Incidence of Oral Lesions in HIV-1-infected Women: Reduction with HAART

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J DENT RES 2004 83: 145
DOI: 10.1177/154405910408300212

RESEARCH REPORTS
Clinical

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J Dent Res 83(2):145-150, 2004

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ABSTRACT

Few studies assess the effectiveness of HAART on reducing the incidence and recurrence of oral lesions. We investigated such changes among 503 HIV+ women over six years in the Women's Interagency HIV Study. The incidence of erythematous candidiasis (EC), pseudomembranous candidiasis (PC), hairy leukoplakia (HL), and warts was computed over follow-up visits after HAART initiation compared with before HAART initiation. Analysis of our data demonstrates a strong decrease in candidiasis after HAART initiation. The incidence of EC fell to 2.99% from 5.48% (RR 0.545); PC fell to 2.85% from 6.70% (RR 0.425); and EC or PC fell to 3.43% from 7.35% (RR 0.466). No changes were seen in HL or warts. Higher HIV-RNA was associated with greater incidence of candidiasis and HL, but not warts. Analysis of these data indicates that recurrence and incidence of candidiasis are reduced by HAART, and that recurrence is reduced independently of CD4 and HIV-RNA.

KEY WORDS: oral candidiasis, hairy leukoplakia, women, HIV, HAART.

Received April 28, 2003; Last revision October 13, 2003; Accepted October 20, 2003

INTRODUCTION

The frequency of oral lesions in human immunodeficiency virus type 1 (HIV) infection is well-established, as are the sentinel roles of those opportunistic infectious conditions in the natural history of HIV infection and AIDS (Greenspan and Greenspan, 2002). Cross-sectional studies of prevalence are numerous (Leigh *et al.*, 1999), but few longitudinal reports of incidence are available, particularly in women (Shiboski, 2002). We previously studied cross-sectional correlates of prevalent oral mucosal lesions in the Women's Interagency HIV Study (WIHS) and showed that pseudomembranous candidiasis was associated with high viral load and low CD4 count, and that hairy leukoplakia was not dependent on CD4 count, controlling for high viral load. In addition, we showed that oral candidiasis and hairy leukoplakia were associated with the use of heroin/methadone, cigarettes, and/or marijuana (Greenspan *et al.*, 2000; MacPhail *et al.*, 2002). Other papers from our group cover salivary gland functional and lesion changes (Mulligan *et al.*, 2000; Navazesh *et al.*, 2000). Few data are available for the assessment of changes in the incidence of oral disease in conjunction with anti-retroviral therapy (Porter and Scully, 1998; Cauda *et al.*, 1999; Arribas *et al.*, 2000; Dios *et al.*, 2000; Cook *et al.*, 2002; King *et al.*, 2002). In a clinic population, we found a decrease in the prevalence of oral candidiasis during the period 7/1990-6/2000, but a significant increase in oral warts (Greenspan *et al.*, 2001). In this study, we explore changes in the incidence of oral mucosal lesions over time in the WIHS. We specifically quantify the effectiveness of highly active anti-retroviral therapy (HAART), which became available during the course of this study, on the incidence of three sentinel oral mucosal lesions: PC, EC, and HL (Ahdieh *et al.*, 2000; Carpenter *et al.*, 2000; Anastos *et al.*, 2002; Gange *et al.*, 2002; Levine, 2002; Yeni *et al.*, 2002).

MATERIALS & METHODS

Study Population

The WIHS is an ongoing prospective study of HIV-1 infection in women, conducted in five locations within the United States. Methods and baseline cohort characteristics have been described previously (Barkan *et al.*, 1998). Briefly, from October, 1994, through November, 1995, 2059 HIV-1-seropositive women were enrolled. All participants provided consent to institutional review board-approved protocols. Every six months, participants were interviewed by means of a structured questionnaire, received physical and gynecological examinations, and provided multiple laboratory specimens. A subset of participants (503 HIV+, 122 HIV-) was invited to undergo comprehensive oral examinations conducted by trained dental examiners at four of the six sites (New York, Chicago, Los Angeles, and San Francisco). The number for each outcome changed slightly because of the exclusion of women with that particular lesion. If a woman had only warts at baseline, she was not included in the incidence

analysis for warts but was included in the recurrence analysis and also in the incidence analysis for the other outcomes.

Study Variables

Oral health measures were documented in a study protocol according to explicit criteria: examination of soft tissue and salivary glands; assessment of caries, plaque, and periodontal disease; and collection of saliva samples and smears from selected lesions. Dental examiners and recorders received formal training in assessing and recording the measures and indices before starting the study and were recalibrated during the study.

