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HIV Disease

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The past 20 years of United States experience with human immunodeficiency virus (HIV) has evolved from an unexplained immune deficiency disorder seen among gay men in San Francisco to a prevalent viral infection that has affected the lives of many individuals from varied backgrounds across the country. Infected individuals can be found in both urban and rural communities and are of all ages, races, and both genders. Undiagnosed or untreated infection with HIV-1, the predominant strain in United States populations, results in progressive loss of immune function marked by depletion of the $CD4^+$ T lymphocytes (CD4), leading to opportunistic infections and malignancies characteristic of acquired immune deficiency syndrome (AIDS).

Several landmarks or events of the first 20 years of our experience with HIV infection are important to note and are shown in the Appendix [1–9]. A preventive HIV vaccine is very technically challenging to construct, largely due to a high rate of spontaneous mutation and HIV strain variation and, therefore is not available. Improved and broad-reaching behavioral HIV prevention efforts will thus remain of critical importance in control of this blood-borne infection in the United States and the global community.

Epidemiology

Much of the information available to the public and health care providers about disease trends comes from surveillance activities at the local and state health departments, with reporting to the Centers for Disease Control and Prevention (CDC). In regard to our nation's integrated HIV/AIDS surveillance system, all states report AIDS cases to the CDC and, as of December 2001, all but five states (California, Pennsylvania, Georgia, Rhode Island, and New Hampshire) had implemented confidential HIV case reporting [10].

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The estimated cumulative AIDS incidence in the United States decreased from 60,747 in 1996 to a plateau of around 41,000 new AIDS cases each year in 1999 through 2001 [11]. Although 462,653 Americans are known to have died of AIDS since the beginning of the epidemic, annual AIDS death rates are in decline [11]. The result is an increasing number of individuals living with AIDS, including more than an estimated 506,154 individuals living with HIV/AIDS through December 2001 [10,11]. To put these numbers in perspective, the number of people who have died of AIDS since the beginning of the epidemic is equivalent in number to over half the population of the state of Montana (902,195), and the number of individuals currently living with HIV/AIDS exceeds the population of Wyoming (493, 782) according to year 2000 census counts (http://factfinder.census.gov/).

United States AIDS surveillance data shown in Table 1 indicates that the largest proportion of AIDS cases to date have occurred among non-Hispanic whites (42%) and men who have sex with men (46%) [11]. Most AIDS cases are diagnosed between age 25 and 44 years for both men and women [11]. Recent trends, however, suggest that in the United States, HIV/AIDS increasingly affects women, racial and ethnic minorities, heterosexual people, young homosexual men, and people over the age of 50 years.

Table 1
Transmission risk and ethnicity of cumulative AIDS cases by gender through December 2001 in the United States

Factor	Male No. (%)	Female No. (%)	Total No. (%)
Exposure category			
Adult/adolescent			
Men who have sex with men (MSM)	368,971 (55)	—	368,971 (46)
Injecting-drug use (IDU)	145,750 (22)	55,576 (39)	201,326 (25)
MSM and IDU	51,293 (8)	—	51,293 (6)
Hemophilia/coagulation disorder	5000 (1)	292 (0)	5292 (1)
Heterosexual contact	32,735 (5)	57,396 (41)	90,131 (11)
Receipt of blood transfusion	5057 (1)	3914 (3)	8971 (1)
Other/risk not reported/identified	57,220 (9)	23,870 (17)	81,091 (10)
Pediatric (<13 years old)			
Hemophilia/coagulation disorder	229 (5)	7 (0)	236 (3)
Mother with or at risk for HIV infection	4113 (88)	4171 (95)	8284 (91)
Receipt of blood transfusion	241 (5)	140 (3)	381 (4)
Other/risk not reported/identified	78 (2)	95 (2)	173 (2)
Ethnicity			
White, not Hispanic	313,034 (47)	30,854 (21)	343,888 (42)
Black, not Hispanic	228,499 (34)	84,681 (58)	313,180 (38)
Hispanic	121,198 (18)	28,554 (20)	149,725 (18)
Asian/Pacific Islander	5354 (1)	803 (1)	6157 (1)
American Indian/Alaska Native	2057 (0)	480 (0)	2537 (0)
Total	670,687 (100)	145,461 (100)	816,149 (100)

Data from Centers for Disease Control and Prevention U.S. HIV and AIDS cases reported through December 2001. HIV/AIDS Surveillance Rep 2001;13(2):1–44; with permission.

Transmission

The primary routes of transmission are sexual (by way of vaginal or anal sexual contact with an infected partner), blood-borne (injecting-drug use where blood is passed in a contaminated syringe from one user to the next or by contaminated blood-product transfusion), and vertical (ie, from mother to child either in utero, during delivery, or postpartum by way of breast milk).

The oral cavity represents a unique site for potential mucosal transmission of HIV. Epidemiologic evidence, however, suggests that oral transmission is rare [12,13], despite detectable virus in saliva and oral mucosal cells of infected persons [14,15]. Several endogenous mucosal antiviral factors such as virus-specific antibodies, mucins, thrombospondin, secretory leukocyte protease inhibitor, and soluble proteins are thought to play a critical role in preventing oral HIV transmission [16].

As of June 2000, 56 health care workers in the United States were documented to have occupationally acquired HIV; none of these documented occupational seroconversions were among dental health care workers [17]. An additional 138 possible occupational transmissions were reported, 6 of which were dental workers without identifiable behavioral or transfusion risks and who reported percutaneous or mucocutaneous occupational exposure to blood or body fluids containing HIV [17]. When a comprehensive report was issued describing circumstances of the exposures and seroconversion rates for occupational exposures though June 1996, it became evident that the rate of seroconversion was extremely low (0.32% for many types of percutaneous injuries to blood of patients in various stages of HIV infection and 0.09% for mucous membrane exposures) [18]. The United States Public Health Service periodically updates the guidelines for management of occupational exposures to HIV and recommendations for postexposure prophylaxis with antiretroviral medications [19].

