



## Incidence of oral candidiasis and oral hairy leukoplakia in HIV-infected adults in North Carolina

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**Objectives.** To establish incidence rates and risk factors for HIV-associated oral candidiasis (OC), oral hairy leukoplakia (OHL), and any HIV-associated oral diseases (HIV-OD).

**Design.** This prospective, cumulative case-control study followed 283 initially oral disease-free HIV-1-infected men and women for 2 years. Incidence rate ratios (IRR) and incidence proportions for OC, OHL, and HIV-OD were estimated. Multivariable analyses using Poisson regression determined the most parsimonious best-fitting model explaining the outcomes.

**Results.** Incidence rate (per 1000 person-months) was 9.3 for OC, 6.8 for OHL, and 13.5 for HIV-OD. Incidence of OC was associated with low CD4 count (adjusted IRR = 3.0 (95% CI = 1.7, 5.1)), smoking (IRR = 1.9 (1.0, 3.8)) and combination antiretroviral therapy (IRR = 0.3 (0.1, 0.8)). Incidence of OHL was associated with low CD4 count, conditional upon smoking status.

**Conclusions.** Low CD4 count and smoking are important risk factors for HIV-associated OC and OHL. Antiretroviral medications are protective for OC but not for OHL.

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Oral candidiasis (OC) and oral hairy leukoplakia (OHL) are the most frequently occurring HIV-associated oral diseases (HIV-OD).<sup>1,2</sup> They serve as important markers of HIV infection,<sup>3,4</sup> viral load,<sup>5-7</sup> and CD4+ T lymphocyte count in the blood (CD4 count)<sup>6-9</sup> and predict

disease progression to AIDS.<sup>9-11</sup> The prevalence of HIV-associated oral diseases (HIV-OD) has decreased since the introduction of highly active antiretroviral therapy (HAART).<sup>12-16</sup> One study reported incident Kaposi's sarcoma,<sup>17</sup> and another reported survival time for OC and OHL after seroconversion,<sup>18</sup> but neither evaluated risk factors. Other follow-up studies demonstrated association of multiple events of OC/OHL with progression to AIDS.<sup>19,20</sup>

While many studies have pointed out risk factors and indicators for HIV-OD using prevalence data, limited information is available regarding independent risk factors established in longitudinal cohorts. Whereas recent studies have reported incidence rates of OC, OHL, and oral warts among women in the Women's Interagency HIV study<sup>21</sup> and OC among women in the HIV Epidemiology Research Study Group,<sup>22</sup> at present there are no published studies evaluating risk factors of incident OC and OHL that address populations of men and women together.

Our overall research questions in this study among HIV-positive individuals were (1) what are the

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independent risk factors/indicators associated with incident OC and OHL, and (2) are OC and OHL similar with respect to occurrence and their risk factors/indicators? The operating hypothesis was that immunosuppression is independently associated with OC/OHL/HIV-OD after adjusting for other covariates such as age, gender, level of education, viral load, sexual orientation, smoking, antimicrobial medications, recreational drug use, and antiretroviral therapy. We had 3 specific aims for this study: (1) to establish incidence rates for OC, OHL, and HIV-OD among HIV-1 positive adults; (2) to establish independent risk factors for development of incident OC, OHL, and HIV-OD; and (3) to evaluate whether the relationship of CD4 count and development of OC, OHL, or HIV-OD was modified by any other measured variable.

## METHODS

### Study data and variables

*Study sample.* Between 1995 and 2000, 631 HIV-positive adults, approximately half of those examined and treated at the infectious diseases clinic of the University of North Carolina (UNC) Hospitals, volunteered to participate in the study and were followed annually for 2 years after giving their signed informed consent. The UNC School of Medicine and UNC Hospitals Committee on the Protection of the Rights of Human Subjects approved the study. During each yearly visit, a trained social researcher interviewed the participant to complete a questionnaire in a private room, requiring about 45–60 minutes. Afterwards, a single calibrated oral medicine trained dental examiner conducted the clinical examination. Assessment of HIV-OD was based on the published standard criteria.<sup>23</sup> Group 1 lesions (lesions deemed to be strongly associated with HIV-1 infection) were considered as defining membership in the HIV-OD group. A medical record review was undertaken usually within 1 month after the examination to ascertain all medical, medication, and laboratory variables used in the study. A second review was undertaken later to cross-check case status, dates, disease outcomes, and laboratory test results to assure that a first event of HIV-OD was not missed in between the study visits.

