Scientific Article

Prevalence of oral soft tissue lesions in HIV-infected minority children treated with highly active antiretroviral therapies

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Abstract

Purpose: *This project studied the prevalence of oral soft tissue disease in HIV-infected children treated with highly active antiretroviral therapy (HAART).*

Methods: *Thirty-eight HIV-infected children participated in the study. Twenty-three of these patients were treated with HAART while 14 received exclusively reverse transcriptase inhibitors (RTI) and served as controls. The children were examined three times at approximately one-month intervals while their health history and laboratory data were abstracted from medical charts. Analyses were performed to determine differences in lesion prevalence between treatment groups as well as between lesion and no lesion groups with regard to immune differences.*

Results: *Thirty patients (79%) had oral lesions detected in at least one visit. There were no differences in specific lesion prevalence between HAART compared with RTI-treated children. However, a trend for more oral candidiasis in the latter group was observed. Subjects with oral soft tissue lesions had lower CD4 counts (P=0.04) and percentages (P=0.01) but similar viral loads when compared to patients without oral soft tissue disease.*

Conclusions: *HAART does not appear to significantly affect oral soft tissue disease prevalence in HIV-infected children. Presence of lesions was associated with decreased immunity and may signal advancing disease.(Pediatr Dent 22:287-291, 2000)*

Oral mucosal pathology is frequently among the first AIDS symptoms seen in HIV-infected children. Diagnosis of this type of lesion may indicate a susceptibility of the patient to opportunistic infections and a probability of rapid progression of disease.[1,2] Thus, early detection of oral soft tissue disease may be used to help diagnose HIV infection, prognosticate progression of the disease, and aid in its therapeutic management.[1,3,4]

The typical anti-HIV treatment in children consists of reverse transcriptase inhibitors (RTI). In most patients, viral resistance to these drugs eventually develops, leading to renewed disease progression and AIDS.[5,6] A relatively new strategy for improving the efficacy of antiretroviral therapy is the use of a combination of agents that inhibit different steps in the HIV life cycle.[7] Protease inhibitors (PI) are part of this combination therapy (highly active antiretroviral therapy or HAART), which has been shown to significantly increase CD4 cell counts and reduce viral loads in tested adults. [7-10] The use of HAART has resulted in widespread optimism that HIV can become a long-term manageable disease.[11]

Most research on oral soft tissue lesions in HIV-infected children was conducted prior to the advent of HAART.[12] The oral effects of this therapy in children have not been reported. Thus, the aims of this project were to study the prevalence of oral soft tissue diseases in HIV-infected children taking HAART and compare it to the prevalence of the same diseases in children treated with RTI alone; and to study the prognostic value of oral soft tissue lesions as reflected by immune differences between lesion vs. no lesion groups.

Methods

Thirty-eight HIV-infected children aged 6 to 18 years (mean=9.8 years) agreed to participate in this study. All subjects were recruited from a University-affiliated pediatric infectious disease clinic. Fifty-eight percent were female and 100% were minorities (84% African American, 16% Hispanic). In all cases viral infection occurred at birth through vertical transmission.

Eligibility for enrollment included active treatment at the pediatric HIV clinic, ambulatory capability, and life expectancy of over three months. All participants' parents or legal guardians signed an informed consent form, which was approved by the Institutional Review Board.

A health history, including past and present medications and laboratory medical data, were abstracted from each subject's medical records and confirmed with the parents and/or legal guardians whenever possible. Enrolled children received three oral examinations approximately one month apart. The subjects were seated in the dental chair and examined by one of two calibrated examiners (M.F. and A.B.). To ensure consistency between the raters, the two clinicians performed and compared separate examinations of 10 patients (Kappa = 0.85). Clinical findings were recorded on a standardized, coded form that was used in a previous study.[12]

During the visual examination, a dental mirror and dental light were used. Salivary glands were palpated and evaluated for abnormalities. Lips, labial and buccal mucosa, tongue, tonsils, floor of month, soft palate, hard palate, and frena were

Received January 26, 2000 Revision Accepted May 12, 2000

Table 1. Frequency and Percentage of Lesions Observed in 38 Patients Detected During at Least One Visit

Lesions	Frequency	Percent (%)
Conventional Gingivitis	19	50
Linear gingival erythema	12	32
Candidiasis	9	24
Pseudomembranous	1	3
Chronic	6	16
Both	2	5
Median Rhomboid Glossitis	3	8
Other Ulcer	6	16
Other Lesions	7	18
Parotitis	1	3
Herpes Labialis	1	3
Herpetic Gingivitis	1	3

visually inspected. All soft tissue findings, including gingival inflammation, were recorded.

