Contemporary profile of oral manifestations of HIV/AIDS and associated risk factors in a southeastern US clinic

Irene Tamí-Maury, DMD, DrPH, MSc[1]; James Willig, MD, MPH[2]; Sten Vermund, MD, PhD[3]; Pauline Jolly, PhD, MPH[1]; Inmaculada Aban, PhD, MS[4]; Jeffrey Hill, DMD[5]; Craig M. Wilson, MD[1]

1 Department of Epidemiology, School of Public Health, University of Alabama at Birmingham
2 Department of Medicine, University of Alabama at Birmingham
3 Vanderbilt Institute for Global Health, Vanderbilt University
4 Department of Biostatistics, School of Public Health, University of Alabama at Birmingham
5 School of Dentistry, University of Alabama at Birmingham

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Correspondence
Dr. Irene Tamí-Maury, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham (Currently at The University of Texas MD Anderson Cancer Center), 6710 Travis St, Apt. #1, Houston, TX 77030. Tel.: +1-(205)-6432493; Fax: +1-(713)-7944730; e-mail: irene.tami@fulbrightmail.org; irenetami@hotmail.com.James Willig is with the Department of Medicine, University of Alabama at Birmingham. Sten Vermund is with the Vanderbilt Institute for Global Health, Vanderbilt University. Pauline Jolly and Craig M. Wilson are with the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham. Inmaculada Aban is with the Department of Biostatistics, School of Public Health, University of Alabama at Birmingham. Jeffrey Hill is with the School of Dentistry, University of Alabama at Birmingham.

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Abstract

Background: Introduction of highly active antiretroviral therapy (HAART) has resulted in a significant decrease of oral manifestations (OMs). The profile and risk factors for OM in those individuals initiating HAART remain understudied in the Southeast of the United States, region of increasing HIV prevalence.
Objective: To determine clinical, socio-demographic, and laboratory characteristics associated with the presence of OM among patients initiating HAART.
Methods: Retrospective review of electronically captured data from patients initiating HAART at a Southeastern US clinic. Prevalence was determined, and risk factors for overall OM, oropharyngeal candidiasis (OPC), and all other OM were evaluated using logistic regression.
Results: In our sample ($n = 744$), majority of individuals were males (75 percent), African-American (50 percent), mean age of 39 years, 42 percent of which reported sex with men (MSM). Two hundred sixty-six had some type of OM. Compared with those without any OM, patients with OM had a lower mean baseline CD4+ T cells count (CD4 count) (331 ± 260 versus 179 ± 244 CD4 cells/mm^3) and higher mean baseline HIV-1 RNA viral load (4.0 ± 1.34 $\log_{10}$ versus 4.6 ± 1.30 $\log_{10}$) ($P < 0.01$). In the logistic regression models seeking to determine factors associated with an increased risk of OM and OPC, the only characteristic associated with the outcome was baseline CD4 value. Being male, African-American, and heterosexual showed a protective role for OM other than OPC.
Conclusion: OM continues to be common despite HAART. General OM and OPC were closely associated with a low baseline CD4 count. Knowledge of risk factors for OM can potentially help clinicians target oral evaluation of HIV-positive individuals.

Introduction

The Southern United States has become the center of the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic in the nation. Six of the Southern states (Alabama, Georgia, Louisiana, Mississippi, North Carolina, and South Carolina) constitute the Deep South, a region that has "some of the highest levels of poverty and uninsured individuals, factors that complicate the prevention and treatment of HIV infection" (1) (p. 970).

Although Alabama has been designated a moderate morbidity state with regards to HIV infection (15,683 cumulative HIV/AIDS cases as of June 30, 2008), new infections are increasingly concentrated in vulnerable populations such as African-Americans, women, and rural populations (2,3). This socio-demographic profile has been historically associated with high poverty rates, which limits the ability of HIV-positive individuals to access health care, including dental care.

Currently, highly active antiretroviral therapy (HAART) regimens have transformed HIV/AIDS from a uniformly fatal

diagnosis into a chronic illness with an expected survival past 70 years of age (4). The goals of HAART are to restore and preserve immunological function and to suppress viral load (VL) maximally and durably, thereby reducing HIV-related morbidity and mortality and improving quality of life (5,6). The use of HAART has been associated with a decrease in the prevalence of most oral opportunistic infections that are associated with HIV infection (7,8). On the other hand, a trend of rising prevalence in oral warts and salivary gland enlargement in patients on HAART has been reported (8).

