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Oral white patches in a national sample of medical HIV patients in the era of HAART

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Abstract – *Objectives:* Several types of HIV-related oral mucosal conditions have been reported to occur during the course of HIV disease progression. Of these, few may be manifested as 'white' lesions and many are noticeable to the patient. This paper examines the relationships between social, behavioral and medical aspects of HIV infection and reporting an occurrence of oral white patches (OWP) by HIV-infected patients. *Methods:* The subjects are participants in all three interviews in the HIV Cost and Services Utilization Study (HCSUS). The subjects were selected using a three-stage probability sampling design. The multivariate analysis is based on 2109 subjects with nonmissing binary outcome variable for all three waves representing a national sample of 214 000 individuals. The multivariate model was fitted using generalized estimating equations (GEE) by implementing the XTGEE command in STATA. *Results:* We estimate that 75 000 persons (35%) reported at least one incident of OWP, of these 14 000 reported having OWP during all three interviews, and that the rate of reporting declined over the three HCSUS waves. The multivariate analysis showed seven variables that were significant predictors of at least one report of OWP. *Conclusions:* Compared with persons on HAART therapy, patients on other regimens or taking no antiviral medications were 23–46% more likely to report an incident of OWP. Compared with whites, African Americans were 32% less likely to report OWP, while current smokers were 62% more likely than nonsmokers. Being diagnosed with AIDS and having CD4 counts less than 500 significantly increased the likelihood of reporting OWP.

Key words: HAART; HIV/AIDS; oral candidiasis; oral symptoms; protease inhibitors

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America has two distinct HIV/AIDS epidemics. The initial epidemic affected predominately gay white males, who typically had health insurance, were educated, and had access to care and resources. The second epidemic affects minority communities already ravaged by lack of services, violence, substance abuse, prejudice, minimal resources, and where HIV disease is just one of many social and health concerns (1). In 1996, at the onset of this study, African Americans, although only 12% of the nation's population, accounted for 41% of adults with AIDS in the US, exceeding for the first time the proportion who were non-Hispanic white (2). Hispanics, just 10% of the nation's population, made up 21% of all AIDS cases. Similarly, women accounted for 20% of all adults with AIDS in 1997, the highest proportion ever reported for that group. These groups, as well as intravenous drug users (IDU), appear most likely to experience difficulty accessing medical care and hence, to have lower outpatient utilization and less treatment with the most recent medications (3, 4). In addition, nonwhites compared with whites and women compared with men are less likely to receive antiretroviral treatment, are more likely to receive treatment at a later disease stage and have fewer outpatient visits (5–7).

There are many oral health problems associated with HIV infection that require the attention of

both medical and dental personnel. In the course of HIV disease progression, the development of oral soft tissue lesions is frequently a sign of declining local and systemic immune function. In patients with advanced HIV disease, treatment of painful lesions of the mouth, oropharynx, and esophagus may improve the ability to eat and to swallow, thereby decreasing problems related to weight loss and adherence to oral treatment regimens (8, 9). The study described in this paper focuses on a general symptom of 'White Patches' reported by patients in various stages of HIV infection. An oral white patch could indicate several non-HIV as well as HIV-related clinical conditions. Among non-HIV-related conditions are reactive hyperkeratotic lesions related to local factors such as trauma or exposure to tobacco and mucosal conditions such as premalignant leukoplakia and oral Lichen Planus. There are, however, HIV-related conditions such as oral candidiasis, hairy leukoplakia and oral warts that can clinically present as a distinct white patch detectable by the patient.

Clinically, oral candidiasis (OC) has several forms, the most common of which is the pseudomembranous variant commonly known as 'thrush'. Thrush presents as creamy or 'cheesy' white or yellowish plaques that are fairly adherent to red or normally colored oral mucosa. Although this type of OC is generally not painful, the erythematous areas associated with the white plaques (mostly exposed after the loss of the pseudomembrane) can become symptomatic. A second form of OC, hyperplastic candidiasis, presents as white or discolored singular or confluent plaques that cannot be wiped off and patients may complain of a burning sensation. These lesions often come to the attention of infected persons by their visible presence in the mouth. In a study of HIV patients with OC there was an inconsistent association between clinical signs, patient symptoms and candidial infection, with half of patients reporting pain or discomfort (10).

