Delayed tooth emergence in children infected with human immunodeficiency virus

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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 children positive and negative for HIV in the exposed and unexposed groups, respectively.

Study Design. A longitudinal study of children positive for HIV and HIV-negative household peers, aged 2 to 15 years was conducted between 1993 and 1996. Emergence status was determined for the maxillary and the mandibular permanent first molars and the central and lateral incisors. A multivariable, discrete time, proportional hazards model was fitted to the data. Median age of emergence for each of the six pairs of teeth 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 were observed for five of the six tooth pairs, with children positive for HIV being less likely to have emergence of the corresponding tooth compared with the children negative for HIV. Age differences for each tooth pair ranged from 0.7 to 1.5 years, with a median emergence age difference of 1.03 years.

Conclusions. Delayed tooth emergence of the permanent dentition was observed in children with HIV. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:442-447)

Each year, approximately 200,000 children are newly infected with human immunodeficiency virus (HIV) worldwide,[1] with 187 new cases in children under 13 years reported by the Centers for Disease Control and Prevention (CDC) for 2013.[2] The development of and access to therapeutic treatments, in particular antiretroviral therapy, have decreased HIV-associated infant mortality and have 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.

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There is evidence in the literature with regard to early deficits in growth, which 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 children positive for HIV appeared delayed compared with that in patients negative for HIV.[6-10] It was significant that 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 delay[9]; disease progression in children with HIV was associated with delayed dental development.[10,11] The findings are consistent across studies, but these studies were limited by their cross-sectional nature, small sample sizes, and limited adjustment for potential confounders other than age (e.g., gender).

A contrasting finding was that from the study by Fernandes et al.,[12] who used panoramic radiographic evaluation and reported no difference in alveolar emergence of the first and second permanent molar or

Statement of Clinical Relevance

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

tooth calcification between children with HIV and the comparison group. 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 regarding tooth emergence timing over a 3-year period between children with HIV and healthy household peers for six selected permanent tooth pairs; the study 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.

MATERIALS AND METHODS

Study population

Children, aged 2 to 15 years, who were vertically infected with HIV 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 3-year prospective oral health study. HIV-negative household peers of the enrolled children positive for HIV, if any, were invited to serve as comparison participants. Sixty-seven HIV-negative household peers agreed to participate.

Identification and enrollment of study participants took place over a 1-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-positive 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 patients.

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

Outcome

Tooth emergence status was determined for each tooth in the six contralateral permanent tooth pairings comprising the maxillary and the mandibular permanent first molars, central incisors, and lateral incisors. These 12 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 contralateral tooth pair. Three calibrated dental examiners performed the clinical assessment of DMFS (decayed, missing, filled surfaces) and dmfs (deciduous teeth) by using the Radike criteria based on 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 as a result of dental caries or periodontal disease. Thus, if not present in the mouth, and not scored as missing because of caries, then the tooth is considered unerupted. An overall 90% agreement between clinical examiners performing these assessments was achieved before initiation of the study.

Follow-up examinations were planned for 6-month intervals from the initial baseline examination over the first 2 years of the study (five consecutive examinations), and 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 the demographic characteristics of HIV-positive 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 by 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 were used to estimate robust standard errors while assuming an unstructured working correlation between examinations.[14] 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