

Full Length Research paper

HIV-related oral lesions as markers of immunosuppression in HIV sero-positive Nigerian patients

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This study was carried out to assess the use of HIV-related oral lesions as markers of immunosuppression defined as CD4+ cell counts <200 cells/mm³ and viral load ≥20,000 copies/ml in HIV positive Nigerian adults. Cross-sectional study on 278 HAART naive adults seen at an AIDS referral Centre. Oral examination was according to the European Community Clearinghouse on oral problems related to HIV infection. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) is reported for oral lesions with plasma HIV-RNA ≥20,000 copies/ml and CD4 counts <200 cells/mm³. The highest PPV (100%) for CD4 <200 cells/mm³ was noticed from Kaposi's sarcoma, oral ulcerations and linear gingival erythema, $P > 0.05$. Lesions with moderate to high PPV for CD4 <200 cells/mm³ were pseudomembranous candidiasis (96.3%; $P = 0.003$), angular cheilitis (96.0%; $P = 0.004$) erythematous candidiasis (94.4%; $P = 0.025$), and melanotic hyperpigmentation (87.1%; $P = 0.040$). Oral hairy leukoplakia was the only lesion significant for HIV- RNA ≥ 20,000 copies/ml (PPV: 89.3%; $P < 0.05$). Oral candidiasis and melanotic hyperpigmentation could be used as markers of immunosuppression depicted by CD4 counts <200 cells/mm³ while oral hairy leukoplakia could indicate HIV- RNA ≥20,000 copies/ml in an adult Nigerian population.

Keywords: HIV/AIDS, CD4 count, Viral load, markers

INTRODUCTION

Many of the clinical features of human immunodeficiency virus (HIV) infection can be attributed to the profound immunological deficiencies which develop in infected individuals. HIV is immunosuppressive because it affects and destroys CD4 cells. There is an inverse relationship between the level of the virus in the blood (viraemia) and the CD4 lymphocyte count (CD4 count). These parameters (CD4 count and viral load) are the central indicators of disease progression and immune status in HIV infected individuals (Beverly and Helbert, 1997; Pinto and Greenberg, 2000).

Presently, the most powerful laboratory immunologic marker of HIV disease progression is the CD4 cell count. Other markers include neopterin, beta 2 – microglobulin, presence of p-24 antigen and HIV – specific immunoglobulin levels (Glick et al., 1994; Arthur-Nouel, 1994). The normal value of CD4 lymphocytes is put at between 500 - 1,500 cells/mm³ (Cotran et al, 1999). A

progressive downward trend in CD4 cells reflects disease progression and decreased life expectancy, even in the absence of symptoms. Also a decline in the CD4 count predisposes the HIV infected individual to a wide range of opportunistic infections.

Since the loss of immune containment is associated with declining CD4 counts, the Centres for Disease Classification (CDC) stratifies patients with HIV infection into three categories on the basis of CD4 counts : CD4 counts ≥ 500 cells/mm³; 200-499 cells/mm³ and < 200 cells/mm³. A CD4 count < 200 cells/mm³ is associated with severe immune suppression and the CDC in 1993 included all HIV - infected persons with such a count as fulfilling an AIDS- defining diagnosis (Beverly and Helbert, 1997).

Laboratory parameters will only partially reflect disease stage and progression. The addition of clinical markers more accurately reflects the overall disease status of the patient. (Glick et al., 1994) Though, the measurement of CD4 counts requires a blood sample and laboratory analysis, the identification of oral lesions can be made during the course of physical examination. These lesions

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are used in several HIV diseases staging and classification designations because of their prognostic significance and their diagnostic simplicity, requiring no sophisticated laboratory tests (Ramirez-Amador et al., 1998; Greenspan and Greenspan, 1991; Scully et al., 1991; Haring, 1990).

Oral lesions are among the earliest clinical manifestations of HIV infection and are associated with HIV- disease progression (Hodgson, 1997). These lesions have been shown to be high predictive markers of severe immune deterioration and disease progression. (Katz et al., 1992; Patton, 2000; Begg et al., 1996; Kolokotronis et al., 1994; Lynch, 1997; Begg et al., 1997; Campo et al., 2002; Gaitan-Cepeda et al., 2005). However, most of these studies had largely been conducted in developed countries and on patients who are homosexual/bisexual and/or intravenous drug users. Considering the potential geographic and gender variability in the presentations of HIV related oral lesions, this study aimed to determine if these lesions could serve as markers of immune suppression in a heterosexual population of HIV-positive adults in a developing country like Nigeria.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Jos University Teaching Hospital (JUTH). The study took place at an AIDS referral centre in JUTH. Informed consent from all the patients was also obtained prior to data collection. It was a cross sectional study involving 278 confirmed HIV positive Nigerian adults living in and around Jos, Nigeria. These patients were those being recruited into the Highly Active Antiretroviral Treatment (HAART) programme of the referral Centre.

