Oral lesions as markers of severe immunosuppression in HIV-infected homosexual men and injection drug users

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Objectives. We examined the diagnostic utility of the presence of oral lesions, individually and in combination, in identifying severe immunosuppression, defined as CD4 cell count under 200.
Study design. Data were collected on 82 HIV-seropositive homosexual men and 82 HIV-seropositive injection drug users who volunteered to participate in a longitudinal study of HIV infection. CD4 cell counts were measured within 24 hours of oral examination.
Methods. Sensitivity, specificity, positive predictive value, negative predictive value, and the odds ratio were computed to assess the association between oral lesions and CD4 less than 200. In addition to the individual lesions, we studied the diagnostic properties of sets of three to six lesions. For each set of lesions, a patient was classified as positive for the set if he or she had one or more lesions in that set.
Results. In homosexual men and injection drug users, individual lesions had low sensitivity, high specificity, and moderate positive and negative predictive values. Odds ratios reflected weak correlation to immunosuppression. When lesion sets were considered in homosexual men, sensitivity rose dramatically with only modest decreases in specificity. The positive and negative predictive values remained almost the same. Similar results for lesion sets were obtained in injection drug users, with greater reduction in specificity but stable positive and negative predictive values. Odds ratios indicated that for homosexual men, the more lesions included in the set, the stronger the correlation with immunosuppression. For injection drug users, strong correlations were observed for all lesion sets.
Conclusions. Analysis of sensitivities and odds ratios in homosexual men suggest that it may be valid to note the occurrence of a greater number of oral lesions than is currently done in staging patients with HIV infection. Among injection drug users, monitoring a larger number of lesions neither improves nor reduces the correlation to severe immunosuppression.
(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82;276-83)

A wide array of clinical signs and symptoms is used to monitor the progression of disease in HIV-infected persons. In addition to CD4 cell count, the staging system proposed by the Centers for Disease Control and Prevention[1] advises the recording of such clinical manifestations as fever, night sweats, weight loss, diarrhea lasting more than 1 month, and the development of oral lesions (hairy leukoplakia, oral candidiasis, and oral Kaposi's sarcoma). Although the measurement of CD4 cell count requires a blood sample and laboratory analysis, the identification of oral lesions such as hairy leukoplakia and oral candidiasis can be made during the course of a physical examination. (Although detection of Epstein-Barr virus is required for definitive diagnosis of hairy leukoplakia, diagnosis is often made based on clinical appearance.) If the development of these or other oral lesions was found to be highly correlated with immunosuppression (defined as CD4 <200 cells per cubic millimeter), then oral lesions could be used as markers of immunosuppression, serving as a prompt to the patient's physician that disease has progressed,

Reviewed by members of the Oral Diagnosis Review Board.
Supported by DE 09545 from the National Institute of Dental Research and by MH 43520 from the National Institute of Mental Health.
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Received for publication Feb. 14, 1996; returned for revision Mar. 13, 1996; accepted for publication Apr. 30, 1996.

1079-2104/96/$5.00 + 0 **7/17/74760**

that the degree of immunosuppression needs to be reassessed, or that a specific treatment should be initiated. It is the purpose of this article to explore the utility and accuracy of oral lesions as markers of immunosuppression in HIV-infected subjects.

According to the CDC staging system for HIV disease,[1] the occurrence of hairy leukoplakia or oral candidiasis signals the progression of disease to clinical category B (the stage of disease that directly precedes the onset of AIDS). Oral Kaposi's sarcoma, less common than either of the other two lesions, is one of the malignant conditions that meets the criteria for the case definition of AIDS. The prognostic significance of these three oral lesions has been well documented,[2-5] primarily in cohorts of HIV-infected homosexual men. In addition to these lesions, there is a host of other lesions that occur in association with the development of HIV disease. These include necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), oral ulcers (varicella-zoster, herpes simplex, or major aphthous-like), linear marginal erythema (previously referred to as HIV-associated gingivitis), noncandidal oral erythematous lesions, and papilloma-like lesions.