Pathogenesis

HIV is a retrovirus that enters human host cells and sets up a productive infection. HIV envelope proteins interact with susceptible target cell surface CD4 receptors and chemokine receptors (CCR5 and CXCR4), leading to fusion followed by virion uncoating, reverse transcription of the RNA genome, nuclear import of the viral preintegration complex, and integration of the double-stranded viral cDNA into the host cell chromosome, thus establishing HIV provirus [20]. Late events in the HIV-infected cell, including downregulation of CD4 to optimize the intracellular environment for viral replication, culminate in assembly and release of new infectious virions [20].

One of the important challenges in the medical management of HIV disease is the ability of the virus to establish latent reservoirs early in the course of infection that ensure persistence of this pathogen even in the face of intensive drug therapy and apparently effective immune response [21,22]. Anatomic

reservoirs have been demonstrated, including lymphoid, central nervous system, and genitourinary compartments, and cellular reservoirs involve a variety of cell types, predominantly the resting memory CD4 T cell [21,22].

Diagnosis

Standard serologic HIV antibody test methods consist of screening enzyme immunoassay or enzyme-linked immunosorbent assay (ELISA) and confirmatory Western blot tests. The HIV test is read as negative, with results returned within 3 to 4 days if the initially run enzyme immunoassay or ELISA is negative. False-negative results are possible in the ''window period'' (usually the 10 to 14 days from infection to seroconversion or development of the HIV antibodies) but may last up to 6 months in rare instances [23]. A ''repeatedly reactive'' enzyme immunoassay or ELISA is the criterion for Western blot testing, and this lengthens the test result notification time frame by up to 1 week. Western blot detects antibodies to HIV-1 proteins including core, polymerase, and envelope with a frequency of false positives of 0.0004% [24].

Technologic advances have resulted in the ability to easily and safely collect and test oral fluids for antibodies to HIV-1 [25]. OraSure (OraSure Technologies, Bethlehem, PA) is a needleless oral fluid–based test for antibodies to HIV that consists of a specially treated cotton pad that is placed between the buccal mucosa and mandibular gingival for 2 minutes to absorb and concentrate immunoglobulin G from oral mucosal transudate and surrounding saliva for application of enzyme immunoassay/ELISA and Western blot tests in a laboratory setting [26]. In 2002, a rapid enzyme immunoassay HIV antibody screening test that yields results in 20 minutes (OraQuick, Abbott Labs, Abbott Park, IL and OraSure Technologies) was approved by the United States Food and Drug Administration for use with blood. Clinical trials continue to improve this rapid test designed for use with oral mucosal transudate. Rapid testing at the point of care facilitates occupational-exposure postexposure-prophylaxis decisions and may have value in identification of newly infected individuals in high prevalence and low return-rate settings.

Dentists may play a role in diagnosing HIV when medical history taking and oral examination reveal risks and clinical signs of possible immune suppression [27]. Oral lesions, specifically intraoral Kaposi's sarcoma, oral candidiasis, and oral hairy leukoplakia, may be the first clinical manifestation of HIV and have been shown to have relatively high positive predictive value for HIV infection in Tanzania and the United Kingdom [28–30]. HIV testing requires written consent in most states and under most circumstances and should be accompanied by pretest and post-test prevention counseling according to CDC guidelines [31]. In addition to private physician's offices, county health departments around the country provide confidential HIV testing.

Disease course and laboratory monitoring

The natural history of untreated HIV infection can be divided into stages: (1) initial viral transmission, (2) acute retroviral syndrome (primary or acute infection) within the first 2 to 3 weeks, (3) recovery and seroconversion within the first 6 weeks, (4) asymptomatic chronic HIV infection that persists over 7 to 9 years, (5) symptomatic HIV infection, and (6) AIDS for 1 to 2 years before death. With effective medical management that suppresses HIV replication in the host cells, all phases of HIV infection can be prolonged and death can be postponed beyond the untreated 10-year to 11-year life span [32].

The 1993 CDC AIDS surveillance case definition [11] incorporates three clinical categories of disease ranging from A to C, with C representing clinical AIDS, as follows:

A = acute HIV infection, asymptomatic disease, or persistent generalized lymphadenopathy
B = symptomatic disease, including development of oropharyngeal candidiasis or oral hairy leukoplakia
C = one of 26 AIDS indicator conditions including, in order of frequency, *Pneumocystis carinii* pneumonia; wasting due to HIV; candidiasis of esophagus, trachea, bronchi, or lungs; pulmonary *Mycobacterium tuberculosis*; Kaposi's sarcoma; cytomegalovirus of any organ other than liver, spleen, or lymph nodes (most commonly the eye); disseminated *Mycobacterium avium*; HIV-associated dementia; and recurrent pneumonia

The clinical staging of HIV disease and the relative risk of developing opportunistic infections have historically relied on the CD4 cell count as the principal laboratory marker of immune status [24]. HIV disease is commonly categorized on the basis of three levels of immunodeficiency: relative immune competence (CD4 cell count $>500/\mu L$; $\geq 29\%$), early immune suppression (CD4 cell count between $200/\mu L$ and $500/\mu L$; 4%–28%), and severe immune suppression (CD4 cell count $<200/\mu L$; $<14\%$) [6].

More recently developed technologies allowing determination of HIV viral load, reported as HIV RNA copies per milliliter, provide a quantitative measurement of viral replication in the blood that is seen as a harbinger of future CD4 cell destruction [33]. Even the most ultrasensitive assay Amplicor HIV-1 Monitor (Roche Diagnostics, Basel, Switzerland) is unable to detect levels below 50 copies per milliliter. Quantitative plasma HIV RNA is useful in diagnosing acute infection, predicting rate of disease progression and overall prognosis in chronically infected patients, predicting the probability of transmission, and for therapeutic monitoring of patient response to antiretroviral therapy [34,35]. A patient with the best prognosis is one with an undetectable plasma viral load and a robust CD4 cell count ($>500/\mu L$), which can only be attained with effective medical management.

Medical management

Medical management for HIV-infected patients consists of two primary objectives: (1) suppression of HIV viremia to maintain immune competence with the use of antiretroviral drugs and management of subsequent drug toxicities, and (2) prevention and treatment of opportunistic diseases that result from immune suppression. Through maximal and durable suppression of viral load and resulting preservation or restoration of immunologic function, quality of life is dramatically improved and HIV-related morbidity (including incidence of opportunistic infections) and mortality are reduced.

