

## Research Team

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## Main Findings

The presence of certain oral diseases can be an important tool for identifying persons living with HIV and assessing the relative progression of their disease. The important aspects of the epidemiology and significance of oral lesions include: (1) indication of HIV infection, (2) predictor of disease progression, (3) entry into, or end points for, clinical trials, (4) determinants of preventative and anti-HIV therapies, and (5) markers for systems of classifying the existence, progression, and prognosis of disease.

## Background

A wide body of scientific research attests to the frequency of oral disease in persons living with HIV disease and AIDS. The most common of these are candidiasis (thrush) and hairy leukoplakia, and they are seen more as CD4 cell counts decrease and HIV disease progresses. Indeed, because the association between oral disease and progression of HIV disease is so strong, it is often used as a marker for assessing the presence of HIV infection and the extent to which HIV has damaged the immune system. Also, particularly in developing countries where large-scale HIV counseling and testing is not yet in place or for persons who may not know of their increased risk of infection, the observation of oral lesions can be an important tool for identifying HIV infection. Recent studies provide important information on factors that likely increase the risk of oral disease; they also rule out certain factors previously thought to be related to oral disease.

## Why this project?

As our collective knowledge of HIV infection and disease has increased, so too has our understanding of the varied clinical and biological importance of HIV-related oral diseases. In the earliest days of the epidemic, oral candidiasis (thrush) was one of the lesions associated with AIDS, particularly among the gay and bisexual men who were part of the first onslaught. Since that time, scientific studies have reinforced, confirmed, and built upon those initial descriptions. While the literature on oral

lesions and HIV is extensive and has been published in a wide range of different scientific disciplines, UCSF researchers have focused on better understanding the natural history of HIV-related oral disease and its relationship to HIV prevention and care.

Because the mouth and throat are easily examined by a wide range of medical professionals and most oral lesions are clearly visible, an improved understanding of HIV-related oral disease can benefit many people living with HIV—even those without access to specialized dental specialists.

## Intervention

A comprehensive analysis of research done over the past two decades demonstrates that the oral manifestations of HIV disease serve as strong indicators of HIV infection, are early clinical features of HIV disease, and can be important warning signs for the imminent progression to AIDS.

### Oral lesions as indicators of HIV infection

Several studies have demonstrated that oral lesions are more common among persons living with HIV than those that are not, and that they serve as a strong predictor for HIV infection. For example, examination of patients from Dar Es Salaam, Tanzania, by Schiodt and colleagues showed that 85% of those diagnosed with oral lesions were later determined to be HIV-positive. Similar studies of patients in Belgium, Greece, and Zaire offer similar results. All in all, there seems to be growing consensus that the presence of hairy leukoplakia or Kaposi's sarcoma (KS), and to a lesser extent other oral lesions such as candidiasis, lymphoma, intraoral herpes simplex or zoster, is highly suggestive of HIV infection. It must, of course, be remembered that all of these lesions can occur outside the context of HIV.

Researchers have noted differences in the prevalence of certain oral diseases among men and women, observing a lower prevalence of these sentinel lesions in women than in men (see Table 1). Gender differences have been identified in the prevalence of hairy leukoplakia and KS.

**Table 1: Reported Prevalence of Oral Disease in Persons Living with HIV**

	<b>Oral Candidiasis</b>	<b>Hairy Leukoplakia</b>
<i>Among Women</i>		
Greenspan D 2000	14%	6%
Shiboski 1997	14%	10%
Shiboski 1996	13%	9%
Schuman 1998	15%	5%
Carpenter 1991	18%	5%
<i>Among Men</i>		
Feigal 1991	7%	20%
Barr 1992	na	20%
Shiboski 1996	24%	22%

There are also commonalities. For both men and women, the most common oral lesion is candidiasis, and the frequency of infections of various types of candidiasis appears more related to the health of the immune system than gender.

**Oral lesions as an early clinical feature of HIV disease**

Because oral lesions occur frequently among persons living with HIV, several research

projects have sought to place them in the natural progression of HIV disease. A better understanding of when oral diseases are likely to occur, from initial infection to life-threatening opportunistic infections, has been sought both by studying their occurrence among those with well-defined dates of infection and by correlating their presence with other clinical markers like CD4 counts.

A study in San Francisco of 80 men with well-defined dates of seroconversion found development of hairy leukoplakia and oral candidiasis at the following rates: 10% within the first year, 30% within three years, and 50% within five years. Another study that included hemophiliac and transfusion product recipients found similar, although slightly lower, incidence figures.

