

# Oral candidiasis in HIV infection: predictive value and comparison of findings in injecting drug users and homosexual men

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The objectives of this study were to compare the relationship of oral candidiasis to HIV status, cohort and CD4+ lymphocyte values in injecting drug users and homosexual men and to examine its impact on prognosis. An oral examination was added to an ongoing longitudinal study of HIV infection. Data obtained at 6-month intervals included smoking, illicit drug use, medication use, symptoms and medical diagnoses, physical examination findings and laboratory data. In this study HIV+ subjects were much more likely to present with oral candidiasis than were HIV- subjects (OR = 6.3,  $P < 0.01$ ). Injecting drug users, regardless of serostatus, were more likely than homosexual men to present with oral candidiasis (OR = 3.0,  $P = 0.001$ ). In both cohorts oral candidiasis was associated with low CD4+ lymphocyte counts and percent ages, and Kaplan-Meier survival estimates showed that subjects with oral candidiasis had a poorer prognosis than those without candidiasis, even after controlling for CD4+ lymphocyte count.

Key words: HIV; oral candidiasis

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Oral candidiasis was one of the opportunistic infections observed in the first reported cases of Acquired Immune Deficiency Syndrome (AIDS) (1-4). Soon after reports of the first cases of AIDS were published, oral candidiasis was identified as a predictor of the development of AIDS in individuals at risk for AIDS (5), and subsequent studies have confirmed this finding (6-12). Although differing prevalence rates for oral candidiasis have been reported, studies of oral manifestations of HIV infection have consistently found oral candidiasis to be one of the most commonly occurring opportunistic diseases in subjects infected with HIV (13-25).

Some of these differences in prevalence rates can be accounted for by differences in study design. It is not yet clear whether transmission category contributes to these differences.

Furthermore, oral candidiasis is an important clinical marker in the management of patients infected with HIV. It is included in HIV staging systems and it is also one of the indicators for prophylaxis against *Pneumocystis carinii* pneumonia in HIV+ individuals (26-31). Therefore, it is important to confirm that findings related to the presence of oral candidiasis are similar among different transmission categories.

The study reported here examined

the relationship between oral candidiasis and cohort and HIV serostatus in two transmission categories: HIV seropositive (HIV+) and HIV seronegative (HIV-) injecting drug users (IDU) and HIV+ and HIV- homosexual men (HM). In addition, we explored the impact of oral candidiasis on prognosis in HIV+ subjects by examining the relationship between oral candidiasis and death or the development of an AIDS-defining disease.

## Methods

Study subjects were already enrolled in a longitudinal study of HIV infection.

The cross-sectional portion of this study included 269 subjects (81 HIV+ and 59 HIV- IDU; 82 HIV+ and 47 HIV- HM) who received the baseline oral examination. For the longitudinal portion of the study, 133 HIV+ AIDS-free subjects (69 IDU and 64 HM) were available. Seventeen subjects (6 IDU and 11 HM) were excluded because they had an AIDS-defining opportunistic disease recorded at the baseline visit. Thirteen additional subjects (6 IDU and 7 HM) who declined to participate in the study after the first dental visit were also excluded.

The two cohorts, IDU and HM, included in this study have been described in a report by LAMSTER *et al.* (25). The cohorts were similar in age and, within serostatus, were also similar in mean level of CD4+ lymphocytes, percent of CD4+ lymphocytes, CD8+ lymphocytes, percent of CD8 lymphocytes and total number of white blood cells at baseline. The proportion of the IDU subjects reporting recent antiviral drug use was slightly greater than that among homosexual men. The cohorts differed markedly in race. Of the IDU, over 70% were black and of the HM, over 80% were white. At the baseline oral examination, the cohorts differed with respect to medical stage of disease, with a greater proportion of IDU than HM having progressed to more advanced disease. The cohorts differed in smoking history, with a higher percentage of IDU reporting a positive smoking history.