Between study visits, subjects received varying levels of routine medical and dental care, depending on severity of general and oral health conditions and access to care. Patients generally received their primary medical care at the UNC Infectious Disease clinic, staffed by physicians with considerable experience in managing patients with HIV disease. Infectious Disease clinicians were not specifically calibrated to diagnose oral lesions for this research study. Community providers were occasionally seen, but no attempt was made to obtain

community providers' clinical records. UNC Hospitals medical records of patients enrolled in the longitudinal study were reviewed for oral/head-and-neck exam findings recorded by all clinicians during the course of routine and urgent care visits.

*Case definition.* Two hundred eighty-three participants were free at baseline of any HIV-OD on clinical examination and by history and were followed for 2 years. For each outcome (OC, OHL, HIV-OD), those who did not develop the condition were controls, and cases were those who developed the disease. Participants who had both OC and OHL at a study visit were included as cases for all 3 outcomes. Participants remaining disease free were censored at the last visit. Those developing a disease of interest stopped contributing person-time to the study as of the event date. Covariate values in the analyses reflect those at the time of developing disease or at the last study visit unless specified as baseline values.

*Data management and variables.* All outcomes and main exposure (CD4 count, typically within a month) data were double-entered for quality assurance, and error checks were performed. Discrepancies and conflicts were resolved by verifying original data on the hard copy questionnaire and medical record review data sheet. The following variables were included in the analyses from each visit: outcome variables—OC, OHL, and HIV-OD; and explanatory variables—age, race, sex, years of education, sexual orientation, smoking, recreational drug use, CD4 count, plasma viral load, antiretroviral therapy, antifungal medication use, and antibiotic use. Standard definitions<sup>24</sup> were used to classify variables.

### Statistical analyses

Univariate distributions were evaluated for the variables in the study for each disease outcome for each year. Bivariable relationships were evaluated between the covariates and each of the 3 potential outcome variables—OC, OHL, and HIV-OD—and with CD4 count as our main explanatory variable. Continuous variables were assessed using *t* tests and analysis of variance. Categorical variables were assessed with odds ratios and chi-squared statistics, using 2-sided tests. Correlations were evaluated between the covariates to help prevent collinearity errors in the models. Because CD4 count was used as the main “exposure” variable, viral load was not used in any of the models because it occurs directly in the causal pathway between the main exposure and outcome.<sup>25</sup> Correlation was evaluated using Pearson's, Spearman's, and Kendall's tau correlation coefficients. Statistical significance was evaluated at .05 level (.1 for interactions).<sup>25</sup> All analysis was done in SAS (V8.2, SAS Institute, Cary, NC).

*Multivariable analyses.* Poisson regression was used to explore the relationship between the putative risk factors and each outcome. Indicator variables with reference cell coding were used. Crude and adjusted incidence densities and incidence rate ratios (IRR) for each of the disease outcomes using log of person-months contributed (offset) were computed using PROC GENMOD. Goodness of fit and over/under dispersion were evaluated using deviance and Pearson chi-squared statistics and their ratio to their respective degrees of freedom.<sup>26</sup> For each disease outcome a full model was first created using all variables suggested in the literature and those associated with the outcomes and CD4 count in bivariable analyses. Interaction terms between CD4 count and important covariates were tested one at a time. The analyses aimed to find the best-fitting and most parsimonious, yet biologically reasonable, model describing the relationship between the disease outcome and explanatory variables. Hierarchically well formulated model structure was used, implying that given any variable in the model, all lower-order components of the variables must also be contained in the model.<sup>27</sup> To reach a final model, we used a manual hierarchical backward elimination approach.

For proceeding further, the full model had to be significantly better than an intercept-only model. Starting with the full model, noncontributory variables were manually removed in sequence through sets of hierarchical models. Because CD4 count was the main explanatory/exposure variable, it was forced into the model even if the effect did not contribute statistically significantly. Precision of IRRs was evaluated using 95% confidence limit ratio (CLR), defined as the ratio of upper and lower 95% confidence limits. Hierarchical sets of models were tested using the likelihood ratio test with alpha set at .05. Regression diagnostics were performed and utility of the models were evaluated by outputting predicted scores.

