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# Oral lesions in HIV+/AIDS adolescents perinatally infected undergoing HAART

**Luis-Alberto Gaitán-Cepeda [1], Anitza Domínguez-Sánchez [3], Noris Pavía-Ruz [2], Rocío Muñoz-Hernández [2], Roberto Verdugo-Díaz [3], Ana-María Valles-Medina [4], Héctor Meráz-Acosta [3]**

[1] Laboratorio de Patología Clínica y Experimental, Facultad de Odontología, Universidad Nacional Autónoma de México, México city
[2] Clínica de Inmunodeficiencia, Facultad de Medicina, Universidad Nacional Autónoma de México, México city
[3] Facultad de Odontología, Universidad Autónoma de Baja California-Mexicali, Mexicali, BC. México
[4] Facultad de Medicina, Universidad Autónoma de Baja California-Tijuana, Tijuana, BC. México

*Correspondence:*
*Lab. Patología Clínica y Experimental*
*Fac. Odontología, UNAM*
*Circuito Institutos s/n, Ciudad Universitaria*
*Coyoacán 04510, D.F*
*México*
*lgaitan@servidor.unam.mx*

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## Abstract

Objective: To assess the prevalence of the oral lesions related to HIV-infection (HIV-OL) in HIV+/AIDS adolescents (=13 years old), and the differences with HIV+/AIDS children (=3 - <13 years old) perinatally infected.
Material and methods: 25 HIV+/AIDS adolescents and 62 HIV+/AIDS children, undergoing Highly Active Antiretroviral Therapy, were orally examined. HIV-OL was diagnosed in accordance with EC-Clearinghouse-World Health Organization. The patients were classified with respect to their immune status in relation with the CD4+ cell counts as moderately immunodeficient; mildly immunodeficient and severely immunodeficient in accordance to the revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years (CDC-USA). The virological status was established in relation to the copies of RNA-HIV-1/mL as follows: with undetectable viral load (UDVL); with low viral load and with high viral load. A chi-square test was performed ($p<0.05$IC95%).
Results: The prevalence of HIV-OL in HIV+/AIDS adolescents was 20% while in HIV/AIDS children was 30.6% ($p>0.05$). Oral candidiasis was the most prevalent oral lesion in both groups. Association ($p<0.05$) of a high prevalence of HIV-OL and oral candidiasis with a high viral load was observed in both study groups.
Conclusions: Adolescents perinatally HIV-infected have a high prevalence of HIV-OL. Oral candidiasis still is the most frequent oral opportunistic infection. Oral lesions could have association to viral failure in HIV+/AIDS adolescents undergoing HAART.

***Key words:*** *HIV+/AIDS children, HIV+/AIDS adolescents, oral lesions, oral candidiasis.*

## Introduction

There is approximately 2.3 million of human immunodeficiency virus (HIV)-infected children in the whole world (1). In Mexico, until November of 2008, the National Center for Prevention and Control of HIV/AIDS (CENSIDA-México) had registered 2,972 cases of HIV+/AIDS in perinatally infected pediatric patients (2). The progression of HIV infection is different in pediatric patients than in HIV+ adult patient. In spite of some confusion and overlapping definitions of different pediatric HIV+ populations, it seems that HIV+/AIDS children have a bimodal progression of the disease: fast progression and slow progression (3). HIV+/AIDS children that are fast progressors die before they are three years old, whereas slow progressor HIV+/AIDS children survive more than three years (3).

Protease inhibitors of HIV-1 introduced in the antiretroviral therapy against HIV in the middle of 90's and their later combination with inhibitors of transcriptase reverse established the highly active antiretroviral treatment (HAART). HAART produced an important decrease of the morbidity-mortality associated to AIDS and an increase in the survival time of the HIV+/AIDS patient (adult or pediatric) (4). Therefore, there has been an increase in the number of perinatally HIV-infected youth and children that require oral and dental health services. However, scientific information regarding the HIV-associated oral lesions (HIV-OL) of perinatally-HIV patients, especially adolescents, is scarce. To contribute to a better knowledge of the perinatally HIV-infected patients, specifically the adolescent population, the main objective of this report was to assess the prevalence of HIV-OL in perinatally HIV-infected adolescents. Additionally, in order to assess if HIV+/AIDS adolescents show a specific distribution frequency of HIV-OL, the prevalence of HIV-OL obtained in HIV+/AIDS adolescents was compared with the prevalence of HIV-OL obtained in a population of perinatally HIV-infected children.