At 6-month intervals, each subject received both a medical and immunological evaluation, as well as a separate oral/dental examination. Data obtained by interview included smoking history, illicit drug use, medication use, symptoms and medical diagnoses over the previous six months. Laboratory data obtained included a total white blood cell count, the number and percentage of CD4+ and CD8+ lymphocytes and the number of CD19+ lymphocytes. The oral examiners were trained in the identification of oral candidiasis and calibration was accomplished using color slides of clinical conditions. Three forms of oral candidiasis were recorded: pseudomembranous candidiasis, erythematous candidiasis and angular cheilitis (32). Pseudomembranous candidiasis was defined as oral mucosal lesions characterized by white curd-like material which when wiped off revealed an underlying erythematous mucosa. If there was no underlying mucosal ery-

thema, or if there was any question about the diagnosis of the lesion, a mucosal smear was taken and examined for fungal hyphae. Otherwise, this condition was diagnosed on the basis of clinical presentation. Erythematous candidiasis was defined as mucosal erythema or irregular depapillation of the tongue (usually primarily filiform papillae) with a mucosal smear of the erythematous area positive for fungal hyphae. Angular cheilitis was defined as erythema, ulceration or fissuring of the labial commissures. Hyperplastic candidiasis was not included because the descriptive clinical diagnoses used for documenting oral findings in this study did not allow differentiation of this lesion from other leukoplakias. Denture stomatitis (limited to within the borders of mucosa covered by a full or partial denture) was recorded, but not included in the analysis because it has not been shown to be associated with immune deficiency.

Mucosal smears were taken using a tongue blade. These were alcohol-fixed, periodic acid-Schiff-stained and examined microscopically for fungal hyphae. Identification of at least 10 fungal hy-

phae was required for a smear to be considered positive.

This study was initiated prior to the 1993 revision of the Centers for Disease Control and Prevention classification of HIV disease. Therefore, AIDS is defined on the basis of opportunistic diseases and does not include the CD4+ lymphocyte count (33).

#### Statistical methods

The first objective of the statistical analysis was to characterize the prevalence of oral candidiasis in HIV+ and HIV- HM and IDU by serostatus and cohort, and to identify hematologic, demographic, and medication use correlates of lesion occurrence. Estimates of the prevalence of oral candidiasis of any type, as well as of each type (pseudomembranous, erythematous and angular cheilitis) considered separately, were compared using Pearson's chi squared statistic and the Mantel-Haenszel procedure (34). In the analyses of oral candidiasis of any type, a subject was considered positive if one or any combination of the three types was present. In measuring association across several four-

Table 1. Prevalences (in %) of different types of candidiasis in injecting drug users and homosexual men

	Injecting drug users <i>n</i> =140			Homosexual men <i>n</i> =129		
	HIV+ <i>n</i> =81	HIV- <i>n</i> =59	<i>P</i> value	HIV+ <i>n</i> =82	HIV- <i>n</i> =47	<i>P</i> value
% Candidiasis (any type)	43.2	10.2	<0.001	19.5	4.3	0.016
% Pseudomembranous	22.2	3.4	0.002	4.9	0	NS
% Erythematous	25.9	3.4	<0.001	9.8	2.1	NS
% Angular cheilitis	18.5	3.4	0.007	8.5	2.1	NS

For all categories, there is a significantly higher prevalence of candidiasis in HIV+ IDU compared to HIV+ HM except for angular cheilitis, where *P*=0.062.

Table 2. Relationship of lymphocyte subsets and white blood cell counts to the occurrence of candidiasis in HIV+ subjects (variation in *n* is due to missing data)

	Without candidiasis		With candidiasis		<i>P</i> -value
	<i>n</i>	Median (min-max)	<i>n</i>	Median (min-max)	
Injecting drug users					
CD4	44	392 (25-1304)	35	207 (3-834)	0.004
CD4%	45	21 (4-41)	35	21 (1-36)	NS
CD8	44	916 (201-2661)	35	640 (191-1983)	0.004
CD19	37	168 (60-418)	33	120 (11-480)	0.010
WBC	46	5.0 (2-12.6)	35	4.0 (1.1-11.2)	0.029
Homosexual men					
CD4	66	324 (9-1185)	16	188 (14-479)	0.078
CD4%	66	22 (2-75)	16	12 (1-35)	0.045
CD8	66	767 (179-2371)	16	748 (223-3684)	NS
CD19	65	106 (20-353)	16	84 (13-272)	NS
WBC	66	4.7 (1.8-10.2)	16	3.7 (1.9-9.6)	NS

Table 3. Distribution of CD4+ lymphocyte counts among HIV+ subjects with candidiasis

CD4+ lymphocyte counts	0-199	200-499	≥500	Total
<b>Injecting drug users</b>				
Any type	15 (43%)	14 (40%)	6 (17%)	35
Pseudomembranous type	9 (50%)	6 (33%)	3 (17%)	18
Erythematous type	9 (43%)	8 (38%)	4 (19%)	21
Angular cheilitis	6 (40%)	7 (47%)	2 (13%)	15
<b>Homosexual men</b>				
Any type	8 (50%)	8 (50%)	0	16
Pseudomembranous type	3 (75%)	1 (25%)	0	4
Erythematous type	4 (50%)	4 (50%)	0	8
Angular cheilitis	3 (43%)	4 (57%)	0	7

fold tables, the common odds ratio (OR) was estimated by the method of MANTEL & HAENSZEL (35). The Wilcoxon rank sum test was used to compare continuous measurements among subjects with and without oral candidiasis.

