals (CI). A *P* value <0.05 was considered statistically significant.

For an emerged tooth, age at emergence was defined as the age at examination minus one-half of the corresponding examination interval¹⁷. Lastly, a probability equation:

$Pr = 1 / 1 + \exp[-(\widehat{\beta}_0 + \widehat{\beta}_1 * X_1 + \widehat{\beta}_2 * X_2)]$ ¹⁸ was used to estimate the median age of emergence for each of the six tooth pairs using the parameter estimates from the regression analysis and setting *p*=0.5 (where: $\widehat{\beta}_0$ = intercept; $\widehat{\beta}_1$ = the parameter estimate for HIV status, X_1 = HIV status (i.e., 1 = HIV+, 0 = HIV-); $\widehat{\beta}_2$ = the parameter estimate for age; and X_2 = age at baseline. All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

Demographics

Descriptive statistics of the study population are presented in Table 1 and includes demographic characteristics of subjects enrolled in the study and those that completed the 36-month follow-up. Of the initial 171 subjects (104 HIV-positive cases and 67 HIV-negative household peers) who were enrolled in this study, 116 subjects (60% of the original HIV-positive and 81% of the original HIV-negative household peers) completed the initial

baseline examination and all subsequent examinations. The majority of children who completed the study were male (52%) with the racial/ethnic distribution being 84% African-American, non-Hispanic, 15% Hispanic, and 1% White, non-Hispanic.

Tooth Emergence

Results of multivariable regression analysis evaluating the association between HIV status and tooth emergence for each of the six permanent tooth pairs are presented in Table 2. Sex and CD₄ counts were not statistically significant and dropped from the model. A statistically significant difference in timing of emergence was observed for five of the six tooth pairs, with HIV-positive children being less likely to have a corresponding tooth emerged than the HIV-negative children. While the maxillary lateral incisor was the only tooth pair in which HIV status was not associated with delayed emergence at a 95% CI (HR=0.45; 95% CI: 0.20, 1.04), the direction of the finding was in agreement with the other five tooth pairs although the upper border of the 95% CI just exceeded 1.0.

The estimated median age of emergence for each of the six tooth pairs are presented in Table 3. HIV-positive cases were older than their HIV-negative household peers at the time of emergence for each tooth from the six tooth pairs. Age differences for tooth pairs ranged from 0.7 to 1.5 years with an overall median emergence age difference of 1.03 years for the six tooth pairs with Maxillary lateral incisor showing the smallest observed age difference at 0.7 years.

DISCUSSION

In this longitudinal prospective cohort study, the major finding was a delayed tooth emergence of the permanent dentition for children with HIV infection compared to their household HIV negative peers. The delayed emergence finding in the HIV children in this study is further confirmed as ‘delayed’ when compared to reported ages for tooth emergence^{19–22}. Moreover, these findings are in accordance with previous cross-sectional reports^{6–10,23}. Strengths of this study included a comparison group comprising healthy household peers of the HIV-infected children to minimize any potential household and neighborhood unmeasured/unmeasurable confounding, and the longitudinal design with repeated measurements over a three-year period. Given that this was a longitudinal prospective cohort study, it provided the inherent strengths of this type of study design, especially as regards outcome measurement and confounder ascertainment. Additionally, our analytic approach, utilizing GEE, accounted for the within subject correlation of repeated observations while adjusting for individual-level covariates with inference for population average effects.

In a previous analysis of a subgroup of our study population comprised of 12 HIV-infected cases and 12 household uninfected peers, Tofsky et al.²⁴ reported 52% of HIV-infected cases presented with an erupted permanent first molar compared to 79% of the HIV- peers and that 57% of the HIV-infected cases had exfoliated specified primary teeth compared to 71% for their peers. In addition, HIV-infected children had a greater dmfs index compared to their household peers; however, the DMFS index was lower in the HIV infected children. These results were most prominent in children aged 6–11 years old which corresponds to ages at

which tooth development is characterized by the *mixed dentition* stage, i.e., the exfoliation of primary teeth and emergence of permanent teeth. These age-specific DMFS data, as reported by Tofsky et al (23) showed that the HIV infected children had lower permanent tooth DMFS scores than their household peers; however, the number of emerged teeth suggests that the observed delayed emergence of permanent teeth in HIV infected children may confound age-specific DMFS scores and thus mask the true caries susceptibility of HIV infected children. That is, in HIV infected children the differences in dental caries rates may be explained by having fewer susceptible surfaces for permanent tooth caries to develop and a correspondingly shorter “window of exposure” for time dependent caries risk factors. This observation is similar to the delayed emergence of both primary and permanent teeth observed in children with early childhood malnourishment and the apparent observed caries lag.^{25–31}