Suppression of HIV viremia

The CDC periodically publishes guidelines for the use of the ever-increasing arsenal of antiretroviral agents [36], using new information about HIV viral dynamics and treatment outcomes from HIV cohort studies and randomized clinical trials. Many treatment efficacy studies are conducted using the United States multicenter pediatric and adult AIDS Clinical Trials Group, the largest HIV clinical trials organization in the world. The issues of when in the HIV disease course to start antiretroviral therapy and which drug combinations to use remain controversial. Treatment is usually offered to all patients with symptoms of HIV infection. Among asymptomatic patients, real and potential risks and benefits must be weighed in consultation with the patient, giving consideration to the patient's willingness and readiness to begin therapy and likelihood of adherence to the regimen, the current level of immune suppression based on the CD4 cell count, and the risk of disease progression as determined by the CD4 cell count and viral load. The most recent consensus opinion is that antiretroviral treatment should be offered to persons with a CD4 cell count $<350/\mu L$ or plasma HIV RNA levels of >55,000 copies per milliliter [36].

Current recommendations for the treatment of HIV-infected patients advise highly active antiretroviral therapy (HAART), consisting of combinations of three or more drugs demonstrated in trials to provide sustained clinical benefit. Regimens generally include at least one protease inhibitor or non-nucleoside reverse transcriptase inhibitor in addition to one or more nucleoside reverse transcriptase inhibitors in order to target HIV replication at more than one stage in the virus life cycle and to allow more complete suppression of replication. See Table 2 for a list of currently available antiretroviral drugs.

Results of therapy are evaluated through the plasma HIV RNA level that is expected to drop by 1.0 $\log_{10}$ at 2 to 8 weeks and to attain undetectable levels (<50 copies per milliliter) at 4 to 6 months after treatment initiation. Although HAART can result in long-term suppression of viral loads to undetectable levels in plasma in some patients, we now know that long-term therapy fails to eradicate virus. Viral levels in plasma generally rebound after single or

Table 2
Toxicities and oral side effects of antiretroviral medications approved by the US Food and Drug Administration for treatment of HIV

Generic name	Proprietary name	Toxicity/oral side effects[a]
Nucleoside analogs or nucleoside reverse transcriptase inhibitors		
zidovudine (AZT, ZDV)	Retrovir	anemia, neutropenia
didanosine (ddI)	Videx	peripheral neuropathy
zalcitabine (ddC)	Hivid	stomatitis, peripheral neuropathy
stavudine (d4T)	Zerit	peripheral neuropathy
lamivudine (3TC)	Epivir	
zidovudine/lamivudine	Combivir	anemia, neutropenia
abacavir (ABC)	Ziagen	hypersensitivity in 2%–5%
abacavir/lamivudine/ zidovudine	Trizivir	hypersensitivity in 2%–5% anemia, neutropenia
Nucleotide reverse transcriptase inhibitors		
adefovir (bis-POM PMEA)	Preveon	
tenofovir (TDF)	Viread	
Non-nucleoside reverse transcriptase inhibitors		
nevirapine (NVP)	Viramune	rare Stevens-Johnson syndrome
delaviradine (DLV)	Rescriptor	rare Stevens-Johnson syndrome
efavirenz (EFV)	Sustiva	
Protease inhibitors		
saquinavir (SQV)	Invirase; Fortovase	
ritonavir (RTV)	Norvir	taste perversion, circumoral paresthesias
indinavir (IDV)	Crixivan	thrombocytopenia, chapped lips, metallic taste, dry mouth
nelfinavir (NFV)	Viracept	
amprenavir (APV)	Agenerase	perioral paresthesias, rare Stevens-Johnson syndrome
lopinavir (LOP)/ ritonavir	Kaletra	

Note: Most of these medications have additional toxicities and side effects (e.g., gastrointensified disturbance, nephrotoxicity, and rashes) not listed here that limit their use.

[a] Reported oral side effects or systemic toxicities relevant to the management of dental patients.

multiple treatment interruptions, possibly due to reseeding from viral reservoirs, fluctuations in the rates of viral production or clearance, or other yet-unknown complex interactions between virus and target cells or immune responses [37].

The complexity of antiretroviral regimens and serious side effects create challenges for patient adherence to the regimen. Drug manufacturers have worked to create drug combination pills (eg, Combivir [zidorudine and lamivudine], and Trizivir [zidorudine, lamivudine, and abacavir] Glaxo-SmithKline, Research Triangle Park, NC) in order to reduce the quantity of pills that need to be ingested daily. Important toxicities that are associated with HAART include lactic acidosis and hepatic steatosis, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, increased bleeding

episodes among patients with hemophilia, osteonecrosis, osteopenia and osteoporosis, and skin rash [36]. Additional oral side effects, including xerostomia, stomatitis and oral ulceration, perioral paresthesias, and bone marrow suppression are listed in Table 2. The consequences of non-adherence to a prescribed drug regimen not only include ineffective viral suppression from obtaining suboptimal levels of the drug but also (and even more critical) risk of development of viral resistance to the drug and drug class. Similar to the growing problem of antibiotic drug-resistant bacterial strains, the HIV-1 genome is prone to development of resistance mutations that decrease the effectiveness of antiretroviral drugs.

Epidemiologic evidence suggests antiretroviral drug-resistant HIV strains can be sexually transmitted [38] and are spreading across the United States. In North American cities, from 1995 to 2000, the proportion of new HIV infections that involved drug-resistant virus increased significantly. High-level resistance to one or more drugs increased from 3.4% to 12.4% of new infections and the frequency of number of resistance mutations in an individual increased from 8.0% to 22.7% [39], suggesting a need for genotype (or phenotype) testing of the patients' virus to the relevant viral genes (eg, protease and reverse transcriptase) as a way to guide future antiretroviral drug selection. Among subjects infected with drug-resistant virus, the time to viral suppression after the initiation of antiretroviral therapy is longer and the time to virologic failure is shorter [39]. Testing for resistance to drugs before therapy begins and when treatment failure arises may now be indicated even for recently infected patients. The development of new drugs will remain necessary for those patients who have failed to respond to all currently available drugs. The institution of more effective and less toxic HAART regimens will also remain necessary.

