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# Clinical implications of the oral manifestations of HIV infection in children

Daniel H. Fine, DMD[a,*], Nanci Tofsky, DDS[b], Evelyn M. Nelson, DMD, MPH[c], Diane Schoen, BSDH, MS[d], Andre Barasch, DMD, MDSc[e]

[a]*Dental Research Center, University of Medicine and Dentistry of New Jersey, New Jersey Dental School, Health Sciences Building, Room C-636, 185 South Orange Avenue, Newark, NJ 07103, USA*
[b]*Department of Pediatric Dentistry, University of Medicine and Dentistry of New Jersey, New Jersey Dental School, Health Sciences Building, Room C-636, 185 South Orange Avenue, Newark, NJ 07103, USA*
[c]*Department of Epidemiology and Health Promotion, New York University College of Dentistry, 345 East 24th Street, New York, NY 10010, USA*
[d]*Department of General Dentistry and Community Health, University of Medicine and Dentistry of New Jersey, New Jersey Dental School, Health Sciences Building, Room C-636, 185 South Orange Avenue, Newark, NJ 07103, USA*
[e]*Department of Diagnostic Sciences, University of Detroit Mercy School of Dentistry, Detroit, MI, USA*

Caries and periodontal disease are among the most common infections known to humans [1,2]. Both diseases are initiated by oral bacteria and are modulated by the host response to these provoking bacteria. Disease occurs as a result of an imbalance between the provoking bacteria and the host response to those bacteria [3]. It is logical to expect, therefore, that alteration of either the provoking agents or the host response to those agents should result in a change in the clinical presentation of disease. In the early

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* Corresponding author.
*E-mail address:* finedh@umdnj.edu (D.H. Fine).


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1980s, when AIDS was first described, it seemed reasonable to conclude that patients with AIDS—because of their reduced capacity to fight infections—should be more susceptible to oral infections such as periodontal disease [4,5]. This proposed susceptibility appeared to be real when it was found that patients with AIDS demonstrated more periodontal disease than did a historical control population derived from the National Health and Nutrition Examination Survey (NHANES) epidemiological database [6]. Not only was a higher prevalence of periodontal disease reported, but the disease appeared to be more destructive [4,7]. Other studies [8,9], however, did not support this conclusion, and challenged the contention that AIDS patients were at increased risk for periodontal disease. In either case, the AIDS patients who demonstrated periodontal disease were adults and therefore possessed a fully developed immune system before they were infected by the HIV virus. A question that remained unanswered at that time related to children who were born with HIV. How would these unfortunate individuals cope with the effects of accumulating dental plaque over time?

Our group postulated that children born with HIV when faced with new antigens, in the form of oral bacteria, might not be capable of mounting a sustained response to these new antigens. In this scenario, periodontal disease and other oral infections would advance, and thus children who were HIV positive would be more susceptible to oral diseases than age-matched, gender-matched, and race-matched controls over time. It was also hypothesized that these oral manifestations may precede AIDS and thus provide an early indication of AIDS. At the time this study began, 1992 to 1994, no case-controlled studies had been performed with respect to pediatric AIDS. Dr. James Oleske, at the University of Medicine and Dentistry of New Jersey (UMDNJ) in Newark, first identified pediatric AIDS as a clinical entity. Over time, Dr. Oleske's program developed into The Children's Hospital AIDS Program (CHAP) in Newark (now known as the Francois Xavier Bagnoud Center at UMDNJ), and this clinic became a center for the study of Pediatric AIDS. In collaboration with Dr. Oleske, our group decided to examine the oral manifestations of Pediatric AIDS.

In 1992, a population of HIV-infected children, under the care of Dr. Oleske's group, was asked to enroll in a multiyear treatment and evaluation study of the oral manifestations of pediatric AIDS. In an effort to have controls for the HIV-infected children, we enrolled their noninfected household peers. Study enrollment began in June 1993 and ended May 1994. The information contained in this report represents a summary of the data obtained in the first longitudinal controlled study of Pediatric AIDS and oral disease.