All the patients included in the study were those who had not been on any form of HAART. Oral lesions were diagnosed clinically, according to the criteria established by the European Community Clearinghouse on oral problems related to HIV infection (Weibe and Epstein, 1997). Demographic and clinical data were recorded on an adapted form. These among others includes: smoking and alcohol history, stage of HIV infection, HIV serotype and oral complaints. Others are immunologic chemistry; presence of HIV related oral lesions and systemic opportunistic infections. Low CD4 counts could also be a result of some systemic conditions apart from HIV infection. Examples of such include; acute viral infections, sarcoidosis, tuberculosis, systemic lupus erythematosus (SLE), some purine metabolic defects and corticosteroid therapy (Beverly and Helbert, 1997). These were considered in our study as possible co-morbidities for the evaluation of CD4 counts. Oral examinations were conducted by a dentist (OOT) with experience in the identification of HIV- related oral lesions. If multiple lesions were found (in the same patient) at the time of clinical evaluation, each lesion was considered independently for the analysis.

Blood (5ml) was drawn for the determination of immunologic parameters (CD4 count and viral load). This was done between 8am – 10am as part of the recruitment exercise for each patient. CD4 count was determined by the Flowcytometric (Cyflow) method (Partec CyFlow Counter®, Partec GmbH D-48161 Münster ·Germany). Viral load measurement was by quantification of viral RNA in peripheral blood with a minimum detectable level of 400RNA copies/ml. This was done using Amplicor® HIV-1 Monitor Test, version 1.5 (Roche-Amplicor®-Roche Diagnostics,

Branchburg, NJ, USA). These tests were done within 12 hours of blood collection (Fryland et al., 2006; Vanprapar et al., 2005).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were checked for specific oral lesions as markers for immunosuppression depicted by CD4 < 200 cells/mm³ and HIV RNA ≥ 20,000 copies/ml. Odds ratio (OR) and 95% confidence interval (CI) for the association of oral lesion with the categorical laboratory markers indicating immune suppression was reported. The results were reported using the “linear – by – linear association” (Mantel-Haenszel) *p* values. *P* values <0.05 were considered statistically significant. Statistical analyses of all data were done using SPSS software version 15.0.

RESULTS

The demographic characteristics of the 267 patients seen are shown in Table 1. 213 (80.1%) patients had clinical AIDS (CDC classification of 1993) at presentation (Table 2). Out of this number, 76 (35.7%) patients had tuberculosis. The overall prevalence of HIV – related oral lesions in this population was 44.2%. Forty - one (15.3%) patients had multiple lesions (maximum of 4 per patient). Oral candidiasis (26.2%) was the most common lesion identified. Others were melanotic hyperpigmentation (11.6%), Oral hairy leukoplakia (10.9%) and xerostomia (8.2%). The female population generally had higher rates for HIV - related oral lesions except for pseudomembraneous candidiasis and xerostomia, *p*>0.05 (Table 3).

The abilities of specific HIV related oral lesions to predict significant immune suppression at CD4 <200cells/mm³ and HIV RNA ≥ 20,000 copies/ml are summarised in Tables 4 and 5. The highest PPV (100%) for CD4 <200 cells/mm³ was noticed from Kaposi's sarcoma, oral ulcerations and linear gingival erythema, *p* > 0.05. Oral candidiasis (pseudomembraneous, erythemathous and angular cheilitis) had the highest OR (11.9, 7.4 and 10.8) *p*<0.05 for CD4 count < 200cells/mm³. The PPV for CD4 <200 cells/mm³ from pseudomembraneous candidiasis, erythemathous candidiasis, angular cheilitis and melanotic hyperpigmentation was significant (87.1 – 96.3; *p* < 0.05). NPV for all the lesions was all in the neighbourhood of 30% for CD4 <200 cells/mm³. All the lesions noticed apart from the general presence of HIV-related oral lesions had low sensitivity for CD4 <200 cells/mm³. Specificity was > 93.7% for all the lesions. (Table 4)

Oral hairy leukoplakia (as a specific HIV related oral lesion) was the only lesion significant for HIV RNA ≥ 20,000 copies/ml (PPV: 89.3, OR: 4.6. CI: 1.4 – 15.8, *p* < 0.05). (Table 5)