Four lesions of interest (Greenspan *et al.*, 1992; EC-Clearinghouse, 1993) in this analysis are:

- pseudomembranous candidiasis (PC), defined as white removable plaques on any oropharyngeal mucosal surface;
- erythematous candidiasis (EC), defined as red areas on any oropharyngeal mucosal surface;
- hairy leukoplakia (HL), defined as white non-removable plaques, sometimes with corrugated appearance, occurring on the lateral or dorsal/ventral tongue; and
- oral warts (WT), defined as single or multiple warts with multiple white spike-like projections, cauliflower-like masses, single projections, or flat lesions.

Quantification of HIV-1 RNA in plasma was performed by means of the isothermal nucleic acid sequence-based amplification (NASBA/Nuclisens) method (Organon Teknika Corp., Durham, NC, USA) in laboratories participating in the NIH/NIAID, Virology Quality Assurance Laboratory proficiency testing program. The lower limit of quantification through 9/97 was 4000 copies/mL based on a 0.1-mL sample input; from 10/97 through 12/98, the lower limit was 400 copies/mL with a 0.2-mL sample input; after 1/99, the lower limit was 80 copies/mL with a 1.0-mL sample input. Lymphocyte subsets were quantified by standard flow cytometric methods in laboratories participating in the NIH/NIAID Flow Cytometry Quality Assessment Program. CD4+ lymphocyte counts were stratified into four categories: < 200, 200-349, 350-500, and ≥ 500 cells/mm^3. HIV RNA counts were stratified into three categories: < 4000, 4000-40000, and ≥ 40000 copies/mL.

At each study visit, self-reported anti-retroviral use since the previous visit was assessed by interviewers who stated the name of each drug (by both brand and generic drug names) and showed participants photo-medication cards. We focused on the three classes of FDA-approved therapies: nucleoside reverse-transcriptase inhibitors (NRTI), including zidovudine, stavudine, zalcitabine, didanosine, abacavir, and lamivudine; protease inhibitors (PI), including saquinavir, indinavir, ritonavir, and nelfinavir; and non-nucleoside NRTIs (NNRTI), including nevirapine, efavirenz, and delavirdine. The definition of HAART was guided by the International AIDS Society-USA Panel (Carpenter *et al.*, 2000; Yeni *et al.*, 2002) guidelines as: (a) two or more NRTIs in combination with at least one PI or one NNRTI (91% of observations classified as HAART); (b) one NRTI in combination with at least one PI and at least one NNRTI (6%); (c) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs (2%); and (d) an abacavir-containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs (1%). Combinations of zidovudine (AZT) and stavudine (d4T) with either a PI or NNRTI were not considered HAART.

Use of any anti-fungal therapy at each visit (since the last visit) included reported use of clotrimazole, nystatin, ketoconazole, fluconazole, itraconazole, amphotericin B, or any "other anti-fungal". Other covariates included self-reported use (yes/no) of cigarettes, heroin/methadone, marijuana, and crack/cocaine.

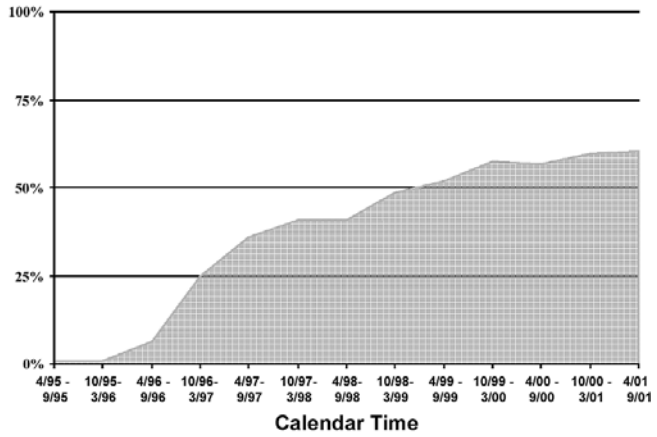

Figure. Prevalence of reported HAART over time.

Statistical Analysis

For each outcome, we examined the trends in incident and recurrent lesions. Incidence of mucosal lesions within the WIHS was investigated among those free of the outcome at baseline, and accumulating all the visits up to and including the first occurrence of the outcome. We used these with the total number of incident events to calculate the incidence rate in terms of "person-visits". Those who were diagnosed with one of these lesions were censored at the time that type of lesion was discovered, but remained at risk for evaluation of development of other lesions.