## Methods

### *Demographics*

The study was designed to obtain data from 104 HIV-infected children and 67 noninfected household peers [10–12]. No effort was made to balance

the groups for age, gender, or race, because in some instances there were multiple household peers, who were neither gender matched nor age matched. Participants were from 2 to 15 years of age at baseline with an overall mean age of $7.7 \pm 3.8$. Control participants (household peers) were selected as follows: The individuals were both (1) HIV negative and (2) residing in the same household as the HIV-infected peer. Sixty-six percent of the controls consisted of natural siblings, some of whom were half-brothers or half-sisters (28%). Six-percent were natural-born children of foster parents unrelated to the HIV-infected child (ie, these parents had a child of their own who was HIV negative). These children were carefully monitored and judged to be HIV negative by report from the physician who was attending the HIV-infected child and also in charge of the family's HIV status report. The presence of the HIV virus—that is, the HIV status of the subjects—was determined by enzyme-linked immunosorbent assay (ELISA) for all HIV-infected children. Using this method, 94% of the control group as HIV negative. The ethnicity of the children was categorized as African American, white, or Hispanic as a result of a questionnaire completed by parent, grandparent, or guardian. All participants—HIV infected and controls—were referred to the Pediatric Dental Clinic at UMDNJ/New Jersey Dental School (NJDS) for all their necessary dental care. Institutional Review Board approval for this research project was obtained prior to the start of the screening process. The study consisted of documenting dental caries, oral lesions, and periodontal disease in the HIV-infected population as compared with their household peers.

All examinations were performed by calibrated investigators and were done at baseline, 6 months, 12 months, 18 months, 24 months, and 36 months following baseline. In addition to dental examinations, medical histories were reviewed for each child at each examination. Three examiners were calibrated at a level of 90% agreement between examiners by comparing their examination results with those of an experienced and recognized examiner at 6-month intervals; that is, as compared with an experienced Radike-calibrated examiner, the criteria used for the diagnosis of dental caries [13]. In addition to the clinical examinations of dental caries, periodontal disease, and soft tissue examinations, bacterial and fungal cultures were taken and thus the full examination took approximately 45 minutes. Parents or guardians received $25 as compensation for time and travel expenses.

### *Dental caries analysis*

Caries were evaluated using conventional decayed, missing and filled surfaces (dmfs for primary teeth and DMFS for permanent teeth) [12,13]. Examinations were done with a mirror and explorer in a well-lit dental chair. For dental caries and tooth eruption studies, analysis was divided into three age groups (2–5-year-olds, 6–11-year-olds, and 12–15-year-olds). Children who completed the baseline examination were enrolled in the study. To

keep bias to a minimum, participants' medical status was coded in an attempt to maintain investigator blindness. All examinations took place in a dental facility at UMDNJ/NJDS that was dedicated to clinical research.

*Oral mucosal lesion analysis*

For oral lesion analysis, each lesion seen on a given individual was counted only once. Baseline evaluation included a complete blood count with differential values, CD4 (T-helper cell lymphocytes), plasma immunoglobulin levels, and a complete soft tissue examination [10]. All laboratory and medical data entered into the patient chart was extracted from the patient record. Associations of oral lesion status and immune status were correlated to these baseline values. As in the case of caries evaluations, data was divided into three groups based on the patient age ranges described in the caries analyses. The oral soft tissue examinations were done by two experienced oral medicine academicians and were performed with a tongue blade and dental mirror [10]. The HIV status of the patient undergoing the examination was not revealed to the examiners, but in specific instances it was clear from the physical condition of the patient that they were seropositive (Table 5). Lesions were documented based on their clinical appearance and recorded with detailed descriptions on standard forms. All soft tissue examinations included thorough evaluation of the lips, buccal mucosa, tongue, soft and hard palate, floor of the mouth, salivary glands, attached and unattached gingivae, and the oropharynx. Fungal and microbial samples also were taken. After each 6-month examination, patients were referred to the dental clinic or to CHAP for dental or medical treatment [10].

*Periodontal disease analysis*

The periodontal examination consisted of several indices including (1) the Modified Patient Hygiene Performance (PHP) Index (PHP-M) [14], (2) the Gingival Index (GI) [15], and (3) the Papilla Bleeding Index (PBI) [16]. In addition, several other parameters were included in the examination as follows: (1) linear gingival erythema (LGE; in mm), (2) pocket depth and recession in mm at four sites per tooth (MB, B, DB, and L), and (3) tooth mobility. LGE (referred to in the past as HIV gingivitis) was defined as a fiery red linear band from 1 to 3 mm in width on or slightly below the gingival margin [11]. Characteristically, the levels of erythema are disproportionate to the amount of plaque seen on the tooth undergoing evaluation. Periodontal interventions were not performed at any time during the study period.

