

## Pediatric HIV-related oral manifestations – a five-year retrospective study

### *Manifestações bucais associadas à infecção pelo HIV em crianças – estudo retrospectivo de cinco anos*

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**ABSTRACT:** The purpose of this study was to carry out a five-year retrospective descriptive follow-up of the oral manifestation frequency, systemic condition and type of medication used in HIV-infected children and adolescents after the introduction of combined antiretroviral therapy. Fifty-eight patients were examined in 2001/2002, and their previous medical and dental records (1997 to 2000) were researched from files. There was an occurrence of 7 new cases of AIDS in a sample of 19 children, while 46.5% of the entire sample (n = 58) progressed as to classification of HIV infection. No difference was noted among the frequencies of oral manifestations, categories of the immunosuppression and viral load categories. The oral manifestations in the group of children and adolescents followed up in this study remained stable, even after treatment with combined antiretroviral therapy. However, a downward trend in the frequency of oral candidiasis and parotid enlargement was noted.

**DESCRIPTORS:** HIV; Oral manifestations; Child; Immunosuppression; Combined modality therapy; Protease inhibitors.

**RESUMO:** O objetivo deste estudo foi realizar um acompanhamento descritivo retrospectivo da frequência de manifestações bucais, da condição sistêmica e do tipo de medicação utilizada em um grupo de crianças e adolescentes infectados pelo HIV após a introdução da terapia anti-retroviral combinada. Cinquenta e oito pacientes foram examinados em 2001/2002, enquanto seus exames médicos e odontológicos retrospectivos (1997 a 2000) foram pesquisados em prontuário. Foram observados 7 novos casos de AIDS em uma amostra de 19 pacientes, enquanto 46,5% da amostra total (n = 58) progrediram quanto à classificação da infecção pelo HIV. Não foram observadas diferenças entre as frequências de manifestações bucais, das categorias de imunossupressão e da carga viral. O quadro de manifestações bucais no grupo de crianças e adolescentes acompanhados neste estudo manteve-se estável, mesmo após a introdução da terapia anti-retroviral combinada. Contudo, foi observada uma tendência de diminuição da frequência de candidíase bucal e hipertrofia de parótidas.

**DESCRIPTORES:** HIV; Manifestações bucais; Criança; Imunossupressão; Terapia combinada; Inibidores de proteases.

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## INTRODUCTION

The development of HIV infection in children has different characteristics to those noted in adults, due mainly to the earlier acquisition of the virus, combined with the immaturity of the immunologic system and other body structures<sup>8</sup>. It is estimated that in Brazil there are approximately 597,000 people infected by HIV, of which 12,800 are children aged between 0 and 14 years<sup>20</sup>. It represents the number of vertically infected children, which is the principal way of HIV transmission in children.

The clinical feature of pediatric HIV infection includes the appearance of various oral lesions, some of which are considered AIDS diagnosis markers, such as recurrent oral candidiasis and chronic enlargement of the parotid<sup>5</sup>. The most frequently associated oral lesions are: candidiasis, herpes simplex infection, linear gingival erythema (LGE), parotid enlargement and recurrent aphthous stomatitis. Other viral and bacterial infections, including periodontal infections are less commonly associated, while hairy leukoplakia and

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Kaposi's sarcoma are rarely seen in HIV-infected children<sup>18</sup>.

The development of antiretroviral drugs for treating HIV infection began with the introduction of zidovudine (AZT) in 1987. Protease inhibitors became available in 1997, and they led to the preparation of therapeutic schemes that provided greater control of viral replication, improving the immunologic response of HIV-infected patients. Broad access to antiretroviral therapy, principally to the combined therapy (two or more drugs), resulted in a better quality of life for such patients<sup>4</sup> and, according to some studies, was responsible for a drop in the prevalence of oral manifestations<sup>1,6,17</sup>.

This study sought to report those observations through a five-year retrospective descriptive follow-up of oral manifestations and systemic conditions (laboratory data and use of antiretroviral therapy) in HIV-infected children and adolescents, after they were treated with combined antiretroviral therapy.

## MATERIAL AND METHODS

### Subjects

The population studied consisted entirely of children treated at the pediatric AIDS clinic of a public university institution of the city of Rio de Janeiro, from March 2001 to February 2002 (n = 307). The oral health (oral manifestations and dental caries) of this population is routinely followed up by a dental team through periodical clinical examinations (usually quarterly), at the same time as medical consultations.

