JADA LANDMARK SERIES
Spotlighting articles from past ADA Journals that have achieved landmark status thanks to their lasting impact on dental care and the dental profession

A total of 375 homosexual males were studied to assess the dental findings, life-style, and risk factors during a 4-year period. At baseline, 136 of the patients were diagnosed as having AIDS, 116 were considered at risk for AIDS, and 123 were considered healthy. In a mean follow-up time of 23 months, nine of the patients at risk for AIDS and five of the patients considered healthy were diagnosed as having AIDS. Kaposi’s sarcoma was the most common oral neoplasm, and candidiasis was the most frequent oral infection. Hairy leukoplakia was found in 28% of the patients, and periodontal disease was found in 17% of the patients. Carriers of the AIDS virus may not be identified easily and control measures in the dental office must be followed.

Oral findings in people with or at high risk for AIDS: a study of 375 homosexual males

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The role of the dental profession in addressing the human immunodeficiency virus epidemic

In February 1986, Dr. Sol Silverman Jr. and his colleagues reported clinical findings among 375 gay men from the San Francisco area who were treated at the oral medicine clinic at the University of California, San Francisco from 1981 through 1985. These patients were diagnosed at various stages of human immunodeficiency virus (HIV) infection or were healthy but at risk of developing infection. This landmark article applied scientific observation to dispel some of the misinformation, panic and fear that accompanied the early days of the epidemic. The recognition of what would become the AIDS epidemic was initiated by astute clinicians, the “founders of the field,” who identified a new syndrome by the process of meticulous categorization of unique findings and unusual
disease manifestations. This article identified many of the issues that are still relevant today: the clinical presentation of the disease, the epidemiology, the disease progression and the transmissibility of HIV.

The article delivers a clarion call, then and now, to dental professionals on their responsibility to collaborate with other members of the primary care team to identify patients early in the course of their HIV disease and to link them to medical care. Knowledge of HIV disease has advanced significantly in the ensuing years, and our understanding of HIV prevention, pathogenesis, diagnosis and medical management has resulted in entirely new health outcomes for those patients who have access to treatment. Because of this, a review of the disease’s evolution in the nearly 30 years since publication of this seminal article is warranted as a reminder to the dental profession to realize our full potential in affecting the course of the HIV epidemic.

**HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIOLOGY**

The number of new HIV diagnoses in the United States has been relatively stable—nearly 50,000 cases per year for the past decade, despite the widespread public health efforts to encourage people to modify their risk behavior. At the time of the report by Silverman and colleagues, 74 percent of people with AIDS in the United States were men who have sex with men; that figure had fallen to 56 percent by 2011. Women now represent a quarter of people diagnosed with HIV in the United States. The majority of men (62 percent) and especially women (82 percent) diagnosed with HIV either are non-white or Hispanic. HIV has become an opportunistic infection in its own right by disproportionately affecting communities with social and economic disadvantages.

HIV infection may present with nonspecific symptoms and findings. For a clinician to recognize, diagnose and properly treat a person with HIV, the possibility of infection first must be considered. Lack of an acknowledged risk factor for HIV acquisition should not dissuade evaluation for the diagnosis. Approximately 20 percent of people living with HIV in the United States are unaware of their HIV-positive serostatus; almost half of all HIV transmissions are attributable to these people (Figure 1). Moreover, knowledge of HIV infection leads to reduced risk behavior. In April 2013, the United States Preventive Services Task Force announced a recommendation for routine HIV screening for all adults aged 15 to 65 years regardless of their lifestyle or perceived risk. These age cutoffs are not fixed, and HIV screening can be a cost-effective strategy for older or younger people, especially in communities with high HIV seroprevalence. At the time of Silverman and colleagues’ article, no screening strategy was available for HIV, the virus that had been discovered as the cause of AIDS. Signs and symptoms were the only marker of infection. Ideally, through routine screening of all adults, people with HIV infection will be identified early, before the advanced clinical presentations described by Silverman and colleagues have had a chance to develop.