A fungal culture of the dorsal tongue was performed for all subjects with a sterile cotton tip applicator. Patients with clinical lesions had an additional culture taken of the affected area. The samples were plated on chromagar and then incubated at 37°C with 5% carbon dioxide for five days. The number of colony forming units and the type of fungal growth were analyzed and are presented elsewhere. Candida colony formation was confirmed with a potassium hydroxide preparation and examination under the light microscope.

Following each examination, all children were referred to dental services and actively encouraged to obtain appropriate treatment whenever it was clinically indicated. At the conclusion of data collection, the parent and/or legal guardian was encouraged to continue routine medical and dental checkups.

Statistical analyses

Comparisons across groups were made using either a chi-square analysis with the appropriate contingency table or a t-test of independent group means. The ANOVA was used to determine correlations of immune parameters to presence or absence of oral lesions in specific treatment groups. These tests were performed at the $P<0.05$ level of significance. SPSS for windows (SPSS Inc. Chicago, IL) was the program used to calculate the statistical tests.

Results

Of 38 enrolled subjects, 95% (N=36) completed all three examinations while two subjects missed one visit each. Twenty-three patients received HAART and 14 received exclusively RTI. For one subject the active antiretroviral treatment could not be determined, and he was excluded from pertinent analyses. Seventy-nine percent of the children had one or more oral lesions detected in at least one visit (Table 1). When conventional gingivitis (CG) was excluded, the percentage of subjects with soft tissue lesions became 53% (N=20). Of these, 65% (N=13) received HAART and 35% (N=7) were treated with RTI alone (P=0.48).

The most common oral lesion was conventional gingivitis (50%), followed by linear gingival erythema (LGE) (32%). Oral candidiasis was diagnosed in nine (24%) children: of these, six (16%) subjects had chronic candidiasis; one (3%) had pseudomembranous candidiasis; and two (5%) had both forms of this disease. All nine diagnoses of candidiasis were confirmed by fungal culture. The prevalence of oral candidiasis in children receiving various HIV treatments is presented in Table 2.

Immune parameters were obtained for 36 patients (laboratory data for two children were unavailable). The CD4 counts for all subjects ranged from 43 to 2017 cells/ml. The subjects' viral load ranged from undetectable (N=9) to 1,155,122 copies/ml. Mean and median values for these parameters are presented in Table 3.

Seven of the children with undetectable viremia were receiving HAART. However, there were no significant differences between HAART and RTI-treated groups with regard to average CD4 counts (590+503, 673+365, respectively; P=0.61), CD4 percentages (23.8+12.9, 27.8+10.9, respectively; P=0.367), or viral load (122,605+263,055, 61,601+206,942, respectively; P=0.48). The median viral loads for the two groups were 13,980 and 2,500 for the HAART and RTI-treated children, respectively.

Children with oral lesions (CG excluded) had a mean viral load of 114,902 + 210,602 copies/ml as compared to children with no lesions who had a viral load of 84,565 + 280,687 copies/ml (P= 0.71). CD4 counts (mean = 487 + 372) and percentages (20% + 12%) for children who had lesions were compared to values for children who had no lesions (784 + 493 and 31% + 10%, respectively). These differences were statistically significant (P= 0.04, P= 0.01 for counts and percentages, respectively).