The immediate goal of this analysis is to compare individual lesions with sets of lesions with respect to their correlation with severe immunosuppression, but our broader aim is to develop recommendations for the use of oral lesions in staging patients with HIV disease. We attempt to identify a constellation of oral manifestations of HIV infection that would be indicative of current immune status that might be useful to a primary care physician faced with the complex problem of treating a newly encountered HIV-infected patient in the absence of an accurate detailed medical history. As the HIV epidemic spreads into underserved populations, individual medical records may be unobtainable or nonexistent as a result of limited access of health care, and patient self-reporting may be less reliable in subjects who do not enjoy the benefits of a stable home and family and community support. Thus we will likely see increasing dependence on simple markers of disease status that can be observed on physical examination for accurate staging and appropriate treatment decisions.

Glick et al.[6] examined the correlation of a wide array of individual lesions to immunosuppression (as measured by CD4 less than 200 and measured within 2 months of oral examination). This article expands on these earlier findings by evaluating the relationship of oral lesions, both alone and in combination, to immunosuppression, as measured by CD4 cell count. Analyses of diagnostic accuracy were conducted separately in HIV-positive homosexual men, and in male and female HIV-positive injection drug users (IDU) to assess whether the same individual lesions, and sets of lesions achieved comparable levels of correlation to CD4 in the two cohorts.

METHODS

Study design

A longitudinal study of the oral manifestations of HIV disease was initiated in two cohorts of volunteers (homosexual men and IDU men and women) in New York City. The sample included both HIV-negative and HIV-positive subjects, with symptoms that range from absent to severe to AIDS in the latter group. Assignment to cohort was based on the probable routes of infection for cohort members. These two cohorts were markedly different with respect to demographic profile, overall health status, oral health, and manifestations of HIV disease. A description of study design and patient characteristics was presented earlier.[7] Detailed information on oral, medical, and laboratory parameters was collected at 6-month intervals over the next 3 years. The data presented in this article come from the baseline oral examinations, most of which occurred between March 1991 and March 1992.

In addition to recording incidence of hairy leukoplakia, oral candidiasis, and oral Kaposi's sarcoma, the oral pathology data collection instrument incorporated a wide range of possible oral manifestations of disease. All medical and laboratory data (including CD4 cell count) were collected within 24 hours of the oral examination. Aside from the aforementioned three lesions, the most commonly observed lesions included gingival lesions (linear marginal erythema, NUP, NUG), noncandidal oral erythematous lesions, and oral ulcers. Although most studies of the progression of HIV disease have focused on homosexual men (because it was in this group that AIDS was first identified), it is not at all clear that the clinical manifestations of HIV identified in homosexual men will parallel those identified in a growing segment of the HIV-infected population—IDU men and women—who comprise 25% of cumulative national AIDS diagnoses as of June 30, 1995.[8] In fact, recent work[9] suggests that these distinct groups differ with respect to the course and duration of HIV disease.

A total of 272 subjects were enrolled in the longitudinal study. This included 48 HIV-negative and 82 HIV-positive homosexual men, and 60 HIV-negative and 82 HIV-positive IDUs. (These totals differ slightly from the totals given in the baseline article[7] because of the addition of data from several subjects who entered later.) Medical evaluation of subjects included a physical examination for current signs and

Table I. Prevalence of oral lesions among HIV-positive subjects by cohort and CD4 cell count

Lesion	Homosexual men CD4 count			IDU CD4 count		
	0-199 (n = 34)	200-499 (n = 37)	>499 (n = 11)	0-199 (n = 22)	200-499 (n = 37)	>499 (n = 20)
Oral candidiasis	8 (24)*	8 (22)	0	15 (68)	14 (38)	6 (30)†
Other leukoplakia (lateral tongue)	4 (12)	2 (5)	1 (9)	6 (27)	6 (16)	3 (15)
Hairy leukoplakia	10 (29)	7 (19)	1 (9)	5 (23)	4 (11)	0†
Oral ulcer	7 (21)	4 (11)	2 (18)	2 (9)	3 (8)	1 (5)
Kaposi's sarcoma	3 (9)	0	0	0	0	0
Linear marginal erythema‡	6 (18)	5 (14)	0	6 (32)	11 (37)	7 (39)
NUP/NUG‡	4 (12)	1 (3)	0	0	3 (10)	1 (6)