*Statistical analysis*

Statistical analysis varied according to the indices used and were conducted as follows. Chi-square analysis was used to determine differences

in ages between groups and compliance with respect to study guidelines and examinations. Significant differences between HIV-positive and HIV-negative participants within each group was performed by a two-tailed Student *t* test, whereas differences within an age group and between the age groups were performed using analysis of variance (ANOVA). For evaluation of differences in oral mucosal lesions, statistical analysis consisted of comparisons across groups using either chi-square analysis of the appropriate contingency table, Fisher exact test, or Student *t* test of independent group means. Analyses were performed using SPSS (SPSS Inc., Chicago, IL). For periodontal disease analysis, comparisons were performed by ANOVA and chi-square analysis. A level of significance of $P = 0.05$ was used in all statistical tests [10–12].

## Results

### *Demographics*

Of the 202 HIV-infected and control participants who were initially identified as potential participants for enrollment in the study, 171 participants (104 HIV-positive and 67 HIV-negative participants), or 85%, were enrolled in the study and participated in the baseline examination (Table 1) [10–12]. Baseline participants were divided into the three racial or ethnic groups as follows: 83% were African American, 2.5% were white, and 15% were Hispanic. Fifty-one percent of the HIV-positive patients were female, whereas 40% of the control population was female. The mean age of the HIV-positive group was $6.6 \pm 3.7$ years, whereas that for the control group was $7.9 \pm 3.7$ years. At the 2-year examination, 121 patients participated, representing 71% of the original population. Of the 121 patients remaining, 68

Table 1
Demographic distribution of study subjects

| | Baseline | | 24 months | | 36 months | |
|---|---|---|---|---|---|---|
| Descriptor | HIV+ | Control | HIV+ | Control | HIV+ | Control |
| n | 104 | 67 | 68 | 53 | 62 | 54 |
| Age[a] | $6.6 \pm 3.7$ | $7.9 \pm 3.8$ | $6.0 \pm 3.6$ | $7.7 \pm 3.8$ | $5.5 \pm 3.2$ | $7.8 \pm 3.8$ |
| Race | | | | | | |
| African American | 82 | 54 | 56 | 44 | 53 | 44 |
| Hispanic | 14 | 12 | 9 | 9 | 8 | 10 |
| White | 8 | 1 | 3 | 0 | 1 | 0 |
| Gender | | | | | | |
| Male | 51 | 40 | 31 | 32 | 28 | 32 |
| Female | 53 | 27 | 37 | 21 | 34 | 22 |

[a] Age differences were significant using analysis of variance at the $P < 0.05$.

*Adapted from* Schoen DH, Murray PA, Nelson E, Catalannotto FA, Katz RV, Fine DH. A comparison of periodontal disease in HIV-infected children and household peers; a two-year report. Pediatr Dent 2000;22:365–9; with permission.

were HIV positive and 53 were HIV negative; thus, there was a loss of 35% of the HIV-positive and 2l% of the HIV-negative participants. An additional 6 HIV-positive patients were lost after the third year. Of the 42 HIV-positive patients who were lost to the study at the 36-month examination, 27 had died and 15 had moved or were lost to follow-up. Of the 13 household peers who were no longer available for examination, 3 had left the study after the death of their household peer, and 10 had moved away or were otherwise unavailable. When the calculations were re-evaluated, taking into consideration the death of participants, the dropout rate was similar for HIV-positive and HIV-negative participants (Table 1) [10–12].

*Caries prevalence and incidence*

Table 2 shows the incidence of caries when the HIV-positive and HIV-negative groups were compared. Examination of the cumulative dmfs shows that caries prevalence was 18% higher in the HIV-positive 2- to 5-year-olds at the 2-year examination, whereas the caries incidence was approximately fourfold lower in the 6- to 11-year-old HIV-infected children as compared with the control group (Table 2); 6- to 11-year-old increment). When the DMFS was compared, however, caries incidence was higher across all age groups in the HIV-negative group (data not shown). Caries incidence was 17% higher in the control group in the 6- to 11-year-olds, and this incidence increased by eightfold in the 12- to 15-year-olds in the HIV-negative group as compared with the HIV-positive group (data not shown). Similar patterns of caries were seen when decayed, missing and filled teeth (dmft for primary teeth and DMFT for permanent teeth) evaluations were compared in the two groups (data not shown). Results of these evaluations suggested that although the caries prevalence and, in some cases, incidence was greater in primary teeth of HIV-positive participants, these participants appeared to demonstrate less caries in their permanent teeth. As seen in Table 3,