Recurrence of mucosal lesions was investigated among women who had first reported a prevalent (*i.e.*, baseline) or incident outcome. All visits after the first occurrence were accumulated and used with the total number of events observed to calculate the recurrence rate. Because of the difficulty in evaluating whether subsequent reports of HL or WT were new events or manifestations of prior events, we evaluated recurrence for only PC, EC, and the combined PC/EC outcome.

Incidence and recurrence rates were calculated separately for those visits that occurred prior to the initiation of HAART ("Pre-HAART") and after HAART initiation. Using these rates, we computed crude (unadjusted) relative risks. To evaluate the occurrence patterns of mucosal lesions before and after HAART initiation, we used two different Poisson regression models that adjusted for time-varying confounding variables. The first model was adjusted for use of anti-fungal medications, smoking, and use of marijuana, cocaine, and heroin/methadone. The second model was adjusted for these variables in addition to CD4 cell counts and HIV RNA levels. These separate models were fit to avoid over-adjustment by markers that may mediate the association of HAART and the development of oral lesions.

RESULTS

The use of HAART increased from 2% to 54% between the beginning and the end of the study (Fig.) (Gange *et al.*, 2002). This increase reflects the introduction of new PI and NNRTI medications as well as the expanded use of these medications among WIHS participants (Ahdieh *et al.*, 2000). Three hundred eighty-two HIV-positive women who were free of all lesions at baseline are included in the incidence analyses, and 239 of these

women initiated HAART during follow-up. Table 1 displays time-varying demographic variables stratified by HAART initiation. There was no significant difference in the prevalence of antifungal use among visits before and after the initiation of HAART ($p = 0.354$). However, there was significantly ($p < 0.001$) lower use of cigarettes (46.3% *vs.* 62.7%) and recreational drugs among visits after HAART initiation. Furthermore, HIV RNA and CD4 levels were significantly lower after HAART initiation. Table 2 displays the incidence rates before and after HAART initiation for EC, PC, either EC or PC, HL, and WT. Relative risk (RR) estimates reflect the relative incidence of each outcome after HAART relative to before HAART. As described in MATERIALS & METHODS, we computed the crude incidence rates and evaluated two multivariate models: Model 1 reflects the RR for HAART, adjusted for reported use of anti-fungals, smoking, marijuana, cocaine, and heroin/methadone; Model 2 reflects the RR for HAART adjusted for those variables in Model 1 and also CD4 and HIV RNA. Overall, our data demonstrate a strong decrease in candidiasis after HAART initiation relative to the time before HAART initiation (Table 2). The incidence of EC fell to 2.99 from 5.48 (RR 0.545); PC fell to 2.85 from 6.70 (RR 0.425); and EC or PC fell to 3.43 from 7.35 (RR 0.466) (Table 2). After further multivariate adjustment of CD4 and HIV RNA levels, all of the RR estimates remained below 1, but the statistical significance of the EC estimate was lost. The rates of HL and oral warts were much lower than the rates of candidiasis, and no significant changes were seen in the time period after HAART initiation.

Recurrence rates (Table 2) were examined for candidiasis only, since the identification of HL and oral warts may reflect persistent rather than recurrent lesions. The rates of recurrence for PC, EC, and the combined outcome were 3-5 times higher than incidence rates. As was demonstrated with the incidence rates, recurrence rates showed a strong decrease after HAART initiation. The magnitude of

Table 1. Summary Statistics among Visits Contributed by 382 Women Free of All Lesions at Baseline

	Percentage of Person-visits with Characteristic Demographic Variables		
	Pre-HAART visits	Visits after HAART Initiation	p value[a]
Current anti-fungal use	16.0	17.2	0.354
Current smoking	62.7	46.3	**< 0.001**
Current marijuana use	25.8	15.7	**< 0.001**
Current crack/cocaine use	33.9	20.0	**< 0.001**
Current heroin use	17.9	12.1	**< 0.001**
HIV RNA (copies/mL)			**< 0.001**
> 40 K	21.3	16.3	
4 K-40 K	30.3	21.9	
< 4 K	48.4	61.8	
CD4+ lymphocyte count (/mm^3)			**< 0.001**
< 200	16.2	25.8	
200-349	25.5	23.6	
350-500	22.6	21.1	
> 500	35.8	29.5	

[a] P value reflects comparison of characteristics pre- *vs.* post-HAART initiation by chi-square tests of association.