*Table entries are frequency (percentage).
†$p < 0.05$ by Mantel-Haenszel test for trend within cohort.
‡Note that sample sizes for gingival lesions among IDU by CD4 group are 19/30/18, after deletion of 12 edentulous subjects.

Table II. Relationship between presence of individual lesions and CD4 cell count (<200 versus >= 200) among HIV-positive subjects

Lesion	OR	95% CI	Sensitivity	Specificity	PPV	NPV
Homosexual Men						
Oral candidiasis	1.5	(0.5, 4.6)	23.5	83.3	50.0	60.6
Other leukoplakia (lateral tongue)	2.0	(0.4, 9.6)	11.8	93.8	57.1	60.0
Hairy leukoplakia	2.1	(0.7, 6.0)	29.4	83.3	55.6	62.5
Oral ulcer	1.8	(0.6, 6.0)	20.6	87.5	53.9	60.9
Kaposi's sarcoma	10.8	(0.5, 216)	8.8	100.0	100.0	60.8
Linear marginal erythema	1.8	(0.5, 6.6)	17.6	89.6	54.5	60.6
NUP/NUG	6.3	(0.7, 58.8)	11.8	97.9	80.0	61.0
IDU						
Oral candidiasis	3.9	(1.4, 11.3)	68.2	64.9	42.9	84.1
Other leukoplakia (lateral tongue)	2.0	(0.6, 6.5)	27.3	84.2	40.0	75.0
Hairy leukoplakia	3.9	(0.9, 16.2)	22.7	93.0	55.6	75.7
Oral ulcer	1.3	(0.2, 7.8)	9.1	93.0	33.3	72.6
Kaposi's sarcoma			NONE OBSERVED			
Linear marginal erythema	0.8	(0.2, 2.4)	31.6	62.5	25.0	69.8
NUP/NUG	0.9	(0.8, 1.0)	0	91.7	0	69.8

OR = odds ratio; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value.

symptoms, as well as a history of signs and symptoms over the last 6 months. Blood was drawn for determination of immunologic markers of disease (including CD4 cell count and CD4 percentage). Prescription drug use was recorded during an interview by a research nurse. Oral lesions were diagnosed by trained calibrated dentists. A diagnosis of oral candidiasis required confirmation by a PAS-stained mucosal smear examined for the presence of fungal hyphae. In making a clinical diagnosis of leukoplakia on the lateral tongue, examiners noted whether or not the lesion was corrugated. Corrugated lesions were recorded as "hairy leukoplakia," and noncorrugated as "other leukoplakia on the lateral tongue." It has been well established that an accurate diagnosis of hairy leukoplakia requires identification of Epstein-Barr virus within the lesional epithelial cells. However, studies of hairy leukoplakia have consistently described a corrugated clinical appearance. Therefore, in this study, these two variants of leukoplakia when present on the lateral tongue were recorded as two distinct clinical diagnoses.

In analyzing the correlation between lesion presence and immune status, severe immunosuppression was defined as a CD4 cell count under 200. The reliance on CD4 cell count as the sole measure of immune status implies that immune function and ultimately disease progression are mediated by this one factor alone. Clearly this assumption is flawed and is one that we ourselves do not endorse. Many research-

ers have noted the shortcomings inherent in the measurement of CD4 (including diurnal variation and interlaboratory variability),[10] whereas still others have identified other HIV-associated laboratory parameters (CD8 cell count and percentage, p24 antigenemia, β2-microglobulin, etc.).[11] However, CD4 has become the principal laboratory marker of HIV-associated immunosuppression; it has been shown to correlate with time to disease progression in HIV-infected patients,[5, 11, 12] and receives tremendous emphasis with respect to staging and treatment recommendations.[1]