Table 2
Caries incidence (dmfs) by age group and HIV status

| | 2- to 5-year-olds | | 6- to 11-year-olds | | 12- to 15-year-olds | |
|---|---|---|---|---|---|---|
| | Cases (n = 36) | Controls (n = 15) | Cases (n = 24) | Controls (n = 28) | Cases (n = 8) | Controls (n = 10) |
| Baseline[a] | 8.2 | 3.5 | 13.9 | 5.0[b] | 0.0 | 0.3 |
| Year 2 | 11 | 6.7 | 10.0 | 4.0[b] | 0.0 | 0.0 |
| 2-year increment | 2.8 | 3.3 | −3.8 | −1.0 | 0.0 | −0.3 |

Values for dmfs represent mean ± standard deviation.

[a] Significant difference between HIV status within specified time period.

[b] Significant difference within particular age groups for specified time periods, analysis of variance, $P < 0.05$.

*Adapted from* Tofsky N, Nelson EM, Lopez RN, Catalannotto FA, Fine DH, Katz RV. Dental caries in HIV-infected children versus household peers: two-year findings. Pediatr Dent 2000;22:207–14; with permission.

Table 3
Number of subjects with 6-year molars present and percentage of subjects with unerupted 6-year molars at baseline age of 6–7 years by HIV status

| | HIV-infected cases (n = 12) | | Control subjects (n = 12) | |
|---|---|---|---|---|
| Tooth | No of cases with tooth present | Percentage of cases with tooth absent | No. of cases with tooth present | Percentage of cases with tooth absent |
| 3 | 6 | 50% | 10 | 17% |
| Mean age ± 50[a] | 7.0 ± 0.0 | | 6.6 ± 5.2 | |
| 14 | 5 | 58% | 9 | 25% |
| Mean age ± 50 | 6.8 ± 4.5 | | 6.4 ± 5.3 | |
| 19 | 7 | 42% | 9 | 25% |
| Mean age ± 50 | 6.7 ± 4.9 | | 6.4 ± 5.3 | |
| 30 | 7 | 42% | 10 | 17% |
| Mean age ± 50 | 6.7 ± 4.9 | | 6.4 ± 5.2 | |

[a] Mean age differences were significant using analysis of variance at the $P \leq 0.05$.

*Adapted from* Tofsky N, Nelson EM, Lopez RN, Catalannotto FA, Fine DH, Katz RV. Dental caries in HIV-infected children versus household peers: two-year findings. Pediatr Dent 2000;22:207–14; with permission.

patterns of tooth eruption were delayed in the HIV-positive group, and thus anywhere from 42% to 58% of the 6- to 7-year-old participants who were observed had one of their four permanent 6-year molars (teeth numbers 3, 14, 19, and 30) missing; whereas only 17% to 25% of the control participants had one of their four permanent molars missing (Table 3). A similar observation was made when retention of primary incisors was studied, and thus a higher percentage of control participants had four primary incisors missing as compared with their HIV-positive household peers (data not shown). This data suggests that HIV-positive participants have more caries in their primary teeth but fewer caries in their permanent teeth, and that this difference is most likely due to the slower eruption pattern with respect to permanent teeth in the case of the HIV-positive participants [12].

### *Oral mucosal lesions analysis*

As shown in Tables 4 and 5, 75% of the HIV-infected patients had oral lesions, whereas only 35% of the controls had lesions. When analyses were performed lesion by lesion there was a clear distinction between HIV-infected and noninfected controls. Candidal lesions made up 38% of the HIV-positive lesions. Only 2% of the controls showed any candidal lesions ($P<0.001$). LGE was seen in 22% of the HIV-positive participants, whereas it was seen in only 3% of the controls ($P<0.02$). Median rhomboid glossitis was seen in 12% of the HIV-positive participants and in only one HIV-negative control ($P\leq0.01$). Conventional gingivitis was seen more frequently in the controls (13%), whereas only 7% of the HIV-infected participants had gingivitis (not significant). Hairy leukoplakia and necrotizing periodontitis

