

# Epidemiology, pathogenesis, and management of human immunodeficiency virus infection in patients with periodontal disease

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According to the U.S. Centers for Disease Control and Prevention, over 1,000,000 people are living with human immunodeficiency virus (HIV) infection in the U.S.A., and an estimated additional 40,000 people are becoming infected annually (12). A significant decrease in the mortality of HIV-infected patients has occurred because of the advent of combination antiretroviral therapy. The improved management of HIV-infected patients has resulted in a decrease in some HIV-associated diseases, but the dramatic increase in the life expectancy of HIV-infected patients has increased the probability of developing chronic diseases, such as chronic periodontitis.

In this review, we will focus on the epidemiology, pathogenesis, and medical management of HIV-infected patients. In addition, we will review the epidemiology, pathogenesis, and management of periodontal diseases associated with HIV infection, with a special emphasis on chronic periodontitis in HIV-infected patients.

## Epidemiology

HIV is transmitted by sexual contact, by contact with infected blood or with blood-containing bodily fluids, and by infected mothers to infants (intrapartum, perinatally or peripartum through breast milk). Oral sex is a less efficient mode of transmission than receptive intercourse, but there have been several reports of documented HIV transmissions (111). Although HIV can be isolated from saliva in a small

proportion of infected individuals, usually at low titers, there is no convincing evidence that saliva can transmit HIV infection. Additionally, saliva contains antiviral factors, such as HIV-specific immunoglobulins, mucins, and thrombospondin-1 (118, 119).

Cofactors for sexual transmission of HIV, such as genital ulcer disease and lack of circumcision, have been identified (42, 43, 106). The level of viral load in the blood of the source patient appears to be the key determinant of transmission risk in needle stick injuries, and similar associations have been shown for mother-to-child transmission and sexual transmission. Virulence differences between HIV strains, and innate resistance to infection by host cells, may also be important factors.

The worldwide pandemic of acquired immunodeficiency syndrome (AIDS) is caused by infection with HIV-1. A distantly related lentivirus, HIV-2, is the cause of an AIDS-like illness, but is less easily transmitted and largely restricted to populations in western Africa and Brazil. Classifying HIV-1 strains into genetically grouped subtypes has revealed distinctly different patterns around the world. The Major (M) group of HIV-1 comprises eight subtypes (clades) – designated A, B, C, D, F, G, H, and J – and four circulating recombinant forms. B is the dominant clade found in the U.S.A. and western Europe, but is rarely seen in sub-Saharan Africa or Southeast Asia where clades A and C or E predominate. There is speculation that these subtype differences account for some of the distinctive features of the HIV epidemics in these regions.

Since the first case descriptions of AIDS, and the identification of the causal role of HIV, 20 million people have died from HIV, and an estimated 38 million people are currently living with HIV infection (133). Sub-Saharan Africa continues to have the largest number of infected individuals and the highest seroprevalence rates. Recently recognized, but rapidly growing, epidemics in the former Soviet Union, China and India are a great cause for concern because the population density of the latter two countries is so high. One statistic that crystallizes the drastic impact of the global AIDS epidemic is the estimate that 14 million children have lost one or both parents to this disease.

In the U.S.A., there have been two distinct epidemics of HIV infection. One has been concentrated among men who have sex with men, and the other among injection drug users, their heterosexual partners and children. Over the past decade, the fastest growth in HIV infection has occurred among this latter group, especially impacting black and Latino women (22). In the past 2 years, another trend has appeared as a result of young men who have sex with men returning to high-risk sexual activity and acquiring both HIV and other sexually transmitted diseases at an increased rate (60).

## Pathogenesis of HIV infection

The HIV virus is a member of the Retrovirus family. It is a single-stranded ribonucleic acid virus with an icosahedral nucleocapsid and a lipid envelope. The virion has two identical copies of ribonucleic acid and carries a reverse transcriptase. The HIV genome consists of three major (*Gag*, *Pol*, *Env*) and six accessory (*Tat*, *Rev*, *Nef*, *Vif*, *Vpr*, *Vpu*) genes. *Gag* codes for internal structural proteins; *Pol* codes for the major enzymes reverse transcriptase, protease, and integrase; and *Env* codes for the gp120 envelope glycoprotein and the gp41 transmembrane protein.

Replication of HIV begins with the binding of gp120 protein to the CD4 molecule, the receptor on the host's T lymphocytes. In order for HIV-1 to fuse to and enter its target cell efficiently, it must also bind to a coreceptor. The two major coreceptors for HIV-1 are the chemokine receptors, CCR5 and CXCR4. Strains of HIV that utilize CCR5 as a coreceptor are referred to as R5 viruses, and strains that utilize CXCR4 as a coreceptor as referred to as X4 viruses. R5 viruses readily infect macrophages and predominate during the early stages of HIV disease, whereas the syncytium-inducing X4 variants tend to emerge dur-

ing a later stage of infection and are associated with increased cytopathogenicity and more rapid T-cell depletion (17, 18, 107).

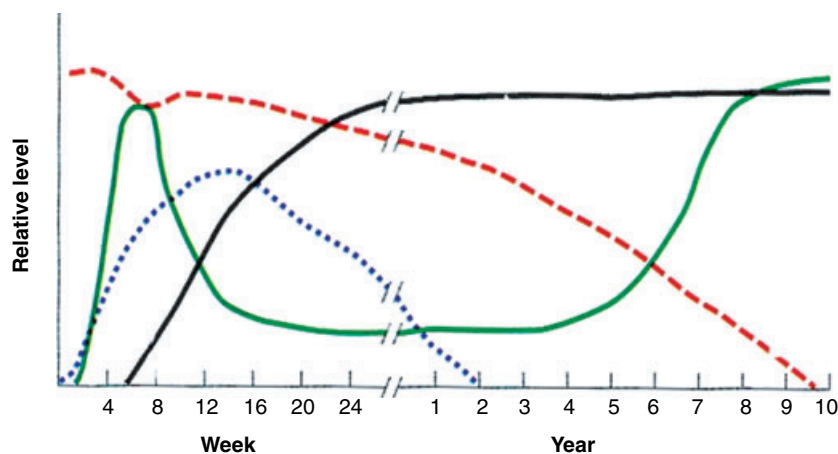
Following binding, the conformation of the HIV viral envelope changes and fusion with the host cell membrane occurs, allowing the HIV genomic ribonucleic acid to be internalized into the target cell. The reverse transcriptase enzyme then catalyzes the reverse transcription of the genomic ribonucleic acid into double-stranded DNA. The DNA translocates into the nucleus, where it is integrated into the host chromosome through another virally encoded enzyme, integrase. This provirus remains latent in the host genome until the host cell is activated. Once activated, the integrated proviral DNA is transcribed into genomic ribonucleic acid and messenger ribonucleic acid, which is translated into essential proteins and enzymes. The viral particle is formed by the assembly of HIV proteins, enzymes, and genomic ribonucleic acid at the cell membrane. The virally encoded protease cleaves the gag-pol precursor to yield the mature virion, which buds off the host cell membrane.

During vaginal or anal intercourse, HIV-1 infects and binds to Langerhan's and dendritic cells and then travels to lymph nodes, where viral replication takes place and infection of CD4 cells occurs. In general, dendritic cells are transporters of HIV and do not primarily support HIV replication. After injection of the virus into blood, HIV-1 is likely to infect dendritic and other monocyte/macrophage lineage cells. Macrophages are persistently infected with HIV and are probably major reservoirs of infection.

Continuous replication of virus occurs in the lymph nodes, with release of virus and infected T cells into the blood. CD4 depletion occurs as a result of HIV-induced cytolysis, cytotoxic T-cell immune cytolysis, or chronic activation in response to the large HIV antigen challenge. HIV-associated cytopathic effects include direct mechanisms, such as the accumulation of unintegrated reverse-transcribed viral DNA, and indirect mechanisms, such as increased plasma membrane permeability, syncytium formation, and induction of apoptosis (16).

## Natural history of HIV infection

HIV disease is a chronic, progressive process with a variable period of clinical latency but no microbial latency. Although HIV may be difficult to recover by culture, during much of this time sensitive assays for HIV nucleic acid have shown that virtually all



**Fig. 1.** Human immunodeficiency virus (HIV) viral infection dynamics. Green solid line: HIV viral load. Black line: HIV antibody. Red dotted line: CD4 count. Blue dotted line: cell-mediated immunity.

patients have evidence of active replication at all times. Levels of viremia are highest directly after infection and are then actively suppressed by a host cellular immune response after a few months (Fig. 1). A set-point is established for the concentration of HIV ribonucleic acid in plasma by 6 months, which is predictive of the subsequent course of HIV disease (78, 115).