Table 2. Oral Candidiasis in Children Receiving Various HIV Treatments

	HAART	RTI	Significance
N	23	14	
Chronic candidiasis	13% (N=3)	36% (N=5)	N.S. (P=0.11)
All Candidiasis	17% (N=4)	36% (N=5)	N.S. (P=0.19)

Table 3. Immune Parameters in 36 Patients

	CD4	CD4 percentage	Viral Load Copies/ml
N	36	36	36
Normal Range	689-1566	33-59	0
Mean	620±455	25±12	100, 576±243, 027
Median	512	25	3,145

Table 4. CD4 Counts and Percentages and Viral Loads for Children with and without Oral Candidiasis

		Mean CD4	Mean CD4 percentage	Viral Load Copies/ml
Chronic Candidiasis				
No	N=29	689±458	27%±12%	77,778±221,368
Yes	N=7	335±330	18%±12%	195,024±320,820
Significance		N.S., P=0.06	N.S., P=0.06	N.S., P=0.26
All Candidiasis				
No	N=28	680±464	27%±12%	80,535±224,922
Yes	N=7	412±375	18%±12%	170,721±304,872
Significance		N.S., P=0.14	N.S., P=0.07	N.S., P=0.36

Children without chronic candidiasis had a mean CD4 count of 689+458 versus 335+330 for children with this lesion (P=0.06). The CD4% was 27+12 for children without chronic candidaisis versus 18% +12% for children with this disease. Children with any candidiasis had a mean CD4 count of 412+ 375 versus 680+375 for children without candidaisis (P=0.14). The respective CD4% was 18+12 and 27+12 (P=0.07). No significant differences in viral loads, CD4 counts or percentages were detected (Table 4).

No other differences were found in anti-HIV therapy or immune parameters between lesion-no lesion groups for all other pathological entities.

Discussion

This report presents results from a prospective, blinded study that followed a population of 38 HIV-infected ethnic minority children for three months. The study focused on changes in oral soft tissue disease patterns in patients treated with HAART as compared to children treated exclusively with RTI.

One of the purposes of this study was to determine the prevalence of oral soft tissue disease in HIV-positive children taking HAART as their antiretroviral regimen. The results indicated a high prevalence of oral lesions in these children, which was similar to the rate of occurrence of similar lesions in untreated children.[1,2,12] Albeit a trend in oral candidiasis was apparent, the current study found no statistical differences in prevalence of total or specific oral lesions in subjects receiving HAART compared with RTI.

Based on reports in adult populations,[13] it was expected that children treated with HAART would exhibit a healthier oral condition. The unexpected finding of no difference in the health of soft tissues may be due in part to: 1) insufficient duration of treatment with HAART; 2) development of viral resistance to PI; and/or 3) poor compliance with medication therapy in the cohort studied.

While the study enrollment criteria required at least six months of HAART therapy, most subjects had been taking this regimen for less than one year, which might be insufficient time for a significant immune reconstitution in children. Additionally, compliance with this complicated therapeutic regimen is often poor, particularly with inner city minority populations. This was reported also by Watson and Farley who found that non-adherence to HAART regimens was common in pediatric HIV-infected patients.[14] In the current study compliance could not be evaluated since medical information was derived from the patients' records which lacked information on adherence to antiretroviral therapy.

Similarly, while development of resistance to HAART is relatively common in children[15,16], this study did not establish prevalence of resistant viruses in the cohort studied. The fact that immune parameters were not significantly different in HAART versus RTI-treated children is consistent with the discussion above and indicates that the former group did not achieve a clear therapeutic advantage. A selection bias may also be involved in that children placed on HAART might have had a worse immune status at the initiation of their therapy. However, changes in immune status in children on HAART were beyond the purposes of this project.

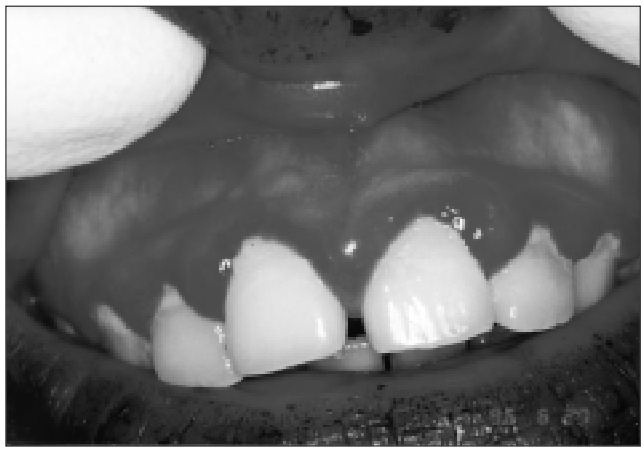

Fig 1. Convenctional gingivitis (plaque-induced) with its characteristic inflammatory signs.