**HUMAN IMMUNODEFICIENCY VIRUS DISEASE PROGRESSION**

In Silverman and colleagues’ study, 14 people who apparently were healthy at initial visit developed AIDS-defining signs and symptoms in less than two years: “As follow-up continues, AIDS undoubtedly will be seen to develop in many more people [in the study group]; however, the predictability remains uncertain.” The assay to detect and quantify the amount of virus in the blood, called the “plasma HIV viral load,” became clinically available in the mid-1990s. The height of the viral load correlates with the rate of disease progression in a person. This transformative assay demonstrated that, while HIV can be clinically latent, it undergoes high-level replication in most people from the very start of the infection. This asymptomatic period, which averages 10 years, is an opportunity for the virus to be transmitted to others and leads to progressive imbalance of the immune system of the infected person. Screening for infection is the best way to identify people during this period. People identified during the acute retroviral syndrome (ARS) phase have a unique opportunity to initiate therapy, which may help preserve the integrity of their immune system and lower the burden of the reservoir of integrated viral DNA that remains in CD4 cells after suppressive therapy. All clinicians need to be aware of the signs and symptoms of ARS, which include fever, maculopapular rash, swollen lymph nodes, pharyngitis (without an exudate) and oral aphthous ulcers. Acute HIV infection is associated with a very high plasma viral load—the most important determinant of viral transmission. Therefore, initiating treatment, especially during acute infection, will mitigate disease progression in the person and interrupt the likelihood of transmitting the virus to others.
At the time of Silverman and colleagues’ article, there were no approved treatments for HIV. Today, there are more than 30 agents. Combination therapy is superior to individual drug therapy in achieving complete suppression of HIV replication, durability of treatment response, prevention of development of HIV drug resistance, and reduced HIV- and non-HIV-associated morbidity and mortality. High levels of adherence (over a lifetime) to treatment are required to achieve long-term success. Improvements in drug tolerability and side-effect profiles and the development of coformulated agents all have contributed to increased patient acceptance and successful outcomes from therapy.

Silverman and colleagues noted, “Nationwide, as well as in San Francisco, the death rate in patients with AIDS approximates 50 percent ... essentially all persons with AIDS will die of the disease, usually within 2 years from the times of diagnosis.” Recent data suggest that people with HIV infection who have an undetectable viral load on therapy and achieve and maintain a CD4 count above 500 cells per milliliter can have a mortality rate equal to that of uninfected people. Such outcomes, which were unimaginable at the time of Silverman’s review, are predicated on initiating therapy at a stage early enough to allow CD4 reconstitution to this level and to remain adherent to treatment indefinitely. The extent of CD4 recovery is less robust if treatment is started at a lower CD4 count, with older age and with incomplete viral suppression. Unfortunately, most people living with HIV in the world are unable to initiate treatment early enough in the course of the disease to accrue the full potential survival benefit.

Silverman and colleagues were prescient in recognizing variable cofactors that “may account for the spectrum of the disease” and “unpredictable outcome.” Today, it is becoming clear that HIV is responsible for pathogenic processes that affect health long before AIDS develops. HIV generates a state of persistent activation of the immune system through direct viral infection, causing imbalance of normal immune function by T-helper cell depletion, disruption of the protective lymphocyte milieu of the intestinal lining, allowing for microbial translocation and creating an environment of elevated stimulatory cytokines that activates neighboring uninfected lymphocytes, causing “bystander” cell death. This state of chronic immune activation is postulated to impair full immune reconstitution on therapy and cause endothelial damage and “premature aging.” The Swiss HIV Cohort Study found that whereas 80 percent of deaths before 1995 were AIDS related, only 16 percent of deaths were AIDS related during the period.
from 2005 to 2009. These data underscore that HIV-associated illness has now shifted from AIDS-defining conditions toward those associated with chronic immune activation and persistent infectious coinfections such as hepatitis C and human papillomavirus (HPV).