## Material and Methods

The clinical status of soft oral tissues was examined in 87 HIV+/AIDS (≥3 years old) perinatally HIV-infected patients confirmed by PCR, ELISA and Western-blot tests. 50 were from the Immunodeficiency clinic, School of Medicine, National Autonomous University of Mexico, México City, while 37 were from the Epidemiology Department, Health Department of Baja California State, Tijuana, México. Both institutions are third level clinic specialized in the diagnosis and treatment of HIV infection in children. All the patients had undergone previous antiretroviral treatments. Inclusion criteria established that patients should have been under HAART (two inhibitors of transcriptase reverse analogue nucleoside plus one protease inhibitor of HIV-1) for at least 6 months. Before the oral examination an informed consent was obtained in writing from each patient´s parents or legal caretakers. The research protocol was approved by the Bioethical and Biosafety Committees at the participant institutions (National Autonomous University of México; Autonomous University of the State of Baja California).

Between January, 2005 and December, 2007, the patients were monitored bimonthly at their respective immunodeficiency clinic. Each visit included detailed medical and oral health examinations. The oral examination was performed by a dental surgeon specialized in oral pathology and oral medicine (LAGC/HMT). HIV-OL were diagnosed in based on the HIV-OL clinical criteria proposed by the EC-Clearinghouse and the World Health Organization (5). The diagnosis of Oral Candidiasis (OC) was confirmed by positive Candida spp. culture on Sabouraud-chloramphenicol medium at 37°C for 48 h and morphological microscopic observation.

The following information was recorded for each patients from the medical record: age, gender, previous antiretroviral therapy, current antiretroviral therapy scheme, CD4+ lymphocyte cell count/mL, and the quantity of RNA-HIV-1 copies /mL in peripheral blood (viral load). CD4 cell count/mL and viral load in peripheral blood were determined within 2 months before the oral examination.

In regard to age the patients were grouped as follows: HIV+/AIDS children group (Chg) formed by children ≥3 - <13 years old and HIV+/AIDS adolescent group (Adg) formed by patients ≥ 13 years old (6). The patients in regard to their immunological status in relation with CD4 cell count were classifies as moderately immunodeficient (Stage 1); mildly immunodeficient (Stage 2) and severely immunodeficient (Stage 3) based on the revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years (CDC-USA) (6). In regard to virological status HIV+/AIDS Adolescents were grouped as follows: with undetectable viral load (UDVL); with low viral load (viral load >50 to <10,000 copies/mL) and with high viral load (viral load >10,000 copies/mL) (7). Due it has not been possible to extrapolate guidelines from adult natural history and therapeutic trials to the pediatric population and because high and persistent plasma levels of HIV in infancy (8), the virological status in children was assessed as: undetectable viral load (UDVL); low viral load (viral load >50 - <100,000 copies/mL) and high viral load (viral load >100,000 copies/mL) (9).

In such a way the Adg was formed by 25 adolescents (14 girls; 11 boys, mean age 12.5 ±12.5; range 13-9). From them 11 adolescents were moderately immunodeficient;

11 were mildly immunodeficient and 3 were severely immunodeficient. In regard to their virological status 4 adolescents had an UDVL, 16 had low viral load and 5 had high viral load. On the other hand the Chg included 62 children (34 girls; 28 boys; mean age 5.5 ±1.9; range 3–12); 34 children were moderately immunodeficient; 23 were mildly immunodeficient; and 5 were severely immunodeficient. In regard to their virological status 21 children had an UDVL, 30 had low viral load and 11 had high viral load.

When evaluating the patient's oral health the examiner was blinded to immunological and virological status. At the beginning of the study, the distribution of patients in the different immunological and virological categories were not significantly different (p>0.05) from Mexico City and from Tijuana. Therefore and only for research purposes, the description of results will be done based on study groups regardless of the geographical location of their clinic.

The prevalence of HIV-OL was established for each study group. The results were analyzed by means of the chi-square test with a confidence level of 95% (p<0.05IC95%) using EPIINFO 5.0 software (CDC-Atlanta, USA).

## Results

Among 87 perinatally HIV-infected patients studied, 23 (26.4%) had HIV-OL. Oral candidiasis was the most prevalent opportunistic oral infection with 19 (21.8%) cases. The most common clinical type of OC was the pseudomembranous one with 11 cases. Seven cases of OC were erythematous candidiasis, and one case of OC was angular cheilitis. The following HIV-OL were identified: Linear gingival erythema (LGE) in 4 (4.6%) patients, Herpes Simplex (HS) in 2 (2.1%), one case of non-specific oral ulcers (NSOU) and one case of parotid gland enlargement (PGE). The number of oral lesions is higher than the number of patients with HIV-OL because 3 patients had, two or more HIV-OL concomitantly.

Among 25 HIV+/AIDS adolescents, 5 (20%) patients had HIV-OL. In contrast, among 62 HIV/AIDS children, 19 (30.6%) had HIV-OL. The difference was no significant (p >0.05). In both study groups OC was the most prevalent oral opportunistic infection.