Because of the first reports of AIDS in 1981, the importance and frequency of the associated oral manifestations (OMs) with HIV infection have been noted (9). The pattern of oral conditions associated with HIV infection differs depending upon the population and factors that have been found to be associated have included socioeconomic status, behavioral factors, laboratory features, and access to health services (10).

The reduction of oropharyngeal candidiasis (OPC) seems to be the main contributor to the overall reduction of OM. The marked decrease of OPC and of all OM following HAART was attributed to immune reconstitution, as measured by the elevation of circulating CD4+ T cells (CD4) after the reduction of viral burden (11). The epidemiology and prevalence of OM during HIV infection are comprehensively documented in the literature from the United States (8,12-14). However, there are few reports from the Southeastern region of the United States (Alabama, Georgia, Louisiana, Mississippi, North Carolina, and South Carolina) on the role that OM play in the HAART era. These states show pronounced rural and urban characteristics that give rise to distinct risk profiles, challenges to surveillance and patterns of access to care compared with other states in the United States (15). Therefore, the purpose of this study was to investigate clinical and socio-demographic factors associated with the presence of OM, especially OPC, in persons with HIV infection initiating HAART who were followed for 2 years in Alabama.

Materials and methods

Study population

The University of Alabama at Birmingham (UAB) 1917 Clinic Cohort is an ongoing single-center, longitudinal HIV observational study established in 1992. Pre-2004, prospective data were collected through in-person interviews, daily medical record abstraction by trained study personnel, and computerized questionnaires. Post-2004, data have been collected in real time through a client/server-based point-of-care electronic medical record (EMR) system.

We selected a subsample of this cohort based on the following criteria: patients must have been at least 19 years old with known HIV infection, entered the 1917 Clinic for the first time between January 2000 and June 2006, initiated or changed HAART regimen at the 1917 Clinic, and they must have had at least four clinic visits within their 2-year follow-up period. The UAB Institutional Review Board approved this protocol.

Diagnosis of oral manifestations

The diagnosis of OM was performed by the attending physicians and recorded in the patient's medical record. Collected data were classified according to the clinical diagnostic criteria of the Clearinghouse on Oral Problems Related to HIV Infection and the World Health Organization's (WHO) Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus (16). All clinical presentations of candidiasis (erythematous candidiasis, pseudomembranous candidiasis, chronic hyperplastic candidiasis, angular cheilitis) were grouped as OPC.

Bivariate analyses

OM was used as a categorical variable dichotomized as with or without OM. Patients with OM were those with a diagnosis of OPC, oral herpes, oral ulcer, oral hairy leukoplakia, Kaposi's sarcoma, undetermined stomatitis, and/or salivary gland swelling. Patients not reporting any OM during the 2-year follow-up period were classified as without OM. The independent variables were: age (continuous variable); gender (male versus female); race/ethnicity (white, African-American, other); insurance status (uninsured, public, private); previous antiretroviral therapy (ART) exposure (*naïve* versus experienced); transmission risk category [men having sex with men (MSM), men having sex with women (MSW), intravenous drug users, other]; baseline CD4 (continuous and <50, 50-199, 200-349, ≥350); and HIV-1 RNA VL (continuous and 0-999, 1,000-9,999, 10,000-49,999, 50,000-100,000, ≥100,000) in a range of 120 days and 30 days after the primary care visit, tobacco use, alcohol use, substance use, and affective mental health disorder. The transmission risk was categorized by highest risk. Hence, a patient that is either MSM or man having sex with women (MSW) who has a history of intravenous drug use (IVDU) was categorized as IVDU. The remaining patients were categorized in the two remaining risk groups for sexual transmission, MSM, and MSW. The following conditions were grouped as affective mental health disorders: depressive disorders, anxiety disorders, and/or bipolar disorders. Frequency counts and percentages were used to estimate the prevalence of OM for the descriptive statistics. OM prevalence was defined as the proportion of patients reporting an OM at any time during the 2-year follow-up period. In order to identify statistical differences between patients with any OM and patients without OM, categorical variables were compared using the χ^2

test or Fisher's exact test, when appropriate. Continuous data were compared using two-sided *t*-tests. Correlation analyses were performed to identify colinearity between independent variables. Pearson and Spearman rank correlation coefficients were calculated. Among the independent variables, baseline VL showed moderate correlation with baseline CD4 count ($r > 0.43$). In order to avoid inflating the variance of the parameter estimated, we opted to drop baseline VL from the model.