DISCUSSION

Many oral lesions are strongly associated with HIV infection. Studies have shown clearly that patients with a CD4 lymphocyte count of less than 200 had more oral

Table 1. Demographic Characteristics of study participants (N = 267)

Variable	Male (109)	Female (158)	Total (267)
Age (years)			
Mean (SD)	41.2 (8.9)	33.3 (8.0)	36.5 (9.2)
Range	25 - 68	19 - 65	19 - 68
Marital Status			
Married	74 (67.9)	65 (41.1)	139 (52.1)
Single	18 (16.5)	34 (21.5)	52 (19.5)
Separated	1 (0.9)	10 (6.3)	11 (4.1)
Divorced	7 (6.4)	8 (5.1)	15 (5.6)
Widowed	9 (8.3)	41 (25.9)	50 (18.7)
Suspected route of transmission			
Heterosexual	99 (90.8)	155 (98.1)	254 (95.1)
Parenteral (Exposure to blood)	5 (4.6)	0	5 (1.9)
Not sure	5 (4.6)	3 (1.9)	8 (3.0)
CDC HIV Clinical disease stage *			
Asymptomatic A	20 (18.3)	43 (27.2)	63 (23.6)
Symptomatic B	39 (35.8)	56 (35.4)	95 (35.6)
AIDS – defining C	50 (45.9)	59 (37.3)	109 (40.8)
CD4 Counts (cells/mm ³)			
Mean (range)	151.1 (3 - 629)	148.1 (3 - 873)	149.3 (3 - 873)
CD4 Counts groups (cells/mm ³)			
< 200	77 (70.6)	113 (72.0)	190 (71.4)
200 – 499	26 (23.9)	42 (26.8)	68 (25.6)
≥ 500	6 (5.5)	2 (1.3)	8 (3.0)
HIV RNA (copies/mL)			
Median (range)	78818 (0 – 1556467)	53064 (0 – 952471)	59181.5 (0 – 1556467)
HIV RNA groups			
<500	9 (8.3)	8 (5.1)	17 (6.4)
500 – 10,000	17 (15.6)	24 (15.3)	41 (15.4)
> 10,000	83 (76.1)	125 (79.6)	208 (78.2)
HIV serotype			
HIV 1	107 (98.2)	158 (100)	265 (99.3)
HIV 1&2	2 (1.8)	0	(0.7)

*CDC classification of 1993

Table 2. Disease Stage using the 1993 Revised CDC Classification System for HIV Infection

CD4+ T cell categories (cells/ mm ³)	Clinical categories		
	A	B	C
	Asymptomatic, acute (primary) HIV	Symptomatic, not A or C Conditions	AIDS Indicator Conditions
≥500	A1 (2)	B1 (4)	C1 (2)
200-499	A2 (31)	B2 (16)	C2 (21)
<200	A3 (29)	B3 (75)	C3 (86)

Persons in categories A3, B3, C1, C2, and C3 have **AIDS** under the 1993 surveillance case definition i.e. 29 + 75 + 86 + 21 + 2 = **213**. This gives **80.1%** for the proportion with AIDS (computed with 266 as the total number due to a missing CD4 count)

Table 3. Prevalence of HIV – related Oral lesions by gender in 267 Nigerian patients

Any Oral Disease	Male n (%)	Female n (%)	Total N (%)
Pseudomembraneous Candidiasis	14 (5.2)	13 (4.9)	27 (10.1)
Angular Cheilitis	11 (4.1)	14 (5.2)	25 (9.4)
Erythematous Candidiasis	6 (2.2)	12 (4.6)	18 (6.7)
Oral Candidiasis	31 (11.5)	39 (14.7)	70 (26.2)
Linear Gingival Erythema	-	2 (0.7)	2 (0.7)
Oral Hairy Leukoplakia	13 (4.9)	16 (6.0)	29 (10.9)
Herpes Simplex	1 (0.4)	5 (1.9)	6 (2.2)
Oral Ulcerations	1 (0.4)	3 (1.1)	4 (1.5)
Kaposi's Sarcoma	2 (0.7)	5 (1.9)	7 (2.6)
Enlarged Salivary Gland	4 (1.5)	5 (1.9)	9 (3.4)
Xerostomia	13 (4.9)	9 (3.4)	22 (8.2)
Melanotic Hyperpigmentation	14 (5.2)	17 (6.4)	31 (11.6)
Presence of Oral lesion	48 (18)	70 (26.2)	118 (44.2)