There are several limitations of this study. First, the large time period (six and twelve month intervals) between examinations did not allow for estimates of the exact age for tooth emergence. Second, the median age of emergence estimates may be imprecise due to the lack of large numbers of age specific observations as well as children presenting with previously emerged teeth at baseline and those not having all six tooth pairs emerged at study completion. However, these estimates would be stable between cohorts¹⁷ and given that the HIV negative subjects’ emergence ages are consistent with other reports it is likely that our findings are a close approximation to the true median emergence ages. Third, data on concurrent health conditions that could potentially impact delayed tooth emergence, including gestational age and nutritional status, was unavailable and may represent uncontrolled confounding, though there was no statistical difference of BMI between HIV positive and negative children. In this regard, the introduction of AZT to some of the children in the period of the study may be a particular concern regarding confounding. The literature on systemic conditions and tooth emergence is sparse and may only include animal models for evidence; there are few systemic conditions known to effect tooth emergence and those unlikely to found in the study sample, e.g., frank endocrine disorders, radiation therapy.³²

Finally, the limited ethnic distribution of the sample (i.e., within eighteen months of the study initiation there were no non-Hispanic White unexposed subjects remaining in the study, and eighty percent of the subjects remaining were of African American descent) precluded estimation of race/ethnic specific tooth emergence estimates.

The effect of antiretroviral therapy on tooth emergence is unknown. The data described here is some 20 years old, however, the study findings remain applicable to those children worldwide either not receiving antiretrovirals or administered an antiretroviral regimen having no tooth emergence effect. A future study of any effect by antiretroviral therapies will serve as a baseline for comparison with the findings presented here.

In conclusion, in our study the primarily minority race/ethnicity HIV-infected children, as compared to HIV-negative household peers, were found to have delayed emergence of the permanent dentition. Median tooth emergence timing in HIV infected children was delayed, on average, by 1.03-years for the six selected permanent tooth pairs compared to their HIV

negative household peers. These findings are in accordance with previously published reports of permanent tooth delay in other studies and support findings of lowered age specific caries risk among HIV infected children, likely due to physiologic delays in growth and development (and tooth emergence) in HIV infected children.

Clinicians should therefore expect a lower age-specific caries rate relative to the non-HIV infected population due to the teeth exposure time to caries risks being less for any given age because of the delayed tooth emergence time and adjust their clinical management, risk assessment, and parent/guardian health communications of young children accordingly. Elucidating the viral-host pathophysiologic mechanism(s) for delayed tooth emergence and other observed growth retardations should be a research priority.

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In this case the subject matter -tooth emergence timing- was not an original study aim. The data was subsequently utilized for a thesis by a co-author and due to various factors then took time to be prepared for publication.

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Statement of clinical relevance

This cohort study presents evidence of delayed tooth emergence in children infected with HIV. Clinical management, risk assessment, and parent/guardian health communications of young children should account for physical developmental delays including those of the oral cavity.

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Table 1

Demographic characteristics of HIV-positive and HIV-negative controls at baseline and for those children completing the full 36-month follow-up

	Baseline		36-months	
	HIV-infected (n=104)	Peer controls (n=67)	HIV-infected (n=62)	Peer controls (n=54)
Age *, years (SD)	6.6 (3.7) **	7.9 (3.8)	5.5(3.2) **	7.8(3.8)
Male (%)	51 (49)	40 (60)	28 (45)	32 (59)
Race (%)				
African American	82 (79)	54 (81)	53 (85)	44 (81)
Non-Hispanic White	8 (8)	1 (1)	1 (2)	0 (0)
Hispanic	14 (13)	12 (18)	8 (13)	10 (19)

Definition of abbreviations SD, standard deviation

* Age reflects age at study entry

** $P < 0.05$

Table 2

Adjusted hazard ratios and corresponding 95% confidence intervals for the emergence of six selected permanent tooth pairs for HIV-positive children compared to HIV-negative household peer controls, adjusted for age at baseline

<i>Tooth</i>	Hazard Ratio *	95% CI
Maxillary 1 st molar	0.21	(0.11, 0.41) **
Maxillary lateral incisor	0.45	(0.20, 1.04)
Maxillary central incisor	0.25	(0.12, 0.53) **
Mandibular 1 st molar	0.26	(0.13, 0.52) **
Mandibular lateral incisor	0.25	(0.13, 0.47) **
Mandibular central incisor	0.34	(0.18, 0.65) **

* For all analyses, estimated hazard ratios are associated with HIV-infected children, with the HIV-negative household peers serving as the reference group.

**
 $P < 0.05$

Table 3

Median age and difference of tooth emergence for the six permanent tooth pairs for HIV-positive children and HIV-negative household peer controls

Tooth	HIV- infected Age (years)*	Peer controls Age (years)*	Difference Age (years)
Maxillary 1 st molar	6.8	5.7	1.1
Maxillary lateral incisor	8.7	8.0	0.7
Maxillary central incisor	7.6	6.5	1.1
Mandibular 1 st molar	6.6	5.7	0.9
Mandibular lateral incisor	8.0	6.5	1.5
Mandibular central incisor	6.7	5.8	0.9

* Median age was calculated using the following probability equation:

$Pr = 1 / 1 + \exp[-(\widehat{\beta}_0 + \widehat{\beta}_1 * X_1 + \widehat{\beta}_2 * X_2)]$ where, $\widehat{\beta}_0$ = the model intercept, $\widehat{\beta}_1$ = the parameter estimate for HIV status, X_1 = HIV status (i.e., 1 = HIV-infected, 0 = peer control), $\widehat{\beta}_2$ = the parameter estimate for age at baseline and X_2 = age at baseline and probability of emergence