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ORIGINAL ARTICLE

Prevalence of oral disease among adults with primary HIV infection*

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OBJECTIVE: To explore the type and prevalence of oral mucosal lesions among adults with primary HIV infection (PHI) compared with HIV-negative adults at high risk for HIV disease, and in relation to HIV viral load.

METHODS: We conducted standardized oral examinations to identify specific oral mucosal lesions among adults with PHI, both *pre-seroconversion* and *post-seroconversion*-recently infected, compared with HIV-negative adults. We compared the group with oral lesions to those without oral lesions with respect to HIV-RNA load and CD4 + T-cell count.

RESULTS: Among 115 adults (predominantly men), pseudomembranous candidiasis was the most common oral lesion among those with PHI, and was found in 4% of the 23 participants in *pre-seroconversion* and in 9% of 69 participants with *post-seroconversion* recent infection, compared with none found among 23 HIV negatives. Among those with PHI, the median viral load was higher and the median CD4 + T-cell count lower among the 15 participants with an oral lesion of any type than among the 77 participants without oral lesions ($P = 0.02$ and 0.04, respectively).

CONCLUSION: This finding suggests that individuals with PHI who have oral lesions may be more likely to transmit HIV because of their higher viral load.
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Keywords: primary HIV infection; candidiasis; oral lesions; viral load

Primary HIV infection (PHI) represents the early stages of infection with the human immunodeficiency virus (HIV), and is defined as a negative or indeterminate HIV antibody test with subsequent seroconversion within 6 months (Hecht *et al*, 2002). It is important to recognize PHI because it is characterized by a very high viral load, and persons at this stage of HIV infection are an important source of new infections (Apoola *et al*, 2002; Gray *et al*, 2004). PHI includes two stages: (1) the acute stage, characterized by detectable HIV RNA, but prior to HIV antibody seroconversion and (2) recent HIV antibody seroconversion (within the past 6 months) during which HIV antibodies are present but immune responses are still maturing. Up to 90% of persons in the acute phase experience an initial influenza-like illness (Schacker *et al*, 1996). However, little is known about other clinical manifestations, such as oral mucosal diseases, that may occur at this early stage of HIV infection (Apoola *et al*, 2002; Hecht *et al*, 2002). Previous studies describing oral lesions in HIV infection enrolled subjects at different stages of HIV infection (Feigal *et al*, 1991; Glick *et al*, 1994; Shiboski *et al*, 1994, 1996, 2001; Patton, 2000), and specific oral lesions such as candidiasis have been found to be associated with a higher HIV viral load (Patton *et al*, 1999; Greenspan *et al*, 2000). However, very few have addressed the study of oral lesions in PHI due to the challenges in identifying individuals at that stage. If specific oral lesions were found to occur in PHI, their early detection may help to identify persons with PHI, and thus prevent further transmission. We hereby describe the type and prevalence of oral mucosal lesions in a sample of adults during primary HIV disease compared to a group of HIV-negative adults at high risk for HIV disease, and in relation to HIV viral load.

Methods

Study population

The OPTIONS Project is an ongoing study at the University of California San Francisco that recruits adults with potential PHI to explore the natural history of early stage HIV infection and the effect of antiretroviral therapy administered to those participants who choose the *option* to do so (Hecht *et al*, 2002). Both persons with suspected acute retroviral syndrome and recent seroconverters (within 6 months) are targeted for recruitment. Participants for screening are either

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self-referred or referred by others, including healthcare workers, HIV testing sites, or community-based organizations (Hecht *et al*, 2002). Participants are classified as *pre-seroconversion HIV infected* if (1) testing using standard EIA HIV-1 antibody testing and confirmatory Western blot is negative or indeterminate, and (2) HIV-1 RNA test or p24 antigen test shows viral antigen, confirmed on repeat testing and followed by HIV antibody conversion. To be classified as *post-seroconversion recently infected* participants have to be HIV antibody positive and have either a documented negative HIV antibody test within the prior 6 months, or a history of having had a negative HIV-1 antibody test within the past 3 years and recent HIV exposures, and a less-sensitive EIA test that is not reactive (Schwarcz *et al*, 2001; Hecht *et al*, 2002). An oral study protocol was incorporated into the OPTIONS study in August 2000, and a consecutive sample of participants was recruited from August 3, 2000 through November 2005.

Variables and measurements

A standardized oral examination, using the diagnostic criteria established by the 1992 US Collaborative Group (Greenspan *et al*, 1992) and the 1993 EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus (EC-Clearinghouse, 1993), was included as part of the study's physical assessment on the day of the initial serologic screening that was used to determine eligibility for the OPTIONS. Oral examinations were conducted by nurse practitioners who were blind to the participants' primary HIV status and trained in the diagnosis of HIV-related oral lesions. The two nurses who performed the oral examinations had received a standardized training (based on a power point presentation and clinical sessions) by a board-certified Oral Medicine specialist. Oral lesions explored included candidiasis (both the pseudomembranous and erythematous types, and angular cheilitis), hairy leukoplakia, aphthous-like ulcers, and warts. Presence of pharyngitis/tonsillitis was also recorded. Due to a logistic issue, some participants had their oral examination performed up to 1 month after the initial screening visit. For the present analysis, we included only those participants who had their oral examinations performed on the day of the screening or within 2 weeks, to avoid misclassification of participants who may have seroconverted between the time of the screening visit and the oral examination visit.

