

# Oral manifestations in human immunodeficiency virus infected pediatric patients receiving and not receiving antiretroviral therapy: a cross sectional study

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*The aim of the study was to assess and compare oral manifestations of human immunodeficiency virus (HIV) infected pediatric patients undergoing antiretroviral therapy (ART) and those not undergoing ART. A cross sectional study included HIV positive children (receiving and not receiving ART) aged 5-15 years, registered at the District Hospital ART Centre, Udaipur, and HIV negative schoolchildren. HIV related oral lesions were diagnosed according to the World Health Organization criteria. Sociodemographic and other related information were also recorded. CD4+ cell count was determined in all study subjects. The  $\chi^2$ -test, stepwise multiple linear regression and logistic regression were used on statistical analysis. In all tests, confidence interval and p-value were set at 95% and  $\leq 0.05$ , respectively. A greater proportion of HIV patients receiving treatment had CD4+ cell count of more than 750 cells/mm<sup>3</sup>. The majority of HIV patients receiving ART for more than three years and only 20% of those not receiving ART were free from any oral lesions. The results of the present study demonstrated ART to be effective in reducing the prevalence of HIV related oral lesions, as already described in the literature; however, unlike previous studies, the present paper reports more valid findings for having included most of the confounding variables.*

**Keywords:** Antiretroviral therapy, highly active; HIV; oral manifestations

## INTRODUCTION

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic is one of the most serious health hazards to affect humanity and the fastest growing threat to humanity today. It remains one of the world's most significant public health challenges, particularly in low- and middle-income countries. According to the Global Health Observatory data Repository, 35 million people were living with HIV worldwide at the end of 2013, with a mortality of 1.5 million (1).

The first symptoms in HIV infected children are oral lesions which have been associated with immune suppression and reduced amounts of serum CD4+ T lymphocytes (2). In chil-

dren, oral lesions are associated with HIV infection and disease progression due to their opportunistic nature and are therefore part of the World Health Organization (WHO) clas-

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Primljeno/Received: 28. 5. 2015., Prihvaćeno/Accepted: 21. 7. 2015.

sification to determine the clinical stage of pediatric HIV disease (3). When HIV status is not known, the lesions provide strong indication of the presence of HIV infection. For this reason, the presence and development of oral lesions are used as entry criteria and end points for prophylaxis and therapy, which explains the weight given to these lesions in HIV prevention and intervention programs (4). The use of new antiretroviral drugs, especially protease inhibitors, has markedly reduced mortality and increased life expectancy in the population infected by HIV. From 1996 till 2012, antiretroviral therapy (ART) averted 6.6 million AIDS-related deaths worldwide, including 5.5 million deaths in low- and middle-income countries. As of December 2012, over 900 000 pregnant women living with HIV globally received antiretroviral prophylaxis or treatment. Coverage of antiretroviral programs for the prevention of mother-to-child transmission (excluding the less effective single dose nevirapine regimen) increased from 57% (51%-64%) in 2011 to 62% (57%-70%) in 2012. From 2001 till 2012, there was a 52% decline in new HIV infections among children (5). Recent studies on ART from developed countries have confirmed reduction in the prevalence of oral lesions among infected adults and children (6, 7). Furthermore, in a recent Brazilian study on HIV-infected children, oral manifestations have been reported to be clinical predictors of highly active ART (HAART) failure (7). However, most of the studies investigating oral manifestations of HIV have been performed in western countries. Also, there is a dearth of information on patients on ART treatment and those not receiving treatment. Therefore, the present study was conducted to assess and compare oral manifestations in HIV infected pediatric patients undergoing ART and those not undergoing ART.

## MATERIALS AND METHODS

### *Study design, study population and study area*

A descriptive cross sectional study included HIV positive children (receiving and not receiving ART) aged 5-15 years, registered at the District Hospital ART Centre, Udaipur, (Rajasthan), and HIV negative schoolchildren enrolled in a nearby school.