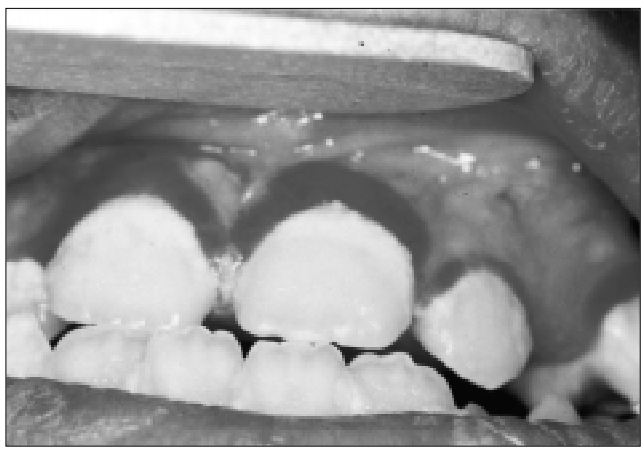

Fig 2. Linear Gingival Erythema (LGE): an erythematous banding without other signs of inflammation.

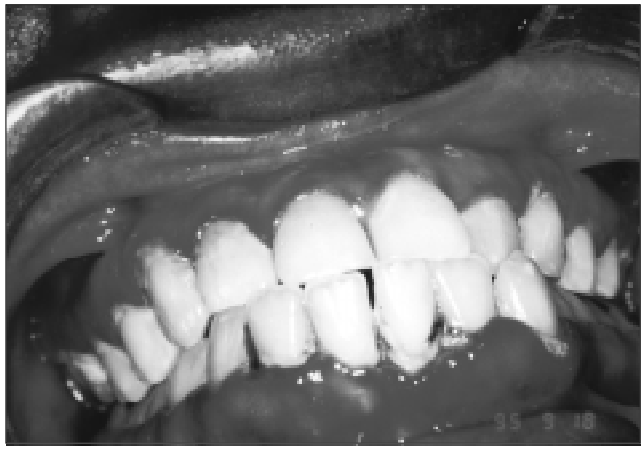

Fig 3. Necrotizing Ulcerative Gingivitis (NUG)

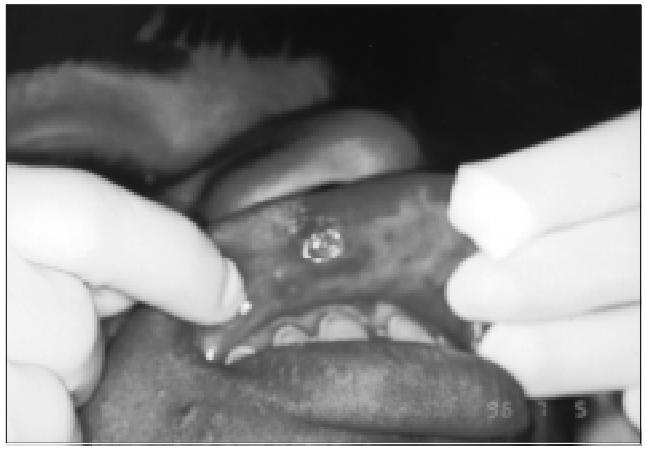

Fig 5. Ulcer (nonspecific)