Oral hairy leukoplakia (OHL) appears as asymptomatic poorly demarcated, hyperkeratotic areas predominantly found on the lateral borders of the tongue; they frequently have a bilateral distribution and may extend to ventral aspects of the tongue. Lesions are often corrugated or hairy in appearance. However, the lesions may present with a flat surface and may also be infrequently observed in locations other than the tongue. Some of the human papilloma virus-induced entities (oral warts) reported to occur in the oral tissues of HIV-infected patients may also assume a white appearance. Because HIV-related oral lesions correspond fairly well with HIV disease staging and success of anti-HIV treatment, detection and further evaluation of an 'oral white patch' by the patient or the health care provider has great significance in the overall HIV disease monitoring (11–13).

Recent advancements in medical treatment of HIV disease make the study of oral health disparities between the 'two faces' of the epidemic increasingly important. The introduction of highly active antiretroviral therapy (HAART) during 1996–1998 has had a profound impact on the course of this disease. This regimen increases survival among persons with HIV by slowing viral replication and thus disease progression (14). AIDS diagnoses and deaths decreased dramatically during 1996 and 1997, and stabilized or declined only slightly in 1998 and 1999, as a result of slower progression of HIV-associated immune deficiency among persons who used HAART (15). The advent of new drug therapies occurred during the course of this study and these therapies have clear implications for oral health. For those who have access to HAART, there appears to be a diminution of frequency and severity of oral lesions, but some adverse effects such as dry mouth and taste disturbances are known to occur (16). The incidence of some oral manifestations associated with HIV has decreased significantly during this period (17). Thus those oral opportunistic infections that were identified early in the epidemic by both medical and dental personnel may not occur as frequently in the era of HAART (18). Studies conducted after 1996 show a range of prevalence rates of 6–35% for OC and approximately 11–25% for OHL depending on the level of immunologic suppression and success of anti-HIV treatment (12, 16, 17, 19). The clinical importance of detecting OC and OHL is related to their predictive value in HIV disease progression (11, 13, 20, 21).

This paper examines self-reporting of oral white patches (OWP), an indicator of OC, by patients with HIV disease in a national probability sample of persons accessing medical care, and its relationships to social, behavioral, and medical aspects of HIV disease in the era of HAART.

Methods

Data collection

The HIV Cost and Services Utilization Study (HCSUS) created a representative national

probability sample, the first of its kind, of HIV-infected adults in medical care in the contiguous US. The population consists of adults at least 18 years old with known HIV infection who made at least one visit for regular, nonemergency care to a nonmilitary, nonprison medical provider from January to March 1996. The 2864 study participants in HCSUS represent approximately 231 400 people with HIV disease in the US. The HCSUS used a multi-staged design to ensure geographic representation, rural and urban areas, large and small clinics, female patients, and African Americans. Baseline interviews were conducted with 2864 subjects between January 1996 and April 1997. A second interview (first follow-up) was conducted with 2466 subjects between December 1996 and July 1997. The second follow-up interview was administered to 2267 subjects from September 1997 to January 1998. The sampling approach adopted by HCSUS used a multistage scientific sampling to randomly select geographic locations in the first stage, providers in those locations at the second stage and patients of those providers in the third stage from comprehensive lists of areas, providers, and patients, respectively. Full details of the design are available elsewhere (22, 23).

Data analysis

This analysis is based on 2109 subjects, representing a national population of 212 050 individuals. These subjects are a subsample of the HCSUS cohort who completed all three interviews; those not completing the three HCSUS waves, while not lost to the study, were excluded from the analysis. In the baseline interview, subjects were asked to report if they had white patches in the mouth; in the first and second follow-ups, they were asked if they had this condition since the previous interview. The response to this question was compared with other variables that characterized demographics, stages of disease, and use of HAART during the course of study. The analysis consists of bivariate comparisons using STATA and multivariate models using STATA's generalized estimating equations (GEE). The GEE method enables us to account for repeated observations from the same subject over time (24, 25), and to fit a multivariate linear model.