### *Official Permission, Ethical clearance and informed consent*

The study protocol was reviewed by the institutional Ethics Committee and was granted ethical clearance. Official permissions were obtained from the District Hospital Anti-Retroviral Therapy Centre, Udaipur (Rajasthan) and the selected school. Parents of the selected children signed the written informed consent form.

### *Inclusion criteria*

- For HIV positive subjects: subjects positive on particle agglutination test for antibodies to HIV (Capillus® Trinity Biotech PLC, Bray, County Wicklow, Ireland) and enzyme-linked immunosorbent assay (ELISA) (Enzygnost® Anti-HIV 1/2 Plus, Behring, Behringwerke AG, Marburg, Germany).
- For controls: systemically healthy subjects.

### *Exclusion criteria*

Subjects with a history of adverse habits like tobacco, betel nut, etc.

### *Sample selection*

Sixty-two HIV positive patients undergoing ART for at least a month and 55 patients not undergoing any treatment and fulfilling the eligibility criteria were randomly selected from patients visiting District Hospital ART centre, Udaipur, from June 2014 to August 2014. Fifty control children of the same age group were randomly selected from a nearby school.

### *Proforma details*

Study proforma consisted of three sections:

1. General information: age, gender, place of residence (urban/rural), socioeconomic status, duration of HIV infection, duration of ART, use of traditional medicine, presence of HIV related systemic disease, and group of children (I, II, III). Socioeconomic status was recorded according to Prasad's classification (8) of socioeconomic status scale based on which it was stratified into 5 categories, viz. Upper High, High, Upper Middle, Lower Middle and Poor.
2. Clinical examination:  
Oral manifestations: HIV related oral lesions were diagnosed according to the WHO criteria (9).
3. Biochemical investigations:  
CD4+ cell count.

Clinical examination was made according to Type III examination as described in the WHO Oral Health Survey Basic Methods, 1997 (10).

### *Infection control*

For examination, well sterile and disposable ice-cream wooden sticks, mouth mirrors and explorers were used. All the universal precautions were followed.

### Statistical analysis

The recorded data were compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of the SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). The  $\chi^2$ -test, stepwise multiple linear regression and multiple logistic regression were used on statistical analysis. In all tests, confidence interval (CI) and the level of significance were set at 95% and  $\leq 0.05$ , respectively.

### RESULTS

Among all HIV positive subjects, 62 (34.7%) subjects were receiving ART and 55 (30.7%) subjects were not receiving ART. The majority of study subjects were in the age range of 11-15 years (62%) and were males (56.9%). The majority of subjects receiving ART were urban residents and those not receiving ART were rural residents. Most of the HIV positive subjects were of lower socioeconomic background. However, the proportion of subjects of higher socioeconomic