Table 4
Oral lesions in HIV-infected and control subjects

| Lesion | % HIV-infected | % Control | Difference |
|---|---|---|---|
| Candidiasis | 38 | 2 | $P < 0.001$ |
| Linear gingival erythema | 22 | 3 | $P < 0.02$ |
| Medical rhomboid glossitis | 12 | 1 | $P < 0.01$ |
| Gingivitis | 7 | 13 | NS |
| Necrotizing periodontitis | 3.8 | 0 | NS |
| Hairy leukoplakia | 2 | 0 | NS |
| Herpes simplex | 3 | 2 | NS |
| Other lesions | 16 | 15 | NS |
| Total lesions | 75 | 35 | $P < 0.001$ |

*Adapted from* Barasch A, Safford M, Catalannotto F, Fine D, Katz R. Oral soft tissue manifestations in HIV-positive vs. HIV-negative children from an inner city population: a two year observational study. Pediatr Dent 2000;22:215–20; with permission.

was seen infrequently, but only in the HIV-positive participants. Herpes simplex virus was seen in a low percentage of both the HIV-positive (3%) and HIV-negative (2%) participants. CD4 counts were obtained in 85 of the 104 HIV-positive participants at baseline. The range of CD4 varied among these individuals as follows: CD4 counts of 0 to 199 for 33% of the participants, CD4 counts of 200 to 499 for 18% of the patients, and CD4 counts of >500 for 49% of the patients. The mean percentage of CD4 to total lymphocytes by age group was as follows: in 2- to 5-year-olds, 29% of the lymphocytes were CD4; in 6- to 11-year-olds, 27% of the lymphocytes were CD4; and in 12- to 15-year-olds, 21% were CD4 lymphocytes [10].

The mean CD4 counts were significantly lowered in patients with candidiasis, but not in patients with LGE, medial rhomboid glossitis, or conventional gingivitis (Table 4). As expected, mean CD4 counts were significantly lowered in the 19 patients who died as opposed to the 85 patients who survived over the course of the study [10].

Table 5
Specific oral lesions in decreased as compared with surviving HIV+ subjects: relationship to CD4 and neutrophil cell counts

| Condition | Deceased (n = 19) | Surviving (n = 85) | *P* value |
|---|---|---|---|
| Mean CD4/mL (SD) | 122 (364) | 656 (496) | <0.0001 |
| Mean neutrophil (SD) | 1980 (1379) | 2164 (1421) | 0.62 |
| Candidiasis | 6 | 26 | 0.58 |
| Linear gingival erythema | 6 | 17 | 0.66 |
| Median rhomboid glossitis | 2 | 11 | 0.81 |
| Other lesions | 3 | 30 | 0.11 |
| Total subjects with lesions | 6 | 72 | 0.002 |

*Adapted from* Barasch A, Safford M, Catalannotto F, Fine D, Katz R. Oral soft tissue manifestations in HIV-positive vs. HIV-negative children from an inner city population: a two year observational study. Pediatr Dent 2000;22:215–20; with permission.

*Periodontal disease analysis*

Table 6 presents the periodontal disease data and indicates changes observed from the baseline examination to 2 years following baseline. Plaque indices as measured by the PHP-M showed a 12-fold increase for the HIV-positive participants (score of $3.49 \pm 9.73$) as compared with a score of $0.30 \pm 8.88$ for the HIV-negative participants. Although the difference was great, it was not statistically significant. In addition, Table 6 compares the GI score, the PBI score, and pocket depths in the two groups. The last column of this table shows the differences between baseline and 2-year follow-up scores, and indicates that there were no significant differences in any category when the two groups were compared. Thus, in spite of the differences in plaque scores, there were no differences observed with respect to gingivitis, bleeding, or pocket depths in the two groups. As mentioned previously, LGE was seen more frequently in the HIV-infected children. This was seen at baseline and then again at the 2-year examination. Although there was no increase in the prevalence of LGE over the 2-year period, there was an increase in the severity of the lesions as reported. Thus, 9% of the participants demonstrated LGE at seven or more sites at baseline and 15% of participants demonstrated this more severe form at the 2-year follow-up examination (data not shown) [11].