In the Adg 5 (20%) cases of OC: 2 cases of pseudomembranous candidiasis; 2 of erythematous candidiasis and one of angular cheilitis, were observed. In the Chg there were 14 (24.2%) cases of OC: 9 pseudomembranous candidiasis and 5 erythematous candidiasis. A non significant (p >0.05) difference was observed in the prevalence of OC between the study groups. One case of HS was diagnosed in each study group while all the cases of LGE, NSOU and PGE were diagnosed in the Chg. The distribution of all oral lesions diagnosed in the study groups is shown in (Table 1).

In regard to immunological status, the highest prevalence of HIV-OL was observed in moderately immunodeficient patients from Adg (36.4%) and among severely immunodeficient patients belonging to Chg (40%). No statistical association (p >0.05) was observed between the higher prevalence of HIV-OL and the immunological category in both study groups. In regard to virological status, the highest prevalence of HIV-OL was observed in HIV+/AIDS adolescents with high viral load (60%) and in HIV+/AIDS children with high viral load (72.7%). A statistical association of high prevalence of HIV-OL and high viral load was observed in both Adg (p 0.01; OR 28.5 IC95% 1 – 1569) and Chg (p 0.002; OR 9.7 IC95% 1 – 63). The highest prevalence of OC was observed in the severely immunodeficient children and in HIV+/AIDS children with viral load >100,000 copies/mL. The association of high viral load and a high OC prevalence was statistically significant in both study groups (p <0.05). The distribution of HIV-OL and OC in the study groups in regard to their immunological and virological status is shown in (Table 2).

**Table 1.** Prevalences of oral lesions related to HIV infection in the study groups.

| | OL-HIV | OC | HS | LGE | NSOU | PGE |
|---|---|---|---|---|---|---|
| **TOTAL (n = 87)** | 23 (26.4%) | 19 (21.8%) | 2 (2.3%) | 4 (4.6%) | 1 (1.1%) | 1 (1.1%) |
| **HIV+/AIDS CHILDREN (n = 62)** | 19 (30.6%) | 14 (24.2%) | 1 (1.6%) | 4 (6.4%) | 1 (1.6%) | 1 (1.6%) |
| **HIV+/AIDS ADOLESCENTS (n = 25)** | 5 (20%) | 5 (20%) | 1 (4%) | ------ | ------ | ---- |

n = number of patients; (%) = prevalence ; OL-HIV = oral lesions related to HIV infection; OC = oral candidiasis; HS = herpes simplex; LGE = linear gingival erythema; NSOU = non-specified oral ulcer; PGE = parotid gland enlargement.

**Table 2.** Prevalences of oral lesions related to HIV infection and oral candidosis in regard to immunological and virological status of the study groups.

| STUDY GROUP | IMMUNE/VIROLOGICAL STATUS | | OL-HIV | OC |
|---|---|---|---|---|
| HIV+/AIDS CHILDREN (n = 62) | IMMUNE STATUS | MODERATE IMMUNODEFICIENCY n = 34 | 11 (32.4%) | 8 (23.5%) |
| | | MILD IMMUNODEFICIENCY n = 23 | 6 (26.1%) | 5 (21.7%) |
| | | SEVERE IMMUNODEFICIENCY n = 5 | 2 (40%) | 2 (40%) |
| | VIROLOGICAL STATUS | UDVL n = 21 | 5 (23.8%) | 3 (14.3%) |
| | | LOW VIRAL LOAD[a] n = 30 | 6 (20%) | 5 (16.7%) |
| | | HIGH VIRAL LOAD[b] N = 11 | 8 (72.7%) p 0.002 OR 9.7 IC95% 1.8 – 63.3 | 7 (63.6%) p 0.002 OR 9.4 IC95% 1.8 – 52.4 |
| HIV+/AIDS ADOLESCENTS | IMMUNE STATUS | MODERATE IMMUNODEFICIENCY n = 11 | ------ | ------ |
| | | MILD IMMUNODEFICIENCY n = 11 | 4 (36.4%) | 4 (36.4%) |
| | | SEVERE IMMUNODEFICIENCY n = 3 | ------ | ----- |
| | VIROLOGICAL STATUS | UDVL n = 4 | ------ | |
| | | LOW VIRAL LOAD[c] N = 16 | 1 (6.3%) | 1 (6.3%) |
| | | HIGH VIRAL LOAD[d] N = 5 | 3 (60%) p 0.01 OR 28.5 IC95% 1.2 – 1569.4 | 3 (60%) p 0.01 OR 28.5 IC95% 1.2 – 1569.4 |

n = number of patients; (%) = prevalence; OL-HIV = oral lesions related to HIV infection; OC = oral candidiasis; UDVL = undetectable viral load; a = VIRAL LOAD >50 - <100,000 copies/mL; b = VIRAL LOAD >100,000 copies/mL; c = VIRAL LOAD >50 - <10,000 copies/Ml; d = viral load >10,000 copies/mL.