TABLE 1. Distribution of study subjects

Variable	HIV patients receiving ART n (%)		HIV patients not receiving ART n (%)	Systemically healthy controls n (%)	Total
	Short term therapy (<3 years)	Long term therapy ( $\geq 3$ years)			
<b>Age (yrs)</b>					
5-10	13 (48.2)	15 (42.9)	19 (30)	25 (40.3)	72 (38)
11-15	14 (51.9)	20 (57.1)	36 (70)	37 (59.7)	107 (62)
<b>Gender</b>					
Male	15 (55.6)	22 (62.9)	29 (50)	36 (58.1)	102 (56.9)
Female	12 (44.4)	13 (37.1)	26 (50)	26 (41.9)	77 (43)
<b>Place of residence</b>					
Urban	17 (62.9)	21 (60)	27 (46)	29 (46.8)	94 (52.5)
Rural	10 (37.1)	14 (40)	28 (54)	33 (53.2)	85 (47.4)
<b>Socioeconomic status</b>					
Upper high	2 (7.4)	2 (5.7)	0	5 (8.1)	9 (4)
High	3 (11.1)	3 (8.6)	0	2 (3.2)	8 (3.3)
Upper middle	5 (18.5)	5 (14.3)	7 (12.7)	15 (27.3)	32 (17.3)
Lower middle	10 (37)	13 (37.1)	23 (41.8)	13 (23.6)	59 (36)
Poor	7 (25.9)	12 (34.3)	25 (45.4)	27 (49.1)	71 (39.3)
<b>Duration of HIV infection (yrs)</b>					
$\leq 2$ years	18 (66.7)	11 (25)	39 (70.9)	-	68 (34)
>2 years	9 (33.3)	24 (75)	16 (29.1)	-	49 (32.7)
<b>Presence of HIV related systemic disease</b>					
Yes	16 (59.3)	15 (46.9)	43 (78.2)	0	74 (42)
No	11 (40.7)	20 (53.1)	12 (21.8)	62 (100)	105 (24.7)
<b>Use of traditional medicine</b>					
Yes	15 (55.5)	15 (37.5)	35 (63.6)	0	65 (37.3)
No	12 (44.5)	20 (62.5)	20 (36.4)	62 (100)	114 (62.7)
<b>CD4+ cell count (cell/mm<sup>3</sup>)</b>					
<250	8 (29.6)	3 (6.3)	27 (49.1)	-	38 (22)
250-750	5 (18.5)	9 (21.9)	22 (40)	-	36 (20.7)
>750	14 (51.9)	23 (71.9)	6 (10.9)	-	43 (24)
<b>Oral lesions</b>					
None	12 (44.5)	28 (80)	12 (21.8)	62 (100)	114 (72)
Linear gingival erythema	0	0	3 (5.5)	0	3 (1.3)
Hairy leukoplakia	0	0	3 (5.5)	0	3 (2)
Angular cheilitis	0	0	4 (7.3)	0	4 (1.3)
Oral ulcers	3 (11.1)	2 (5.7)	4 (7.3)	0	9 (4.7)
Candidiasis	10 (37)	1 (2.8)	21 (38.2)	0	32 (15.3)
Hyperpigmentation	2 (7.4)	4 (11.4)	8 (14.5)	0	14 (3.3)
<b>Total</b>	27 (15.1)	35 (19.6)	55 (30.7)	62 (34.6)	179 (100)

HIV = human immunodeficiency virus; ART = antiretroviral therapy

TABLE 2. Prevalence of HIV related oral lesions among HIV positive subjects

Variable	Oral lesions n (%)		p-value
	Present	Absent	
<b>Age</b>			
5-10 years (n=47)	17 (36.2)	30 (63.8)	0.68
10-15 years (n=70)	35 (50)	35 (50)	
<b>Gender</b>			
Male (n=55)	20 (36.4)	35 (63.6)	0.54
Female (n=62)	32 (51.6)	30 (48.4)	
<b>Place of residence</b>			
Urban (n=65)	19 (29.2)	38 (58.5)	0.11
Rural (n=52)	33 (63.5)	27 (51.9)	
<b>Socioeconomic status</b>			
Upper high (n=4)	1 (25)	3 (75)	0.023*
High (n=6)	2 (33.3)	4 (66.7)	
Upper middle (n=17)	5 (29.4)	12 (70.6)	
Lower middle (n=46)	21 (45.7)	25 (54.3)	
Poor (n=44)	23 (52.3)	21 (47.7)	
<b>Duration of HIV infection (yrs)</b>			
≤2 years (n=68)	23 (33.8)	45 (66.2)	0.05*
>2 years (n=49)	29 (59.2)	20 (40.8)	
<b>Presence of HIV related systemic disease</b>			
Yes (n=74)	39 (52.7)	35 (47.3)	0.004*
No (n=43)	13 (30.2)	30 (69.7)	
<b>Use of traditional medicine</b>			
Yes (n=65)	21 (32.3)	44 (67.8)	0.89
No (n=52)	31 (59.6)	21 (40.4)	
<b>CD4+ cell count (cell/mm<sup>3</sup>)</b>			
<250 (n=38)	25 (65.8)	13 (34.2)	0.044*
250-750 (n=36)	19 (52.8)	17 (47.2)	
>750 (n=43)	8 (18.6)	35 (81.4)	
<b>HIV positive subjects</b>			
<b>On ART (n=62)</b>			
<3 years (n=27)	15 (55.5)	12 (44.4)	0.032*
≥3 years (n=35)	7 (20)	28 (80)	
<b>Not on ART (n=55)</b>			
	43 (78.2)	12 (21.8)	
<b>Total (n=117)</b>			
	52 (44.5)	65 (55.5)	