Results

Table 1 presents national estimates of HIV/AIDS population's (212 050) response to the question about the presence of white patches in the mouth from January 1996 to January 1998. The N,N,N response indicates that at none of the three interviews during this period were OWP reported. The Y,N,N response indicates that persons reported OWP at the first interview, but not subsequently. The other six possible combinations are shown similarly.

About two-thirds of the estimated population did not report having OWP at any of the three interviews. Seven percent or 14 000 people continuously reported OWP. In the initial phase of the study, more than one quarter of the population, 54 205 persons reported having OWP. In the last phase of the study this percentage declined to 15% or 31 638 individuals.

Table 2 presents bivariate distributions for those selected characteristics. Only 25% of persons 50 years of age and older reported OWP, compared with 37% for their younger cohorts. African Americans reported less OWP than the other ethnic groups. Current smokers, the unemployed, those with an AIDS diagnosis, and those with low CD4 counts have higher percentages of OWP. The responses to types of drug therapies taken do not show distinctive patterns in the bivariate analysis.

Table 1. Response patterns for the three interviews

White patches response	Percentage	Projected population	OWP in initial phase	OWP in second phase	OWP in last phase
N,N,N	65	137 197			
Y,N,N	9	19 339	19 339		
N,Y,N	5	9819		9819	
Y,Y,N	7	14 056	14 056	14 056	
N,N,Y	3	6521			6521
Y,N,Y	3	6793	6793		6793
N,Y,Y	2	4307		4307	4307
Y,Y,Y	7	14 017	14 017	14 017	14 017
	100	212 050	54 205	42 199	31 638

Table 2. Percentage and number of persons with oral white patches by characteristics

Variable	Category	Estimated population with OWP	Percentage of population with OWP	Estimated population without OWP	Total population
Ethnicity	White	37 946	36	66 592	104 538
	African American	21 408	31	47 078	68 486
	Hispanic	12 684	40	19 034	31 718
	Other	2816	39	4492	7308
	Total	74 853	35	137 197	212 050
Age	18–34	26 246	37	45 479	71 725
	35–49	42 655	37	73 913	116 568
	50+	5952	25	17 805	23 757
	Total	74 853	35	137 197	212 050
Smoking	Never	16 838	29	41 191	58 029
	Past	14 982	30	34 367	49 349
	Current	42 992	41	61 638	104 631
	Total	74 812	35	137 197	212 009
Employment status	Employed (full/part-time)	26 416	26	74 578	100 994
	Not employed	48 436	44	62 618	111 054
	Total	74 853	35	137 197	212 050
Medications	HAART	45 395	36	81 443	126 838
	Poly-drug therapy	18 523	34	36 154	54 677
	Mono-drug therapy	2064	37	3527	5590
	No ARV	6280	32	13 509	19 789
	Total	72 261	35	134 633	206 894
Diagnosed with AIDS	No, never	24 679	22	85 658	110 337
	At some point	50 174	49	51 494	101 668
	Total	74 853	35	137 152	212 004
Latest reported CD4 count	≥500	12 791	22	44 215	57 007
	200–499	26 711	33	53 838	80 549
	50–199	20 025	47	22 793	42 818
	0–49	10 279	64	5819	16 098
	Total	69 806	36	126 665	196 471

Thirty-six percent of those taking HAART report OWP, compared with 32% of those not taking any antiviral medications.

Table 3 presents multivariate analysis using the response to the OWP question as the dependent variable and the characteristics of the population as covariates. The table presents the odds ratio of having OWP for each characteristic compared with a reference group within the category. For example, females are 10% more likely to report OWP than males, which is the reference group; this difference is not significant. However in the case of ethnicity, African Americans with an odds ratio of 0.68 are 32% less likely than whites to report OWP, and this result is statistically significant. Similarly, compared with the youngest age group, older persons with HIV/AIDS are 33% less likely to report OWP. Compared with nonsmokers, current smokers are 1.6 times more likely to report OWP, and those who are unemployed are twice as likely to report OWP. Being diagnosed with AIDS and having CD4 counts less than 500 significantly increase the likelihood of reporting OWP. Persons with CD4 counts less than 50 are 3.6 times more likely to report the condition than those with CD4 counts of 500 and more. The odds ratios increase as the CD4 counts decline. Comparing HAART with other regimens, those taking poly-drug therapy are 23% more likely, and those on mono-drug or taking no antiviral medication are 47% and 46%, respectively, more likely to report OWP.