The second major objective of the analysis was to study the impact of candidiasis at the baseline oral examination on the subsequent risk of death or the development of an AIDS-defining disease in the HIV+ population. Proportional hazards regression methods were used in order to accommodate censoring and to adjust for variable length of follow-up in studying the relationship between candidiasis and progression of disease (36). Use of regression methods allowed for simultaneous control of confounding factors that may have affected our assessment of this relationship (e.g., CD4+ lymphocyte count, prescription drug use, etc.). The outcome measurement used in these models was the time from the baseline oral examination to death, or to the development of an AIDS-defining opportunistic disease (33), whichever occurred first. The exact date of death was available for every subject who died during the course of the study. Length of time to the diagnosis of AIDS was calculated as the midpoint between the first visit at which a diagnosis of AIDS was made and the nearest previous visit. The proportion of subjects surviving without AIDS as a function of time was estimated by the method of KAPLAN & MEIER using Greenwood's formula to generate 95% confidence intervals (CI) (37).

## Results

### Cross-sectional analysis

Consistent with previously reported studies, the presence of oral candidiasis was clearly associated with HIV status (Table 1). HIV+ subjects, both IDU and HM, were much more likely to

present with oral candidiasis than were HIV- subjects (IDU: HIV+ 43.2%, HIV- 10.2%,  $P < 0.001$ ; HM: HIV+ 19.5%, HIV- 4.3%,  $P = 0.016$ ). A seropositive subject had odds more than six times greater than a seronegative subject of presenting with oral candidiasis at the baseline visit ( $P < 0.001$ , adjusted for cohort). An increased risk in HIV+ versus HIV- IDU subjects was observed for each of the three types of candidiasis examined separately. In HM there were fewer cases of oral candidiasis and significance was observed only when all forms of candidiasis were combined. For all HIV+ versus HIV- subjects, adjusted for cohort, an estimated odds ratio (OR) of 9.8 was found for pseudomembranous candidiasis ( $P < 0.001$ ); 8.0 for erythematous candidiasis ( $P < 0.001$ ); and 5.6 for angular cheilitis ( $P = 0.002$ ). Candidiasis was

diagnosed in a higher percentage of IDU than HM. We observed that, when compared with HM, IDU subjects were at increased risk of candidiasis (OR = 3.0,  $P = 0.001$  adjusted for serostatus). Similar results were obtained when each type of candidiasis was studied separately.

In the HIV+ IDU cohort, oral candidiasis appeared to be related to several measures of immune function (Table 2). HIV+ IDU subjects with candidiasis tended to have lower CD4+ lymphocyte counts ( $P = 0.004$ ), CD8+ lymphocyte counts ( $P = 0.004$ ), CD19+ cell counts ( $P = 0.010$ ) and white blood cell counts ( $P = 0.029$ ) than subjects without candidiasis. In the cohort of HIV+ HM, we observed a marginally significant relationship between the occurrence of oral candidiasis and low CD4+ lymphocyte count ( $P = 0.078$  for number and  $P = 0.045$  for percent) (Table 2). No other significant relationships were observed between the presence of candidiasis and other hematologic variables in HM.

Table 3 shows the distribution of CD4+ lymphocyte counts for subjects diagnosed with each type of candidiasis. Among HIV+ IDU with oral candidiasis, the occurrence patterns for the three types of candidiasis are strikingly similar. Although the number of HIV+ homosexual men with candidiasis is small, the pattern appears to be similar

Table 4. Relationship of candidiasis and demographic variables, smoking and alcohol use among HIV+ subjects (variation in *n* is due to missing data)