HIV = human immunodeficiency virus; ART = antiretroviral therapy; test applied:  $\chi^2$ -test; \*statistically significant difference at  $p \leq 0.05$

status was greater among those receiving ART than among those not receiving ART. Around 70% of those not receiving ART had HIV infection for less than two years. The majority (63.6%) of subjects not receiving ART were on traditional medicine. Around half of the HIV positive subjects not receiving ART showed CD4+ cells count of less than 250 cells/mm<sup>3</sup>, whereas the majority of subjects receiving ART had CD4+ cells count of more than 750 cells/mm<sup>3</sup>. Only 20% of

TABLE 3. Stepwise multiple linear regression analysis with HIV related oral lesion as dependent variable

Model	R	R <sup>2</sup>	F-value	p-value
HIV related oral lesion				
1	0.134 <sup>a</sup>	0.045	129.12	0.000 <sup>a</sup>
2	0.812 <sup>b</sup>	0.421	136.77	0.000 <sup>b</sup>
3	0.914 <sup>c</sup>	0.435	99.56	0.000 <sup>c</sup>
4	0.856 <sup>d</sup>	0.512	97.812	0.000 <sup>d</sup>
5	0.843 <sup>e</sup>	0.662	94.333	0.000 <sup>e</sup>
a. Predictors: (Constant), Presence of systemic disease.				
b. Predictors: (Constant), Presence of systemic disease, not receiving ART therapy.				
c. Predictors: (Constant), Presence of systemic disease, not receiving ART therapy, Duration of HIV infection.				
d. Predictors: (Constant), Presence of systemic disease, not receiving ART therapy, Duration of HIV infection, CD4+ cell count.				
e. Predictors: (Constant), Presence of systemic disease, not receiving ART therapy, Duration of HIV infection, CD4+ cell count, socioeconomic status.				

HIV = human immunodeficiency virus; ART = antiretroviral therapy

TABLE 4. Odds ratio (OR) and 95% confidence interval (CI) for HIV related oral lesions according to multiple logistic regression

Independent variable	HIV related oral lesion OR (95% CI)
Socioeconomic status: low/high	4.434* (2.361-13.521)
Duration of HIV infection: ≤2 years/>2 years	0.671* (0.136-2.888)
Presence of HIV related systemic disease: yes/no	5.777* (1.654-5.892)
CD4+ cell count: ≤250/>250	1.999* (0.129-3.688)
Patient receiving ART therapy: not receiving ART/receiving ART	5.634* (2.341-9.888)

HIV = human immunodeficiency virus; ART = antiretroviral therapy; \*statistically significant at  $p \leq 0.05$

HIV positive subjects receiving ART for more than three years had oral mucosal lesions. Among those not receiving ART, 78.2% of subjects had oral mucosal lesions (Table 1).

Bivariate analysis revealed significant association of the presence of oral lesions with socioeconomic status ( $p=0.023$ ), duration of HIV infection ( $p=0.05$ ), presence of HIV related systemic disease ( $p=0.004$ ), CD4+ cell count ( $p=0.044$ ) and ART treatment ( $p=0.032$ ) (Table 2). According to multivariate modeling, the best predictor of the presence of oral lesions was the presence of HIV related systemic disease, followed by ART therapy, with variances of 4.5% and 42.1%, respectively. Duration of HIV infection, CD4+ cell count and socioeconomic status also predicted the presence of oral lesions with the variances of 43.5%, 51.2% and 66.2%, respectively (Table 3). Multiple logistic regression analysis depicted that patients not receiving ART had 5.634 (odds ratio) ( $p \leq 0.05$ ) times greater risk of developing oral lesions

than those receiving ART. Table 4 shows the significant odds ratios of 3.51, 0.512, 2.789, 1.916 and 5.27 for socioeconomic status, duration of HIV infection, presence of HIV related systemic disease, CD4+ cell count and group (ART treatment), respectively.