## RESULTS

Overall, among Group-1 lesions, 51/283 (18%) participants developed OC, 37/283 (13%) developed OHL and 4 participants developed linear gingival erythema. Very few participants developed Group 2 or Group 3 lesions. For example, 3 participants developed minor aphthous ulcers and 1 developed focal epithelial hyperplasia. Table I shows incidence proportion (IP) in percent of study sample, incidence rates (IR) in events/1000 person-months, and crude IRRs with their 95% confidence intervals (CIs). The overall incidence rate (per 1000 person-months) of OC was higher than OHL (9.305 vs. 6.763; but less than HIV-OD at 13.547). Persons with low CD4 count had higher incidence of OC/OHL/HIV-OD compared to those with higher CD4

counts. High viral load, low baseline CD4 count, and smoking were significantly associated with higher incidence of OC/OHL/HIV-OD. Those with higher education, males, bisexuals, and those under antifungal therapy had higher incidence of OHL. Antiretroviral therapy was protective for OC and HIV-OD outcomes.

### Oral candidiasis

Significantly more people with low baseline CD4 count, with low CD4 count at end of study, with high viral load, and not under any antiretroviral medication developed OC. Proportion of OC cases was slightly higher among women, blacks, those age 30-39, those with lesser education, current smokers, those under antifungal therapy, and those reporting being bisexual (Table I).

Table II shows the full and final Poisson regression models explaining incident OC. The final model included CD4 count, current smoking, and antiretroviral therapy as significant risk factors for incident OC. After adjusting for antiretroviral therapy and current smoking, those with low CD4 count were 3.0 times as likely to develop OC compared to those with higher CD4 count (IRR (CI) = 3.0 (1.7, 5.1)). Current smokers were almost twice as likely to develop OC compared to not-current smokers after adjusting for covariates (IRR = 1.9 (1.0, 3.8)). Antiretroviral combination therapy (IRR = 0.3 (0.1, 0.8)) showed “protective” effect after adjusting for CD4 count and current smoking.

Because the type 3 *P* value for smoking–CD4 count interaction in the full model was close to the alpha level, we evaluated IRRs in different cross-categories of CD4 count and current smoking. Though there was no statistically significant interaction, the IRRs between the subgroups varied substantially. Current smokers with low CD4 count were most at risk for developing OC. Low CD4 count and smoking increased the risk of OC in the absence of each other. These effects were evident in unadjusted IRR estimates and adjusted estimates. Compared to the final model, the unadjusted low CD4 count–current smoker IRR was confounded upwards away from the null by 8.4%. The trend for risk of OC was similar when evaluated in unadjusted or fully adjusted models.

### Oral hairy leukoplakia

Significantly more men, current smokers, persons with low baseline CD4 count, those with low CD4 count at end of study, and those with high viral load developed OHL. Proportions of OHL cases were slightly higher among those with more than 12 years of education, those under antifungal therapy, men who have sex with men (MSM), and those with high viral load at baseline, as shown in Table I.

Table III shows the full and final Poisson regression models for explaining incident OHL. Based on the final

**Table I.** Incidence of OC/OHL/HIV-OD disease occurrence (incidence proportion (IP) in percent; incidence rate (IR) per 1000 person-months; incidence rate ratio (IRR) includes 95% confidence interval (CI))