## Discussion

Our findings offer insights on oral lesions in perinatally HIV-infected adolescents and children. The prevalence of HIV-OL, OC, LGE, HS, and NSOU found in the Chg is in accordance to previously reports in the scientific literature. The reported prevalence of HIV-OL is from 28.9% to 69% (10,11); from 2.9% to 67% respect to OC (10-12); from 1.9% to 4% in regard to LGE and from 1.3% to 6.5% with respect to HS (10-12). The prevalence of HIV-OL and of OC found in the Chg is very similar to that previously reported in Mexican HIV+/AIDS children (12). In 2001 a prevalence of 29.2% and 20.8% to HIV-OL and to OC, respectively was reported (12). This data suggests that the prevalence of HIV-OL in Mexican perinatally HIV-infected children has not diminished in the last years.

Only one case (1.4%) of PGE was diagnosed in the Chg. The prevalence of PGE in HIV+/AIDS children is from 8.8% to 47% (12). PGE has been related to slow progression of HIV disease (13). If this assumption is true,

perinatally HIV-infected adolescents should had had a higher prevalence of PGE during their childhood. We have no data to confirm or reject this assumption. An experimental protocol design ex-profeso will be necessary to confirm this proposal. The presence of Oral Hairy Leucoplakia (OHL) in HIV+/AIDS children is controversial. The prevalence of OHL reported in HIV+/AIDS children ranges from 2% to 6.7% (10,11), although some authors consider that this opportunistic viral infection is rare or absent in HIV+/AIDS children (10,11). We can not affirm or deny that perinatally HIV-infected children will develop OHL during adolescence or adulthood. A future research in regard to this issue is necessary. None of the children and adolescents observed by us had OHL.

In spite of the increase of perinatally HIV-infected adolescents, scientific information about this particular population is scarce (14). With regard to the lesions of the oral soft tissues in perinatally HIV-infected adolescents, and to the best of our knowledge, this is the first report that describes the prevalence of HIV-OL in HIV+ adolescents. In this sample of Mexican perinatally HIV-infected patients the lower prevalence of HIV-OL observes in the Adg can be explained by the fact that LGE and PGE are classified as oral lesions strongly related to HIV+ children (5). Both lesions were present in the Chg but were absent in the Adg. However the most frequent opportunistic oral infection does not change.

Clinical events of HS are closely related to stress and to emotional imbalance (15). Owing to the fact that depression, bereavement and anxiety is a characteristics of the HIV+ adolescent's personality (14), the Adg should have shown the highest prevalence of HS. However, in HIV+ adolescents only one case of HS was diagnosed. The present report is of a cross over study and this could explain the lower prevalence of HS. A cohort study would be necessary to clarify this issue.

We observe in both study groups close association of high viral load with a high prevalence of HIV-OL and OC. This finding supports the usefulness of the HIV-OL and the OC as clinical markers of viral failure in HIV+/AIDS children and adolescents undergoing HAART. Oral candidiasis has been proposed as clinical markers of HIV-infection progression (16), however, we do not found association of higher prevalence of OC with HIV+ adolescents severely inmunodeficient. The small sample of this particular study population could explain this fact. If the prognostic value of OC is present in HIV+/AIDS adolescents, it should be assessed.

The pattern of the progression of HIV-infection in children and adolescents trends to behave as a chronic disease, and therefore their psychosocial needs resemble the needs of the chronically ill patients rather than the terminally ill ones (17). The increase of life expectancy observed in perinatally HIV-infected children and adolescents and the need to improve their quality of life will increase their demand of oral health services. HIV+ patients with HIV-OL have a lower quality of life than HIV+ patients without oral lesions (18). Untreated oral disease may interfere with talking, chewing and swallowing and lead to weight loss and malnutrition. Therefore professional oral health care plays an important role in improving and maintaining health-related quality of life in HIV-patients (18). Consequently the responsibility of the dentist for being able to identify HIV-OL in HIV+/AIDS children and adolescents is important (10,11). An anticipatory comprehensive HIV-infant oral care program, consisting of oral health risk assessment at regularly scheduled dental visits, early regular dental assessment, counseling sessions for parents during the regular dental visits or additional scheduled visits if a child is deemed at risk, has been proposed (19). Due to the findings obtained in the present report, it is suggested that the oral care program should also include adolescents and include preventive strategies against oral opportunistic infections and it should necessarily include outreach and incentives to reinforce attendance and oral health education.

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