Multivariable analyses

Clinical and demographic factors associated with OM during the 2-year follow-up period were investigated in this cohort. Odds ratios and 95% confidence intervals (CIs) were used in the multiple logistic regression analysis to determine the presence of OM with respect to demographic variables and baseline CD4 count. A multiple logistic regression model for estimating the probability of having OM was constructed using a stepwise selection algorithm with entry and exit *P*-value criteria of 0.05 and 0.10, respectively. Separate models to determine factors associated with OPC and other OM were conducted as well. OPC status was the binary variable of interest for the second model because OPC represented the most frequent OM in this sample. As an exploratory analysis, a third model was built using all other OM (Kaposi's sarcoma, undetermined stomatitis, and salivary gland swelling) as the binary variable of interest.

CD4 count measurement, which was used as a covariate, was modified into a categorical variable with four different groups: group I (0-49 cells/mm^3), group II (50-199 cells/mm^3), group III (200-349 cells/mm^3), and group IV ($\geq$350 cells/mm^3). Other explanatory variables (covariates) used to assess association with either OM, OPC, or other OM status included age (in years), gender, race, insurance status, previous antiretroviral therapy exposure, transmission risk category, history of tobacco use, history of alcohol use, history of substance use, and affective mental health disorder. Death during the study period was excluded as a predictor variable from all the models because our outcome of interest was presence/absence of oral manifestations. All tests of hypotheses were two-tailed, and all *P*-values less than 0.05 were considered significant.

Statistical Package for Social Sciences Software (SPSS 18 for Windows; SPSS Inc., IL, USA) was used for all of the statistical analyzes.

Results

Descriptives

The study sample consisted primarily of men (75.3 percent) with a mean age of 39 $\pm$ 9.2 years. Approximately half of the sample was white (48.0 percent), and close to half was African-American (49.9 percent). Self-identified HIV risk factors were as follows: 42.3 percent MSM, 27.8 percent MSW, 8.6 percent intravenous drug users, and for 21.2 percent the HIV risk was not identified. The prevalence of OM was 35.8 percent. Patients with any type of OM were more likely to have higher baseline VL and lower baseline CD4 counts ($P < 0.01$) (Table 1). Individuals with public insurance coverage were more likely to have OM (40.6 percent). Individuals who died during the study period were more likely to have had any type of OM (7.9 percent). In this sample population, the most common OM detected was OPC (74.9 percent), followed by oral herpes (10.4 percent), oral ulcer (9.1 percent), oral hairy leukoplakia (3.2 percent), and other OM (2.4 percent) (Table 2).

Multiple logistic regression analyses

The stepwise modeling strategy resulted in a logistic regression model for OM that retained baseline CD4 counts (Table 3) as an important covariate. Regression coefficients achieved statistical significance for baseline CD4 counts. History of alcohol use exhibited a trend toward a statistically significant increased risk of OM (*P*-value = 0.07). It is important to highlight that patients having baseline CD4 counts below 50 cells/mm^3 were six times more likely to develop any OM than patients with 350 cells/mm^3 or more. There was an evident trend of increased likelihood of OM with CD4 depletion ($P < 0.01$). Point and interval estimates for odds ratios associated with each covariate and associated *P*-values are presented in Table 3.

The stepwise multiple logistic regression model for OPC retained the same covariate (baseline CD4 counts), which achieved statistical significance (Table 4). A patient with baseline CD4 count less than 50 cells/mm^3 was eight times more likely to have OPC [adjusted odd ratio (OR adj) = 8.19; 95% confidence interval (CI): = 4.92–13.66; $P < 0.01$] than a patient with baseline CD4 count equal to or greater than 50 cells/mm^3.