Characteristic	Level	OC			OHL			HIV-OD		
		IP	IR	IRR (CI)	IP	IR	IRR (CI)	IP	IR	IRR (CI)
Overall		18.0	9.305	—	13.2	6.763	—	25.3	13.547	—
CD4+ cells at event (cells/μl)	<200	31.7	14.027	3.1 (1.8, 5.3)	20.5	8.724	2.2 (1.2,3.9)	40.7	18.714	2.3 (1.3, 4.1)
	≥ 200	11.8	4.593	1	10.2	4.064	1	19.1	8.056	1
Smoking	Current	19.9	8.553	2.2 (1.1, 4.5)	14.7	6.330	2.6 (1.2, 5.3)	27.9	12.764	2.1 (1.1, 4.3)
	Never/Former	13.9	3.899	1	10.0	2.598	1	20.5	6.029	1
Antiretroviral medication	Combination	16.4	2.238	0.2 (0.1, 0.8)	12.0	4.662	0.9 (0.4, 2.5)	20.8	2.736	0.3 (0.1, 0.9)
	Monotherapy	15.9	7.668	0.8 (0.5, 1.5)	13.8	5.747	1.2 (0.6, 2.4)	25.6	12.399	1.0 (0.6, 1.9)
	None	23.1	9.221	1	12.2	4.847	1	28.1	11.929	1
Age (years)	40+	14.7	5.415	0.9 (0.3, 2.9)	11.9	4.345	0.5 (0.2, 1.4)	23.1	8.273	0.7 (0.2, 1.8)
	30-39	22.5	9.476	1.5 (0.5, 5.0)	13.9	6.084	0.7 (0.3, 1.9)	27.7	12.969	1.0 (0.4, 2.7)
	18-29	14.3	6.309	1	18.2	8.197	1	26.3	12.739	1
Sex	Female	18.7	7.868	1.2 (0.6, 2.2)	6.1	2.649	0.4 (0.2, 0.9)	20.8	9.062	0.8 (0.4, 1.6)
	Male	17.7	6.715	1	16.6	6.571	1	27.2	11.069	1
Race/ethnicity	White	14.6	4.406	0.5 (0.3, 1.0)	13.8	3.602	0.6 (0.3, 1.2)	20.8	6.644	0.6 (0.3, 1.1)
	Black	19.7	8.368	1	12.9	6.028	1	27.4	12.167	1
Sexual orientation	MSM	14.8	4.878	0.6 (0.3, 1.3)	19.8	5.216	1.1 (0.6, 2.2)	29.4	9.042	0.8 (0.4, 1.7)
	Bisexual	26.1	8.645	1.1 (0.5, 2.4)	13.5	8.726	1.9 (0.9, 4.1)	25.7	11.857	1.1 (0.5, 2.5)
	Heterosexual	17.2	7.791	1	9.9	4.658	1	23.2	10.801	1
Antifungal	Yes	24.1	8.000	1.2 (0.5, 2.7)	30.6	13.976	3.6 (1.9, 6.4)	41.4	16.666	1.8 (0.9, 3.6)
	None	17.3	6.911	1	10.7	3.939	1	23.1	9.541	1
Baseline CD4+ (cells/μl)	<200	25.9	9.942	1.9 (1.1, 3.2)	20.4	8.235	2.3 (1.3, 4.0)	37.9	14.719	1.71 (1.0, 3.0)
	≥ 200	13.4	5.358	1	9.1	3.659	1	19.3	8.585	1
Education level	12+ years	15.3	4.509	0.5 (0.3, 0.9)	18.0	7.202	1.8 (1.0, 3.3)	25.5	9.352	0.8 (0.5, 1.5)
	<12 years	19.6	8.888	1	10.1	3.983	1	25.2	11.211	1
Recreational drug use	Current	15.8	5.371	0.8 (0.3, 1.9)	14.3	5.050	0.6 (0.3, 1.5)	23.3	6.400	0.6 (0.2, 1.6)
	Former	21.6	7.845	1.2 (0.6, 2.3)	9.7	4.170	0.5 (0.3, 1.0)	24.6	11.036	1.0 (0.5, 1.8)
	Never	13.3	6.702	1	19.7	7.837	1	27.9	11.555	1
Viral load (cp/ml)	≥ 20,000	5.9	15.113	5.2 (2.9, 9.4)	7.7	8.166	2.1 (1.2, 3.8)	12.4	18.957	3.0 (1.7, 5.3)
	< 20,000	31.2	2.896	1	16.9	3.853	1	37.5	6.230	1

MSM, Men who have sex with men.

**Table II.** Poisson regression models for incidence density for OC

Variable	Level	Full model			Final model		
		Estimate	SE	P	Estimate	SE	P
Intercept		-4.91	0.76	<.0001	-5.54	0.39	<.0001
CD4+ cells/μL at event (ref: ≥ 200)	<200	0.80	0.76	.2887	<b>IRR</b>	<b>95% CI</b>	<.0001
					3.0	1.7, 5.1	
Smoking (ref: never/former) CD4+*, smoking	Current	0.56	0.47	.2320	1.9	1.0, 3.8	.0500
		0.22	0.80	.7863			
		<b>IRR</b>	<b>95% CI</b>	<b>P</b>			
Antiretroviral medication (ref: none)	Combination	0.3	0.1, 0.9	.0344	0.3	0.1, 0.8	.0203
	Monotherapy	0.9	0.5, 1.7	.7760	0.8	0.4, 1.4	.3979
Age (years) (ref: 18-29)	40+	0.6	0.2, 2.0	.3898			
	30-39	0.9	0.3, 3.5	.9539			
Sex (ref: men)	Women	1.1	0.5, 2.3	.7820			
Race/ethnicity (ref: black)	White	0.6	0.3, 1.3	.1870			
Sexual orientation (ref: heterosexual)	MSM	0.7	0.3, 1.7	.4687			
	Bisexual	1.5	0.6, 3.8	.3432			
Antifungal (ref: none)	Yes	0.7	0.3, 1.9	.5413			
Baseline CD4+ cells/μL (ref: ≥ 200)	<200	1.2	0.6, 2.4	.5991			
Education (ref: < 12 years)	12+ years	0.7	0.4, 1.4	.3518			
Recreational drug use (ref: never)	Current	0.8	0.3, 2.2	.7050			
	Former	0.8	0.4, 1.6	.5138			