Prevention and treatment of opportunistic disease

Evidence-based guidelines for preventing exposure among HIV-infected persons to 19 opportunistic pathogens, preventing first episodes of disease by chemoprophylaxis or vaccination, and preventing disease recurrence are made available to the health care community by the United States Public Health Service and the Infectious Diseases Society of America [40]. The most recent edition includes guidance for discontinuing primary and secondary prophylaxis among persons whose CD4 cell counts have improved in response to HAART. Recommendations vary according to specific pathogen, duration of CD4 cell count increase, threshold level of CD4 cell count and, in the case of secondary prophylaxis, duration of treatment of the initial episode of disease [40]. The most common HIV-associated opportunistic disease that causes morbidity and death is *Pneumocystis carinii* pneumonia. Primary and secondary prophylaxis, generally with trimethoprim/sulfamethoxazole, is now initiated when the CD4 cell count falls below 200/μL and is discontinued when the CD4 cell count increases above 200/μL for $\geq$3 months in response to HAART [40]. In addition to trimethoprim/sulfamethoxazole, other drugs

used to prevent opportunistic infections that have the potential to suppress the bone marrow and reduce elements of the complete blood count include cidofovir, dapsone, ganciclovir, pyrimethamine, rifabutin, and sulfadiazine [40].

Hepatitis viral coinfections are important to recognize among HIV-infected adults. Hepatitis C virus (HCV) infection is an increasing concern because many patients are infected with both HIV and HCV [41]. The CDC recommends that all HIV-infected patients be screened for HCV because certain populations, especially injecting-drug users and hemophiliacs, are at increased risk for HCV infection and HCV-related disease and because knowledge of HCV status is critical for management of all HIV-infected patients, particularly to interpret and manage elevated liver-related tests [40]. Studies indicate that among patients in an urban United States cohort, HCV infection does not substantially alter the risk of dying, developing AIDS, or responding immunologically to HAART, especially after accounting for differences in HAART administration and effectiveness [42]. HCV viral loads and HCV-related liver disease, however, do progress more rapidly in HIV/HCV coinfected patients than in patients infected with HCV alone [43,44]. The dental care team should be alert to the potential for altered drug metabolism and coagulopathies associated with liver failure.

Tuberculosis, the most common infectious disease in the world, is an important problem among HIV-infected adults in the United States, particularly among drug users and indigent patients [45]. In developed countries, introduction of HAART and changes in CD4 cell counts have lead to marked decreases in tuberculosis incidence [46]. Tuberculin skin tests (purified protein derivative by the Mantoux method) are recommended for all HIV-infected patients at initial HIV diagnosis and annually for those with increased likelihood of exposure to *Mycobacterium tuberculosis* [40], although anergy testing to detect false negative skin tests is no longer recommended [47]. An HIV-infected patient with a positive skin test, read as induration of $\geq$5 mm, should undergo chest radiography and clinical evaluation to rule out active tuberculosis and should subsequently undergo 9 months of treatment for latent tuberculosis if no treatment had previously been completed [40]. The dental care provider should maintain a heightened awareness for the cardinal clinical signs of tuberculosis, including fatigue, weight loss, coughing up blood, low-grade fever, and night sweats, and should refer a worrisome patient to a primary care physician or infectious disease specialist for evaluation.

HIV-associated oral mucosal lesions and periodontal disease

Oral manifestations of HIV have been important in identification of patients harboring the HIV virus and in predicting the decline in their immune system. Several consensus classification schemes for HIV-associated oral lesions in adults [48,49] and children [50] have been developed to help

the provider identify and diagnose these lesions and to track HIV oral disease findings around the globe. Oral candidiasis and oral hairy leukoplakia appear to be the first and second most common oral opportunistic infections associated with HIV [51]. Other HIV-associated infections and manifestations include linear gingival erythema, necrotizing ulcerative gingivitis, periodontitis or stomatitis, herpes simplex virus ulcers, cytomegalovirus ulcers, major aphthous ulcers, oral warts, Kaposi's sarcoma, non-Hodgkin's lymphoma, and HIV salivary gland disease [52].

Oral candidiasis most often results from *Candida albicans* infection and clinically presents either as the pseudomembraneous variant (Fig. 1), described as white or yellow spots or plaques that may be located in any part of the oral cavity and can be wiped off to reveal an erythematous surface that may bleed, or the erythematous variant, described as red areas usually located on the palate and dorsum of the tongue but occasionally located on the buccal mucosa [49]. Hairy leukoplakia (Fig. 2), caused by the Epstein–Barr virus, is presumptively diagnosed by clinical appearance as asymptomatic, nonremovable, flat or vertically correlated bilateral whitish/gray lesions on the lateral margins of the tongue [49]. Oral candidiasis and oral hairy leukoplakia have been associated with immune suppression (as measured by reduced CD4 cell counts) and viremia (as measured by high HIV RNA quantity in plasma) [53–55]. These lesions have also been shown to predict progression to AIDS, even independently of CD4 cell count [56,57].

A recent systematic review of the scientific literature showed that nystatin, clotrimazole, itraconazole, ketaconazole, and fluconazole are effective in treating oral candidiasis in HIV-positive populations [58]. Infectious disease experts have suggested a protocol to reduce the development of azole-resistant *Candida* strains and emergence of less susceptible non-*albicans* strains [59].