In that period (2001-2002), the dental team examined 160 children and/or adolescents. Their previous medical and dental records were researched in files, and those that had at least 3 complete annual examinations in the period between 1997 to 2002 were included in the research. Consent was obtained from the person responsible for each patient and the study was approved by the local ethics committee.

The study period was divided into five groups of annual intervals, according to the period of the examination:

- Interval 1 (I1) - March 1997 to February 1998.
- Interval 2 (I2) - March 1998 to February 1999.
- Interval 3 (I3) - March 1999 to February 2000.
- Interval 4 (I4) - March 2000 to February

2001.

- Interval 5 (I5) - March 2001 to February 2002.

### Data collection procedures

The patients of the I5 Group (2001/2002) were examined by a trained professional and the criteria for diagnosing the principal lesions associated to HIV infection in children were those described by EC-Clearinghouse (1993)<sup>10</sup> and Ramos-Gomez *et al.*<sup>18</sup> (1999). The extrabuccal examination consisted of a visual inspection of the face and palpation of the cervical, submandibular and submentonian lymph nodes and parotid glands; the intrabuccal examination was performed using an oral mirror, wooden spatula and flashlight to improve illumination. Soft tissues were examined in the following sequence: lips, buccal mucosa, tongue, floor of the mouth, hard and soft palate and gums<sup>18</sup>.

Information on previous records of oral manifestations of the sample of Groups I1 to I4 (1997 to 2000) was researched in the dental files, while the medical files of all the patients included in the study were researched to find out what type of medication was used, data on CD4+ cell count and viral load, as well as the classification of the clinical stage of the disease<sup>8</sup>.

The resulting data was stored in a databank created by the SPSS Program, version 11.0 (SPSS Inc., Chicago, USA). Descriptive statistics was used to analyze the data.

## RESULTS AND DISCUSSION

### Description of sample

It was discovered that not all of the 58 children chosen for I5 (2001/2002) had the complete examination (doctor and dentist) for all intervals of the study. In this case, only 33 patients qualified (56.9%). However, all the patients chosen had at least 3 complete examinations from I1 to I5. Additionally, of those 58 patients, 46 (79.3%) began the follow-up in this study in I1, and 12 (20.7%) in I2. There was no difference as to sex and as to age, the latter increased with time because the same children were followed up for 5 years, as seen in Table 1. Regarding the distribution of the categories of exposure of the patients to the HIV virus, 55 patients (94.9%) had been vertically contaminated, while only two cases (3.4%) resulted from blood contamination (transfusion) and one case (1.7%) had unknown way of contamination.

HIV disease in children is classified through a system<sup>8</sup> that combines the presence of clinical

symptoms (N - no symptoms, A - mild symptoms, B - moderate symptoms, C - serious symptoms) and the degree of immunosuppression (1 - none, 2 - moderate, 3 - serious). Fifty-four patients (93.1%) already showed, at the start of follow-up, some symptom of the disease (classification A, B or C), and this number rose to 56 (96.5%) patients in I5.

The proportion of the number of patients with AIDS (classification: N3, A3, B3, C1, C2 or C3) at the start (I1/I2) and at the end of the follow-up (I5), was 39 and 46 children, respectively. The progress of HIV infection in children is different to that in adults, because they can develop the HIV infection as fast progressors (they evolve to AIDS in the first two years of life), intermediate progressors (they show only mild symptoms during the first five years of life) or non-progressors (they did not develop the disease until eight years of age). However, the majority of children develop the disease as an intermediate progressor, similar to the findings of this study<sup>4</sup>.

The evolution of HIV infection to the AIDS

stage or death can be influenced by various factors, among which are the early appearance of clinical symptoms and the presence of generalized lymphadenopathy<sup>19</sup>. It could be suggested that the occurrence of 7 cases of AIDS in the sample, in the five years of follow-up, may be due to the fact that the majority (93.1%) already showed some clinical symptoms of the infection at the beginning of the study, as well as a high frequency of lymphadenopathy, as Table 2 shows.

### Laboratory data

The values of CD4+ cells, viral load, in addition to the classification of the sample of each interval of the study into immunosuppression groups, according to criteria established by the Centers for Disease Control and Prevention (1994)<sup>8</sup> can be seen in Table 3.