MSM, Men who have sex with men.

\*Interaction term.

**Table III.** Poisson regression models for incidence density for OHL

Variable	Level	Full model			Final model		
		Estimate	SE	P	Estimate	SE	P
Intercept		-5.75	0.89	<.0001	-6.89	0.72	<.0001
CD4+ cells/ $\mu$ L at event (ref: $\geq$ 200)	<200	1.56	0.87	.0712	1.59	0.84	.0577
Smoking (ref: never/former)	Current	2.20	0.73	.0025	1.77	0.74	.0159
CD4+*, smoking		-1.66	0.88	.0582	-1.49	0.88	.0701 <sup>#</sup>
		<b>IRR</b>	<b>95% CI</b>		<b>IRR</b>	<b>95% CI</b>	
Antifungal (ref: none)	Yes	2.2	1.1, 4.3	.0292	2.8	1.5, 5.4	.0016
Sex (ref: men)	Women	0.4	0.1, 0.9	.0310	0.5	0.2, 1.1	.0622
Recreational drug use (ref: never)	Current	0.4	0.2, 1.0	.0504			
	Former	0.4	0.2, 0.7	.0043			
Age (years)	40+	0.3	0.1, 0.7	.0086			
(ref: 18-29)	30-39	0.5	0.2, 1.3	.1712			
Race/ethnicity (ref: black)	White	0.6	0.3, 1.2	.1098			
Sexual orientation (ref: heterosexual)	MSM	0.7	0.3, 1.4	.2501			
	Bisexual	1.8	0.7, 4.4	.2018			
Baseline CD4+ cells/ $\mu$ L (ref: $\geq$ 200)	<200	1.6	0.7, 3.3	.2503			
Antiretroviral medication (ref: none)	Combination	0.7	0.3, 1.8	.4958			
	Monotherapy	0.9	0.5, 1.9	.8291			
Education (ref: <12 years)	12+ years	2.0	1.1, 3.7	.0181			

MSM, Men who have sex with men.

\*Interaction term.

<sup>#</sup>Retained in the model because the model changed significantly if the interaction was removed, and because interactions are recommended to be evaluated at a higher alpha level.<sup>25</sup>

model, after adjusting for CD4 count, antifungal medication and current smoking, women were about half as likely to develop OHL compared to men (IRR = 0.5 (0.2, 1.1)). Those under antifungal medication were about three times as likely to develop OHL compared to those not under antifungals after adjusting for CD4 count, current smoking, and gender (IRR = 2.8 (1.5, 5.4)).

Current smokers with low CD4 count were most at risk for developing OHL. Both low CD4 count and smoking increased the risk of OHL. These effects were evident in unadjusted IRR estimates and adjusted estimates (Table III). Based on the final model and compared to those with high CD4 count who were not current smokers, those with low CD4 count who were current smokers were 6.5 times as likely to develop OHL, those with low CD4 count who were not current smokers were 4.9 times as likely to develop OHL, and those with higher CD4 count who were current smokers were 1.3 times as likely to develop OHL (Table III). Compared to the final model estimate, the unadjusted low CD4 count–current smoker IRR was confounded upwards away from the null value by 62.71%. The trend for risk of OHL was similar in unadjusted and fully adjusted models.

**HIV-associated oral diseases**

Table IV shows the Poisson regression models for HIV-OD. The final model included CD4 count, current

smoking status, and antiretroviral medication. Based on the final model, those with lower CD4 count were more than twice as likely to develop HIV-OD compared to those with higher CD4 count (IRR = 2.4 (1.3, 4.2)) after adjusting for current smoking status and antiretroviral therapy. After adjusting for covariates, current smokers were twice as likely to develop HIV-OD compared to not-current smokers (IRR = 2.0 (1.1, 3.9)); whereas combination antiretroviral therapy (IRR = 0.2 (0.1, 0.8)) was protective for developing HIV-OD compared to those not under any antiretroviral therapy.