The hallmark of HIV disease is profound immunodeficiency, resulting primarily from a progressive deficiency of a subset of T lymphocytes, the helper T cells or CD4 cells. Even during the asymptomatic stage of HIV infection, viral replication and CD4 cell destruction occurs at a high rate, resulting in the destruction of  $10^9$  CD4 cells daily and in the replacement of only 6–7% of the total CD4 cells each day (48).

Natural history studies have established a series of CD4 thresholds below which the risk of specific opportunistic infections rises greatly. This has proven to be enormously valuable in targeting diagnostic evaluations and utilization of specific prophylactic regimens. The ultimate outcome of untreated HIV disease is progression to AIDS and eventual death in nearly all patients. Better clinical care (especially prophylaxis of opportunistic infections) extends survival considerably, and combination antiretroviral therapy can reverse even severe immunodeficiency, dramatically reducing the risk of opportunistic infections and mortality.

There is substantial interpatient variability in the course of HIV disease, which remains largely unexplained. The viral load set-point accounts for most of the variability seen in the speed of HIV disease progression. ‘Long-term nonprogressors’ are a small subgroup comprising  $\approx 5\%$  of all HIV-infected individuals (identified in several natural history studies), who have had relatively normal CD4 counts and no

HIV-related disease for 10 years or longer, even without antiretroviral therapy. These patients are characterized by low levels of plasma viremia and normal immune function. Host genetic factors, such as mutations in the chemokine receptors and certain human leukocyte antigen types, have been identified in some individuals (71); however, the precise role of these recognized and unrecognized genetic factors remains unclear.

### Primary HIV infection (acute HIV infection)

In most patients the time of initial HIV infection is not known. Primary HIV infection is a transient symptomatic illness associated with high HIV replication and an expansive immunologic response (55). Signs and symptoms occur in 40–90% of new HIV-1 infections, usually present within days to weeks after the initial exposure and may last for a few days to several weeks. The most common signs and symptoms are fever, fatigue, a maculopapular rash, headache, lymphadenopathy, pharyngitis, and myalgias. Mucocutaneous ulcers, involving the buccal mucosa, gingiva, palate, and/or esophagus, with or without candidiasis, can appear in 10–20% of patients (101, 130). Severe and prolonged symptoms appear to be correlated with more rapid disease progression (28). Because the recombinant enzyme-linked immunosorbent assay, commonly used to diagnose established HIV infection, is usually negative at this stage, diagnosis depends upon HIV-1 ribonucleic acid testing. Estimates are that only 20% of patients seek care for symptoms related to primary HIV infection. Identifying a greater number of patients at the onset of infection is important for preventing further transmission, and there may be some therapeutic benefit of early antiretroviral therapy.

## Asymptomatic phase of HIV infection

This variable period, during which there is ongoing viral replication, is also characterized by progressive CD4 cell depletion. The average patient has a viral load set-point of  $\approx 30,000$  copies/ml of HIV-1 ribonucleic acid and loses 50 CD4<sup>+</sup> T cells per year. In most patients there are no symptoms of HIV infection, or its complications, for many years. There are, however, three compelling reasons for the early identification of HIV-infected, asymptomatic patients: (i) behavioral changes can lower or eliminate the risk of further transmission of HIV; (ii) prophylactic regimens to prevent life-threatening opportunistic infections can be utilized based on CD4 cell risk staging; and (iii) if antiretroviral treatment is initiated before the late stages of HIV disease, immune deterioration can be halted or reversed before complications develop.

## Early manifestations of HIV disease

There is no single pattern for the clinical course of HIV disease. Many patients report no major symptoms before an AIDS-defining event. However, there are a series of manifestations that are not HIV-specific but occur more commonly in HIV-infected patients: these include bacterial pneumonia, especially caused by *Streptococcus pneumoniae*, herpes zoster, new onset or major flares of psoriasis and seborrheic dermatitis, salmonella septicemia, and increasingly frequent or severe recurrences of anogenital herpes simplex viral disease. Most of these events are associated with moderately advanced immunodeficiency and are quickly followed by an AIDS-defining event if HIV infection is not recognized and prophylaxis initiated. Two exceptions are herpes zoster (which may precede AIDS by years) and tuberculosis. Any of these entities in an individual with a history of HIV risk behavior, or simply in an otherwise healthy young adult, should raise the possibility of HIV infection.

The absolute value of the CD4 count is the best-established surrogate marker to predict time to AIDS, risk of specific opportunistic infections, or death, especially once counts have fallen from the normal range of 800–1200 to  $\leq 300$ . The CD4 percentage alone, although more reproducible over time, is somewhat less accurate prognostically. The median time from detection of a CD4 cell count of  $< 200$  cells/ $\mu\text{l}$  to the development of an AIDS-defining diagnosis is 12–18 months in patients not receiving antiretroviral therapy (57). Combining an HIV-1 viral load

measurement with a CD4 count provides a very accurate prediction of the risk of developing AIDS in treatment-naïve patients who are starting antiretroviral therapy. For example, a 35-year-old man with a CD4 T-cell count of 300 and an HIV viral load of 300,000 copies/ml has a 4.2% chance of progression to AIDS-defining diagnosis in 6 months, compared with a 1.0% chance for a similar patient with a viral load of 3,000 copies (97).

## Clinical features of AIDS

There is a consistent group of about 12 major complicating diseases that are common among patients with advanced HIV disease. A few conditions are restricted by geographic background or HIV risk factor and therefore are not equally likely to occur in all patients. The rank order of first AIDS-defining conditions, reported by the Centers for Disease Control and Prevention, is as follows: *Pneumocystis pneumonia* (42.6%); esophageal candidiasis (15%); wasting (10.7%); Kaposi's sarcoma (10.7%); disseminated *Mycobacterium avium* infection (4.8%); *Mycobacterium tuberculosis* (4.5%); cytomegalovirus disease (3.7%); HIV-associated dementia (3.6%); recurrent bacterial pneumonia (3.0%); and toxoplasmosis (2.6%) (54).

### *Pneumocystis pneumonia*

*Pneumocystis* is a fungus that has proven difficult to propagate *in vitro*, so there is relatively little known about its biologic or epidemiologic properties. It appears to be widely distributed in nature, and antibody studies suggest most people become exposed to *Pneumocystis* during childhood (99). Recently, the taxonomy has been revised with the recognition that *Pneumocystis carinii* is actually a rodent pathogen, whereas the organism responsible for human disease has been named *Pneumocystis jirovecii*. (124) *Pneumocystis* is a prototypic opportunistic pathogen that was initially implicated in human disease in nursery outbreaks among malnourished infants in post-World War II Europe. Before AIDS, *Pneumocystis* was encountered in the U.S.A. exclusively in congenitally immunodeficient or iatrogenically immunosuppressed transplant and cancer patients. It was therefore quickly recognized as a unique occurrence when previously healthy homosexual men began to be diagnosed with this disease in the early 1980s. Most AIDS patients with *Pneumocystis pneumonia* have CD4 counts of  $< 200$ , although patients with higher counts and with symptoms such as oral thrush, fever, and weight loss, are also at high risk

(56). Re-infection, rather than re-activation, may account for some cases of *Pneumocystis* pneumonia, but secondary cases or outbreaks have not been well documented. Before the widespread use of primary *Pneumocystis* pneumonia prophylaxis and effective antiretroviral therapy, *Pneumocystis* pneumonia occurred in 70–80% of patients with AIDS, and the course of treated *Pneumocystis* pneumonia was associated with a mortality of 20–40% (8, 95).

Proliferation in the alveoli, leading to an exudative response, produces the typical disease. Hematogenous dissemination occurs in some cases, and extrapulmonary involvement at numerous sites has been reported. Fever and dry cough with slowly progressive dyspnea (often over 4 weeks) are common symptoms. Hypoxia is the most characteristic laboratory abnormality. The chest radiograph typically demonstrates diffuse, bilateral symmetrical interstitial infiltrates; however, the chest radiograph may be normal in early disease. No culture, antigen detection or serologic diagnostic procedure is available, so diagnosis rests on histologic identification of the cysts or trophozoites from bronchoalveolar fluid or induced sputum, or on direct immunofluorescent staining (8, 36).