The results of the viral load levels are described from I2 to I5, because in I1 the examination for qualifying the viral load for routine clinical use was not yet available. The results are shown in log of number of copies of viral particles per ml of

**TABLE 1** - Description of the sample - sex and age. Rio de Janeiro, 2002.

Interval	n	Sex n (%)		Age		
		Male	Female	Interval	Mean	S.D.
I1	46	22 (47.8)	24 (52.2)	1.3 - 13	5.3	2.9
I2	53	24 (45.3)	29 (54.7)	0.6 - 13.8	6.1	3.0
I3	51	23 (45.1)	28 (54.9)	1.5 - 14.3	7.2	3.0
I4	50	24 (48.0)	26 (52.0)	2.4 - 14.6	7.8	2.7
I5	58	28 (48.3)	30 (51.7)	3.6 - 16	9.2	2.8

S.D.: standard deviation.

**TABLE 2** - Frequency of the principal oral manifestations associated with HIV infection in children. Rio de Janeiro, 2002.

Oral manifestation	I1 (n = 46) n (%)	I2 (n = 53) n (%)	I3 (n = 51) n (%)	I4 (n = 50) n (%)	I5 (n = 58) n (%)
General	39 (84.8)	43 (81.1)	39 (76.5)	36 (72.0)	47 (81.0)
Except lymphadenopathy	20 (43.5)	22 (42.2)	20 (39.2)	17 (34.0)	16 (27.6)
Lymphadenopathy	33 (71.7)	34 (64.2)	31 (60.8)	27 (54.0)	42 (72.4)
Pseudomembranous candidiasis	4 (8.7)	2 (3.8)	1 (2.0)	3 (6.0)	5 (8.6)
Erythematous candidiasis	5 (10.9)	6 (11.3)	5 (9.8)	2 (4.0)	2 (3.4)
Angular cheilitis	3 (6.5)	1 (1.9)	1 (2.0)	-	1 (1.7)
Enlargement of parotids	7 (15.2)	6 (11.3)	5 (9.8)	1 (2.0)	1 (1.7)
Linear gingival erythema (LGE)	1 (2.2)	5 (9.4)	2 (3.9)	4 (8.0)	6 (10.3)
Herpetic infections	1 (2.2)	1 (1.9)	-	3 (6.0)	-

the plasma sample. The CD4+ cell count and the viral load are parameters used for evaluating the progression of the disease and for knowing when to begin the antiretroviral treatment<sup>4</sup>.

Even though the independent predictor of progression of the disease seemed more effective in adults<sup>16</sup>, the evaluation of the viral load in vertically infected children takes into account that the patient is already born with high levels of RNA-HIV, which tend to decline slowly during the first years of life, sometimes even without any antiretroviral medication. However, it is believed that in children older than 30 months, viral load levels higher than 100,000 copies/ml and a CD4+ lymphocytes count below 15% indicate increased risk of progression of the disease to the AIDS stage or death<sup>4</sup>. In this study, the frequency of serious immunosuppression (%CD4 < 15%) varied from 30.0 to 37.7% of the sample, and although the viral load levels analyzed in log form did not show a difference from interval to interval, these were very high (averaging above 100,000 copies/ml after I3), and may be related to the progression of the disease observed in the sample.

### Antiretroviral therapy

The type of antiretroviral therapy is described

in Table 4. The use of combined antiretroviral therapy increased with time, and in the case of the patients shown in Table 4 as not using any medication, this means that up to that time there was no clinical and/or laboratory indication for beginning therapy<sup>4</sup>. The results show that monotherapy is no longer suitable as a therapeutic scheme for treating HIV disease, and the combination of drugs may vary specifically from patient to patient, according to the infection markers<sup>4,9</sup>. The time of use and the type of therapy can influence the evaluation of its impact on the patient's oral and systemic condition (which is why more studies are necessary with more follow-up) and/or of the case-control type for clarifying that relation.

### Oral manifestations

Table 2 shows the frequency of the principal oral lesions during the follow-up period (1997-2002).

Oral manifestations are frequently found in HIV-infected children, and in some cases are the first clinical sign of the disease<sup>14</sup>. In this study, no difference was noted among the frequencies of lesions between the consecutive intervals of the study, because in all the intervals, more than 70% of the patients showed some type of manifestation.