Current smokers who had low CD4 count were most at risk for developing HIV-OD. Based on the final model, compared to those with high CD4 count who were not current smokers, those with low CD4 count who were current smokers were 4.8 times as likely to develop HIV-OD. This IRR estimate was similar to the unadjusted low CD4 count–current smoker IRR value. The trend for risk of HIV-OD was similar in unadjusted and fully adjusted models.

Figure 1 shows the predicted IRR for OC, OHL, and HIV-OD from models similar to the respective final models, using CD4 count as a continuous variable.

**DISCUSSION**

This study provides the first analysis of incidence densities of HIV-associated oral diseases in a mixed-race

**Table IV.** Poisson regression models for incidence density for HIV-OD

Variable	Level	Full model			Final model		
		Estimate	SE	P	Estimate	SE	P
Intercept		-4.1421	0.69	<0.0001	-5.1139	0.39	<0.0001
					<b>IRR</b>	<b>95% CI</b>	
CD4+ cells/ $\mu$ L at event (ref: $\geq 200$ )	<200	0.62	0.73	0.3996	2.4	1.3, 4.2	0.0031
Smoking (ref: never former)	Current	0.85	0.47	0.0669	2.0	1.1, 3.9	0.0443
CD4+*, smoking		0.03	0.78	0.9704			
		<b>IRR</b>	<b>95% CI</b>				
Antiretroviral medication (ref: none)	Combination	0.2	0.1, 0.7	0.0155	0.2	0.1, 0.8	0.0224
	Monotherapy	0.9	0.5, 1.8	0.8208	0.9	0.5, 1.7	0.7557
Age (years) (ref: 18-29)	40+	0.4	0.1, 1.1	0.0704			
	30-39	0.7	0.2, 2.0	0.4928			
Sex (ref: men)	Women	0.7	0.3, 1.6	0.4199			
Race/ethnicity (ref: black)	White	0.6	0.3, 1.3	0.1866			
Sexual orientation (ref: heterosexual)	MSM	0.7	0.3, 1.5	0.3174			
	Bisexual	1.0	0.3, 2.7	0.9457			
Antifungal (ref: none)	Yes	1.3	0.5, 3.0	0.5844			
Baseline CD4+ cells/ $\mu$ L (ref: $\geq 200$ )	<200	1.2	0.6, 2.5	0.6639			
Education (ref: <12 years)	12+ years	1.2	0.7, 2.3	0.5346			
Recreational drug use (ref: never)	Current	0.6	0.2, 1.9	0.4415			
	Former	0.3	0.4, 1.5	0.4033			

MSM, Men who have sex with men.  
\*Interaction term.

and mixed-gender population-based study. A recently published study<sup>21</sup> has examined incidence rates of HIV-associated OC and OHL in a cohort of HIV-infected women and demonstrated that incidence of OC has been reduced in the post-HAART era. Some follow-up studies have examined OC and OHL,<sup>17-20,28,29</sup> but have not included all major potential risk factors, nor did they report incidence densities or IRRs. Boutler et al<sup>28</sup> evaluated factors associated with replication of EBV—the causative agent of OHL—but not OHL as a disease. From a multicenter longitudinal study using prevalent cases, Shiboski et al<sup>29</sup> concluded that men were at greater risk than women for OC and OHL. Lifson et al<sup>18</sup> reported a cumulative incidence proportion of 31% for OC and 41% for OHL over a 5-year follow-up period but did not evaluate risk factors. Hilton et al<sup>20</sup> evaluated 152 HIV-infected hemophiliacs using repeat-measure transitional models and concluded that history of OC predicts OC after adjusting for CD4 count. We found that CD4 count and cigarette smoking are independent risk factors for OC and OHL.