Statistical methods and determination of lesion sets

To study the association between CD4 cell count and lesion presence within cohort, HIV-positive subjects were divided into three groups on the basis of CD4 cell count (0 to 199, 200 to 499, and 500+), and the proportion with each particular lesion was estimated within group. The Mantel-Haenszel extension test for trend was used to test whether CD4 groups differed with respect to lesion presence.[3]

To assess the diagnostic utility of oral lesions as markers of immune status, we computed the sensitivity, specificity, positive predictive value, and negative predictive value of each lesion as a marker of immunosuppression (i.e., CD4 cell count under 200). Thus sensitivity is defined as the probability of lesion presence among those with CD4 under 200; specificity is the probability of lesion absence given CD4 greater than or equal to 200. The positive predictive value is the likelihood of immunosuppression (CD4 < 200) given that the lesion is present; the negative predictive value is the likelihood of a CD4 cell count greater than or equal to 200 when the lesion is not present. In addition to the above diagnostic parameters, the odds ratio relating lesion presence to immunosuppression is calculated along with a 95% confidence interval for this value.[14] The odds ratio is defined as the odds of immunosuppression given lesion presence over the odds of immunosuppression given lesion absence. An odds ratio of 1 would indicate no relationship between lesion presence and immune status. An odds ratio greater (less) than 1 would indicate that subjects with the lesion are at higher (lower) risk of severe immunosuppression than subjects without the lesion.

After the relationships between individual lesions and immune status were evaluated, analyses were performed to evaluate various sets of lesions as markers of immunosuppression. Lesions found to be associated with a reduced CD4 cell count were used in defining lesion sets. A subject was considered positive for a set if any of the lesions in the set were observed and negative if none of the lesions was present. Once the various sets of lesions were defined, we evaluated their diagnostic performance (relative to CD4 < 200) with the same quantities used above in evaluating individual lesions. In confirmatory analyses, results were adjusted for recent prescription drug use in accord with the method of Mantel and Haenszel for stratified data.[15] The Breslow-Day test was used to test for possible effect modification by prescription drug use.[14] All analyses were conducted separately by cohort.

RESULTS

CD4 cell counts were available for all 82 homosexual men and all but three IDU (96%). Table I presents the prevalences of each type of oral lesion within CD4 category by cohort. Overall the IDU presented with higher rates of every type of lesion except for hairy leukoplakia, oral ulcers, and Kaposi's sarcoma. Among homosexual men, there tended to be higher risks of oral candidiasis, hairy leukoplakia, Kaposi's sarcoma, linear marginal erythema, and NUP/NUG in HIV patients with lower CD4 cell counts. However, none of these differences achieved statistical significance. In the IDU cohort, we observed significant associations between CD4 level and the occurrence of oral candidiasis and hairy leukoplakia; the risk of other leukoplakia (lateral tongue) was also higher among subjects with low CD4 cell counts, but this difference was not significant. The risks of oral ulcer, linear marginal erythema, and NUG/NUP did not tend to increase with lower CD4 cell counts among HIV-positive IDU.

The data in Table II further describe the association between each individual lesion type and the risk of immunosuppression. In the homosexual men, we observe relatively modest nonsignificant odds ratios characterizing the relationship between low CD4 and the occurrence of oral lesions. None of the odds ratios is much higher than 2, except for the NUP/NUG and Kaposi's are odds ratios, which are large but which are nonetheless nonsignificant because of the low prevalence of these lesions in this cohort. Somewhat higher odds ratios for oral candidiasis and hairy leukoplakia were observed in the IDU cohort, but only one of these relationships (oral candidiasis) proved significant at the $\alpha = 0.05$ level.