**HUMAN IMMUNODEFICIENCY VIRUS TRANSMISSION IN DENTAL SETTINGS**

Silverman and colleagues reported no documented cases of AIDS in dental professionals who were not in the classified high-risk groups. According to the Centers for Disease Control and Prevention, no dental health care professionals are among the 57 health care providers in the United States documented to have seroconverted following a specific exposure from a known HIV-infected patient. The 2003 Guidelines for Infection Control in Dental Health-Care Settings updated previous recommendations, including those in place when Silverman and colleagues reported their findings. Today, the adoption of universal precautions (treating all people the same because HIV and hepatitis infections may be clinically silent) and use of postexposure prophylaxis have greatly reduced the risk of occupational transmission of HIV from patient to provider and vice versa.

**ORAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS DISEASE**

Silverman and colleagues reported multiple oral findings associated with immunosuppression: 53 people with oral Kaposi sarcoma, 13 with other oral cancers and 248 with *Candida*. With access to current HIV therapies, the prevalence of oral lesions reported by Silverman and colleagues of 65 percent has decreased to approximately 30 percent, with oral pharyngeal candidiasis still the most frequent manifestation. An increase in the frequency of HPV-associated oral lesions has been reported. These lesions are associated with older age and require years to develop (Figure 2).

For those who are unaware of their HIV infection, the presence of an oral lesion can be the earliest sign of a new infection. Regardless of a decreased prevalence of oral lesions in general, or an increased prevalence of HPV specifically, the oral manifestations and conditions of HIV disease are critically important insomuch as they affect overall quality of life and can serve as important surrogate markers of seroconversion or treatment failure among those currently in care. The importance of performing a definitive intraoral and extraoral examination cannot be overemphasized.

**SCREENING FOR HUMAN IMMUNODEFICIENCY VIRUS DISEASE IN THE DENTAL SETTING**

A rapid HIV test using oral fluids was approved in 2004. With its high sensitivity and specificity, the test offers reliable results typically in less than 20 minutes. The dental practice site remains a largely untapped venue for performing HIV testing, especially since many of the previous barriers, including mandatory pretest and posttest counseling, have been removed. Dental care offers opportunities to serve at-risk people who are otherwise unlikely to be tested or to receive preventive medical services. Using data from the 2005 National Health Interview Survey, Pollack and colleagues reported that there are an estimated 3.6 million Americans at significant risk of developing HIV infection who have never been tested. Nearly three-quarters of these people have seen a dentist within the past two years. Pollack and colleagues concluded that in areas with an HIV-prevalence rate greater than 0.1 percent, it is reasonable to assume that HIV screening in the dental setting could be a cost-effective initiative to identify people who are unaware of their HIV-positive serostatus. Additionally, studies have repeatedly demonstrated that dental patients are widely receptive to being tested for HIV in the dental setting.

The dental profession can play a crucial role in addressing the HIV epidemic. As Silverman and colleagues urged in their seminal publication, dentists should identify cases through the recognition of oral lesions that serve as markers of HIV infection. However, with the advent of the HIV rapid test using oral fluids, dental professionals can now effectively screen for HIV.
disease in their practice settings and refer patients for medical care well before the presentation of oral lesions.

CONCLUSIONS
After almost three decades, the prescience shown by Silverman and colleagues serves as a reminder to oral health practitioners that their role is to screen for HIV infection, recognize manifestations of HIV-associated disease and establish linkage to care with HIV-experienced providers. Moreover, people living with HIV infection may be seeing their oral health care provider but not their primary care provider. Best practices dictate that a collaborative care practice model would yield optimal outcomes for the overall health of HIV-infected people. It is important that oral health care providers have a referral network in place and have developed a process for cross-disciplinary collaboration.

Although many lives have been lost in the over quarter-century since Silverman and colleagues published their landmark article, the loss has spurred a drive to develop effective tools to combat the AIDS epidemic. The advances that have been made in battling this epidemic are impressive and rank among the greatest accomplishments of modern medicine. These gains are fragile and could be reversed as they depend on ongoing individual adherence to medications, potent public health and community advocacy, uninterrupted access to treatment and strong support from dedicated health care providers. Diligence among oral health professionals was critical at the time when Dr. Silverman and colleagues published their article, and it remains so today.

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