Statistical analysis

Standard summary statistics (mainly proportions) were used to describe sample characteristics. We used Fisher's exact test to compare the prevalence of specific oral lesions between participants with PHI *pre-seroconversion* and *post-seroconversion* HIV infection, and between participants with PHI (both pre- and post-seroconversion) and HIV-negatives. We used the nonparametric Mann–Whitney rank-sum test to compare participants with any oral lesions to participants without oral lesions with respect to (1) HIV RNA viral load, and (2) CD4 + T-cell count.

Results

Among the 235 participants who were recruited into the OPTIONS study between August 3, 2000 and November 30, 2005, 115 received an oral examination either on the day of the serologic screening (82% of the participants) or within 2 weeks. Among 92 participants with PHI, 23 were *pre-seroconversion* HIV infected and 69 were *post-seroconversion* recently infected (Table 1). Twenty-three participants who received an oral examination on the day of the serologic screening were subsequently found to be HIV-negative, and served as controls for this study. Both participants with PHI and those who were HIV-negative were predominantly male (96% and 83%, respectively), between 20 and 39 years of age (73% and 65%, respectively), and white (79% and 57%, respectively).

Pseudomembranous candidiasis was the most common oral lesion among those with PHI, and was found in 4% of those in *pre-seroconversion* HIV and in 9% of those with *post-seroconversion* recent infection, compared with none found among HIV-negative participants (Table 1). Aphthous ulcers were present in both the group with PHI and among HIV negatives, and the frequency did not differ between groups. Fisher's exact test of association comparing the prevalence of oral lesions between participants with PHI *pre-seroconversion* and *post-seroconversion* yielded no statistically significant difference. Similarly, no difference was found when comparing participants with PHI with HIV negatives with respect to oral lesions. However, among participants with PHI, the median viral load was significantly higher among the 15 participants found to have an oral lesion of any type (273 343 copies ml^{-1}) than among the 77 participants without oral lesions (86 548 copies ml^{-1}; $P = 0.02$). Furthermore, the

Table 1 Distribution of oral lesions among adults with primary HIV infection (PHI) by HIV serostatus

	Participants with PHI (n = 92) *Antibody seroconversion status*		
Oral lesions	*Pre- (acute)[a] (n = 23)*	*Post- (recent)[a] (n = 69)*	*HIV-negative participants[a] (n = 23)*
Candidiasis			
Pseudomembranous	1 (4)	6 (9)	0
Erythematous	0	4 (6)	0
Wart	0	0	1 (4)
Aphthous ulcer	0	6 (9)	2 (9)
Pharyngitis/tonsillitis	1 (4)	3 (4)	2 (9)

Values are expressed as *n* (%).
[a]Fisher's exact test of association comparing the prevalence of oral lesions between participants with PHI pre-seroconversion and post-seroconversion yielded no statistically significant difference. Similarly, no difference was found when comparing participants with PHI with HIV negatives with respect to oral lesions.

median CD4 + T-cell count among those with any oral lesion was significantly lower (420 cells mm^{-3}) than among those without lesions (552 cells mm^{-3}; $P = 0.04$).

Discussion

HIV infection progressively compromises systemic and local immunity until the host succumbs to opportunistic infections that significantly affect the mucosal sites, the oral mucosa included (Challacombe and Sweet, 2002). Early treatment of acute HIV infection may lead to slower declines in CD4 + T-cell counts (Hecht *et al*, 2006). Antibody tests are unreactive and diagnosis at this stage of HIV infection relies mainly on the p24 antigen or HIV-1 RNA tests. Oral lesions may represent important early symptoms associated with PHI and may potentially contribute to its early detection. In a recent study, 81% of individuals with PHI reported that they would be very likely to seek attention if they developed oral ulcers after unprotected sex (Stekler *et al*, 2006). Although we did not observe any statistically significant difference in the prevalence of oral lesions overall when HIV-positive and HIV-negative participants were compared, there was a difference in the type of oral lesions seen in each group. Oral candidiasis was not reported in any HIV-negative subject, but was present in 4% of *pre-seroconversion* and 9% of *post-seroconversion* HIV-infected participants. Furthermore, we found that oral lesions in participants with PHI were associated with higher viral loads and lower CD4 counts. This finding may suggest that individuals with PHI who have oral lesions may be more likely to transmit HIV because of their higher viral load.

These preliminary results from a study with a small sample size suggest a need for larger studies to further evaluate the role of oral lesions in PHI. The recognition and diagnosis of PHI remains a challenge, and it has been suggested that future efforts aimed at increasing the diagnosis of PHI should focus on increasing the knowledge of symptoms and healthcare-seeking behavior (Stekler *et al*, 2006).

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