In the homosexual men, none of the estimated sensitivities exceeded 30% (see Table II). In contrast, each of the oral lesions was highly specific (83% to 100%). The positive predictive values (of greater interest here) did not tend to be much higher than about 50%, except for the rare lesions (Kaposi's sarcoma

Table III. Definitions of lesion sets

Set	Number of lesions	Lesions included*
1	3	OC, HL, KS
2	4	OC, HL, KS, LME
3	4	OC, HL, KS, NUP/NUG
4	4	OC, HL, KS, OL-LT
5	5	OC, HL, KS, LME, NUP/NUG
6	5	OC, HL, KS, LME, OL-LT
7	5	OC, HL, KS, NUP/NUG, OL-LT
8	6	OC, HL, KS, LME, NUP/NUG, OL-LT

*OC = oral candidiasis, HL = hairy leukoplakia, KS = Kaposi's sarcoma, LME = linear marginal erythema, NUP/NUG = necrotizing ulcerative periodontitis or gingivitis, OL-LT = other leukoplakia (lateral tongue)

and NUP/NUG). The negative predictive values were all close to 60%. In the IDU cohort, oral candidiasis displayed a sensitivity of 68%, much higher than any of the sensitivities for homosexual men or any of the other sensitivities in the IDU. As in the homosexual men, specificities in the IDU were very high, except for oral candidiasis and NUP/NUG. The positive predictive values were uniformly low in the IDU cohort, whereas the negative predictive values ranged from 60% to 80%.

On the basis of these results, we defined a number of "sets" of lesions with a view to identifying a group of lesions that appeared to correlate most strongly with immunosuppression in the two HIV-infected populations. Because oral candidiasis, corrugated hairy leukoplakia, and oral Kaposi's sarcoma are already incorporated in most staging systems for HIV infection, these three lesions were included in every defined set of lesions. To this core set, we added other lesions (one at a time, two at a time, and three at a time) that appeared from earlier analyses to be related to the decline in CD4 cell count: linear marginal erythema, NUP/NUG, and other leukoplakia (lateral tongue). This resulted in the identification of eight sets of three to six lesions as shown in Table III. For each set of lesions, a binary indicator variable was defined; this indicator assumed the value 1 if the patient was diagnosed with any of the lesions in the set, and 0 if the patient had none of the specified lesions.

As with the individual lesions, first we computed the proportion of HIV-positive patients in each CD4 category who were positive for any lesion in that "set." Entries in Table IV indicate that all of the lesion sets exhibit a significant association with the CD4 cell count among the homosexual men. Among IDU, only four sets reached statistical significance with respect to correlation with CD4: sets 1, 3, 4, and 7. These four sets were those that did not include linear marginal erythema as one of the diagnostic lesions. Because linear marginal erythema is so highly prevalent in the IDU cohort and seems to bear no association with CD4 cell count, adding this lesion to the set only served to reduce the correlation between CD4 and lesion presence.

The diagnostic properties of the lesion sets were similarly evaluated (see Table V). Regardless of cohort, the use of lesion sets over individual lesions substantially improved the correlation between oral lesions and severe immunosuppression. This conclusion is supported by a comparison of the odds ratios presented in Tables II (for individual lesions) and V (for lesion sets). Among homosexual men, taking into account the occurrence of all six HIV-associated oral lesions (lesion set 8) resulted in the strongest association between the presence of oral lesions and immunosuppression (OR = 4.2, $p < 0.05$). Among IDU, large odds ratios were obtained for all eight lesion sets.

Comparing sensitivity estimates in Tables II and V reveals that combining lesions into sets greatly improves the sensitivity of oral lesions as markers of immunosuppression. Sensitivities for lesion sets in the homosexual men ranged from 50% to 74% (as compared with 9% to 29% for individual lesions) with only modest reductions in specificities (between 60% and 71%). Observed sensitivities in the IDU also increased dramatically when considering lesion sets instead of individual lesions (73% to 86% versus 0% to 68%) but with more pronounced decreases in specificity (39% to 63%). The positive predictive values for lesion sets were very close to those for individual lesions both for homosexual men (53% to 58%) and for IDU (35% to 43%). Negative predictive values increased slightly for homosexual men (from 60% to 63% for individual lesions to 67% to 76% for lesion sets) and for IDU (from 70% to 84% for individual lesions to 84% to 89% for lesion sets).