	HIV+ Injecting drug users		HIV+ Homosexual men	
	Total <i>n</i>	<i>n</i> (%) Candidiasis	Total <i>n</i>	<i>n</i> (%) Candidiasis
<b>Race</b>				
White	7	1 (14)	71	13 (18)
Hispanic	14	6 (43)	7	3 (43)
Black	60	28 (47)	2	0
Asian/Pacific islander	0	0	2	0
<b>SES</b>				
Unskilled laborer	15	3 (20)*	0	-
Semi-skilled	24	14 (58)	9	1 (11)
Skilled	16	10 (63)	9	1 (11)
Minor professional	21	7 (33)	29	9 (31)
Professional	1	0	35	5 (14)
<b>Sex</b>				
Male	53	23 (43)	82	-
Female	28	12 (43)	NA	-
<b>Current smoking</b>				
No	8	3 (38)	57	12 (21)
Yes	73	32 (44)	25	4 (16)
<b>Alcohol use</b>				
None	43	15 (35)	41	9 (22)
<1 drink/wk	11	5 (45)	35	6 (17)
>1 drink/wk	19	11 (58)	6	1 (17)

\* $P = 0.05$  for % with candidiasis across categories.

Table 5. Relationship of candidiasis to prescription drug use in HIV+ subjects (no significant associations were found in either cohort)

		Injecting drug users		Homosexual men	
		n	n (%) Candidiasis	n	n (%) Candidiasis
Acyclovir use	No	73	33 (45)	53	9 (17)
	Yes	4	1 (25)	27	7 (26)
Antiviral use (other)	No	29	12 (41)	42	7 (17)
	Yes	48	22 (46)	38	9 (24)
Antibiotic use	No	39	14 (36)	39	7 (18)
	Yes	38	20 (53)	41	9 (22)
Antifungal use	No	65	29 (45)	61	15 (25)
	Yes	12	5 (42)	19	1 (5)

to that in IDU. Thus, at least cross-sectionally, there is no evidence from these data that the type of candidiasis is related to the level of immune deficiency as measured by CD4+ lymphocyte count.

In a cross-sectional assessment of the relationship of oral candidiasis to demographic characteristics and drug use (Tables 4 and 5), no significant associations were found in either cohort between candidiasis and age, race, sex, current smoking, alcohol consumption, acyclovir or other antiviral drug use, antibiotic use, or antifungal use. Differences in prevalence of candidiasis across categories of socioeconomic status (SES) were observed in the IDU cohort.

#### Longitudinal analysis

The remainder of the analysis includes only those 69 IDU (23 women and 46 men) and 64 HM who were HIV+ and AIDS-free at the time of the baseline oral examination and for whom follow-up data were available. A comparison between subjects who were lost to follow-up and those who remained revealed minimal differences with respect to CD4+ cell count, stage of disease or presence of candidiasis (data not shown). In the longitudinal sample, the prevalence of oral candidiasis in the HIV+ IDU cohort remained significantly higher than that in the HIV+ HM cohort ( $P=0.001$ ). This is true for the occurrence of the pseudomembranous type ( $OR=9.4$ ,  $P=0.001$ ) and for the erythematous type ( $OR=4.2$ ,  $P=0.005$ ). For angular cheilitis, IDU had a higher, but not significantly higher, prevalence. The distribution of CD4+ cell counts was similar between the two cohorts. Among IDU, 30% of subjects had CD4+ cell counts in the range of 0–199; 45% had CD4+ counts of 200–499 and 25% had CD4+ counts  $\geq 500$ .

The corresponding values in HM were 36%, 50% and 14%.

Subjects were followed for a median of 29 months (based upon censored observations) with a range of 1.9 to 33.8 months. Cohort specific medians were comparable (29.4 for the IDU and 25.6 for HM). Of the HIV+ IDU, 17 (24.6%) developed AIDS or died during the follow-up period (3 women and 14 men). Ten (58.8%) of these had CD4+ lymphocyte counts less than 200 at baseline; 6 (35.3%) had CD4+ counts between 200 and 499 at baseline. Five (29.4%) had reported antifungal drug use during the 6 months prior to the baseline oral examination, whereas only 8% of the subjects who had either survived without AIDS or were lost to follow-up at the time of analysis reported antifungal drug use.

While we studied HM for comparison, we chose to focus on IDU in the longitudinal analysis because the prevalence of candidiasis was much greater in this population. Proportions of subjects who progressed to AIDS or who died were compared among subjects with and without oral candidiasis at baseline. Thirty AIDS-free IDU subjects presented with oral candidiasis at base-