The strength of our study is that it is the first to report independent risk factors from multivariable models for incidence of OC, OHL, and HIV-OD in a mixed-race and mixed-gender population of HIV-infected adults. Owing to the original design of the parent study being one of an observational natural history study of oral disease in HIV-infected adults, OC and OHL diagnoses were based on standardized presumptive diagnostic criteria without biopsies, cultures, smears, and evaluation of treatment

response. Use of presumptive clinical criteria could raise concern for potential misclassification. The accepted consensus criteria for definitive diagnosis of OHL is demonstration of Epstein-Barr virus (EBV) in the lesion tissue in the presence of characteristic histologic features. Alternatively a presumptive OHL diagnosis would be strengthened by lack of response to antifungals or demonstration of immunodeficiency. Definitive diagnosis of pseudomembranous candidiasis relies upon response to antifungal drugs, although *Candida albicans*—positive smears or culture may support diagnosis in cases of antifungal resistance. There are no accepted definitive criteria for erythematous candidiasis, although detection of *C albicans* or response to antifungals may help establish the diagnosis.<sup>23</sup> Hyperplastic candidiasis, which is rare and more difficult to determine by clinical appearance, was not included in the study. The 2 main diseases, OC and OHL, have distinct clinical presentations that can be easily differentiated as suggested by the presumptive diagnostic criteria.<sup>23</sup>

An additional limitation of our study was the lack of information documenting the time since either the initial HIV infection event or seroconversion in the study population, thus limiting our ability to analyze the influence of HIV disease duration on the incidence data. Also, we acknowledge that annual follow-up may be too long an interval to study episodic diseases such as OC and OHL in a meaningful way to evaluate risk factors for time-to-event outcomes. We confirmed the recording of first/repeat events of diseases by

reviewing medical records following the individual study visits and by conducting a second medical record review just prior to data analysis. We ascertained good data quality through multiple data entry, multiple record review, and cross-checking missing and out of range values.

During modeling to ascertain potential etiological mechanisms, we followed the suggestions by Rothman and Greenland<sup>25</sup> that variables falling in the direct causal pathway should not be used as covariates in the same model. Plasma viral load is an antecedent to CD4 counts for compromising mucosal defenses through various mechanisms.<sup>30</sup> Because CD4 count was our main exposure variable, plasma viral load was precluded as a covariate. Antiretroviral therapies, on the other hand, may not be equally successful in reducing viral load for substantial periods. Their effect on CD4 count therefore would be variable and indirect. Most medications are secreted in the saliva and may have an effect on the oral microorganisms either directly or through a common side effect such as xerostomia. This provided a rational basis for considering antiretroviral therapy as a potential confounder of the CD4 count–OC/OHL/HIV-OD relationships.

Whereas various studies have discussed prevalence of HIV/AIDS and associated diseases before and after institution of HAART, a comparable definition of HAART in these studies was not found. Our study was initiated before development of the now widely used US Department of Health and Human Services guidelines,<sup>31</sup> and data were collected during the phase of initiation and establishment of HAART. Therefore our data does not lend itself suitable to a HAART/nonHAART type of dichotomization. To evaluate antiretroviral treatment as a paradigm, we categorized antiretroviral therapy into a 3-level variable: no therapy, monotherapy, and any combination therapy. We found antiretroviral therapy to show “protective” effects (IRRs < 1) for OC and HIV-OD. This clear demonstration contrasts to some reports that have suggested a reverse relationship.<sup>20,32</sup> We attribute the discrepancy to differences in defining antiretroviral therapy and in variable construction for analysis. In our analyses, combination antiretroviral therapy was consistently protective in crude, bivariable, fully adjusted models and final models where it was involved (for OC and HIV-OD).

Use of antifungal medications persisted in our models for OHL. It has been suggested that some individuals with OHL may have had OC in the immediate past that had resolved at examination. Because the medication was still being used, the association was observed. We tried to address this issue in 2 ways. First, after developing the final model, we tested for history of candi-

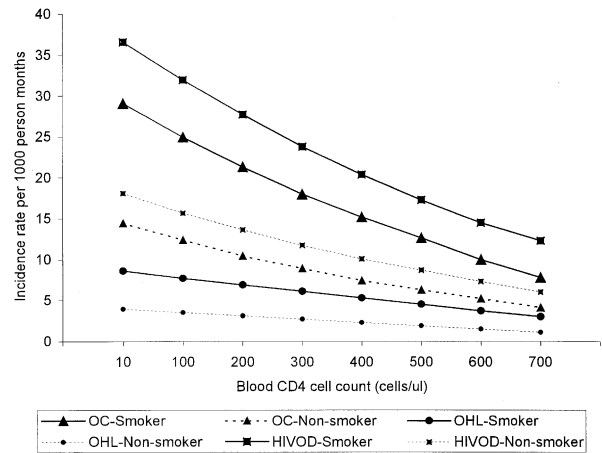


Fig 1. Predicted OC, OHL, and HIV-OD incidence rates for current smokers and nonsmokers by CD4+ cell count (cells/μL) at event: final models corresponding to each disease outcome, adjusted for antiretroviral therapy, using CD4+ cell count as a continuous variable.