Because prescription drug use is associated with both the occurrence of oral lesions and CD4 cell count, we reevaluated the CD4/lesion set odds ratios within subgroups defined by whether or not the patient reported use of antibiotic, antifungal, or antiviral drugs during the last 6 months. Results were the same regardless of recent antibiotic or antiviral drug use. However, the data suggested that the relationship between CD4 and lesion set positivity was stronger for subjects who reported recent antifungal drug use compared with those who did not use antifungal drugs in the cohort of homosexual men. Results did not vary with antifungal drug exposure in the IDU cohort.

DISCUSSION

The primary purpose of this study was to assess whether groups of lesions were more helpful than individual lesions in identifying immunosuppression in

Table IV. Positivity of lesion sets among HIV-positive subjects by cohort and CD4 cell count.

	Homosexual Men CD4 count			*IDU CD4 count*		
Lesion set	*0-199 (n = 34)*	*200-499 (n = 37)*	*>499 (n = 11)*	*0-199 (n = 22)*	*200-499 (n = 37)*	*>499 (n = 20)*
1	17 (50)*	13 (35)	1 (9)†	16 (73)	15 (41)	6 (30)†
2	19 (56)	15 (41)	1 (9)†	17 (77)	19 (51)	10 (50)
3	21 (62)	14 (38)	1 (9)†	16 (73)	17 (46)	7 (35)†
4	19 (56)	15 (41)	2 (18)†	18 (82)	18 (49)	8 (40)†
5	23 (68)	16 (43)	1 (9)†	17 (77)	20 (54)	10 (50)
6	21 (62)	17 (46)	2 (18)†	19 (86)	22 (60)	12 (60)
7	23 (68)	15 (41)	2 (18)†	18 (82)	20 (54)	9 (45)†
8	25 (74)	17 (46)	2 (18)†	19 (86)	23 (62)	12 (60)

*Table entries are frequency (percentage).
†$p < 0.05$ by Mantel-Haenszel test for trend within cohort.

Table V. Relationship between lesion sets and CD4 cell count (<200 versus > = 200) among HIV-positive subjects.

Lesion set	*OR*	*95% CI*	*Sensitivity*	*Specificity*	*PPV*	*NPV*
Homosexual Men						
1	2.4	(0.97, 6.1)	50.0	70.8	54.8	66.7
2	2.5	(1.0, 6.3)	55.9	66.7	54.3	68.1
3	3.6	(1.4, 8.9)	61.8	68.8	58.3	71.7
4	2.3	(0.9, 5.7)	55.9	64.6	52.8	67.4
5	3.8	(1.5, 9.7)	67.6	64.6	57.5	73.8
6	2.5	(1.0, 6.1)	61.8	60.4	52.5	69.0
7	3.8	(1.5, 9.7)	67.7	64.6	57.5	73.8
8	4.2	(1.6, 11.0)	73.5	60.4	56.8	76.3
IDU						
1	4.6	(1.6, 13.5)	72.7	63.2	43.2	85.7
2	3.3	(1.1, 10.1)	77.3	49.1	37.0	84.9
3	3.7	(1.3, 10.7)	72.7	57.9	40.0	84.6
4	5.4	(1.6, 17.9)	81.8	54.4	40.9	88.6
5	3.1	(0.99, 9.4)	77.3	47.4	36.2	84.4
6	4.3	(1.1, 16.2)	86.4	40.4	35.8	88.5
7	4.3	(1.3, 14.4)	81.8	49.1	38.3	87.5
8	4.0	(1.1, 15.0)	86.4	38.6	35.2	88.0

OR = odds ratio, 95% CI = 95% confidence interval, PPV = positive predictive value, NPV = negative predictive value.