line (9 women and 21 men); 39 did not (14 women and 25 men). The results of four different Cox regression models using data from these subjects are shown in Table 6. Variables are shown on the table headings. All models were adjusted for CD4+ cell count ( $<200$  vs  $\geq 200$ ), sex and antifungal drug use during the 6 months prior to the baseline examination. As can be seen from Model 1, oral candidiasis at baseline is a strong predictor of subsequent risk of AIDS or death, even after adjustment for antifungal drug use, sex and immune status (CD4+ lymphocyte count below or above 200). Model 1 gives an estimated relative risk of 3.8 associated with the presence of oral candidiasis at baseline ( $P=0.029$ ). Subjects who reported antifungal drug use in the six months before the baseline examination and subjects with CD4+ cell counts below 200 were at increased risk of AIDS or death in IDU. Men appear to be twice as likely to suffer the onset of AIDS or death compared to women, but this difference is not statistically significant. The last three models shown illustrate the effects of each type of candidiasis individually. Only angular cheilitis shows a significant relationship to prognosis when considered alone.

We re-fitted these regression models, combining IDU and HM and adjusting for cohort. The estimates obtained from this analysis were very close, but slightly weaker than those obtained from the IDU data. None of the relative risks for cohort (IDU vs HM) differed significantly from 1.0, indicating that survival was not significantly different between the cohorts once CD4 cell count, antifungal use and candidiasis are accounted for.

Figure 1 shows the Kaplan-Meier survival estimates for IDU subjects with and without candidiasis, stratified

Table 6. Estimated relative risks ( $P$ -values) from proportional hazards regression models with outcome defined as time to the development of an AIDS-defining disease or death (whichever occurred first) among HIV+ IDU subjects who were AIDS-free at baseline

Model	Low CD4 ( $<200$ vs $\geq 200$ )	Antifungal (yes or no)	Gender (male vs female)	Any cand.* (vs none)	Ps. cand.* (yes vs no)	Er. cand.* (yes vs no)	AC* (yes vs no)
1	2.1 (NS)	3.3 (0.052)	1.9 (NS)	3.8 (0.029)			
2	2.9 (0.052)	2.4 (NS)	2.0 (NS)		2.0 (NS)		
3	3.2 (0.039)	3.1 (0.062)	2.1 (NS)			1.2 (NS)	
4	2.7 (0.067)	4.1 (0.020)	1.9 (NS)				4.6 (0.006)

\* Any cand.=any candidiasis; Ps. cand.=pseudomembranous candidiasis; Er. cand.=erythematous candidiasis; AC=angular cheilitis.

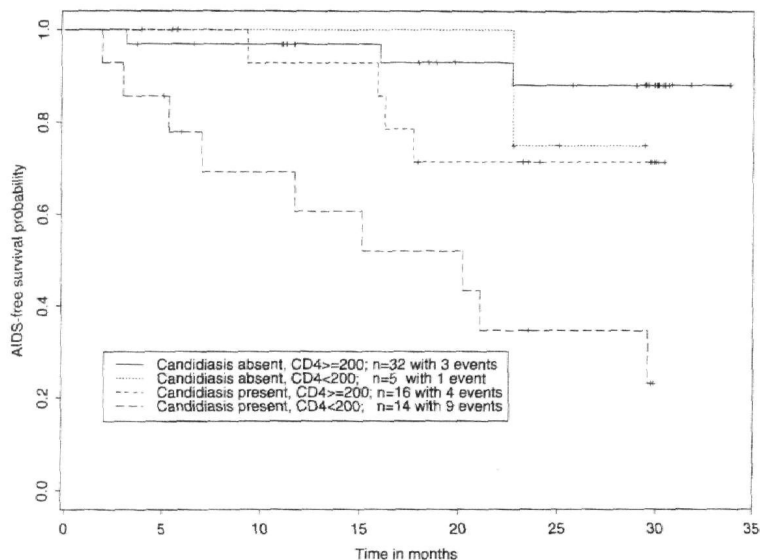


Fig 1. AIDS-free survival probability in IDU by presence of oral candidiasis and CD4 cell count ( $<200$  vs  $\geq 200$ ); event is development of an AIDS-defining condition or death.

by CD4+ cell count (0–199 versus 200+).

Results are the same as that of the regression models: subjects without candidiasis at baseline had a better prognosis than those with candidiasis, even after controlling for CD4+ level. The estimated proportions of subjects progressing to AIDS or death after 24 months of follow-up are 12% (95% CI: 0–25%) for subjects with CD4+  $\geq 200$  and no candidiasis, 25% (CI: 0–67%) for subjects with CD4+  $< 200$  and no candidiasis, 29% (CI: 5–52%) for subjects with CD4+  $\geq 200$  and candidiasis present, and 65% (CI: 38–93%) for subjects with both risk factors (CD4+  $< 200$  and candidiasis present).