The third multiple logistic regression model for the other OM retained different covariates (sex, race, and HIV transmission risk), all of which achieved statistical significance but played protective roles (Table 5). Being male (OR adj = 0.22; CI = 0.08-0.61; $P < 0.01$), African-American (OR adj = 0.41; CI = 0.19-0.89; $P < 0.01$), and MSW (OR adj = 0.29; CI = 0.10-0.83; $P < 0.01$) was associated with the presence of one of the other OM.

Discussion

Despite the fact that antiretroviral (ARV) drugs have been associated with a decrease in the prevalence of most oral opportunistic infections, the oral cavity is still a common site

Table 1 Clinical and Socio-Demographic Factors among HIV Patients Who Initiated Care between January 2000 and June 2006 Stratified by Presence or Absence of Oral Manifestations (n = 744)

Characteristics	All patients, *n* (%)	Without OM, *n* (%)	With OM, *n* (%)	*P*-value
Age in years (mean ± SD)	39 ± 9.2	39 ± 9.6	38 ± 8.4	0.26
Gender				0.70
Female	184 (24.7)	116 (24.3)	68 (25.6)	
Male	560 (75.3)	362 (75.7)	198 (74.4)	
Race/ethnicity				0.17
White	357 (48.0)	236 (49.4)	121 (45.5)	
African-American	371 (49.9)	229 (47.9)	142 (53.4)	
Other	16 (2.2)	13 (2.7)	3 (1.1)	
Insurance status				<0.05
Uninsured	173 (23.3)	109 (22.8)	64 (24.1)	
Public	302 (40.6)	180 (37.7)	122 (45.9)	
Private	269 (36.2)	189 (39.5)	80 (30.1)	
Antiretroviral therapy naïve				0.19
No	351 (47.2)	234 (49.0)	117 (44.0)	
Yes	393 (52.8)	244 (51.0)	149 (56.0)	
Death during the study period				
No	708 (95.2)	463 (96.9)	245 (92.1)	<0.01
Yes	36 (4.8)	15 (3.1)	21 (7.9)	
Transmission risk category				0.82
MSM	315 (42.3)	201 (42.1)	114 (42.9)	
MSW	207 (27.8)	138 (28.9)	69 (25.9)	
IVDU	64 (8.6)	39 (8.2)	25 (9.4)	
Other	158 (21.2)	100 (20.9)	58 (21.8)	
Mean baseline CD4 (cells/uL)	276 ± 264.3	331 ± 259.8	179 ± 244.3	<0.01
Baseline CD4 (cells/uL)				
<50	173 (23.9)	65 (14.0)	108 (41.5)	<0.01
50-199	170 (23.4)	101 (21.7)	69 (26.5)	
200-349	151 (20.8)	112 (24.1)	39 (15.0)	
≥350	231 (31.9)	187 (40.2)	44 (16.9)	
Mean baseline $\log_{10}$				
HIV RNA (copies/mL)	4.2 ± 1.36	4.0 ± 1.34	4.6 ± 1.30	<0.01
Baseline viral load				<0.01
0-999 copies/mL	142 (21.2)	110 (25.2)	32 (13.7)	
1,000-9,999 copies/mL	92 (13.7)	73 (16.7)	19 (8.2)	
10,000-49,999 copies/mL	132 (19.7)	100 (22.9)	32 (13.7)	
50,000-99,999 copies/mL	99 (14.8)	62 (14.2)	37 (15.9)	
≥100,000	205 (30.6)	92 (21.1)	113 (48.5)	
History of tobacco use				0.86
No	450 (60.5)	288 (60.3)	162 (60.9)	
Yes	294 (39.5)	190 (39.7)	104 (39.1)	
History of alcohol use				0.14
No	608 (81.7)	398 (83.3)	210 (78.9)	
Yes	136 (18.3)	80 (16.7)	56 (21.1)	
History of substance use				0.94
No	589 (79.2)	378 (79.1)	211 (79.3)	
Yes	155 (20.8)	100 (20.9)	55 (20.7)	
Affective mental health disorder				
No	332 (44.6)	207 (43.3)	125 (47.0)	0.33
Yes	412 (55.4)	271 (56.7)	141 (53.0)	
Total number of patients	744 (100.0)	478 (64.2)	266 (35.8)	

OM, oral manifestations; SD, standard deviation; MSM, men having sex with men; MSW, men having sex with women; IVDU, intravenous drug use; CD4, CD4+ T cell count; HIV, human immunodeficiency virus.