HIV infection. Although the importance of hairy leukoplakia, oral candidiasis, and Kaposi's sarcoma to the staging of HIV disease is recognized, this study sought to determine if incorporation of other lesions would improve the ability to distinguish between severe and mild immunosuppression.

This analysis demonstrates that specific sets of oral lesions are superior to individual lesions in the strength of their association with severe immunosuppression. Our conclusion is that correlation to immune status can be enhanced, and disease monitoring improved, if a broader range of oral lesions is considered in staging HIV-infected patients. This analysis did not address each individual lesion's importance in assessing immune function adjusted for the presence of the other lesions; this would have been appropriate had our aims included assessment of the biologic relevance of specific lesions in the progression of disease. In contrast, it was our objective to develop recommendations for clinicians evaluating new patients with respect to immune status in order to make appropriate treatment and testing decisions for those patients. We contend, on the basis of these results, that more detailed information on oral pathology can prove useful in the patient care setting and that recommendations vary depending upon HIV-transmission category of the individual patient.

Overall, the low positive predictive values observed in this analysis would argue against the use of individual lesions in monitoring severe immunosuppression in either cohort of subjects. The median positive predictive value across both cohorts, 48%, indicates that a patient who presents with one of the oral lesions in the lesion sets has about even odds of severe immunosuppression (in the absence of other clinical or laboratory information). However, the

negative predictive values were fairly high, signifying that the absence of oral lesions can be taken as a clinical indicator that CD4 has probably not yet declined below 200 cells. The odds ratios that related immunosuppression to lesion presence were uniformly low in both cohorts and indicated weak association between the diagnosis of an individual lesion and CD4. Dramatic increases in sensitivity were observed in both cohorts, however, when combinations of lesions were considered. This was anticipated, as it is easier for a patient to be positive for a lesion set than for an individual lesion. Conversely, specificities were reduced by the use of lesion sets. The positive and negative predictive values for combinations of lesions changed very little compared with those for individual lesions. Although the median odds ratio for individual lesions was 2.0, the median for lesion sets rose to 3.8, revealing a much higher correlation to severe immunosuppression. In homosexual men, the strongest correlation to CD4 was obtained when considering the largest lesion set (set 8), which took into account all six HIV-related oral lesions. In contrast, all lesion sets displayed high correlations to CD4 in the IDU cohort. Results did not appear to be strongly influenced by recent prescription drug use in either cohort.

Although identification of immunosuppression is improved by monitoring additional oral lesions, the specific lesions to be monitored depend on the characteristics of the individual subject. On the basis of the data provided by the two HIV-positive cohorts participating in our study, it appears that in homosexual men it may be worthwhile to include a greater number of oral lesions in staging HIV patients; whereas in the IDU cohort, large and small lesion sets do equally well in discriminating between severe and mild immunosuppression. One can argue then the reasonableness of two distinct approaches to staging disease in HIV-infected IDUs. First, one need not record a larger number of lesions in order to improve staging among IDU patients; a small number of lesions is just as effective. Alternatively, in the absence of information about the method of HIV acquisition, one can use the largest lesion set as a correlate of immune status because it performed well in both cohorts.

Why does the correlation between oral lesions and CD4 depend on cohort? One possible explanation might lie in a comparison of the "background" rates of oral lesions in the two HIV-negative cohorts. In the HIV-negative homosexual men, we see very low prevalence rates for oral lesions; this is in striking contrast to the HIV-negative IDU cohort where we see a high prevalence of oral lesions.[7] Given that homosexual men do not tend to develop HIV-associated oral lesions in the absence of HIV infection, any lesions that develop in the HIV-positive patient can be taken as a sign of increasing immunosuppression. Conversely, HIV-negative IDU subjects experience a much greater risk of oral lesions that have been associated with HIV infection; thus there is less benefit in noting the occurrence of a greater number of oral lesions in HIV-positive IDU. It is likely that the condition of the oral cavity before HIV infection can influence oral lesion development once infection with HIV occurs and immunosuppression becomes more severe. An earlier report[7] noted the disparity in the prevalence of oral lesions between homosexual men and IDU. In addition to route of virus acquisition, the two patient cohorts studied and compared in this article differ markedly with respect to a variety of factors. On average, the IDU men and women have less education, lower incomes, poorer overall oral health, and are more likely to be homeless than the men in the homosexual cohort. We also observed differences in ethnic background and smoking habits. Furthermore, results from Paik et al.[9] suggest differences in the course of HIV disease among IDU and homosexual men, in that IDU men and women experience more severe symptoms than homosexual men at a given CD4 level.