Discussion

This paper provides a national perspective on the HIV/AIDS epidemic as it moves through the critical years involving the introduction of HAART. Although there was no clinical examination associated with this study which was limited to self-report data, the subjects were asked on three occasions whether they have white patches in their mouth. Those who responded positively to this question may have noticed it themselves, or their

Table 3. Longitudinal analysis predicting oral white patches

Variable	Category	Odds ratios	SE	*P*-value	95% CI	
					Lower	upper
Gender	Male			(reference)		
	Female	1.10	0.16	0.534	0.82	1.47
Ethnicity	White			(reference)		
	African American*	0.68	0.09	0.002	0.53	0.87
	Hispanic	0.95	0.13	0.723	0.72	1.26
	Other	0.91	0.25	0.745	0.53	1.58
Age	18–34			(reference)		
	35–49	0.91	0.10	0.401	0.73	1.13
	50+*	0.67	0.13	0.042	0.46	0.99
Education	BA/BS			(reference)		
	Some college	0.86	0.13	0.313	0.64	1.15
	High school degree	0.80	0.13	0.164	0.58	1.10
	Some high school	0.80	0.14	0.202	0.57	1.13
Exposure	Males, sex with males			(reference)		
	IV drug user	1.00	0.14	0.997	0.76	1.32
	Heterosexuals	0.85	0.15	0.358	0.61	1.19
	Other (transfusions, etc.)	0.69	0.14	0.067	0.46	1.03
Smoking	Never			(reference)		
	Past	1.07	0.16	0.631	0.80	1.44
	Current*	1.62	0.21	0.000	1.27	2.08
Dental insurance	Private insurance			(reference)		
	No dental coverage	0.80	0.12	0.139	0.60	1.07
	Medicaid + dental coverage	1.04	0.16	0.786	0.77	1.41
	Medicaid, no dental coverage	0.97	0.16	0.837	0.70	1.34
Living arrangement	Living with someone			(reference)		
	Living alone	1.10	0.10	0.285	0.92	1.32
Employment status	Employed (full/part-time)			(reference)		
	Not employed*	2.05	0.23	0.000	1.64	2.56
Drinking	Do not drink			(reference)		
	Moderate: 1–2/day	0.93	0.09	0.435	0.76	1.12
	Regular: >2 drinks/day	1.02	0.11	0.844	0.82	1.27
Medications	HAART			(reference)		
	Poly-drug therapy*	1.23	0.11	0.018	1.04	1.47
	Mono-drug therapy*	1.47	0.18	0.002	1.15	1.87
	No ARV*	1.46	0.20	0.006	1.12	1.91
Diagnosed with AIDS	No			(reference)		
	Yes*	1.28	0.14	0.025	1.03	1.58
Latest CD4 count	≥500			(reference)		
	200–499*	1.26	0.14	0.043	1.01	1.58
	50–199*	1.87	0.26	0.000	1.42	2.47
	0–49*	3.61	0.64	0.000	2.55	5.11

*$P \leq 0.05$.

physician or dentist may have told them that they have the condition.

The results of this study show that nationally at least 75 000 persons with HIV/AIDS receiving medical care had one or more instances where they reported white patches in their mouth during the period of this study. However, the data show that the rate of reporting declined. Seventy-four percent of those reporting OWP reported it during the first interview when HAART was not available, while only 42% reported the condition during the third interview when HAART was more readily available. The analyses substantiated this relationship. Although the bivariate distribution shows that 36% of HCSUS subjects taking HAART report OWP, compared with 32% of those not taking any antiretroviral medications, the multivariate analysis, when all characteristics are taken into account, shows that those not taking HAART are more likely to experience OWP. Our findings based on patients reporting of OWP are consistent with clinical studies that assess OC clinically. Both self-reported and clinical assessed OC are related to declining immune status, smoking, and AIDS diagnosis.