## DISCUSSION

Oral manifestations are observed commonly in adults and children with HIV infection (11,12). ART is known to suppress HIV replication and helps in immune reconstitution in HIV patients. An association between oral mucosal lesions and immunosuppression has already been documented (13, 14). Hence, this study compared the HIV related oral lesions in patients undergoing ART and those not taking any treatment.

In the present study, candidiasis was evidenced to be the first most common oral lesion, followed by oral ulcers and mucosal hyperpigmentation. A similar prevalence of candidiasis and oral ulcer was observed by *Leggott* (1992) (15) (13%) and *Alexio et al.* (2010) (16) (4%). Oral candidiasis has also been reported as the most common oral lesion among HIV infected subjects in Thailand (17). Among South African pediatric patients, oral candidiasis was most common, followed by oral ulcers (18). Oral lesions may have negative impact on the nutritional health of the children by reducing food intake as a result of discomfort during eating (14). In another review of published reports, *Enwonwu* (19) revealed that malnutrition may induce mucosal disruptions predisposing candidiasis. The prevalence of mucosal hyperpigmentation in the present study was consistent with the findings reported by *Hamza et al.* (2006) (20), which might be attributed to the increased melanin production in the epithelium associated with the increased release of alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH) (21).

The presence of systemic disease was found to be the best predictor of oral lesions in the present study. Similar association has also been reported by *Ranganathan et al.* (2010) among pediatric HIV patients from South India (22, 17). The presence of oral lesions has significant effects on the health related quality of life in HIV patients. Dysphagia caused by oral lesions might cause malnutrition and continuous clinical deterioration (4).

In the present study, oral lesions showed greater prevalence in the lower socioeconomic group subjects as compared to the upper socioeconomic group subjects. *Noce* (2009) reviewed the association between socioeconomic status and HIV-associated oral lesions in Rio de Janeiro from 1997 to 2004 and concluded that socioeconomic status was associated with immunosuppression and prevalence of oral lesions (23). In confirmation to previous research, duration of

HIV infection was also observed as one of the predictors of oral lesions among HIV patients in the present study, indicating that worsening in the prevalence of oral lesions also varied significantly with the increasing duration of HIV infection, which is consistent with a previous study (24).

The patients on ART had a significantly increased CD4 cell count as compared to those not receiving ART in the present study. Moreover, those on long term therapy (>3 years) had better immunosuppression in terms of CD4 cell count than those on short term therapy. Retrospective review of electronically captured data from patients initiating HAART at a south-eastern US clinic elicited significant association of CD4+ cell count and presence of oral lesions (25). *Petruzzi et al.* (2013) (26) also report similar findings among south Brazilian patients. *Gullick et al.* (1997) (27) and *Pakkar et al.* (1998) (28) report that the gradual CD4 cell count rise is likely to reflect the generation of new cells by peripheral expansion of pre-existing T cell clones or generation of thymically derived naive cells in ART patients.

The use of traditional medicine did not show any association with the presence of oral lesions in the present study, an observation that is in agreement with that reported earlier in Tanzania (29). It is crucial to learn more about the nature and composition of these plant medicines and their potential interactions with drugs that are used for the management of HIV/AIDS and its associated opportunistic diseases.

In confirmation of the findings reported by *Tappuni and Fleming* (11) and *Pinheiro et al.* (2009) (30), the present study revealed significantly fewer HIV-related oral manifestations among patients receiving ART (35.4%) than in the non-ART group (78.2%). This might be an expression of reconstituted immune system as a result of ART. However, on the other hand, some authors (30) found an increase in salivary gland disease and a striking increase in oral warts in some patients, probably as a complication of ART. No such adverse effects were observed in the present study.

Notably, in the present study, the patients on ART for more than three years had a significantly lower prevalence of oral lesions than those on long term therapy, which corroborates the findings of a previous study (31).