## Discussion

The development of oral candidiasis is a complex process involving changes in both the host and the organism. An increased risk of developing candidiasis has been associated with a variety of factors, including acquired immunologic (disorders primarily cell-mediated immune deficiency), xerostomia, malignant tumors and chemotherapy, steroid and antibiotic therapy, and iron deficiency anemia (38). It is clear that the development of oral candidiasis is common and significant in individuals infected with HIV. The multiple factors that contribute to its development must be considered when evaluating an indi-

vidual patient and determining their significance for that individual. As the numbers of HIV infections continue to increase in association with injecting drug use, it has become increasingly important to determine if there are differences in significance associated with the development of opportunistic infections that may affect the clinical management of these individuals.

With regard to the relationship of oral candidiasis to serostatus, these results were consistent with those of other studies. Both IDU and HM HIV+ subjects were much more likely to present with oral candidiasis than were HIV- subjects. Nevertheless, in this study, when we compared results in IDU with those in HM, IDU overall had a higher prevalence of oral candidiasis. The reason for this is not clear. We were not able to identify any factors that would explain this difference. We did not observe a relationship between the presence of oral candidiasis and smoking or any of the demographic or social factors we examined such as age, race, sex, or current employment status, nor did we see a significant relationship between the use of antibiotic or antifungal medications and the presence of oral candidiasis. The higher, though not significant, prevalence of oral candidiasis in HIV- IDU suggests that, among IDU, there are factors other than HIV that affect the development of oral candidiasis. However, these factors remain un-

clear. The racial distribution between the two cohorts is significantly different and there does appear to be an increased risk of candidiasis among black and hispanic subjects, although this difference does not reach significance. Also, the status of the oral cavity prior to HIV infection may influence the occurrence of candidiasis after infection. We have previously reported that the IDU demonstrated more periodontal disease and more plaque accumulation than the HM. This may influence the oral microflora (25).

The difference in the clinical appearances of pseudomembranous and erythematous candidiasis has been the subject of much discussion. It is tempting to suggest that one type precedes the other. However, this relationship was not supported by findings in this study nor in previously reported studies. We found no evidence that the type of candidiasis was related to the level of immune deficiency (Table 3). Other studies that have examined the relationship between pseudomembranous and erythematous candidiasis and progression to AIDS have found no difference in the time to progression to AIDS between subjects with these two types of candidiasis (39,40). Thus, the reasons for the differing clinical presentations of oral candidiasis remain to be identified.

Longitudinal studies of HIV infection have demonstrated the predictive significance of immunologic markers such as the CD4+ lymphocyte count, CD4+, CD8+ lymphocyte count, and CD4+/CD8+ ratio as well as the impact of the presence of clinical markers such as hairy leukoplakia and oral candidiasis (41–52). The relationship between oral candidiasis and the low CD4+ lymphocyte count seen in this study is consistent with that observed in other studies (23, 28, 52, 53). This association between oral candidiasis and CD4+ lymphocyte count is important because it suggests that oral candidiasis could be used as a marker of immune status when CD4+ lymphocyte counts are not readily available (23). While other studies have found a relationship between immunologic variables such as CD8+ and CD19+ lymphocyte counts and oral candidiasis, when these apparent relationships were found in this study, they appeared to be due to the correlation of these variables with CD4+ count. SAAH and colleagues reported a significant interaction between candidiasis and

CD4+ count of  $\leq 200$  in a cohort of HM (11). This interaction was not observed in the present study. We note, however, that the study reported by SAAH *et al.* focused only on homosexual men with candidiasis, whereas in the present study most cases of candidiasis occurred in IDU.

The strength of oral candidiasis as a marker of progression of disease is again confirmed by the study reported here. Controlling for CD4+ lymphocyte count, candidiasis and antifungal drug use, IDU and HM were at roughly equal risks of death or developing AIDS. Furthermore, we found that although either a CD4+ lymphocyte count  $< 200$  or the presence of oral candidiasis at baseline increased the risk of death or the development of AIDS, the prognosis was much worse if both of these were present at the initial evaluation.

Except for the higher prevalence of oral candidiasis among both HIV+ and HIV- IDU when compared to HM, the results of this study demonstrate similar findings in HIV+ IDU compared to HM. A strong impact of oral candidiasis on outcome in HIV+ IDU has also been demonstrated and this impact was similar to that found when results in both cohorts were combined. The low prevalence of oral candidiasis in the cohort of HIV+ HM precluded a meaningful comparison of its predictive value in the two cohorts.

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