Education, risk exposure, dental insurance, and whether or not the person lives alone, do not affect

the likelihood of reporting OWP. However, if a person is unemployed, the likelihood of reporting OWP increases significantly. While the ability to work is a functional measure often related to physical health status, it may also point to more subtle issues affecting this population. In this analysis we controlled for disease status, therefore other factors may be operating here. Persons who are unemployed may have more stress, less support, and may be overly concerned with their condition that in turn may lead to more likelihood of reporting symptoms.

Age is a predictor in that older persons in the study are 33% less likely to report OWP when compared with the youngest age group. The age effect may, in part, be explained by older persons' ability to cope with and survive HIV disease as a result of knowledge, education, and preventive health practices. These factors may help explain why older people report less OWP than the youngest group who tend to have less of these resources, and less access to dental care. This supposition appears to be confirmed by another HCSUS analysis by Dobalian et al. (26), which found that older persons tended to have more access to dental care.

While the relationship between age and resource mobilization appears clear, the association between ethnicity and reporting of oral symptoms is less so. In our analysis, African Americans were less likely to report OWP; this finding was unexpected. We first examined the characteristics of subjects lost to the study between the baseline and the second follow-up interviews to see if differences in those dropping out may have influence on this finding. We found that African Americans were more likely to drop out of the study but for those who dropped out, there were no differences between African Americans and whites in their rate of reporting OWP.

Previous HCSUS findings lead us to expect that African Americans would be more likely to have OWP and other oral manifestations of HIV/AIDS. The HCSUS findings indicate that African Americans have less access, use dental care less frequently, are less likely to receive HAART (27, 28), and tend to have more oral health issues, than their white counterparts (26). Cunningham et al. (28) found that several other groups, including males and female drug users, female heterosexuals, people with less education, and those uninsured and insured by Medicaid, were also less likely to receive HAART. With regard to access to state of the art medical care, Gifford et al. (29) found that while 18% of white patients participated in an HIV medication trial during the study period when several potent new antiretrovial medications were being tested, about 10% of African American patients and 11% of Hispanic patients participated in a clinical trial. The study also found that patients who were cared for in private health maintenance organizations were also less likely to participate in trials than those with fee-for-service insurance. In addition, participation of African American patients in trials did not increase during the study period, and these patients were more likely to drop out of the research. The investigators speculated that African American and Hispanic patients' limited attempts to obtain experimental HIV medications might reflect lack of awareness of clinical trials in their communities, as well as suspicion and distrust of trials and researchers. African American patients were also less than half as likely as white patients to try to obtain an experimental HIV medication.

One possible explanation for the lower rates of OWP among African Americans may be differences in reporting. Any study using self-reported data is subject to this limitation. Patton found in a study of 245 HIV/AIDS patients' self-assessment of oral opportunistic infections, 66% of whom were African American, that there was a tendency to under report the presence of oral lesions (30). In contrast to the African American pattern of reporting OWP, in another HCSUS study (31), Hispanics had higher rates than whites in reporting another common symptom, that of oral dryness. These observations may reflect real differences in symptom prevalence or may be attributable to the differences in reporting rates among ethnic groups.

In our study, persons with CD4 counts less than 500 are more likely to report OWP than those with CD4 counts of 500 and more. Comparing HAART with other regimens, those taking poly-drug therapy are 23% more likely, and those on mono-drug or taking no antiretroviral medication are 47% and 46%, respectively, more likely to report OWP. Because HAART slows viral replication and depletion of CD4 cells, and CD4 cell loss accounts for a major part of the immunosuppressive effect of HIV disease, those taking antiretroviral medications are more likely to report less oral manifestations of the disease.

Our study showed that while taking HAART decreased the likelihood of reporting OWP, certain demographic and socioeconomic factors still

contribute to a greater burden of oral disease among more vulnerable patient groups. Although considerable speculation remains about the relationship between demographic and socioeconomic factors, oral symptoms, and unmet need for care in the era of HAART, one thing is certain: the new face of the AIDS epidemic has created a gap between whites and minorities, older and younger patients, and employed and unemployed persons; and HAART has widened that gap.

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