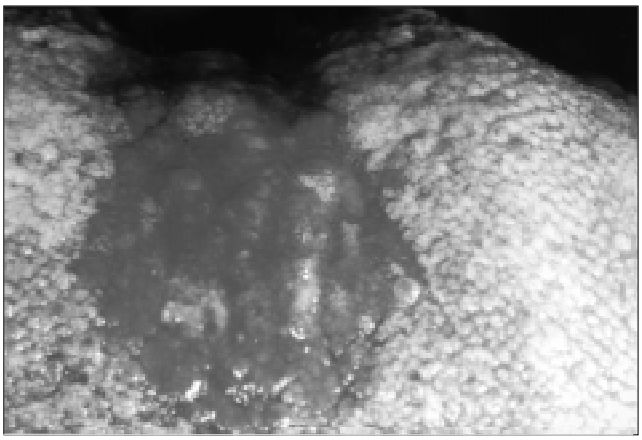

Fig 4. Median Rhomboid Glossitis

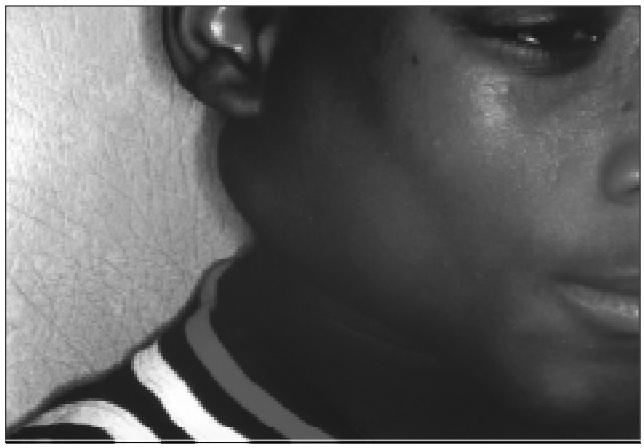

Fig 6. Chronic idiopathic parotitis. This lesion has been associated with a good prognosis.

Despite no significant change of oral disease in children taking HAART, the frequency of types of oral lesions did vary in this study compared to previous studies. [1,2,12,17,18] The most common oral lesion of all 38 children in this study was conventional gingivitis, which occurred in one half (n=19) of the subjects. In an earlier study by Barasch,[12] which included these children, only 6.9% of the HIV-infected subjects had this lesion, which was considered unrelated to the HIV infection. It is interesting to note that Barasch et al. associated a diagnosis of conventional gingivitis with better immunity and slower progression of disease.

LGE was the second most common lesion in this HIV-infected population (32%, N=12). This lesion is characterized by linear erythema of the facial and interproximal gingival margins and is typically unresponsive to improved oral hygiene.[19] This prevalence is similar with the one reported previously by Barasch[12] but higher than reported by other authors.[20] There is no evident explanation for this discrepancy in LGE prevalence. However, this may be due to the fact that LGE is a newly reported lesion and its diagnosis is only based on subjective clinical observations. Since neither the etiology nor the significance of LGE are well understood, analyses regarding this lesion were not undertaken.

It is interesting to note that oral candidiasis was only the third most common lesion in the current study and seen clinically in 24% of the subjects. In contrast, OC was the most frequently seen oral lesion in HIV-infected children in previous studies, with incidence reported to be as high as 70%.[1,2,12,17,18] In those studies subjects were not treated with HAART when evaluated for oral disease, whereas in the present study, more than half of the children were on this regimen. Since this particular lesion is most commonly associated with rapid disease progression and a poor prognosis, further research is needed to evaluate the significance of decreased prevalence of candidiasis in HIV-infected children taking HAART.

Another purpose of this project was to study the relationship of specific clinical oral conditions to a patient's immune status. Frequency of oral lesions was analyzed in relation to CD4 counts and percentages and viral load, and significant differences were found in the former two parameters. This confirms that oral soft tissue lesions are related to decreased immune surveillance and may be prognosticators of disease progression in HIV-infected children. Although no significant differences were found in analyses for individual lesions, a clear trend was found for candidiasis, which is consistent with a number of other studies. [2,12,16,21,22]

The present findings should be interpreted with caution since the study was small and omitted significant data, such as compliance with antiretroviral therapy. Additionally, the population studied consisted exclusively of inner city minority subjects. The data presented may not apply to other populations.

Conclusions

1. Oral soft tissue lesions are common in HIV-infected children.
2. No significant differences were found in oral lesion prevalence or immune indicators between HAART and RTI-treated subjects.
3. Oral soft tissue lesions are associated with lower CD4 counts and percentages but similar viral loads.

This study was supported by NIDCR grant #DE 10592, the Northeastern Minority Oral Health Research Center.
The authors wish to thank Evelyn Varagiannis, study coordinator, Rene Lopez, Director of the statistical core, and Dr. Dieudonne, Francois Xavier Bagnoud Clinic, Department of Pediatrics at University Hospital, Newark NJ, for their invaluable help in this study.

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