Table 4. Ability of specific HIV related oral lesions to predict immune suppression (CD4 <200 mm³) in 267 Nigerian patients

Any Oral Disease	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR	CI (95%)	P value
Pseudomembraneous. Candidiasis	13.7	98.7	96.3	31.4	11.9	(1.6 – 89.3)	.003
Angular Cheilitis	12.6	98.7	96.0	31.1	10.8	(1.4 – 81.6)	.004
Erythematous. Candidiasis	8.9	98.7	94.4	30.2	7.4	(0.9 – 56.4)	.025
Linear Gingival Erythema	1.1	100	100	28.8	∞	∞	.370
Oral Hairy Leukoplakia	11.6	90.8	75.9	29.1	1.3	(0.5 – 3.2)	.576
Herpes Simplex	2.1	97.4	66.7	28.5	0.8	(0.1 – 4.4)	.794
Oral Ulcerations	2.1	100	100	29.0	∞	∞	.203
Kaposi's Sarcoma	3.7	100	100	29.3	∞	∞	.091
Enlarged Salivary Gland	2.1	93.4	44.4	27.6	0.3	(0.1 – 1.2)	.069
Xerostomia	9.5	94.7	81.8	29.5	1.9	(0.6 – 5.8)	.261
Melanotic. Hyperpigmentation	14.2	94.7	87.1	30.6	3.0	(1.0 – 8.8)	.040
Presence of Oral lesion ^φ	51.1	72.4	82.2	37.2	2.7	(1.5 – 4.9)	.001

PPV, Positive predictive value (percentage of people with the lesion who actually have CD4 <200 cell/mm³); NPV, negative predictive value (percentage of people without the lesion who have CD4 ≥ 200 cells/mm³); ∞, infinity; φ; Presence of one or more of the separately listed oral lesions

lesions (Begg et al., 1997; Margiotta et al., 1999; Croser et al., 1991). We recorded a similar finding in our study where 86.2% of the total HIV-ROs identified were in the group of patients with CD4 counts < 200 cells/mm³.

Our study shows that subjects with oral candidiasis (pseudomembraneous, erythematous candidiasis, angular cheilitis) and melanotic hyperpigmentation were predictive of a CD4 count of <200cells/mm³. A similar study had shown that while oral lesions were not predictive of progression among subjects with CD4 ≥ 200 cells/mm³, they were highly predictive of progression among those with CD4 < 200cells/mm³ (Begg et al., 1997). Erythematous candidiasis was the only oral lesion significantly associated with CD4 counts <200cells/mm³ in a Zambian study (Hodgson, 1997). This is in contrast to a study conducted in England which showed that the presence of erythematous candidiasis was not related to

advanced HIV disease, rather, pseudomembraneous candidiasis, oral hairy leukoplakia and mucosal ulcerations were those significantly associated with advanced HIV disease (Palmer et al., 1996). These discrepancies might be as a result of other demographic and/or underlying clinical factors. Also, in our study, the presence of oral candidiasis indicated that subjects with this lesion are at higher risk of immune suppression than subjects without the lesion. This association has also been reported in 192 confirmed HIV positive Tanzanians (Matee et al., 2000). Generally, we observed in our study that the presence of HIV-related oral lesions was strongly related to immune suppression (defined as CD4 <200cells/mm³ and HIV RNA > 20,000 copies/ml). Katz et al., (1992) reported that HIV related oral lesions may not be diagnostic of immunodeficiency, as some patients may have these lesions at high CD4 counts while others

Table 5. Ability of specific HIV related oral lesions to predict immune suppression (HIV RNA $\geq 20,000$ copies/ml) in 267 Nigerian patients

Any Oral Disease	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR	CI (95%)	P value
Pseudomembraneous. Candidiasis	12.9	94.4	84.0	32.4	2.2	(0.8 – 6.1)	.094
Angular Cheilitis	10.4	94.4	81.0	31.8	1.2	(0.5 – 3.1)	.228
Erythematous. Candidiasis	8.0	95.8	81.3	31.5	1.7	(0.5 – 5.4)	.286
Linear Gingival Erythema	1.2	100	100	30.9	∞	∞	.346
Oral Hairy Leukoplakia	15.3	95.8	89.3	33.3	4.6	(1.4 – 15.8)	.015
Herpes Simplex	3.1	98.6	83.3	31.0	2.4	(0.3 – 21.0)	.453
Oral Ulcerations	2.5	100	100	31.2	1.5	(1.4 – 1.6)	.181
Kaposi's Sarcoma	2.5	100	100	31.2	1.2	(0.2 – 6.3)	.181
Enlarged Salivary Gland	4.3	98.6	87.5	31.3	3.9	(0.5 – 32.0)	.259
Xerostomia	9.8	94.4	80.0	31.6	1.7	(0.6 – 4.7)	.282
Melanotic. Hyperpigmentation	13.5	90.3	75.9	31.6	1.7	(0.7 – 4.2)	.418
Presence of Oral lesion ϕ	51.5	70.8	80.0	39.2	2.4	(1.4 – 4.1)	.002