Trimethoprim-sulfamethoxazole is the treatment of choice, because it is as effective as pentamidine isethionate with much lower toxicity. Patients with moderate-to-severe disease, as defined by an alveolar-arterial gradient of  $>35$  mmHg, or room air arterial oxygen  $pO_2$  (pressure of oxygen) of  $<70$  mmHg, should receive corticosteroids as soon as possible after starting *Pneumocystis* pneumonia therapy, in order to reduce the inflammatory response caused by lysis of organisms. The recommended duration of therapy is 21 days. Alternative regimens include intravenous pentamidine for severe disease, and dapsone + trimethoprim, or primaquine + clindamycin or atovaquone, for mild-to-moderate disease (8). Prevention of *Pneumocystis* pneumonia was one of the most important advances in care during the first decade of the AIDS epidemic. *Pneumocystis* pneumonia prophylaxis should begin when a patient's CD4 cell count is  $<200$  cells/ $\mu$ l, or after treatment of *Pneumocystis* pneumonia, and should be maintained until there is adequate immune reconstitution with effective antiretroviral therapy. Trimethoprim-sulfamethoxazole is the most effective agent and can be taken either daily or three times a week. Alternative regimens include oral dapsone and aerosolized pentamidine.

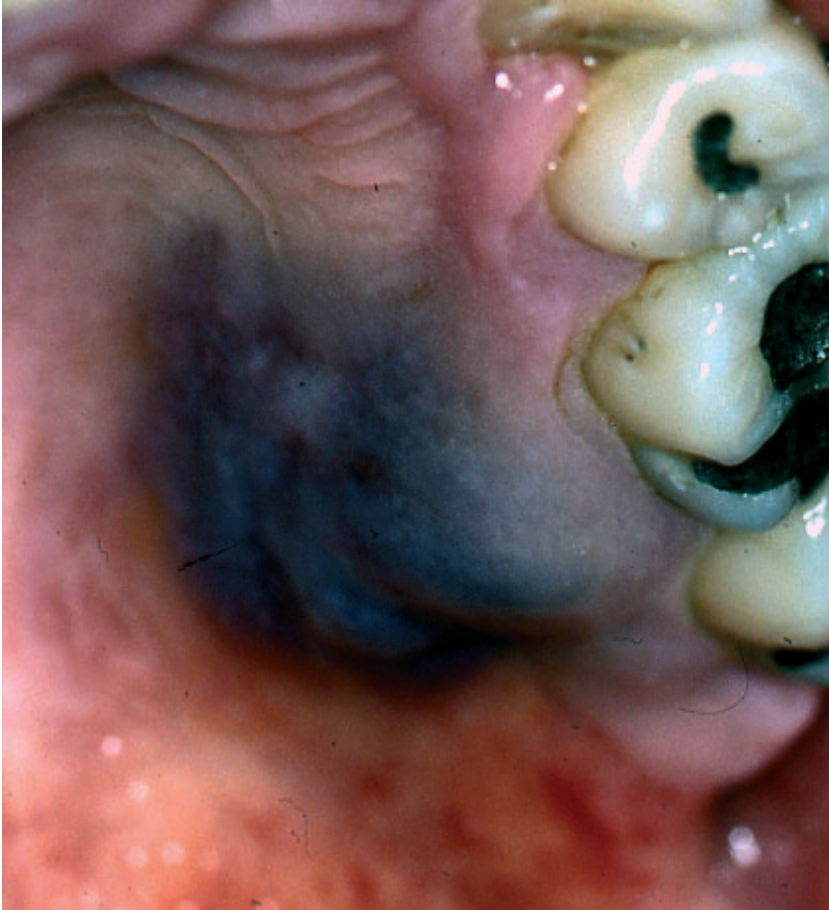
### Kaposi's sarcoma

Kaposi's sarcoma is a low-grade vascular malignancy that is associated with human herpesvirus-8, also

known as Kaposi's sarcoma-associated herpesvirus. There are four epidemiologic forms of Kaposi's sarcoma: classic; African; organ transplant-associated; and AIDS-associated. Although Kaposi's sarcoma has been reported among all risk groups for HIV infection, it is most common in homosexual or bisexual men. HIV infection may promote human herpesvirus-8 replication indirectly by impairing the immunity of the host (79), or induce tumorigenesis directly through the production of inflammatory cytokines (34). Since the introduction of potent antiretroviral therapy, the incidence of Kaposi's sarcoma has declined markedly in HIV-infected patients (68), although the prevalence of human herpesvirus-8 infection has remained relatively constant (88). The histologic features of Kaposi's sarcoma lesions are characterized by whorls of spindle-shaped cells with leukocytic infiltration and angiogenesis.

Clinical manifestations of Kaposi's sarcoma can be variable, ranging from minimal cutaneous disease to extracutaneous spread, resulting in significant morbidity and mortality. Skin lesions most commonly appear on the lower extremities, face, and genitalia, are papular with a reddish, purplish hue, and are often associated with lymphedema. Oral involvement may occur in up to 60% of patients, frequently involving the palate (Fig. 2), gingiva and dorsum of the tongue (30, 35, 104). Intra-oral lesions may be easily traumatized, resulting in bleeding, ulceration, and secondary infection (32). Gingival involvement may result in alveolar bone destruction and loss of teeth (103). Involvement of the gastrointestinal and respiratory tract, as well as of other solid organs, may also occur.

A skin biopsy confirms the diagnosis and rules out bacillary angiomatosis. Staging by tumor size, immune status, and severity of systemic illness helps to predict survival (84). There is no curative treatment for Kaposi's sarcoma, but potent antiretroviral therapy, local or systemic chemotherapy, and immunotherapy have all been utilized to palliate symptoms, shrink the tumor, and prevent disease progression. Potent antiretroviral therapy alone has been demonstrated to reduce the size of existing lesions and possibly improve survival, with or without chemotherapy (1, 49, 127), and therefore should be utilized in all patients with HIV-associated Kaposi's sarcoma. Local therapy with topical alitretinoin gel, intralesional vinblastine, external beam irradiation, laser therapy, or cryotherapy may be utilized for cosmesis or palliation in individual lesions (23). Systemic chemotherapy with liposomal anthracyclines is indicated for patients with extensive disease (37).



**Fig. 2.** Kaposi's sarcoma in the palate.

### ***M. avium* complex disease**

The atypical mycobacteria, *M. avium* and *Mycobacterium intracellulare*, are soil and water organisms widely distributed throughout the world. Because they are difficult to distinguish they are usually referred to as *M. avium* complex. *M. avium* complex is transmitted through inhalation, ingestion, or inoculation via respiratory or gastrointestinal tracts (8), whereas direct person-to-person transmission appears unlikely. HIV-infected patients with very advanced disease (a CD4 count of <50) are at risk for the development of disseminated *M. avium* complex infection.

Disseminated *M. avium* complex usually presents in an indolent, nonspecific manner with fever, weight loss, fatigue, diarrhea, abdominal pain, and anemia. A characteristic syndrome with hepatosplenomegaly reflects massive infiltration of the reticuloendothelial viscera by *M. avium* complex. Skin, lungs, and brain are rarely major sites of involvement. Biopsy and acid-fast staining of affected organs is a reliable means of diagnosis, but blood culture on appropriate media is usually sufficient because there is high-level mycobacteremia in most patients.

As *M. avium* complex organisms are resistant to standard antimycobacterial drugs. The macrolides clarithromycin and azithromycin are the main therapeutic agents, with the addition of at least one agent, usually ethambutol, to prevent resistance (8). As relapses are common, secondary prophylaxis should be continued until there is significant immune reconstitution and a sustained (>6 months) increase in CD4 cell counts to >100 cells/ $\mu$ l. An immune reconstitution inflammatory syndrome, characterized by lymphadenitis and fever without mycobacteremia, has been described among patients with subclinical or established *M. avium* complex disease who begin antiretroviral therapy, similarly to the paradoxical reactions observed with tuberculosis (98). This syndrome may be benign and self-limited, or severe and require systemic anti-inflammatory medications.

### ***M. tuberculosis* disease**

The World Health Organization estimates that tuberculosis is the cause of death in 11% of all AIDS patients (29). Primary infection, re-activation of latent tuberculosis infection, and re-infection with

new strains are all important contributors to the high rate of tuberculosis in HIV patients. HIV-infected persons with a positive tuberculin skin test have a 7–10% annual risk of developing active tuberculosis compared with a 5–10% lifetime risk in an HIV-uninfected person. Patients with tuberculosis also have a higher HIV viral load and a more rapid progression of their HIV disease than comparable patients not infected with tuberculosis (8, 134).