## Discussion

In early studies, patients stricken with AIDS appeared to be more susceptible to periodontal disease, a classical example of a disease whose outcome is determined by an interplay between the host and its response to the infecting parasite [17,18]. The clinical data were supported by a biological explanation that suggested that patients with AIDS demonstrated a reduction in CD4 T-lymphocytes, known as helper cells. Thus, it was speculated that this form of immunodeficiency would lead to a reduced ability of affected patients to mount a protective response to oral plaque bacteria [5,19]. Therefore, in the case of AIDS, the host fails, the bacterial parasite prevails, and periodontal disease is manifested as a destructive and more prevalent disease in this population [7,17,19]. Conclusions that supported this hypothesis were not based on case-control studies but rather on a co-mingling of scientific logic and anecdotal clinical cases [8,9]. For the most part, this hypothesis was supported by data derived from patients who reported to dental clinics because they were in need of dental treatment [5,6,20]. In the vernacular of clinical research, this is known as self-selection. To be more specific, HIV-infected and/or AIDS patients came to the dental clinic because they had periodontal disease; on the other hand, patients who were HIV positive or who had AIDS who did not have periodontal disease visited their physician and had little or no contact with their dentist. As a result, it appeared that there was a greater prevalence of periodontal disease in HIV-positive/AIDS

Table 6
Plaque, gingivitis, bleeding, and pocket depth at baseline and 2 years in HIV+ as compared with control subjects

| | Baseline | | | | Year 2 | | | | Delta | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HIV+ | SD | Control | SD | HIV+ | SD | Control | SD | HIV+ | SD | Control | SD |
| PHP-M/tot | 36.7 | 8.27 | 37.6 | 7.17 | 40.1 | 6.11 | 37.9 | 5.20 | 3.49 (n = 57) | 9.73 | 0.30 (n = 46) | 8.88 |
| GI | 0.82 | 0.52 | 0.86 | 0.39 | 1.14 | 0.25 | 1.1 | 0.26 | 0.32 (n = 47) | 0.52 | 0.26 (n = 47) | 0.38 |
| PBI | 0.46 | 0.58 | 0.35 | 0.47 | 0.34 | 0.44 | 0.39 | 0.39 | −0.13 (n = 52) | 0.64 | 0.05 (n = 44) | 0.40 |
| PD | 2.09 | 0.30 | 2.14 | 0.34 | 21 | 0.22 | 2.30 | 0.22 | 0.06 (n = 54) | 0.28 | 0.17 (n = 45) | 0.28 |

*Abbreviations:* PHP-M/tot, plaque index [14]; GI, Gingival index by Loe and Silness [15]; PBI, papillary bleeding Index of Muhlemann [16]; PD, pocket depth.

*Adapted from* Schoen DH, Murrary PA, Nelson Catalannotto FA, Katz RV, Fine DH. A Comparison of periodontal disease in HIV-infected children and household peers: a two year repart. Ped Dent 2000;22:365–9; with permission.

patients, because most, if not all, of the HIV-positive/AIDS patients seen by dentists had periodontal disease [21]. These reports were confounded by the fact that little was known about AIDS and its chronology at the time [19,22]. Some of the cases seen were dramatic and the periodontal disease observed was very destructive, at times showing bare bone with no tissue covering [4,18].

The anecdotal nature of these reports led to efforts to perform case-control studies in which cases of HIV infection, or patients with frank AIDS were balanced with age-matched, gender-matched, and race-matched control participants [8,21]. In these studies, a true relationship between HIV infection and periodontal disease was not as obvious [8,21]. One interpretation of results derived from these later studies suggested that patients with HIV had no greater susceptibility to periodontal disease than did their uninfected healthy counterparts. Before scientists were ready to rule out a relationship between HIV and periodontal disease, however, there was a series of specific issues that needed clarification [23]. One such issue related to the age at which the participant acquired the disease [19,22,24]. It was hypothesized that the younger the patient was when he or she acquired HIV, the more susceptible that individual would be to oral infection. With that in mind, our studies were designed to examine manifestations of oral diseases seen in patients born with HIV infection whose host capacity to deal with common oral infections was assumed to be altered [19,22,24]. To reduce examiner bias, we chose to observe both participants and controls at regular 6-month intervals, in a case-controlled study. In general, very few differences were noted when the two groups were compared. Our results did not demonstrate any differences in prevalence or incidence of either gingivitis, periodontal disease, or caries in the HIV-positive population as compared with their controls. The oral soft tissue data did show some difference and can be summarized succinctly as follows. Although oral soft tissue lesions were common in HIV-infected children, these findings were anticipated. Thus, the prevalence of oral lesions overall was significantly higher in the HIV-positive participants as compared with controls. Candidiasis, LGE, and medial rhomboid glossitis were the most common lesions seen, although LGE was found predominantly in the older children. Oral candidiasis was associated with lower CD4 counts, but not with higher mortality. Thus, candidiasis did not serve as a good predictor of mortality in this population.