diasis as an additional variable. It was not significant ( $P = .8$ ), and did not alter any of the effect estimates appreciably. Second, we conducted separate analyses restricted to those who did not have OC or a history of OC. In both of these analyses, neither the effect estimates for any factor in the final model nor the variables constituting the model changed appreciably. Antifungal medication remained significant. Therefore, we seek new arguments to explain this association. More likely explanations might involve misdiagnosis of OHL as OC in a busy clinical setting or the use of antifungal medications as preventive therapy.

Higher prevalence of OHL among men is a major point of discussion in the literature with no clear explanations forthcoming.<sup>33</sup> In our study, the IRR of OHL among women was lower than men. To look for an explanation, we found differences in prevalence of smoking habits and drug use between men and women. We could not test for multiway interaction in this study owing to sample size restrictions. Sexual transmission of EBV may occur,<sup>34</sup> and receptive oral sex among MSMs may contribute to the difference in OHL incidence between the sexes. One possible explanation is that individuals who engage in receptive oral sexual practices are at risk for acquiring oral sexually transmitted diseases (eg, syphilis, gonorrhea, and human papilloma virus) and other microbial pathogens whose natural sites are genital and rectal tissues. Coinfections with other microorganisms may alter the oral milieu and, in turn, promote clinical EBV disease. Further evaluation of these habits could probably provide an explanation for the difference between sexes.

It may be argued that antiviral medications other than antiretrovirals suppress the replication of many human herpesviruses, including EBV, and likely have an effect on OHL incidence. We did not find any association between antiviral medications and OHL in bivariable analyses that could warrant their inclusion in multivariable models.

Smoking was a significant independent risk factor for OC, OHL, and HIV-OD. This is the first time that smoking has been demonstrated to be an independent risk factor for incident OHL in a race- and gender-mixed population-based study. Furthermore, the effect modification with CD4 count is an important piece of new information. If smoking and low CD4 count are both considered "exposures," there appears to be a dose-response association because each of these "exposures" increases the risk of OHL in the absence of the other, and their joint effect is of greater magnitude. These observations were consistent through bivariable fully adjusted and the final models, though the effect estimates were lower in the final model.

Cigarette smoking is considered a doubtful risk factor for OC.<sup>35</sup> In our study, for OC, the main effect for smoking was significant; the interaction between smoking and CD4 was not statistically significant. Yet the stratum-specific IRR for CD4 count—smoking groups suggests substantially different estimates between groups with a hint of a dose-response type of relationship as for OHL. Again, as for OHL, the observation that this association was generally similar in the bivariable fully adjusted model and the final models suggests that among HIV-infected adults smoking should be considered as an important risk factor for OC and that its interaction with CD4 count should be evaluated further. Cigarette smoke may contribute particulate matter, noxious chemicals, and heat that can modify more local factors. Salivary alterations caused by cigarette smoke may also modify infectivity of EBV in some unknown way, though once the epithelial cell is infected, cigarette smoke/saliva may not have a direct effect on EBV.

In conclusion, our study indicates that CD4 count and smoking are important risk factors for OC and OHL, and that combination antiretroviral therapy is protective for OC. Use of antifungal medications as a risk factor for OHL among HIV-infected persons needs further clarification. HIV-infected adults' oral mucosal disease risk profile would benefit from antiretroviral therapy to maintain or reconstitute the immune system and smoking abstinence or cessation efforts.

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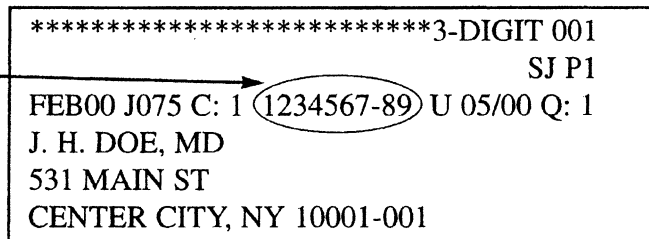
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