Tuberculosis can occur in HIV patients regardless of the CD4 count, but the frequency and severity rise, and the manifestations change, as the CD4 count falls. Lacking effective cell-mediated immunity, patients with advanced HIV disease experience re-activation of dormant tuberculosis infection at a high rate, but do not develop the immune responses that produce the characteristic lung cavities and productive sputum seen in HIV-uninfected patients. The majority of patients have pulmonary diseases with upper lobe infiltrates, with or without cavitation, and a productive cough with a sputum smear positive for acid-fast rods. However, at CD4 T-cell counts of <50 cells/ $\mu$ l, extrapulmonary disease (pleuritis, pericarditis, and meningitis) is common.

In HIV-infected patients, tuberculosis infection is defined by a tuberculin skin test of  $\geq 5$  mm, but patients with more severe immunodeficiency are often anergic. Sputum samples for acid-fast rods smear and culture should be obtained from patients with pulmonary symptoms, but needle aspirates and tissue biopsies may be necessary for diagnosis of extrapulmonary tuberculosis. Among HIV-infected patients with relatively intact immune function, the yield of sputum smear and culture is similar to that of HIV-uninfected patients (121). Nucleic acid amplification tests are helpful in providing rapid identification of tuberculosis, if positive, but false negatives may occur (140).

For sensitive isolates, standard therapy appears to work as well as in HIV-negative patients. Combination therapy, directly observed therapy, and intermittent dosing (twice or thrice weekly) are strategies often employed to provide effective therapy, to prevent acquired drug resistance during therapy, and to maintain a relatively short duration of therapy (6–9 months) (8). Treatment for drug-susceptible tuberculosis in HIV-infected adults should include an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months (8). Drug-resistant tuberculosis epidemics have been centered in AIDS treatment facilities in several countries and are characterized by very high early mortality rates.

Therapy for possibly resistant tuberculosis is best guided by sensitivity testing. Strict adherence to isolation protocols is vital in avoiding nosocomial infection.

There are significant drug interactions between rifamycins and commonly used antiretrovirals (protease inhibitors and nonnucleoside analog reverse transcriptase inhibitors), requiring adjustments in both regimens if concurrent treatment is started. The optimal time for initiating antiretroviral therapy during tuberculosis therapy is unknown and is an area of active study. Early initiation of antiretroviral therapy might decrease HIV disease progression, but is associated with a relatively higher incidence of side-effects and deterioration of tuberculosis; this is termed a paradoxical reaction, which is presumed to develop as a consequence of immune reconstitution (11).

### Cytomegalovirus disease

Cytomegalovirus is a double-stranded DNA virus in the herpesvirus family, which establishes a latent infection with intermittent asymptomatic shedding and is commonly acquired through sexual or other exposure to infectious oral or urogenital secretions. About half of normal adults are seropositive. Along with disseminated *M. avium* complex, cytomegalovirus syndromes occur in patients with advanced stages of HIV disease who are either not receiving, or have failed to respond to, antiretroviral therapy. The majority of infections derive from re-activation of a latent infection.

Cytomegalovirus disseminates throughout the body and persists in a proviral state and therefore re-activation can occur anywhere. Loss of cellular immune control allows replication of the latent virus. A complex interaction between the virus and host appears to contribute to the distinct patterns of cytomegalovirus disease that are associated with different types of immunodeficiency. For instance, cytomegalovirus pneumonia is common in organ transplant patients, but not in AIDS patients where retinitis and gastrointestinal tract involvement are most common. Cytomegalovirus hepatitis is especially common in liver transplant recipients. Retinitis with visual impairment and eventual blindness is the major cytomegalovirus morbidity in AIDS patients (4). The gastrointestinal tract can be involved at any site: manifestations include oral and esophageal ulcers, gastritis and enteritis; and colitis and intestinal perforation (25). Increasingly, central nervous system cytomegalovirus disease is recognized in the form of polyradiculopathy, encephalitis, and ventriculitis (62).

Cytomegalovirus viremia, which generally accompanies end-organ disease, can be diagnosed by polymerase chain reaction, antigen assays, or blood cultures (8). Cytomegalovirus retinitis is diagnosed by the characteristic pattern of hemorrhage and exudate on ocular fundus examination. Diagnosis of cytomegalovirus colitis or pneumonitis may require biopsy confirmation because secretions are often positive as a result of asymptomatic shedding of cytomegalovirus in AIDS and other immunocompromised patients (25, 110).

Ganciclovir, valganciclovir, foscarnet, and cidofovir have all been approved for the treatment of cytomegalovirus disease in AIDS. Valganciclovir is the only oral formulation, and all have substantial toxicity potential. Cytomegalovirus retinitis can be treated with oral valganciclovir, intravenous ganciclovir, foscarnet or cidofovir, and ganciclovir intraocular implants, depending upon the location and severity of the lesions (8). Cytomegalovirus colitis or esophagitis can be treated with intravenous ganciclovir or foscarnet for 3–4 weeks. After induction therapy, chronic maintenance is necessary until there is significant immune reconstitution with antiretroviral therapy. Primary prophylaxis has not been routinely used because of the toxicity and expense of the agents, although pre-emptive therapy in patients with cytomegalovirus viremia, and no evidence of organ system disease, is currently under study.

### Toxoplasmosis

*Toxoplasma gondii* is a protozoon that causes disease when there is a re-activation of latent tissue cysts. Primary infection occurs after eating undercooked meat containing tissue cysts or as a result of ingestion of oocysts shed in cat feces. Seroprevalence rates vary substantially between different populations: 50–75% in certain European countries and 15% in the U.S.A. (8, 51, 74). Toxoplasmosis usually occurs in patients with CD4 counts of <100, with the greatest risk among patients with a CD4 count of <50.

The most common clinical presentation of *T. gondii* infection among AIDS patients is a focal encephalitis, with headache, confusion or motor weakness, and fever that progresses without treatment to seizures, stupor, and coma (8). A computerized tomography scan or magnetic resonance imaging of the brain will typically reveal multiple, contrast-enhancing lesions with edema. The typical clinical presentation, plus focal lesions on the head (as visualized by computerized tomography or magnetic resonance imaging) in an HIV-positive patient with *T. gondii* antibodies, is usually sufficient to

begin therapy. Characteristically symptomatic and radiologic improvement is evident after 1–2 weeks of treatment. Diagnostic brain biopsy may be needed if there is no response.

A combination of pyrimethamine and sulfadiazine is standard and reliably effective, but often not tolerated for long-term use. Clindamycin can substitute for sulfadiazine. Trimethoprim-sulfadiazine was also reported, in a small randomized trial, to be effective and well tolerated (132). Acute therapy should be continued for at least 6 weeks, and long-term suppression is needed until there is adequate immune reconstitution with antiretroviral therapy.

### Cryptococcal disease

*Cryptococcus neoformans* is a widely distributed soil fungus and associated with pigeon and other bird droppings. The polysaccharide capsule is antiphagocytic and a major virulence factor. Cryptococcal infection usually begins as a subclinical pulmonary infection, leading to silent hematogenous dissemination. Before the advent of antiretroviral therapy, ≈5–8% of HIV-infected patients developed disseminated cryptococcosis (80). The majority of infected patients had CD4 cell counts of <50/mm<sup>3</sup>. Re-activation of foci seeded during primary infection occurs when immunity is compromised, although unlike other opportunistic infections, cryptococcal disease can also occur in apparently normal, HIV-negative subjects.

Cryptococcosis in AIDS patients most commonly occurs as subacute meningitis. Mild headache and low-grade fever may be the only features. Classic meningeal features, such as a stiff neck and photophobia, are uncommon, as are major mental status compromise. Widespread dissemination involving the lungs, pleura, mediastinal nodes, and the skin is probably frequent but rarely recognized, because meningitis is easily confirmed and further diagnostic efforts are not made. Cerebrospinal fluid is usually only mildly abnormal, but cerebrospinal fluid cryptococcal antigen and culture are almost always positive. The serum cryptococcal antigen is usually also positive.

Intravenous amphotericin B is the mainstay of acute therapy, and the addition of 5-fluorocytosine may be helpful (8). Long-term suppression with oral fluconazole is highly effective. The use of fluconazole to prevent fungal disease in HIV-infected patients with low CD4 counts is effective at lowering the incidence of cryptococcal and candidal disease, but not mortality (100). Owing to a lack of mortality benefit and concern about fluconazole-resistant candida, routine use of this prophylactic regimen is not recommended.

## Oral manifestations of HIV

Oral manifestations of HIV were identified early in the history of the HIV epidemic. Kaposi's sarcoma, oral candidiasis, and oral hairy leukoplakia were found to be strongly associated with HIV infection and its progression to AIDS (31, 96, 116). A number of other oral lesions were subsequently identified to be associated with HIV. These included major-aphthous ulcers and necrotizing periodontal diseases. Many of the lesions caused by viruses, bacteria, and fungi in HIV-infected patients have the same appearance in the oral cavity and in other parts of the body. In the following sections, we focus some of the common oral lesions associated with HIV infection, including oral candidiasis, oral hairy leukoplakia, and major aphthous-like ulcers.