As this was an institutional study including a single institution, all HIV patients on standardized triple drug regimens were included in the present study, thus ensuring removal of the confounding effect of different drug regimens. The confounding effect of other variables was taken in consideration through mathematical modeling, which was deficient in previous researches. Quality-assured laboratory assays were performed in a single nationally accredited laboratory. The cross sectional nature of the present study

limited the validity of the study to a certain extent, enhancing the need of future longitudinal studies on the same issue. Besides, further studies are necessary to access the HIV-infected children groups using other combinations of ART.

## CONCLUSION

Reduction in oral lesions among AIDS patients on ART was clearly demonstrated in the present study. Our study proposes that oral lesions may be considered as clinical markers of virologic failure in HIV-infected patients receiving ART. Hence, there is a need to centralize research efforts in poor countries to support standardized studies in order to explore the use of oral lesions as surrogate markers for the initiation of ART and prophylaxis of opportunistic diseases. There is also a need to integrate oral health care into the general medical care of these children to ensure regular screening for oral lesions and appropriate early management.

## ACKNOWLEDGEMENT:

Authors would like to express their appreciation to the research centre, College of Applied Medical Sciences and the deanship of scientific research at King Saud University for funding this research.

## Abbreviations:

AIDS – *Acquired Immunodeficiency Syndrome*

ART – *Anti retroviral therapy*

HIV – *Human Immunodeficiency virus*

MSH – *Melanocyte stimulating hormone*

## NOVČANA POTPORA/FUNDING

Nema/None

## ETIČKO ODOBRENJE/ETHICAL APPROVAL

Nije potrebno/None

## SUKOB INTERESA/CONFLICT OF INTEREST

Autori su popunili *the Unified Competing Interest form na www.icmje.org/coi\_disclosure.pdf (dostupno na zahtjev)* obrazac i izjavljuju: nemaju potporu niti jedne organizacije za objavljeni rad; nemaju financijsku potporu niti jedne organizacije koja bi mogla imati interes za objavu ovog rada u posljednje 3 godine; nemaju drugih veza ili aktivnosti koje bi mogle utjecati na objavljeni rad./All authors have completed the *Unified Competing Interest form at www.icmje.org/coi\_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.*

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## SAŽETAK

## Oralne manifestacije u pedijatrijskih bolesnika zaraženih virusom humane imunodeficijencije na antiretrovirusnoj terapiji i bez nje: presječno istraživanje

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*Cilj istraživanja bio je procijeniti i usporediti oralne manifestacije u pedijatrijskih bolesnika zaraženih virusom humane imunodeficijencije (HIV) koji primaju antiretrovirusnu terapiju (ART) i onih koji ne primaju ovu terapiju. Ovo presječno istraživanje uključilo je HIV pozitivnu djecu (djecu koja primaju ART i djecu koja ne primaju ART) u dobi od 5-15 godina, registriranu pri Centru za ART u Pokrajinskoj bolnici u Udaipuru te HIV negativnu školsku djecu. Oralne promjene povezane s HIV-om dijagnosticirane su prema kriterijima Svjetske zdravstvene organizacije. Prikupljeni su socio-demografski te ostali podaci za svu djecu uključenu u ispitivanje. U svim je određen broj CD4+ stanica. U statističkoj analizi primijenjen je  $\chi^2$ -test te postupna višestruka linearna regresija i logistička regresija. U svim testovima interval vjerodostojnosti i vrijednost p utvrđeni su na razini od 95% odnosno  $\leq 0,05$ . Broj CD4+ stanica veći od 750 stanica/mm<sup>3</sup> zabilježen je u većem postotku HIV bolesnika na ART. Bez oralnih promjena bila je većina HIV bolesnika koji su primali ART duže od tri godine, ali samo 20% onih koji nisu primali ART. Rezultati ovoga istraživanja pokazuju da ART učinkovito snižava učestalost oralnih promjena povezanih s HIV-om, što je već prije opisano u literaturi. Međutim, za razliku od prijašnjih ispitivanja, nalazi prikazani u ovom radu imaju veću vrijednost, jer uključuju većinu čimbenika koji bi mogli utjecati na rezultate.*

**Ključne riječi:** antiretrovirusna terapija, visoko aktivna; virus humane imunodeficijencije; oralne manifestacije