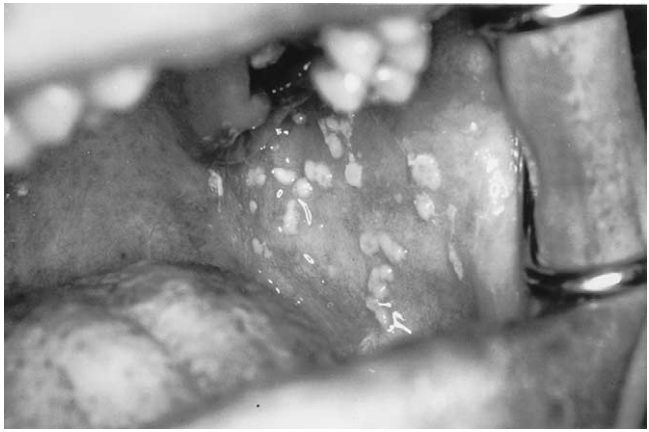

Fig. 1. Oral pseudomembraneous candidiasis of left buccal mucosa in a 34-year-old white man with AIDS.

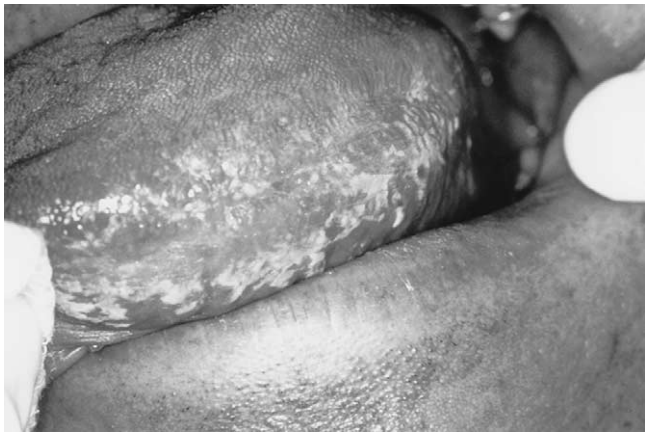

Fig. 2. Oral hairy leukoplakia of the left lateral border of the tongue in a 32-year-old white man with AIDS.

Topical antifungals should be considered first-line candidates for treatment of initial or recurrent cases of oropharyngeal candidiasis in HIV-infected patients, provided there is no esophageal involvement, the patients' CD4 cell counts are $>50/\mu L$, and the patients are currently receiving or expected to receive HAART [60]. For episodes of oropharyngeal candidiasis with concurrent esophageal involvement or where patients have a CD4 cell count of $<50/\mu L$, are not receiving or anticipating HAART, and have a high viral load, the algorithm suggests a systemic oral azole such as fluconazole as the more appropriate treatment choice [60]. Management of oral candidiasis and other HIV-associated oral diseases is covered in Table 3.

Gender differences in oral disease prevalence have been recognized and may become more important as HIV infection incidence increases among women. The most common oral lesion among women is oral candidiasis, with oral hairy leukoplakia and Kaposi's sarcoma being relatively uncommon [61]. Two large multicenter longitudinal cohorts of HIV-positive and HIV-negative at-risk women have been established in the United States. Each cohort, the HIV Epidemiology Research Study [62] and the Women's Interagency HIV Study [63], showed a similar prevalence among the HIV-positive group of candidiasis (14%–15%), hairy leukoplakia (6%–7%), ulcers (3%), warts (<1%), and Kaposi's sarcoma (<1%).

Improvements in oral health brought on presumably by HAART's restoration of immune function and reduction in viral load have been demonstrated by decreasing prevalence of the most common opportunistic oral lesions over time [64]. A retrospective review of oral lesions among 1280 HIV-infected patients seen in San Francisco between 1990 and 1999 demonstrated decreases in oral candidiasis, hairy leukoplakia, and Kaposi's sarcoma; no changes in aphthous ulcers; and increases in salivary gland disease and oral warts (up to sixfold for those on HAART) [65].

Table 3
Management of oral opportunistic disease associated with HIV/AIDS

Oral opportunistic disease	Treatment considerations	Medications	Drug dose regimen
Fungal infections			
Pseudomembranous candidiasis (thrush) or erythematous/atrophic candidiasis	Candidiasis treatment should be continued for 2–3 d after the disappearance of clinical signs (typically 10–14 d of therapy)	nystatin (Mycostatin) 200,000 U pastille	1 pastille dissolved slowly 4–5 times/d
	Topical administration is useful until CD4 cell count drops below 150–200.	nystatin (Mycostatin) 100,000 U/mL oral suspension	2–5 mL qid, rinse for 2 min and swallow
	Azole-resistant strains may develop	nystatin (Mycostatin) 100,000 U vaginal troche	Dissolve 1 troche 3–5 times/d; less cariogenic. Indicated for patients with xerostomia
		clotrimazole (Mycelex) 10 mg troche	Dissolve 1 in mouth 5 times/d
		ketoconazole (Nizoral) 200 mg	2 tablets stat, then 1 tab qd with meal
		fluconazole (Diflucan) 100 mg	2 tablets stat, then 1 tab qd with meal
		itraconazole (Sporonox) 100 mg	2 caplets after meals
Angular cheilitis		nystatin-triamcinolone acetonide (Mycologll) ointment, 1% clotrimazole ointment, 2% miconazole ointment	Apply to affected areas after meals and at bedtime
Viral infections			
Human papilloma virus [condyloma acuminatum (venereal wart)]	High recurrence rate with all forms of treatment; surgical removal.	Topical application of podophyllin resin	25% in compound tincture of benzoin weekly for up to 6 wk

Epstein–Barr virus infection [oral hairy leukoplakia]	Treatment is not necessary and instituted only upon patient's request, can be surgically removed or treated with acyclovir.		
Recurrent herpes simplex virus infection	Rapid institution of therapy will reduce lesion severity.	acyclovir (Zovirax) 200 mg valacyclovir (Valtrex) 500 mg	1–3 tablet 5 times/d for 10 d 2 caplets tid for 10 d
Varicella zoster virus infection [herpes zoster; shingles]	Involvement of ophthalmic division requires opthalmologist consultation; treatment may prevent post-herpetic neuralgia.	acyclovir (Zovirax) 800 mg famciclovir (Famvir) 125 mg	1 tablet 5 times/d for 10 d 4 tablets tid for 7 d
Cytomegalovirus infection	Referral for evaluation for systematic and ocular cytomegalovirus involvement and itravenous or oral gancyclovir.		
Bacterial infections			
Linear gingival erythema [formerly HIV-G]	Scaling of affected areas.	0.12% chlorhexidine (Peridex, Periogard)	0.5 oz bid rinse for 30 s and spit
Necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis [formerly HIV-P], and necrotizing stomatitis	Debridement and dental prophylaxis.	Irrigation with povidone-iodine (10% Betadine) 0.12% chlorhexidine (Peridex, Periogard) metronidazole (Flagyl) 250–500 mg clindamycin (Cleocin) 150 mg amoxicillin/clavulanate (Augmentin) 250 mg	 0.5 oz bid rinse and spit 1 tablet qid for 7 d 1 caplet qid for 7 d 1 tablet tid for 7 d