### Oral and esophageal candidiasis

Oral candidiasis is the most common oral lesion associated with HIV infection, although it is also found in patients who exhibit immunosuppression, including patients with diabetes and those receiving chemotherapy for cancer. It is also seen in conjunction with the use of broad-spectrum antibiotics. The four classical forms of candidiasis (47) found in the oral cavity are discussed below.

*Pseudomembranous candidiasis.* Pseudomembranous candidiasis ('thrush') is classically described as a white, patchy, 'curd-like' lesion that can be removed by rubbing (Fig. 3). The underlying mucosa appears

erythematous and may bleed. The lesion appears most commonly on the buccal and labial mucosa, palate, and tongue. A biopsy of the lesion typically demonstrates psoriasiform epithelial dysplasia.

*Erythematous candidiasis.* Erythematous candidiasis is characterized by mild-to-moderately intense erythematous patches (Fig. 4). Because of the presence of a number of 'red' lesions in the oral cavity, this lesion is frequently overlooked or misdiagnosed. The lesion can be distinguished from other intra-oral 'red' lesions by cytological smears. A cytological smear of this lesion, using Periodic acid-Schiff stain, reveals *Candida* hyphae. These lesions can occur anywhere but are commonly found on the dorsal surface of the tongue and palate.

*Angular cheilitis.* Angular cheilitis is characterized by fissuring at the corners of the lip and is usually found associated with other forms of intra-oral candidiasis. Differential diagnosis of this lesion includes vitamin B12 deficiency or poorly fitting dentures. A cytologic smear positive for *Candida* will confirm the diagnosis.

*Hyperplastic candidiasis.* Hyperplastic candidiasis appears as a white lesion that does not rub off. Cytologic smears of these lesions are positive for *Candida*. The key to differentiating hyperplastic candidiasis from other similar white lesions, such as oral hairy leukoplakia, is by its response to antifungal therapy.



**Fig. 3.** Pseudomembranous candidiasis characterized by the white 'curd-like' material on the buccal mucosa.



**Fig. 4. Erythematous candidiasis on the palate.**

In addition to the four forms of candidiasis listed above, linear gingival erythema is suspected to be, at least partly, caused by *Candida* infection and thus could be considered as a form of intraoral candidiasis (50). The role of *Candida* infection in periodontal diseases in HIV patients will be discussed in the section on periodontal diseases. The reported prevalence of oral candidiasis in HIV-infected patients has varied considerably between studies primarily because of differences in the populations which were studied and the criteria used for diagnosis (i.e. whether suspected lesions were smeared for *Candida*). The colonization of *Candida* is greatly influenced by factors such as oral hygiene, tobacco use, and use of antifungal medications, which vary between risk groups (76). In a cross-sectional study, Lamster et al. reported significant differences in the prevalence of candidiasis in different populations of patients with HIV infection (63). Sixteen per cent of the HIV-infected homosexual men had candidiasis compared with 46% of the HIV-infected injecting drug users. This difference in the prevalence of candidiasis between these two risk groups was not associated with CD4 cell number, but may be accounted for by the poor oral hygiene and a high percentage of smokers in the injecting drug user cohort. However, the prevalence of oral candidiasis is increased when the number of CD4<sup>+</sup> lymphocytes falls below 200 cells/mm<sup>3</sup>, regardless of the population being studied (59). The advent of effective antiretroviral therapy has resulted in a decreased prevalence of

candidiasis, although it still occurs in a significant number of patients with HIV infection (128).

The importance of intra-oral *Candida* infection in predicting the progression to AIDS, and eventual death, in HIV-infected patients has been reported (7), even when controlling for CD4 cell numbers. Because of the complex inter-relationship of the innate and acquired immune system in controlling *Candida*, the presence of *Candida* infection suggests that deficiencies may exist in both. This may help to explain the predictive value of *Candida* infection, independently of CD4 cell counts.

Oral candidiasis can be treated with topical antifungal agents, such as nystatin pastilles (200,000 units) or clotrimazole troches (10 mg), which are dissolved in the mouth five times daily. The effectiveness of these treatments is dependent upon patient compliance. The use of systemic antifungal agents, such as fluconazole (200 mg starting dose followed by 100 mg once daily), may be indicated for patients when topical treatment fails to control the infection. Patients who develop oral candidiasis while concurrently taking antifungal medication should be referred to a physician immediately.

#### **Oral hairy leukoplakia**

The lesion known as 'oral hairy leukoplakia' was initially described in the early 1980s and was shown to be strongly associated with HIV infection (46). In fact, the presence of oral hairy leukoplakia was initially considered to be pathognomonic for HIV infection;

however, oral hairy leukoplakia was found to occur in other immunosuppressed patients (126). The lesion typically presents as asymptomatic white corrugations on the lateral border of the tongue (Fig. 5). Clinically, these lesions may be confused with pseudomembranous candidiasis and hyperplastic candidiasis; however, hairy leukoplakia does not rub off and is not affected by treatment with antifungal agents. The prevalence of these lesions, as reported previously, was found to range from 9 to 25% of HIV-infected patients (31, 57, 63, 96, 116). The advent of more intensive antiviral therapy has decreased the occurrence of oral hairy leukoplakia in HIV-infected patients (58).

Diagnosis of this lesion is confirmed by biopsy, with demonstration of the presence of Epstein–Barr virus in the basal epithelial cells (21). It is thought that immunodeficiency allows activation of the Epstein–Barr virus within the oral mucosa, leading to oral hairy leukoplakia (46). Furthermore, the number of intra-epithelial Langerhan’s cells is decreased, or totally absent, in oral hairy leukoplakia (20) and their presence in patients with oral hairy leukoplakia was shown to be inversely correlated with HIV load.

Because oral hairy leukoplakia is typically asymptomatic and not associated with any significant morbidity, treatment is not usually required. If treatment is necessary for esthetic or other reasons, acyclovir has been demonstrated to cause regression of oral hairy leukoplakia (105). Although oral hairy leukoplakia itself is not associated with morbidity, the presence of oral hairy leukoplakia may indicate an increased risk for progression to AIDS. In a study prior to the advent of potent antiretroviral therapy, Greenspan et al. (46) found that 47% of the HIV-positive patients who developed oral hairy leukoplakia subsequently developed AIDS within 2 years.

### Major aphthous-like ulcers

Phelan et al. (96) described the presence of large aphthous-like oral ulcers in HIV infection. These lesions are usually > 1 cm in diameter, and are deeper and persist for longer than a typical recurrent aphthous ulcer. These ulcers tend to be painful and hinder a patient’s ability to eat. Typically, major aphthous-like ulcers occur in nonkeratinized oral mucosa, but have been found in other parts of the gastrointestinal tract, including the esophagus, rectum, and anus. Differential diagnosis of these ulcers includes ulcers caused by herpes simplex virus, varicella-zoster virus, cytomegalovirus, *M. tuberculosis*, and *M. avium-intracellulare*. The prevalence of these ulcers appears to be low (<3% in most studies) (63, 96), and they are usually associated with a low CD4 cell number. The etiology of these ulcers is unknown; however, Birek et al. (9) reported the presence of *Helicobacter pylori* in 71% of the ulcers they examined, suggesting that this bacteria may play a role in the pathogenesis of these ulcers.

Treatment with thalidomide (200 mg daily) has been shown to result in the complete healing of major aphthous-like ulcers in a majority of treated patients (53). Other treatments for these ulcers include oral prednisone and topical corticosteroids (70).

## Periodontal diseases in HIV-infected patients

### History and epidemiology

Periodontal pathology associated with the HIV-infected patient can be classified into three distinct categories: (i) linear gingival erythema;



Fig. 5. Oral hairy leukoplakia of the left lateral border of the tongue.

(ii) necrotizing ulcerative periodontal diseases, including necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis, and necrotizing ulcerative stomatitis; and (iii) enhanced progression of chronic adult periodontitis.