Table 2. Incidence Rates and Relative Risks for Oral Lesions

	EC[a]	PC	EC or PC	HL	WT
Prevalent cases	46	50	52	47	2
Women contributing data	413	414	414	410	452
Incidence rate (first events/person-visits)					
Pre-HAART	5.48 (76/1386)	6.70 (95/1418)	7.35 (101/1374)	2.54 (40/1576)	0.62 (11/1770)
After HAART initiation	2.99 (39/1305)	2.85 (34/1195)	3.43 (40/1167)	2.35 (31/1321)	0.59 (10/1708)
Crude incidence RR[b]	**0.545**	**0.425**	**0.466**	0.925	0.942
(p-value)	**p = 0.0021**	**p < 0.0001**	**p < 0.0001**	p = 0.7432	p = 0.8914
Adjusted incidence RR Model 1[c]	**0.656**	**0.485**	**0.477**	0.897	0.864
(p-value)	**p = 0.0365**	**p = 0.0004**	**p = 0.0002**	p = 0.6584	p = 0.7511
Adjusted incidence RR Model 2[d]	0.723	**0.494**	**0.520**	1.02	0.848
(p-value)	p = 0.1219	**p = 0.0012**	**p = 0.0012**	p = 0.9543	p = 0.7254
Recurrence rate (subsequent events/person-visits)					
Pre-HAART	29.98 (131/437)	21.23 (86/405)	23.33 (105/450)		
After HAART initiation	15.40 (71/461)	14.01 (80/571)	15.70 (95/605)		
Crude incidence RR	**0.514**	**0.660**	**0.673**		
(p-value)	**p < 0.0001**	**p = 0.0074**	**p = 0.0052**		
Adjusted incidence RR Model 1	**0.550**	**0.657**	**0.664**		
(p-value)	**p < 0.0001**	**p = 0.0084**	**p = 0.0073**		
Adjusted incidence RR Model 2	**0.659**	0.746	**0.707**		
(p-value)	**p = 0.0126**	p = 0.0919	**p = 0.0265**		

[a] Erythematous candidiasis (EC), pseudomembranous candidiasis (PC), either EC or PC, hairy leukoplakia (HL), and oral warts (WT).
[b] Relative risks (RR) measures risk of outcome after HAART relative to before HAART.
[c] Model 1 is adjusted for reported use of anti-fungals, smoking, marijuana, cocaine, and heroin/methadone.
[d] Model 2 is adjusted for these variables and CD4 and HIV RNA.

Table 3. Multivariate Relative Risk Estimates for Predictors of Oral Mucosal Lesions

	EC	PC	EC or PC	HL	WT
Incidence					
Reported use of any anti-fungal (yes/no)	**0.479***[a]	1.029	0.976	1.411	0.216
Current smoking (yes/no)	1.529	**1.749***	**1.667***	0.930	0.866
Current marijuana (yes/no)	0.874	0.780	0.766	1.288	1.299
Current crack/cocaine (yes/no)	1.409	1.095	0.989	0.999	0.520
Current heroin/methadone (yes/no)	**1.879***	1.116	1.254	1.111	**3.246***
HIV RNA > 40 K	**3.508***	**3.551***	**2.991***	**2.962***	1.164
HIV RNA 4 K-40 K	1.409	**1.735***	1.442	**2.273***	1.005
HIV RNA < 4 K	Ref	Ref	Ref	Ref	Ref
CD4 < 200	0.901	1.452	1.373	**2.978***	1.130
CD4 200-349	0.759	0.899	0.886	**2.459***	0.595
CD4 350-500	0.755	1.429	1.440	1.274	1.143
CD4 > 500	Ref	Ref	Ref	Ref	Ref
Recurrence					
Reported use of any anti-fungal (yes/no)	1.327	0.707	**0.685***		
Current smoking (yes/no)	1.410	0.935	0.810		
Current marijuana (yes/no)	0.976	1.117	1.233		
Current crack/cocaine (yes/no)	1.316	1.340	1.249		
Current heroin/methadone (yes/no)	1.081	0.777	0.767		
HIV RNA 40 K	**2.108***	**2.417***	**1.696***		
HIV RNA 4 K-40 K	**1.133**	**1.908***	**1.521***		
HIV RNA < 4 K	Ref	Ref	Ref		
CD4 < 200	0.949	1.276	1.448		
CD4 200-349	1.142	1.602	**1.770***		
CD4 350-500	1.210	1.347	1.470		
CD4 > 500	Ref	Ref	Ref		

[a] Asterisk indicates significance of relative risk from 1.0 at p = 0.05 level, adjusted for HAART use as described in Table 2.

these reductions was similar to those described for incidence, and generally persisted after adjustment for demographic variables (Model 1) and markers of disease progression (Model 2). Table 3 displays the association of other variables with the incidence and recurrence of the oral mucosal lesions studied *via* the multivariate models. Both smoking and heroin/methadone use were associated with incidence of oral candidiasis, while heroin/methadone use was also strongly associated with oral warts. HIV viral load > 40 K was generally associated with incidence and recurrence of candidiasis (EC at > 40 K HIV, RNA RR for incidence was 3.508 and RR for recurrence was 2.108; and for PC, RR for incidence was 3.551 and for recurrence was 2.417). HIV viral load > 40 K was generally associated with incidence of HL but not warts. The only lesion associated with CD4 was HL, with an increased risk of HL for those women with CD4 counts < 200 cells/mm^3.