(*continued on next page*)

Table 3 (*continued*)

Oral opportunistic disease	Treatment considerations	Medications	Drug dose regimen
Neoplasms			
Kaposi's sarcoma	Debridement and dental prophylaxis in area of gingival involvement.	Chemotherapy: intralesional vinblastine sulfate systemic single or multiagent therapy for widespread disease	0.2–0.4 mg/mL/cm^2 of lesion
		Sclerosing therapy: 1% or 3% sodium tetradecyl sulfate	0.1–0.2 mL/cm^2 of lesion
	Radiation therapy: 1–12 d treatment		
	Surgical debulking for esthetics		
	Carbon dioxide laser excision		
Other conditions			
HIV–salivary gland disease	Chewing or sucking sugarless candy		
	Commercial artificial saliva substitutes		
	Avoid products containing caffeine and alcohol		
	Topical fluoride therapy should be considered for patients with persistent xerostomia		
		pilocarpine (Salagen) 5 mg	1 tablet tid before meals; may increase to 7.5 mg tid
Major aphthous ulcerations		fluocinonide (Lidex) ointment 0.05% mixed 50-50 with Orabase	apply coat to ulcer qid
		clobetasol proprionate (Temovate) ointment 0.05% mixed 50-50 with Orabase	apply coat to ulcer qid

	dexamethasone (Decadron) elixir 0.5 mg/5 mL	5 mL oral rinse and spit 3–4 times/d
	intralesional injection of triamcinalone acetonide 3 mg/mL	1.3 mL every third day for 12 d Use local anesthesia first.
Systemic steroids for severe cases; physician consult recommended.	prednisone 20 mg	1 tablet tid for 7 d
	dexamethasone elixir 0.5 mg/5 mL	15 mL oral rinse and swallow qid for 7 d
Physician consult recommended.	thalidomide (Thalomid) 100 mg	2 tablet bid for 5 d, then 2 tablets qd for 9 d

A nested case-control study was conducted among a cohort of HIV-seropositive patients at Grady Hospital in Atlanta, Georgia to assess rates of and risk factors for oral warts (Fig. 3). Incident cases of oral warts (prevalence 2.6%) were significantly more likely to have been diagnosed in 1999 than they were in 1997 to 1998. Multivariate analysis indicated that the risk of oral warts was associated with a decrease in HIV RNA level in the 6 months before diagnosis of oral warts, suggesting that increases in this lesion in the era of HAART may, in part, be related to immune reconstitution [66].

Salivary gland dysfunction may be caused by HIV infection itself, by inflammatory processes such as CD8 lymphocyte proliferation, by a not-yet-identified (possibly herpes viral) infection of the gland, or by medication side effects and can result in xerostomia, with increased dental caries risk [67]. Among the Women's Interagency HIV Study cohort, HIV serostatus was

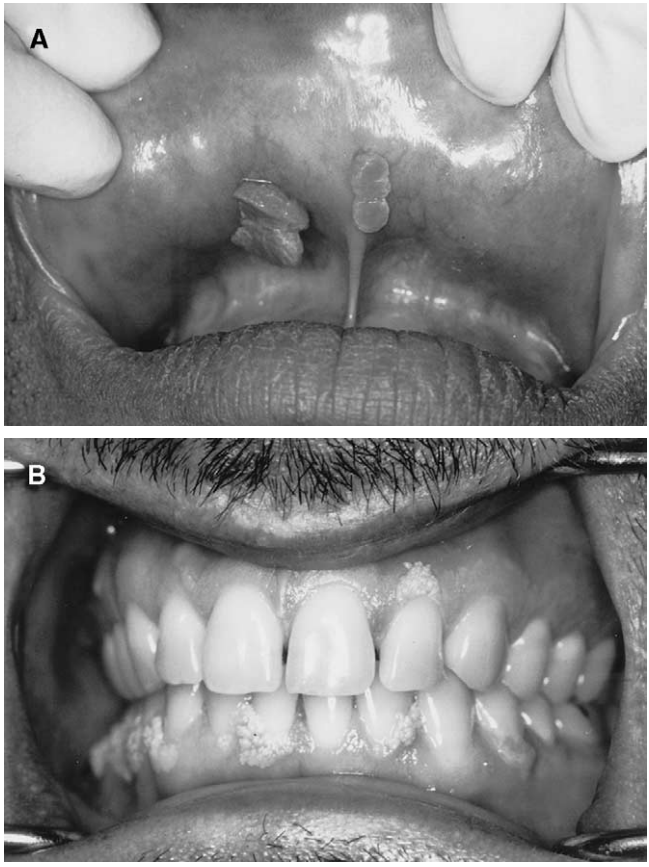

Fig. 3. (*A*) Human papilloma virus–associated condyloma acuminatum of the maxillary labial mucosa present for 3 years in an HIV-infected 36-year-old black man. (*B*) Human papilloma virus–associated gingival papillomas in an HIV-infected 31-year-old white man with a CD4 cell count of 65/μL.