Initially, reports describing necrotic lesions of the periodontium and intense marginal gingival erythema in HIV-infected patients were published in the mid-1980s (41, 136, 137). These acute necrotic lesions, which involved the destruction of the underlying bone, were termed HIV-associated periodontitis (HIV-P), and a distinct type of gingival erythema, refractory to standard plaque control, was termed HIV-associated gingivitis (HIV-G) (137). However, when it was realized that these lesions can occur in non-HIV-infected patients, a new terminology was developed. The current American Academy of Periodontology terminology for HIV-G lesions is linear gingival erythema, and for HIV-P lesions is necrotizing ulcerative periodontitis (50, 61). In addition to linear gingival erythema and necrotizing ulcerative periodontitis, necrotizing ulcerative gingivitis also occurred more frequently in HIV-infected patients (63). Because of their similar clinical appearance and treatment, most studies have tended to classify necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis together as necrotizing periodontal lesions (86, 112).

Initially, the epidemiology of these HIV-associated periodontal lesions was problematic because many of the early studies failed to have appropriate control groups, and demonstrated significant selection bias (65). Furthermore, the lack of definitive diagnostic criteria for these lesions also contributed to the wide variation in their reported prevalence between studies. For example, studies reported the prevalence of linear gingival erythema as ranging from 0 to 50% (65, 73, 109, 125, 138). However, the majority of the better controlled studies reported a prevalence of linear gingival erythema to be less than 10% prior to the advent of the highly active anti-retroviral therapy (64, 114). The prevalence of necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis also varied, but most studies reported an incidence of less than 5% for these necrotizing periodontal lesions (64, 114).

Since the advent of newer, more effective, antiviral therapies, the incidence of periodontal lesions has dramatically decreased. Ceballos-Salobrena et al. (13) studied the prevalence of oral lesions in HIV-infected patients receiving highly active anti-retroviral therapy and reported the prevalence of HIV-associated periodontal and gingival lesions (necrotizing ulcerative

gingivitis/necrotizing ulcerative periodontitis/linear gingival erythema) combined to be 0.6% in their population. Other studies have not reported such dramatic decreases in HIV-associated periodontal lesions (94). However, in patients who have not received effective antiretroviral therapy, the incidence of these lesions remains elevated. This problem is particularly acute in developing countries where the lack of adequate medical and dental care, along with poor oral hygiene, has led to an increase in the prevalence of HIV-associated periodontal lesions (85).

Although the association of linear gingival erythema and necrotizing periodontal diseases with HIV infection has been well documented, the effect of HIV infection on the progression of chronic periodontal disease remains unclear. Although studies have suggested that chronic periodontal disease is more prevalent in HIV-infected patients, others have failed to find an association. An early report, before the advent of highly active anti-retroviral therapy, suggested that older HIV-infected patients with existing chronic periodontal disease have an accelerated progression of their periodontal disease (6). Since many HIV-infected patients are living to older ages because of improved antiretroviral therapies, the possibility exists that some patients with existing periodontal disease may experience accelerated periodontal attachment loss. Reports on the prevalence of chronic periodontitis in HIV-infected patients have also varied widely because of the different prevalence of periodontal disease in populations studied and the lack of a consistent definition of periodontal disease among the studies (64, 114). Because of these methodologic problems, it has been difficult to ascertain the true prevalence of moderate to severe chronic periodontitis in HIV-infected patients.

## Diagnosis and etiology of periodontal disease in HIV-positive patients

### Linear gingival erythema

Linear gingival erythema is defined as a gingival manifestation of immunosuppressed patients, which is characterized by a distinct linear erythema limited to the free gingival margin (Fig. 6) (50). The lack of response of linear gingival erythema lesions to conventional periodontal therapy, including plaque control, and root planing and scaling, is a key diagnostic feature of linear gingival erythema because it is difficult to distinguish linear gingival erythema clinically from severe gingivitis in patients with poor plaque control. It has been reported that the extent of



**Fig. 6.** Linear marginal erythema, present as distinct red banding of the lingual gingiva.

linear gingival erythema may be influenced by the use of tobacco (125).

Another key diagnostic feature of linear gingival erythema is its association with *Candida* infection. Grbic et al. (45) found that oral candidiasis was closely associated with the presence of linear gingival erythema. Other investigators subsequently demonstrated the presence of *Candida* species in linear gingival erythema lesions in addition to the typical periodontal pathogens found in patients with chronic periodontitis (10, 52, 66). The etiology of the linear gingival erythema is now thought to involve the invasion of the gingival tissue by *Candida* species in immunosuppressed patients. Gomez et al. (39) studied the histopathology of linear gingival erythema lesions in HIV-infected patients and compared them to severe gingivitis in non-HIV-infected patients. Histologic evaluation of the linear gingival erythema revealed increased numbers of polymorphonuclear leukocytes and immunoglobulin G-producing plasma cells, whereas inflammatory gingivitis in HIV-negative individuals contained predominately T cells and macrophages. Polymorphonuclear leukocytes are known to be the primary cell involved in controlling *Candida* infection after the fungus enters the tissue. It is postulated that inadequate 'priming' or activation of the polymorphonuclear leukocyte by cytokines allows *Candida* infection to persist in immunodeficient patients (66). Because of the evidence that *Candida* infection is the primary etiology of linear gingival erythema, the American Academy of Periodontology has classified linear gingival erythema as a 'gingival disease of fungal origin' (50). The presence of *Candida* within the gingival tissues can explain the inability of conventional periodontal therapy to control linear gingival erythema.

It is presently unclear whether linear gingival erythema progresses to more severe forms of periodontal disease, although it suspected that linear

gingival erythema may be a precursor to the necrotizing ulcerative periodontal diseases in HIV-infected patients. Interestingly, in a study by Patton (92), linear gingival erythema had a positive predictive value of 70% in predicting which patients would progress to having CD4<sup>+</sup> cell counts of <200. However, necrotizing ulcerative periodontal diseases had a positive predictive value of <50%. These data illustrate the importance of identifying linear gingival erythema in HIV-infected patients.

#### **Necrotizing diseases of the periodontium in HIV-infected patients**

Necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis are two related periodontal lesions that have been found in both HIV-infected and noninfected patients (Figs 7 and 8). The American Academy of Periodontology has classified them together as necrotizing periodontal diseases (86, 112). Necrotizing ulcerative gingivitis typically presents as ulceration of the interdental papilla with gingival bleeding and severe pain (112). The lesion is commonly described as having a 'punched out' appearance of the intraproximal papilla, and the affected area typically appears to be covered with a fibrinous pseudomembrane. For a diagnosis of necrotizing ulcerative gingivitis to be made, the lesion must exhibit all three signs. Necrotizing ulcerative periodontitis lesions are identical in appearance to necrotizing ulcerative gingivitis lesions, with the exception that necrotizing ulcerative periodontitis lesions extend into the alveolar bone. Patients with necrotizing ulcerative periodontitis frequently present with exposed bone, gingival recession, and tooth mobility. Other signs and symptoms of necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis may include oral malodor, lymphadenopathy, fever, and malaise; however, these findings are inconsistent. Several case reports have described the



**Fig. 7.** Necrotizing ulcerative lesion with a pseudomembrane present on the buccal gingiva between the two premolar teeth.



**Fig. 8.** Necrotizing ulcerative periodontitis on the maxillary anterior teeth, characterized by the appearance of 'punched-out' papilla and exposed intraproximal bone.

extension of necrotizing ulcerative periodontitis lesions into the adjacent maxillary and mandibular bone, leading to the osteonecrosis and sequestration of the surrounding bone (93, 135). This particular disease entity has been termed necrotizing ulcerative stomatitis.

Although necrotizing ulcerative gingivitis was seen before the advent of HIV infection, cases of necrotizing ulcerative gingivitis have been strongly associated with HIV infection. A recent study (117) evaluated the HIV serostatus of patients who presented with necrotizing ulcerative gingivitis to a dental clinic and had no

previous signs or symptoms of HIV infection. Of the patients with necrotizing ulcerative gingivitis, 69% were found to be HIV seropositive. This result indicates that patients who present with necrotizing ulcerative gingivitis should be strongly advised to have an HIV antibody test performed and that necrotizing ulcerative gingivitis may present frequently as the initial sign of HIV infection. It has also been shown that the probability of developing necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis increases with decreasing CD4<sup>+</sup> cell counts. For example, studies have shown that HIV-infected

patients with  $<200$  CD4<sup>+</sup> cells are 20.8 times more likely to have necrotizing ulcerative periodontitis than those with  $>200$  CD4<sup>+</sup> cells (102).

The relationship of necrotizing ulcerative gingivitis to necrotizing ulcerative periodontitis is unclear; however, because of their similar appearances, necrotizing ulcerative gingivitis may be a precursor to necrotizing ulcerative periodontitis (86). There is also controversy regarding whether necrotizing ulcerative gingivitis associated with HIV infection is different from necrotizing ulcerative gingivitis associated with other types of immunosuppression.