Table 2 Distribution of Oral Manifestations in the HIV Cohort (n = 268*)

Characteristics	Number of patients	Percent
Oropharyngeal candidiasis	281	74.9
Oral herpes	39	10.4
Oral ulcer	34	9.1
Oral hairy leukoplakia	12	3.2
Others	9	2.4
Total	375†	100.0

* Number of patients with at least one oral manifestation from January 2000 to June 2008.
† Some patients had more than one oral manifestation.
HIV, human immunodeficiency syndrome.

for the occurrence of lesions in HIV-infected patients on HAART. In this study, 35.8 percent of the patients were diagnosed with at least one OM during the 2-year follow-up period. This prevalence is comparable with previous reports from industrialized countries (17), and the prevalence reported in a population from North Carolina (37.5 percent), which is also in the Southeastern region of the United States (15).

It was interesting that history of tobacco use and history of alcohol use were not significantly associated with OM. In several previous studies, the association between tobacco use and OM has been proven to be significant (18,19). Even more, smoking tobacco seems to play a major role in a number of malignancies in patients who are HIV-positive, especially oral squamous cell carcinoma (20). In 2006, Mercante et al. (12) suggested that in their study sample, the incorporation of protease inhibitors in the therapeutic regimens in recent years has resulted in decreasing the incident of many morbidities (including OM), therefore making more difficult to establish strong association between the presence of OM and smoking tobacco. However, the reader should consider that in our sample, the information about tobacco use, along with history of alcohol and substance use, was obtained when the patient started care at the 1917 Clinic and did not reflect either the current use of tobacco or dose of tobacco exposure, which have been reported in previous studies to be lower after HAART initiation (21).

Greenspan et al. (8) reported a dramatic increase in oral warts, mostly associated with the use of protease inhibitors.

Table 3 Clinical and Socio-Demographic Determinants of Oral Manifestations* in the HIV Cohort

	Bivariate analyses	Multivariate analyses		
Independent variable	Crude OR†	Adjusted OR†	95% CI‡	*P*-value
Baseline CD4 (cells/uL)				
<50	7.04	6.09§	3.82-9.69	<0.01
50-199	2.87	2.59	1.63-4.11	<0.01
200-349	1.46	1.41	0.85-2.32	0.18
≥350 (ref)	1.00	1.00		

* MODEL: OM versus no OM. The following variables are also adjusted for in this multivariate model: age, gender, race, insurance status, antiretroviral therapy naïve, transmission risk category, baseline CD4 (cells/uL), tobacco use, alcohol use, substance use, affective mental health disorder.
† Odds ratios (OR), significant association ($P < 0.05$).
‡ Confidence interval (CI).
§ *P*-trend 0.01.
HIV, human immunodeficiency syndrome; OM, oral manifestations; OPC, oropharyngeal candidiasis; CD4, CD4+ T cell count.

Table 4 Clinical and Socio-Demographic Determinants of Oropharyngeal Candidiasis* in the HIV Cohort

	Bivariate analyses	Multivariate analyses		
Independent variable	Crude OR†	Adjusted OR†	95% CI‡	*P*-value
Baseline CD4 (cells/uL)				
<50	9.37	8.19§	4.92-13.66	<0.01
50 to 199	3.80	3.45	2.07-5.73	<0.01
200 to 349	1.58	1.52	0.86-2.69	0.15
≥350 (ref)	1.00	1.00		

* MODEL: OPC versus no OM. The following variables are also adjusted for in this multivariate model: age, gender, race, insurance status, antiretroviral therapy naïve, transmission risk category, baseline CD4 (cells/uL), tobacco use, alcohol use, substance use, affective mental health disorder.
† Odd ratios (OR), significant association ($P < 0.05$).
‡ Confidence interval (CI).
§ *P*-trend 0.01.
HIV, human immunodeficiency syndrome; OM, oral manifestations; OPC, oropharyngeal candidiasis; CD4, CD4+ T cell count.