**TABLE 3** - Percentage of CD4+ cells, frequency of the degree of immunosuppression and viral load levels, of each interval of the study (I1-I5). Rio de Janeiro, 2002.

Variable		I1 (n = 46)	I2 (n = 53)	I3 (n = 51)	I4 (n = 50)	I5 (n = 58)
%CD4	Mean	18.7	19.8	21.0	20.1	20.6
	S.D.	10.7	11.6	11.7	10.5	11.5
Serious immunosuppression (< 15%)	n (%)	16 (34.8)	20 (37.7)	17 (33.3)	15 (30.0)	20 (34.5)
Moderate immunosuppression (15-24%)	n (%)	12 (26.1)	11 (20.8)	11 (21.6)	14 (28.0)	15 (25.9)
No immunosuppression (> 24%)	n (%)	18 (39.1)	22 (41.5)	23 (45.1)	21 (42.0)	23 (39.6)
Viral load (log)	Average ± S.D.	-	4.3 ± 1.1	4.1 ± 1.1	4.2 ± 0.9	4.2 ± 1.0

S.D.: standard deviation.

**TABLE 4** - Type of antiretroviral therapy, adhesion and time of use (I1-I5). Rio de Janeiro, 2002.

Antiretroviral therapy	I1 (n = 46)	I2 (n = 53)	I3 (n = 51)	I4 (n = 50)	I5 (n = 58)
	% (n)				
None	23.9 (11)	11.3 (6)	9.8 (5)	4.0 (2)	15.5 (9)
Monotherapy	10.9 (5)	1.9 (1)	-	-	-
Double therapy	65.2 (30)	64.2 (34)	52.9 (27)	46.0 (23)	36.2 (21)
Triple therapy with protease inhibitor	-	22.6 (12)	37.3 (19)	48.0 (24)	43.1 (25)
Triple therapy without protease inhibitor	-	-	-	2.0 (1)	5.2 (3)

That fact was also observed by various studies, where oral manifestations occurred, regardless of constant medical treatment<sup>3,7,11,13,14</sup>.

However, when lymphadenopathy was excluded, a downward trend in the frequency of lesions could be seen (Table 2). Lymphadenopathy was diagnosed in the majority of the children in all the intervals (Table 2), and this frequency can be expected in the case of immunodeficient patients<sup>3</sup>.

Candidiasis is one of the most frequent oral manifestations in HIV-infected patients and is considered a sign of a poor prognosis of the disease<sup>15</sup>. The study of Aguirre *et al.*<sup>1</sup> (1999) proved the decline of the occurrence of this lesion in adults after the introduction of antiretroviral therapy with protease inhibitors, due mainly to the patient's improved immunological condition. In the study of Flanagan *et al.*<sup>12</sup> (2000), no difference was noted between the prevalence of oral manifestations among the groups of children treated with double therapy and with triple therapy with protease inhibitors. There was just a tendency for candidiasis to be observed more frequently in the group treated without a protease inhibitor. In this study, the frequency of candidiasis observed in I1 (17.4%) was already lower than that of other studies (22%<sup>10</sup>; 24%<sup>12</sup>), while a high frequency of the use of double therapy was noted. These two factors may have

contributed to the observation of a decline in the observation of the lesion over time<sup>6</sup>.

Linear gingival erythema was seen more frequently in the final intervals of the study (Table 2), although evidence has already been found that this lesion is more common in children over 12 years<sup>2</sup>, like in the majority of the children of I4-I5 of this study.

Enlargement of the parotids tended to drop with time, although some authors relate it to a good prognosis of the disease<sup>15</sup> and with an increase in the lymphocytary infiltrate<sup>17</sup>. Among the less frequent lesions noted were herpetic infections (prevalence varying from 0 to 6.0%), and this figure agrees with the majority of the reports in the literature<sup>3,18</sup>.

## CONCLUSIONS

The frequency of oral manifestations in the group of children and adolescents followed up in this study remained stable, even after the introduction of combined antiretroviral therapy. However, a downward trend in the frequency of oral candidiasis and parotid enlargement was noted. There was no difference in the frequency of the immunosuppression groups, while there was an increase in the use of combined antiretroviral therapy, principally with protease inhibitors.

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Received for publication on Mar 27, 2003

Sent for alterations on Aug 19, 2003

Accepted for publication on Dec 12, 2003