Initial studies of the microbiology of necrotizing ulcerative periodontitis lesions reported a bacterial flora similar to that found in HIV-seronegative patients with chronic periodontal disease (82, 102). However, in a more recent study, Paster et al. (91) examined the subgingival microbial profile of subjects with necrotizing ulcerative periodontitis, chronic periodontitis, and periodontally healthy subjects using polymerase chain reaction-amplified checkerboard DNA–DNA hybridization. They concluded that pathogens associated with chronic periodontitis were not associated with necrotizing ulcerative periodontitis in HIV patients. Cobb et al. (15), using electron microscopy, compared the microbiology of necrotizing ulcerative periodontitis in HIV-infected subjects with necrotizing ulcerative gingivitis lesions of HIV-negative subjects. They found that spirochetes, zones of aggregated polymorphonuclear leukocytes, and necrotic cells typically found in necrotizing ulcerative gingivitis lesions were also found in necrotizing ulcerative periodontitis lesions, suggesting that the two lesions had a similar microbiology and pathogenesis. However, candidal invasion was also present in the majority of gingival biopsies of necrotizing ulcerative periodontitis lesions in HIV-infected subjects, suggesting that *Candida* infection plays an important role in the development of HIV-associated necrotizing ulcerative periodontitis (87). Because of the presence of *Candida* in both linear gingival erythema and necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis lesions, the possibility exists that linear gingival erythema is a precursor to the development of necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis.

#### Chronic periodontitis in HIV-infected subjects

As more aggressive antiretroviral therapies have led to increased life expectancies of HIV-infected patients, the probability that these patients will develop a more aggressive form of chronic periodontitis is increased. Barr et al. (6) demonstrated that HIV-

seropositive patients  $\geq 35$  years old and with  $<200$  cells CD4 cells per mm<sup>3</sup> had significantly increased progression of periodontal disease relative to an HIV-seronegative control group. Other investigators (77, 131, 142) have confirmed the finding that HIV-positive patients may have an enhanced rate of periodontal attachment loss and that it is associated with decreased CD4<sup>+</sup> cell counts. Maticic et al. (75) demonstrated that elevated HIV viral load in serum and gingival crevice fluid was associated with increased periodontal attachment loss. Ndiaye et al. (85) studied the extent of periodontal disease in an HIV-infected population in Senegal that was not receiving antiviral or antimicrobial therapy. They found that the number of subjects with sites of  $\geq 6$  mm of attachment loss was significantly higher in an HIV-infected cohort compared to an HIV-noninfected group. The effect of HAART and more aggressive antimicrobial therapies on the rate of periodontal attachment loss is unknown. Furthermore, it should be noted that the prevalence of periodontal disease varies greatly between different risk groups (45).

#### Microbiology and host response of HIV-infected patients with chronic periodontitis

A number of studies have compared the subgingival microbiota from HIV-infected subjects with HIV-noninfected controls. A majority of the studies have demonstrated that the prevalence of periodontal pathogens appears to be similar between HIV-infected and HIV-noninfected subjects (40, 81, 129, 143). In a recent study, Alpagot et al. (2) demonstrated that sites colonized with *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans* were most likely to be found in sites with progressive periodontal disease in HIV subjects. In addition to finding the typical periodontal pathogens in HIV-infected subjects, a number of studies have demonstrated the presence of opportunistic bacteria and *Candida* species (66, 143). The role of *Candida* in the etiology of accelerated periodontal attachment loss seen in HIV patients is unknown, but several possibilities exist. *Candida* may be an opportunistic organism that plays no direct role in the pathogenesis of periodontal attachment loss in HIV-infected patients but is simply present because of a weakened host response in the periodontal pocket. However, *Candida* could potentially play a more direct role in the pathogenesis of periodontal disease by damaging the sulcular and junctional epithelium and thus allowing the entry of bacteria and fungi into the underlying gingival connective tissues. *Candida* has also been shown to elicit a significant pro-inflammatory cytokine response (27),

which could contribute to the increased periodontal attachment loss seen in HIV-infected patients. In addition to *Candida* and other fungal species, opportunistic bacteria that are rarely found in the pockets of HIV-noninfected patients have been demonstrated in HIV-infected patients (143). The role, if any, of these bacteria in the pathogenesis of chronic periodontal disease in HIV-infected patients is unknown.

The role of viruses in the pathogenesis of chronic periodontal disease in HIV-infected patients has been examined. Mardirossian et al. (72) reported the increased prevalence of human herpesviruses 6, 7, and 8 in gingival biopsies and dental plaque samples from HIV-infected subjects. Their results demonstrated that at least one of these three human herpesviruses was found in 90% of the gingival biopsies and in 62% of the plaque samples from HIV-infected subjects, whereas only 43% of the HIV-noninfected subjects demonstrated one of these three viruses. However, it is not known whether these viruses play a role in the pathogenesis of chronic periodontitis in HIV-positive subjects and/or whether the periodontium is a passive reservoir for human herpesviruses 6, 7, and 8.

The periodontium of HIV-positive patients with either gingivitis or periodontitis demonstrates a decreased CD4/CD8 ratio, similar to the ratio of CD4/CD8 seen in peripheral blood (122). In addition to altered T-cell subsets, increased levels of leukocytes have been found in the inflamed gingiva of HIV-infected patients (83). However, polymorphonuclear leukocytes from immunodeficient HIV-infected patients have been shown to be dysfunctional and were not able to phagocytose adequately and kill bacteria (67). Furthermore, Steinsvoll et al. (123) showed that serum immunoglobulin G responses to specific plaque bacteria were decreased in HIV-infected patients with immunodeficiency. These findings suggest that the immune response to periodontal pathogens is altered in HIV-infected patients, and that the inability of the host response to control periodontal pathogens effectively leads to a hyper-inflammatory response in the inflamed periodontium of HIV-infected patients.

Grbic et al. (44) found that gingival crevice fluid levels of the pro-inflammatory cytokine, interleukin- $\beta$ , were elevated in sites with  $\geq 5$  mm of probing depth in HIV-positive patients when compared with HIV-noninfected controls. Alpagot et al. (3, 129), in a 6-month longitudinal study of attachment loss in HIV-infected patients, demonstrated that sites which exhibited at least 2 mm of clinical attachment loss had significantly higher levels of interferon- $\gamma$ , neutrophil elastase, and  $\beta$ -glucuronidase. Other investi-

gators have confirmed the finding of elevated levels of pro-inflammatory cytokines in the gingival crevice fluid of HIV-infected patients (5). Therefore, the pathogenesis of chronic periodontal disease may be related to increased levels of pro-inflammatory cytokines in HIV-positive patients.

### Management of periodontal diseases in HIV-positive patients

The management of periodontal lesions in HIV-infected patients has changed little since the initial discovery of these lesions (113, 114, 137). Because the etiology of linear gingival erythema and necrotic periodontal lesions (necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis) may involve an interaction between bacteria and *Candida*, the treatment of HIV periodontal lesions involves controlling both. Initial treatment for the linear gingival erythema and necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis lesions in HIV-infected individuals involves gross scaling and root planing to remove plaque and calculus deposits, and the debridement of necrotic tissue, when present. In conjunction with root planing and scaling, subgingival irrigation, with either providone-iodine solution or 0.12% chlorhexidine rinse, should be considered for the treatment of both linear gingival erythema and necrotic periodontal lesions. Furthermore, oral rinsing with 0.12% chlorhexidine rinse, two to three times daily, should be used as an adjunctive therapy for several months. If initial treatment fails to control the lesions, the use of systemic antibiotics and/or systemic antifungals should be considered. Before starting an antifungal/antibiotic regimen, consultation with the patient's physician is warranted. If an HIV-infected patient develops linear gingival erythema or necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis while concurrently taking systemic antifungal therapy, the possibility of resistance to the antifungal agent should be discussed with the patient's physician.

Antibiotics should be used with caution owing to an increased overgrowth of *Candida albicans* and other microflora associated with HIV infection. To prevent overgrowth of opportunistic microorganisms, the concurrent use of 0.12% chlorhexidine rinses or antifungal agents, such as nystatin oral rinse or mycostatin (Myclex) troches, has been recommended. If antibiotics are necessary, narrow-spectrum antibiotics, such as metronidazole, should be considered. Metronidazole has a minimal effect on the anaerobic gram-positive bacterial flora; these bacteria help to prevent overgrowth with *Candida* (114, 137).