A more in-depth look at the caries data did demonstrate an increase in caries prevalence in the primary dentition in the HIV-positive population; however, the results were not significant. No increase in incidence or prevalence was seen when the HIV-positive population was compared with its control population. It is clear that caries is a multifactorial disease and thus involves an infecting organism, dietary factors, and exposure to fluoride and host factors. In the study presented in this article, we attempted to control for some of these confounding variables by comparing HIV-positive patients to their household peers. Several assumptions were made that were

unsubstantiated. It was assumed that diets would be more similar in the same household as opposed to other households. Thus, it was speculated that use of fluoride toothpastes would be similar, oral hygiene would be similar, and so forth, in these two groups. Although these assumptions have yet to be proved, it is obvious that the children in these studies—whether HIV positive or HIV negative—had a greater caries exposure than did HIV-positive children as previously reported [27]. This finding, demonstrating that caries is no greater in HIV-infected children as compared with their household peers, all drawn from the Newark area [25], is central to the conclusions drawn from these studies and illustrates the value of the study design.

The finding of less decay in the permanent dentition in the HIV-infected population was unexpected. This finding suggested that perhaps the reduced caries in the permanent dentition seen in the HIV-positive group could be due to the fact that teeth in the HIV-positive group had less exposure to caries-provoking agents than did their matched control population. Because the caries process is known to take anywhere from 9 to 36 months, the reduced decay found in the permanent dentition of HIV-positive participants could have been due to the fact that these teeth erupted later and thus were susceptible to decay-provoking agents for a shorter period of time [26]. Evaluation of the presence and quantity of caries-producing microorganisms in the two groups failed to reveal any differences that could shed additional light on the relationship of these findings to decay (data not shown). As a result, tooth-eruption patterns were evaluated in a more exhaustive manner. In summary, this part of the study suggested that HIV-positive participants have more caries in their primary teeth but fewer caries in their permanent teeth, and that this difference in pattern is most likely due to the slower eruption pattern with respect to permanent teeth in the case of the HIV-positive participants.

There are three points that need to be highlighted with respect to our study design and the findings derived from the study as designed. First, and most important, the study demonstrated the need to include a valid control group and to follow these participants over time. This point was best demonstrated by the caries portion of the study. Studies that had reported high caries prevalence among HIV-infected children were routinely compared with national norms at one point in time. For example, Valdez et al [27] reported that HIV-infected children had a DMFT score that was 1.5-fold higher that the national norm (0.8) for 9-year-olds. In this study, Valdez et al [27] examined a mixed dentition and compared these children with the national sample. In our study, we also found that the HIV-infected children in the mixed dentition stage (in this case, 7.7-year-olds) had higher caries prevalence than that seen in the national sample (.59 for the national sample of 8-year-olds and 0.79 for our sample). The incidence of DMFS was 3.8-fold higher, whereas the DMFT was 2.8-fold higher than in the national norm. These caries scores, however, were not higher than those seen in our control

group from Newark. Therefore, all children in our study had a higher level of caries when compared to the national norm [25]. Had we not used a control group, our conclusions would have been similar to data reported previously.