**Oral lesions predict progression to AIDS**

Certain mouth and throat lesions, notably oral candidiasis and hairy leukoplakia, feature in all HIV/AIDS classification, staging, and prognosis systems currently in use, including the 1986 and 1993 definitions of AIDS by the U.S. Centers for Disease Control and Prevention. The World Health Organization also uses oral lesions as important criteria for diagnosing AIDS in places where laboratory tests such as HIV serology or CD4 counts may not be available.

In fact, a mathematical analysis comparing oral candidiasis and disease progression found it to be an accurate predictor of the imminent onset of AIDS—even when adjusting for CD4 cell counts. This was true for two different groups studied, representing different modes of transmission and

different clinicians, suggesting that the results may be broadly applicable. The researcher in this study (Hilton, in press) concluded that a history of candidiasis indicates that the patient is at high risk of AIDS and that a recent episode of candidiasis suggests that the patient should be monitored very closely for AIDS.

An analysis of three San Francisco male cohorts found that those subjects with oral candidiasis or hairy leukoplakia at initial examination developed AIDS more rapidly than those with normal oral mucosal findings (see Table 2). Similar results were found among HIV-positive women in Rwanda (Linden, et al., 1992), although the prevalence of candidiasis was lower. Researchers in Toronto found that the development of several common oral diseases (oral candidiasis, hairy leukoplakia, and herpes zoster) were the clinical features most significantly associated with progression to AIDS.

Researchers have also noted that this highly predictive value of a candidiasis diagnosis is true of both the pseudomembranous candidiasis (which appears as distinctive patches) and the subtler erythematous candidiasis (which appears as a red rash). This is particularly important for those who may be dependent on this diagnosis for knowledge of their infection or their imminent progression to AIDS, since the latter is easily overlooked during oral examination.

**Table 2: Progression to AIDS and Oral Disease**

	<b>AIDS within six months</b>
Hairy leukoplakia	6%
Candidiasis	31%
Both	9%
Normal	1%

## Selected Key Findings

### Oral disease is highly indicative of HIV infection

Certain oral diseases are strong indicators of HIV infection. However, more subtle variations can be missed during routine examination, resulting in a lost opportunity for diagnosis and treatment.

- A high percentage of those diagnosed with oral lesions will be persons who are living with HIV.
- Hairy leukoplakia and KS are most closely associated with HIV infection, as are (to a lesser degree) candidiasis, lymphoma, and intraoral (in the mouth) herpes simplex or zoster.
- Both pseudomembranous (patches) and erythematous (red rash) candidiasis are equally predictive, but the latter is often missed in routine oral examinations.

### There are variations and similarities by gender

While both men and women get HIV-related oral diseases, it is more common among men.

- Similar types of oral mucosal lesions affected women and men.
- The most common type of oral lesion among women and men is oral candidiasis.
- Gender differences have been identified in the prevalence of hairy leukoplakia and KS.
- The prevalence of HIV-related oral disease is lower among women than men.

### Oral disease is a strong predictor of imminent progression to AIDS

The detection of HIV-related oral diseases should be considered a strong predictor of the imminent (within six months) onset of AIDS. This is particularly important for treating those without access to other laboratory data with which to assess disease progression.

- Since the earliest years of the epidemic, HIV-related oral diseases have been used to gauge disease progression.
- Certain oral diseases, particularly hairy leukoplakia and/or oral candidiasis, place patients at the threshold of AIDS, in most cases even after controlling for CD4 count.

## Recommendations

Having substantial knowledge about HIV-related disease is of little benefit if that knowledge is not used to benefit people living with or at risk from HIV. Unfortunately, too many physicians fail to correctly diagnose and treat these diseases. Substantial and intensive educational efforts are needed to enhance the capacity of clinical providers to quickly and accurately identify these oral diseases and to refer their patients to appropriate follow-up counseling and testing, prevention, and care services.

Proper diagnosis should also be used more widely to identify persons living with HIV in areas where widespread counseling and testing are otherwise unavailable. In addition, it can be used to identify persons living with HIV who are unaware of their risk, including women unknowingly at risk from their partners.

## Lessons Learned/Challenges

Additional research is needed to understand more about the impact of HIV disease on the normal immune protections of the mouth and throat, as well as factors that can strengthen or weaken that protection. Questions also remain around the mechanism(s) for sustaining certain oral diseases even after treatment. For example, it is still not known exactly how the Epstein-Barr virus (EBV) continues to fuel outbreaks of hairy leukoplakia. Does the EBV remain present in certain cells or does continuous re-infection occur from an outside source? Increasing our knowledge about the causes of oral diseases will help people living with HIV prevent their reoccurrence.

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## Materials Available

Additional information is available on the following web sites:

- Oral AIDS Center: <http://itsa.ucsf.edu/~ucstoma/oac.htm>
- AIDS Research Institute at UCSF: <http://ari.ucsf.edu>.

You can also write to:  
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