Table 5 Clinical and Socio-Demographic Determinants of Other Oral Manifestations* in the HIV Cohort

	Bivariate analyses	Multivariate analyses		
Independent variables	Crude OR†	Adjusted OR†	95% CI‡	*P*-value
Sex				
Male	0.54	0.22	0.08-0.61	<0.01
Female (ref)	1.00	1.00		
Race				
White (ref)	1.00	1.00		
African-American	1.96	0.41	0.19-0.88	<0.01
Other	2.54	1.05	0.13-8.68	0.96
Transmission risk				
MSM	0.71	1.06	0.42-2.68	1.06
MSW	0.48	0.29	0.10-0.83	<0.01
IVDU	0.63	0.54	0.14-2.13	0.38
Unknown (ref)	1.00	1.00		

* MODEL: Other OM versus no OM. The following variables are also adjusted for in this multivariate model: age, gender, race, insurance status, antiretroviral therapy naïve, transmission risk category, baseline CD4 (cells/uL), tobacco use, alcohol use, substance use, affective mental health disorder.

† Odd ratios (OR), significant association ($P < 0.05$).

‡ Confidence interval (CI).

OM, oral manifestations; MSM, men having sex with men; MSW, men having sex with women; IVDU, intravenous drug use; CD4, CD4+ T cell count; HIV, human immunodeficiency virus.

Contrary to their results, we did not find any evidence of oral warts. However, it is important to consider the fact that their population was studied from 1990 to 1999, 10 years earlier than the time frame for this study and in the pre-HAART era.

The most common OM in this sample was OPC, representing 74.9 percent; which is similar to several reports from developed (17,21) and developing countries (22-25).

As OPC was the most commonly detected OM, representing three quarters of all the OM reported by our study population, it was decided to use this particular lesion as the main outcome in the second logistic regression model. The goal was to control for the same potential confounders in the first model (OM = yes/no) and to find the best fitting, most parsimonious and biologically reasonable model to describe the relationship between OPC and a set of clinical and socio-demographic factors.

Although in the univariate and bivariate analysis, there were differences in the relative importance for some of the independent variables, logistic regressions for OM and OPC were consistent in finding low baseline CD4 counts as the most important risk factor. The immune suppression that results from destruction of CD4 cells by the process of viral replication in the lymphocytes potentially elevates the susceptibility of developing OM, especially OPC (26). Previous published reports showed a link between alcohol consumption and HIV disease progression, which may involve the oral cavity (27).

However, this cohort did not have a statistically significant association between the presence of OM and alcohol use, or between the presence of OPC and alcohol use.

When cohort indicators were tested to assess their association with other OM, excluding OPC (Table 5), variables like sex, race, and HIV transmission risk showed statistical significance. Being male, African-American, and MSW showed a protective role for having any OM except OPC. However, one must keep in mind that this particular statistical analysis is exploratory, and the result should be viewed with caution due to the small number of cases with other OM (Kaposi's sarcoma, undetermined stomatitis, and/or salivary gland swelling).

Our findings should be interpreted with caution because data were not collected for the purpose of this study. An important limitation of our study relates to the fact that specific antiretroviral components of each HAART regimen were not analyzed. Unfortunately, we also cannot overrule under-report or misclassification of OM. However, our prevalence is comparable with the prevalence reported by other cohorts in the United States and other developed countries (15,17,21). At the 1917 Clinic, as in many other HIV clinics around the United States, it is the treating general clinician, not a dental health professional who performs the intraoral examination most of the time. Therefore, it is necessary to implement strategies for dental/oral training of health professionals, or integrate dentists into the HIV care team, in order to increase the accuracy of the OM diagnosis and treatment implementation. This will subsequently improve the overall health of the HIV patient.

Based on our findings, OM were found in 36 percent of HIV patients entering care at the 1917 Clinic in the 2-year study period. Because of their prevalence, especially in those patients with low baseline CD4 counts, training in the detec-

tion and treatment of OM are important components to HIV care. The accessibility of the oral cavity and the clinical relevance of oral HIV lesions cannot be overlooked or underestimated. Also, additional studies, preferably prospective cohort studies, are needed to accurately estimate the prevalence of OM associated with HIV infection. HIV infected individuals reporting the occurrence of these OMs should be monitored more closely with a team approach between primary care HIV providers and oral health professionals with a more aggressive diagnostic surveillance for these common conditions.

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