Second, our study illustrated the need to use valid statistical measures for comparison of HIV-positive and HIV-negative groups. This is best demonstrated by studies of plaque levels in the HIV-positive participants. Thus, although plaque levels were elevated in the HIV-infected group, statistical comparison failed to demonstrate significance and periodontal disease and gingivitis levels did not correlate with plaque levels. Differences did not hold up to statistical comparison partially because of the large variation in plaque scores from individual to individual. In addition, microbial analysis by quantitative immunofluorescence of specific periodontal pathogens that included *Porphyromonas gingivalis, Prevotella intermedia, Wolinella recta, Eikenella corrodens, Actinobacillus actinomycetemcomitans,* and *Capnocytophaga gingivalis,* and normal plaque residents such as *Streptococcus sanguis* and *Actinomyces viscosus* in each individual plaque sample failed to disclose any differences in individuals and between the groups (data not shown) [20]. We assumed that the HIV-infected children had taken more antibiotics over the 2-year period and this was indeed the case, but our documentation was not reliable enough to include in this report. Although no statistical differences were found in any of the categories examined, the data on pocket-depth progression was intriguing and thus there was less pocket-depth progression in the HIV-infected group than in the control group. One could assume that an increase in antibiotic usage could explain the reduction in pocket depth found in the HIV-infected children. It could also be assumed that gingivitis, and particularly papillary bleeding, would also be reduced as a result of antibiotic usage. In summary, the HIV-infected group demonstrated increased plaque levels, equivalent gingivitis levels over time, less bleeding, and less pocket progression as compared with the control group.

As a third and final point with respect to interpretation of results gathered from this study, it is important to relate our findings to the treatment that patients received during the study period. The children in this study received excellent medical and dental care. When AIDS was first discovered no treatment was available and, therefore, the early observations were completely unhampered by clinical intervention. In later studies, however, patients were placed on a whole regimen of antimicrobial and antiviral medications [18,23]. Undoubtedly, these interventions could have had an effect on reducing the microbial challenge and on boosting the immune response of the compromised host [23]. Interventions such as these make it difficult to interpret the data, particularly in light of the numerous confounding factors that are present in this population of children. Treatment, however, is part of the disease as it is viewed today and this effect will become more evident in the future. All studies should take this into account. The only way to control for this fact is to recognize that the disease cannot be studied without taking into account the accompanying treatment.

In conclusion, keeping in mind the three final thoughts described above, the oral manifestations of AIDS that were anticipated prior to the start of this study were not observed over the course of the study. Undoubtedly, studies attempting to relate clinical conditions to HIV status is confounded by the overwhelming problems caused by the disease itself and the intervening care provided to these unfortunate children [23]. These factors can have a profound effect on analysis of data derived from these patients. At the start of the study, we expected to find more disease prevalence and incidence in this immunocompromised patient population. This expectation would have been even greater had it been known that plaque levels would be elevated in the HIV-positive group over the course of the study. Nevertheless, anticipated changes were not seen and, aside from typical oral lesions and prolonged retention or delayed eruption of permanent teeth, clinical differences expected to occur in the HIV-positive group were not observed to be different when the participants in the HIV-positive group were compared with their household peers. No differences were observed with respect to caries and periodontal disease prevalence. Oral mucosal lesions were more common in the HIV-infected group, but these did not prove to be of diagnostic significance. It is clear that a completely different interpretation could have resulted from this study if controls had not been analyzed in parallel to the HIV-infected population.

Research often produces more questions than answers. This study is no exception. We began by speculating that children born with HIV, with their accompanying poorly developed immune systems, would be more vulnerable to oral infections than would their household peers. Our results, for the most part, did not bear this out; however, the results found posed several new questions. It is clear that an HIV infection takes time to develop into the clinical syndrome called AIDS. This period of time, the incubation period, varies from individual to individual and translates into a reduced capacity for the infected individual to respond to a challenge. This response also appears to vary from individual to individual. Thus, even in children born with an HIV infection, the disease that is classified as AIDS is initiated at different times after birth in different individuals. Is it possible to distinguish between oral infections in children with HIV as compared to children with frank AIDS? Can any of the oral manifestations observed in these children predict future systemic failures? For example, candidiasis is seen more frequently in children with HIV/AIDS. This observation does not, at this time, appear to be predictive of systemic conversion. It is unclear, however, whether examination of children at 3-months intervals would show a better correlation between oral infections and systemic manifestations than would examinations performed at 6-month intervals. Furthermore, it is possible that more frequent oral examinations would provide data that oral infections precede lowered CD4 counts and thus act as predictors of lowered CD4 counts. If this is, indeed, the case, it could lead to more aggressive treatment that could lower

mortality. These are only a few of the issues that need to be addressed in the future to determine whether oral manifestations of AIDS can be shown to assist in the early diagnosis of AIDS.

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