DISCUSSION

Between visits before and those after the initiation of HAART, there was no significant difference in the prevalence of antifungal use (p = 0.354). However, there was significantly (p < 0.001) lower use of cigarettes (46.3% *vs.* 62.7%) and recreational drugs among visits after HAART initiation. Furthermore, HIV RNA and CD4 levels were significantly lower after HAART initiation. These trends reflect changes that might occur after HAART initiation, as well as the characteristics of those who initiate therapy (Ahdieh *et al.*, 2000; Cook *et al.*, 2002). During the six years of the study, HAART was associated with reduced incidence of OC. However, concomitant significant reduction was not seen in the incidence of HL, nor was there a change in the incidence of warts. The relationship of candidiasis to HAART still held after adjustment for several behavioral variables as well as CD4 and HIV RNA. Furthermore, it is interesting to note that the effect of HAART is attenuated (RR estimates are closer to 1.0) but not eliminated after adjustment for CD4 and HIV RNA. This suggests that some, but perhaps not all, of the effect of HAART on PC/EC may be mediated by changes in CD4 cell count and HIV RNA levels.

The estimated RR for each lesion after HAART initiation was attenuated (closer to 1.0) after multivariate adjustment of variables on Model 1. Each of the Model 1 estimates remained significantly below 1, suggesting that the demographic differences after HAART initiation do not account for the change in incidence rate. In general, it seems that oral candidiasis is reduced after HAART, in keeping with the overall changes in morbidity and mortality among HIV-infected people since the introduction of HAART (Palella *et al.*, 1998). As we and others have reported (Palacio *et al.*, 1997; Shiboski *et al.*, 1999; Greenspan *et al.*, 2001), both smoking and heroin/methadone use are associated with OC. In this study, we found that oral warts are also strongly associated with heroin/methadone use. However, we did not record the increases in the incidence of warts that have been reported in clinic populations (Leigh *et al.*, 1999; Greenspan *et al.*, 2001; Greenwood *et al.*, 2002). There are few reports about the effect of HAART on HPV infection. A recent study did not find a reduction in anal HPV DNA levels after the initiation of HAART (Palefsky *et al.*, 2001).

CD4 counts showed no relationship with oral lesions except for HL. The significant relationship observed with high viral load for both OC and HL is consistent with reports from earlier studies (Margiotta *et al.*, 1999; Greenspan *et al.*, 2000; Patton *et al.*, 2000). HL may be a more sensitive marker, since the risk increases with increasing viral load. The relative risk for incidence of PC also increases with increasing viral load.

We and many others have shown the sentinel role of oral opportunistic infections in the natural history of HIV infection and AIDS. The data reported here relate to oral disease in women, and show reductions during therapy with HIV infection. Of significance is the observation that oral candidiasis recurrence rates were quite high, the incidence of recurrent lesions being about 5 times as high as the incidence of an initial event. Recurrence rates declined after HAART as with incidence rates, but they still remained about 5 times higher than the incidence rates after HAART. Other changes in oral disease—including xerostomia, caries, and periodontal disease—in participants in the WIHS are reported in recently submitted papers.

We believe that this is the first report of the incidence of common oral mucosal lesions in HIV-infected women, and of the effects of HIV therapy on oral mucosal lesion incidence and recurrence in that population.

ACKNOWLEDGMENTS

Data in this manuscript were collected by the Oral Substudy of the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Joan Phelan); The Connie Wofsy Study Consortium of Northern California (Deborah Greenspan. John S. Greenspan); Los Angeles County/Southern California Consortium (Roseann Mulligan); Chicago Consortium (Mario Alves); and Data Coordinating Center (Alvaro Muñoz, Stephen J. Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases, with supplemental funding from the National Cancer Institute, the National Institute of Child Health & Human Development, the National Institute on Drug Abuse, and the National Institute of Dental and Craniofacial Research (U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-HD-32632, U01-AI-34993, U01-AI-42590, M01-RR00071, and M01-RR00083).

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