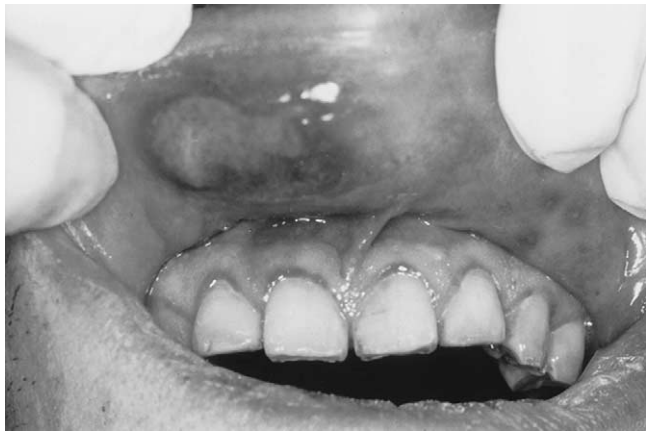

Fig. 4. Major aphthous ulcer and linear gingival erythema in a 45-year-old white man with a CD4 cell count of 10/μL.

related to salivary gland disease as assessed by glandular enlargement (4.3% of HIV seropositive), tenderness (6.9%), and absence of saliva on palpation (26.6%). For the 576 HIV-positive women, the viral load was significantly related to parotid gland enlargement and enlargement/absence of parotid saliva on palpation [68]. Treatment with HAART caused regression of HIV-associated lymphoepithelial cysts of the parotid gland with associated parotid gland swelling and facial disfigurement [69].

Gingival (Fig. 4) and periodontal diseases have been described among HIV-infected patients, both as the likely immune-mediated diseases such as linear gingival erythema and necrotizing ulcerative periodontitis and as chronic adult periodontitis. In necrotizing ulcerative periodontitis, an increasingly rare condition [64], there is usually pain, rapid loss of attachment, and tooth mobility. Exposure destruction or sequestration of bone may be seen from ulceration and necrosis, but pocketing may be minimal due to the concurrent loss of hard and soft tissues [49]. There is growing consensus that, while being classified as distinct periodontal diseases at the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions [70], these are the same diseases seen in non–HIV-infected populations, with the initiation, progression, and presentation being modified by HIV [71].

Dental treatment considerations

Regular oral health care for people with HIV should be integrated into the ongoing maintenance of their overall health and well-being. An analysis of dental claims data from HIV-infected adults served by the Minnesota Access to Dental Care Program showed that regular attenders received more diagnostic and preventive care and less restorative, endodontic, periodontic,

Table 4
Common or important potential drug interactions in delivering dental are for HIV-infected adults

Drugs for management of oral disease or procedure	Drugs for management of HIV disease or opportunistic disease	Contraindications and potential consequences of drug interactions
Meperidine	Acyclovir[a]	Increased meperdine effect
Vancomycin	Amphotericin B[a]	Nephrotoxicity
Midazolam, triazolam	Amprenavir, Saquinavir, Delaviridine, Indinavir, Lopinavir/ritonavir, Nelfinavir, Nevirapine, Ritonavir, Saquinavir, Fluconazole[a]	Contraindicated: inhibits cytochrome P450 enzymes, resulting in increased benzodiazepine levels
	Rifampin	Reduces activity of benzodiazepines
	Efavirenz	Inhibits and induces cytochrome P450 CYP3A4 enzymes, exerting a variable effect on concentrations on concurrently administered drugs that utilize this pathway
Nonsteroidal anti-inflammatory drugs, amphotericin B, aminoglycosides	Cidofovir	Nephrotoxicity
Clarithromycin	Rifabutin	Contraindicated: decreases clarithromycin 50% and increases rifabutin four-fold
	Cisapride, pimozide, terfenidine	Potentially fatal arrhythmias
	Indinavir	Increases clarithromycin levels 53%
	Delaviridine	Increases clarithromycin half-life
	Efavirenz	46% incidence rash and clarithromycin level decreases 39%
	Fluconazole[a]	Increases clarithromycin blood levels
	Rifampin	Inhibits cytochrome P450 and prolongs half-life of rifampin
	Saquinavir	Blood levels of both drugs increase: clarithromycin 45% and saquinavir 177%
	Ritonavir	Increases blood levels of clarithromycin
Opiate analgesics	Fluconazole[a]	Inhibits cytochrome P450 enzymes, resulting in increased opiate levels
Fluconazole	Atovaquone, warfarin, saquinavir, phenytoin, oral hypoglycemics, rifabutin, cyclosporine	Inhibits cytochrome P450 enzymes, resulting in increased levels of atovaquone, warfarin, saquinavir, phenytoin, oral hypoglycemics, rifabutin, and cyclosporine

	Cisapride	Potential life-threatening arrhythmias
	Rifampin and rifabutin	Reduces fluconazole levels, inhibits cytochrome P450, and prolongs half-life of rifabutin and rifampin
Itraconazole	Saquinavir	Increases levels of saquinavir
	Indinavir	Increases indinavir levels of 70%
	Terfenadine, cisapride, astemizole, triazolam[a], lovastatin, simvastatin, rifampin, rifabutin, phenytoin, or phenobarbital	Contraindicated
	Loratadine, cyclosporine, oral hypoglycemics, calcium channel blockers, and digoxin	Increases levels of loratadine, cyclosporine, oral hypoglycemics, calcium channel blockers and digoxin
	Carbamazepine, didanosine, and isoniazid	Decreases levels of itraconazole
	H2 blockers, omeprazole, antacids, or sulcrafate	Impairs gastric absorption of itraconazole
Ketoconazole	Isoniazid	Decreases ketoconazole effect
	Rifampin	Decreases activity of both drugs
	Terfenadine and cisapride	Potential for fatal arrhythmias
	H2 blockers, antacids, proton pump inhibitors, and nonenteric coated didanosine	Impairs gastric absorption of ketoconazole
	Nevirapine	Contraindicated
	Indinavir	Increases indinavir levels 70%
	Ritonavir	Increases blood levels of ketoconazole
	Rifampin, rifabutin	Reduces activity of ketoconazole, inhibits cytochrome P450, and prolongs half-life of rifabutin and rifampin
Metronidazole	Astemizole, terfenadine	Potential for fatal arrhythmias
	Coumadin, lithium	Increases levels of coumadin and lithium
	Alcohol, disulfiram	Mild disulfiram-like reactions (flushing, headache, nausea, vomiting, cramps, sweating)
Erythromycin, ciprofloxicin	Rifampin, rifabutin	Inhibits cytochrome P450 and prolongs half-life of rifabutin and rifampin

[a] Drug used by physicians for management of opportunistic diseases that may also be used by dentist for oral disease management; each potential interaction is listed only once in the table.

removable prosthodontic, and oral surgical treatment, with nearly the same total mean treatment cost as those who were nonregular attenders. These authors concluded that "mainstreaming people with HIV into the community oral health care system to receive ongoing primary dental health care is essential to maintaining their oral health and quality of life" [72]. As the evolving epidemiology of HIV suggests, the vast majority of known HIV-infected people in the United States are healthy, are on HAART therapy, and are thus seeking dental treatment in the community setting.