PPV, Positive predictive value (percentage of people with the lesion who actually have HIV RNA $\geq 20,000$ copies/ml); NPV, negative predictive value (percentage of people without the lesion who have HIV RNA $< 20,000$ copies/ml); ∞ , infinity; ϕ ; Presence of one or more of the separately listed oral lesion

do not have them despite low CD4 counts. Notwithstanding, a study conducted on sero-positive Haemophiliacs has shown that advanced stage of immune suppression and presence of oral lesions were significantly associated ($p = 0.040$) (Ficarra et al., 1994). A similar work, this time on HIV infected women, gave the odds ratio (OR) for the association between oral lesions and CD4 cell counts as 8.9 indicating a strong positive association with the level of immunosuppression (Shiboski et al., 1994).

We observed that individuals with oral hairy leukoplakia (OHL) were 4.6 times more likely to have a viral load $> 20,000$ copies/ml than individuals without OHL. Another study had shown that when an HIV-infected individual presents with OHL, there was a modest twofold increased likelihood of his or her viral load being 20,000 copies or greater (Patton et al., 1999). OHL is a frequent finding in patients with HIV and indicates advanced immunosuppression (Husak et al., 1996)

Both oral candidiasis and oral leukoplakia have been accepted to be of value in staging and classification schemes for HIV disease (Begg et al., 1997; Margiotta et al., 1999; Greenspan, 1997; Gebic and Lamster, 1997; Kolokotronis et al., 1994). In addition to their role in the diagnosis of HIV infection and as indicators of the progress of HIV disease, they are also used as clinical correlates of CD4 counts (Greenspan, 1997). We surmise from our study that oral candidiasis could be used as markers of immune suppression depicted by CD4 counts < 200 cells/mm³ in our patients. Similarly, oral hairy leukoplakia could indicate viraemia i.e. HIV RNA $> 20,000$ copies/ml in the same population. This strong association could make these lesions a useful tool for

identifying progression of HIV infection, monitoring antiretroviral therapy and serve as markers for immune suppression; particularly where CD4 count and viral load cannot be determined routinely.

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Appendix 1

PHOTOGRAPHS OF SOME PATIENTS SEEN

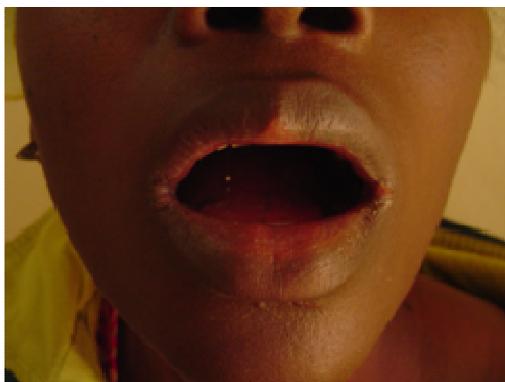
Pseudomembranous Candidiasis (Thrush)



Erythematous Candidiasis



Angular Cheilitis



Appendix 1. cont.

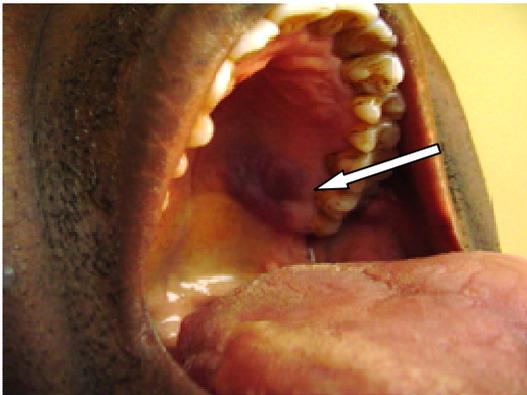
Herpes Simplex (Extra and intra-oral)



Hairy Leukoplakia (HL)



Kaposi's sarcoma



Appendix 1 cont.

Oral Ulcers



Salivary Gland Disease (Parotid Gland Enlargement)



Melanotic Hyperpigmentation