The socioeconomic differences between the two groups led us to question whether members of the IDU cohort experienced greater difficulty in obtaining health care than did the members of the homosexual cohort. As an informal evaluation of this difference, we compared the two cohorts with respect to medications prescribed. Surprisingly, rates of antiviral, antibiotic, and antifungal drugs prescribed were almost identical,[7] probably because most members of the IDU cohort were under treatment at an infectious disease clinic. This result suggests that subjects in the IDU cohort had adequate access to medical care and does not explain why results differed by cohort.

Although appropriate drug treatment may be prescribed, this does not imply that treatment protocol is followed by the individual patient. Although we have no data on compliance to address this point directly, we can report that the prevalence of oral candidiasis declined in both cohorts from the baseline visit to the third follow-up visit 1 year later; moreover, the 21% decline in the IDU men and women (from 43% to 34%) was more pronounced than the 10% decline observed in the homosexual men (from 20% to 18%). These figures do not imply that compliance was substantially lower in the IDU cohort.

Glick et al.[6] examined the relationship of the occurrence of individual oral lesions (Kaposi's sarcoma, oral candidiasis, hairy leukoplakia, NUP, xerostomia, herpes simplex virus, and major aphthous

ulcers) to severe immunosuppression (CD4 < 200) in HIV-positive subjects. In general, correlations estimated from our data for individual lesions were not as strong as those observed by Glick et al.[6] This finding may be due to the degree of immunosuppression in the populations studied. The mean CD4 cell count in our sample was 305 for the homosexual men and 355 for the IDU men and women. The mean CD4 for the entire sample in the Glick et al. study was closer to 200.

Comparisons of estimates of the diagnostic utility of oral lesions may be strongly influenced by patient selection. If patients were sampled because they were known to be affected by oral lesions, then the implication of choosing "marker positive" patients is to increase the rates of true-positive and false-positives, resulting in a higher observed sensitivity and a lower observed specificity than would exist in a randomly selected sample. This bias in estimation leads to uninterpretable results because the alteration in sensitivity and specificity would be merely an artifact of sampling design and not a true representation of the population at large. Similarly, if subjects were selected on the basis of CD4 cell counts, the estimates of positive and negative predictive values would be biased. The odds ratio is invariant to sampling fractions and thus can be used to make valid comparisons regardless of the method of patient selection. Because the entry criteria in this study did not select or exclude subjects on the basis of either lesion status or CD4 cell count, we believe that the estimates presented herein are largely unbiased insofar as a volunteer sample is representative of the population as a whole. This may not be the case in other studies in which the availability of patients often depends on their oral health status.

The importance of oral lesions as early indicators of HIV progression is emphasized by findings that both oral candidiasis and hairy leukoplakia are predictors of the onset of AIDS or death in HIV-positive patients.[1-5] In this article, we have relied on CD4 cell count as a laboratory marker of immunosuppression. The correlation between CD4 and survival time is not perfect, however, and the use of surrogate markers as valid endpoints in clinical studies has been questioned.[16] The results presented here must be extended to look at the correlation of individual lesions and combinations of lesions with the development of AIDS-defining clinical diagnoses and death. We are currently examining the prognostic importance of individual lesions and lesion combinations in predicting AIDS-free survival in these same two cohorts of subjects. Results may further influence recommendations with respect to the monitoring and treatment of men and women with HIV disease.

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