Complications from treatment, such as dry socket, postoperative pain and infection, prolonged bleeding, and delayed wound healing, occur occasionally in dental practice. They are usually minor and non–life threatening in patients without an underlying severe coagulopathy or neutropenia. Management is generally easily accomplished in outpatient settings. Limited numbers of studies are available to directly guide clinicians on the risk of postdental procedure complications [73]; however, treatment complication rates among HIV-infected adults treated in large clinic settings, even before the initiation of HAART, were low [74], and rates of risk elevating severe thrombocytopenia (<50,000 cells per cubic millimeter) and neutropenia (<500 cells per cubic millimeter) are below 1% among patients across the spectrum of HIV disease [75]. Given the significant association of thrombocytopenia and neutropenia with HIV RNA >20,000 copies per milliliter, CD4 cell counts <200/μL, and AIDS indicator illness [75], platelet and neutrophil counts are less likely to be suppressed in HIV-infected patients successfully managed on HAART. Nevertheless, antibiotic coverage has been recommended before oral surgery or periodontal procedures for the rare patient with neutrophil cell count below 500/mm^3 [76]. Recommendations for antibiotic coverage are not dependent on CD4 cell count.

When considering studies comparing dental extraction complications between HIV-positive and HIV-negative adults, a prospective study by Dodson [77] conducted in a hospital outpatient clinic between 1993 and 1996 provides the strongest design [73]. In this study sample of 76 HIV-positive and 75 HIV-negative patients, postextraction complications were of similar types (dry sockets, 3%; local infection, 3%; delayed healing, 4%–7%; and prolonged pain, 9%–12%). Overall complication rates were not significantly different by serostatus, and the complications were minor, self-limiting, and readily treated [77].

Using a case-control design, Miller and Dodson [78] demonstrated that HIV-positive patients do not have a significantly increased risk of having a serious odontogenic infection requiring inpatient management compared with HIV-negative patients. Subsequently, comparing HIV-positive and HIV-negative patients who did have serious odontogenic infections requiring admission to the hospital for management, the HIV-infected group had significantly more febrile (>38.0°C) days, more intensive care unit stays, and longer stays than control patients; however, the overall

length of hospital stay, admission temperatures, number of fascial spaces involved, percentage of patients requiring operating room care, and number of days intubated were not significantly different between groups [79].

In managing any dental patient taking systemic medications to control an underlying disease state, an awareness of drug interactions is important. Common or important potential drug interactions the dentist should recognize in caring for HIV patients are shown in Table 4 [80]. For dental practices providing oral or conscious sedation for phobic HIV-infected patients, an understanding of interactions of certain protease inhibitors with the benzodiazepines through inhibiting cytochrome P450 isoenzymes is needed. This interaction may result in a prolongation of the benzodiazepine half-life, resulting in a greater risk of respiratory depression for a given dose of the benzodiazepine.

Summary

Much has been learned about HIV disease during its first 20 years of existence in North America. The virus can now be successfully suppressed by HAART therapy, yet complete viral eradication from the body has not been demonstrated, and HIV transmissions continue to occur at an alarming rate. With support of the immune system, many HIV-infected patients will avoid oral and systemic opportunistic illnesses (or at least significantly prolong their time to onset). The number of HIV-infected patients under dental care is expected to increase in the future. Thus, dentists are fortunate that oral health care can be provided safely in the community setting for all but the very sickest of AIDS patients.

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Appendix Important events in the chronology of the HIV epidemic in the United States—first 20 years

1981—First case reports of *Pneumocystis carinii* pneumonia associated with unexplained immune deficiency in the United States [1].

1983–84—Scientists at Institute Pasteur in France and National Institutes of Health in the United States identify HIV as a blood-borne virus that causes AIDS [2].

1984—Oral hairy leukoplakia, later to be recognized as an oral marker of symptomatic HIV infection and immune suppression, was first identified among gay men in San Francisco [3,4].

1985—US Food and Drug Administration (FDA) approves the first HIV antibody test. Blood products begin to be tested for HIV in the United States.

1987—AZT [zidovudine (Retrovir), Glaxo Smith Kline, Research Triangle Park, NC] becomes the first anti-HIV (antiretroviral) drug approved by the FDA.

1992—Centers for Disease Control and Prevention (CDC) scientists report first and only dentist-to-patient HIV transmission [5]. Kimberly Bergalis, who apparently got HIV from her HIV-infected dentist Dr. David Acer, unsuccessfully petitions the US Congress to force health care workers to be tested for HIV. First clinical trial of combination antiretroviral drug therapy is held.

1993—CDC adult and adolescent AIDS case definition expanded to include immune suppression ($CD4^+$ T-lymphocyte cell counts of less than 200 μL or a $CD4^+$ percentage of less than 14) and additional opportunistic infections [6]. AIDS becomes the most common cause of death for males aged 25 to 44 years in the United States [7].

1995—FDA approves the first HIV protease inhibitor class drug, saquinavir [(Invirase), Hoffman-LaRoche, Inc., Nutley, NJ].

1995–96—Introduction of HIV viral load measurement tests allow better monitoring of combination drug therapy. Known as highly affective antiretroviral therapy (HAART), multiple classes of drugs used in combination produce significant improvement in immune status by reducing HIV viral replication.

1996—CDC reports annual AIDS deaths dropped in the United States for the first time [8].

1997—CDC reports the first case of probable HIV transmission through ''deep kissing'' or oral sex in the presence of periodontal disease [9].

1998–99—Failures of HAART are attributed to developing HIV drug-resistance patterns.