Following initial treatment, additional visits may be necessary to remove plaque, calculus, and other deposits and to provide strict plaque control instruction. The continued use of antimicrobial mouthrinses, such as chlorhexidine, have been shown to be an effective therapeutic aid in preventing the recurrence of linear gingival erythema and necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis (137). Although reports and controlled studies have shown this therapy to be generally effective in reducing the acute symptoms of linear gingival erythema and necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis, and in halting the progression of the necrotic lesions, the response to treatment does vary. The response to treatment is dependent on a number of factors, including the level of the patient's immunodeficiency, degree of compliance with home care instructions, and use of tobacco.

Because of the potential increased risk of periodontal disease progression, HIV-infected patients should be placed on a more frequent recall schedule and carefully monitored for the progression of periodontal attachment loss. The treatment of periodontal disease in a majority of HIV-infected patients would be similar to the treatment of HIV-noninfected patients. No significant differences in the incidence of post-scaling bacteremias were reported between HIV-infected and HIV-noninfected patients following root planing and scaling (69). Although no controlled studies on the incidence of complications following periodontal surgery in HIV-infected patients have been performed, several studies (38, 108) have found no differences in the incidence of complications and infections following extraction of teeth in HIV-infected and HIV-noninfected patients. However, another contradictory study found an increased rate of post-extraction complications in HIV-infected patients who demonstrated severe immunodeficiency (26). Therefore, an evaluation of the patient's immunocompetence should be performed before any elective oral surgery.

## Treatment of HIV

Currently, there are four classes of U.S. Food and Drug Administration-approved antiretroviral agents: (i) nucleoside and nucleotide analog reverse transcriptase inhibitors; (ii) nonnucleoside analog reverse transcriptase inhibitors; (iii) protease inhibitors; and (iv) entry (fusion) inhibitors (Table 1). Eradication of HIV cannot be achieved with currently available

antiretroviral regimens because the pool of latently infected CD4 cells is established early in the course of HIV infection and persists even with prolonged suppression of plasma viremia (14, 24, 33, 139). The goals of treatment, therefore, are to reduce HIV-related morbidity and mortality, improve the quality of life, restore and preserve immunologic function, and suppress viral load maximally and durably (24).

The nucleotide analog reverse transcriptase inhibitors were the first class of antiretrovirals developed and have activity for both HIV-1 and HIV-2. After intracellular phosphorylation, the nucleotide analog reverse transcriptase inhibitors compete for incorporation into the growing proviral DNA chain, resulting in premature termination of chain elongation. The nucleotide reverse transcriptase inhibitor, tenofovir, contains one phosphate group and therefore needs only to be diphosphorylated intracellularly. Nucleotide analog reverse transcriptase inhibitors remain the backbone of combination regimens, and several single-pill formulations of two nucleotide analog reverse transcriptase inhibitors are available [zidovudine + lamivudine (Combivir), abacavir + lamivudine (Epzicom), and tenofovir + emtricitabine (Truvada)]. Lactic acidosis/hepatic steatosis is a potentially life-threatening complication of several nucleotide analog reverse transcriptase inhibitors (especially d4T, ddI, and ZDV), which may be related to inhibition of the gamma polymerase of cellular mitochondrial DNA (19). The onset may be insidious, presenting with nonspecific gastrointestinal symptoms, such as nausea, vomiting and abdominal pain, or rapidly progressive, resulting in hepatic failure, pancreatitis, and respiratory failure. A hypersensitivity reaction is a potentially life-threatening complication of abacavir, which usually presents within the first 6 weeks after initiation, as high fever, diffuse skin rash, malaise, and abdominal pain. The primary treatment for both complications is discontinuation of the nucleotide analog reverse transcriptase inhibitors. Other adverse effects of nucleotide analog reverse transcriptase inhibitors include bone marrow suppression, peripheral neuropathy, pancreatitis, hepatotoxicity, peripheral lipoatrophy, and visceral adiposity (24).

Nonnucleoside analog reverse transcriptase inhibitors inhibit the HIV-1 reverse transcriptase by binding closely to the active site, locking it in an inactive conformation. They are not active against HIV-2. Nonnucleoside analog reverse transcriptase inhibitors are highly potent but are subject to rapid emergence of resistance because a single-step mutation can confer resistance, and often cross-

**Table 1.** Antiretrovirals

Drug	Trade name	Dose	Food restriction	Adverse effects	Drug-drug interactions
<b>Nucleoside and nucleotide reverse transcriptase inhibitors</b>					
Abacavir (ABC)	Ziagen	300 mg bid or 600 mg daily	None	Hypersensitivity reaction in 2-9%, rash, headache, nausea, vomiting	
Didanosine (DDI)	Videx EC	400 mg daily ( $\geq 60$ kg) 250 mg daily ( $< 60$ kg)	Empty stomach	Pancreatitis, peripheral neuropathy, lactic acidosis	Tenofovir
Emtricitabine (FTC)	Emtriva	200 mg daily	None	Headache, nausea, insomnia	
Lamivudine (3TC)	Epivir	300 mg daily or 150 mg bid	None	Headache, dry mouth,	
Stavudine (d4T)	Zerit	40 mg bid ( $\geq 60$ kg) 30 mg bid ( $< 60$ kg)	None	peripheral neuropathy, pancreatitis, diarrhea	
Tenofovir (TDF)	Viread	300 mg daily	None	Nausea, diarrhea, acute renal insufficiency, Fanconi syndrome	DDI
Zidovudine (AZT, ZDV)	Retrovir	300 mg bid	None	Anemia, neutropenia, nausea, vomiting, headache, myalgia, myopathy	

Table 1. Continued

Drug	Trade name	Dose	Food restriction	Adverse effects	Drug-drug interactions
<b>Nonnucleoside reverse transcriptase inhibitors</b>					
Delavirdine (DLV)	Rescriptor	400 mg tid	None	Rash, fatigue, transaminitis	Antiarrhythmics Anticonvulsants Immunosuppressants Oral contraceptives Statins Clarithromycin Fluvastatin Ketoconazole Methadone Rifampin Rifabutin Sildenafil Warfarin
Efavirenz (EFV)	Sustiva	600 mg daily (at bedtime)	Empty stomach	Rash, transaminitis, abnormal dreams, drowsiness, dizziness, hyperlipidemia	
Nevirapine (NVP)	Viramune	200 mg daily for 14 days; then 200 mg bid	None	Rash, transaminitis	

**Table 1.** Continued

Drug	Trade name	Dose	Food restriction	Adverse effects	Drug-drug interactions
<b>Protease inhibitors</b>					
Amprenavir (APV)	Agenerase	1400 mg bid		Diarrhea, nausea, vomiting, transaminitis, rash	Antiarrhythmics Anticonvulsants Antifungals corticosteroids Immunosuppressants Narcotics Neuroleptics Oral contraceptives Statins Sedative/hypnotics Clarithromycin desipramine Rifampin Rifabutin Sildenafil Theophylline
Atazanavir (ATZ)	Reyataz	400 mg daily or 300 mg + RTV 100 mg daily	With food	Hyperbilirubinemia, transaminitis, PR interval prolongation	
Fosamprenavir (f-APV)	Lexiva	1400 mg bid or 1400 mg + RTV 200 mg daily or 700 mg + RTV 100 mg bid		Diarrhea, nausea, vomiting, transaminitis, rash	
Indinavir (IDV)	Crixivan	800 mg tid 800 mg + RTV 100 mg bid	If taken with RTV no restriction	Nephrolithiasis, hyperbilirubinemia, transaminitis, taste perversion	

Table 1. Continued

Drug	Trade name	Dose	Food restriction	Adverse effects	Drug-drug interactions
Lopinavir/ ritonavir (LPV)	Kaletra	Three capsules bid	With food	Diarrhea, nausea, vomiting, dyslipidemia, transaminitis, taste perversion	
Nelfinavir (NLF)	Viracept	1250 mg bid or 750 mg tid	With food	Diarrhea, nausea, vomiting, transaminitis	
Ritonavir (RTV)	Norvir	100–400 daily or bid for pharmacologic boosting	With food	Nausea, vomiting, abdominal pain, transaminitis	
Saquinavir hard gel cap	Invirase	1000 mg + RTV 100 mg bid	With food	Nausea, vomiting, diarrhea, transaminitis, headache	
Saquinavir soft gel cap	Fortovase	1200 mg tid or 1000 mg + RTV 100 mg bid	With food	Nausea, vomiting, diarrhea, transaminitis, headache	
Tipranavir	Aptivus	500 mg + RTV 200 mg bid	With food	Nausea, vomiting, diarrhea, transaminitis, hypercholesterolemia	
<b>Entry/fusion inhibitor</b>					
Enfuvirtide (T-20)	Fuzeon	90 mg sq bid	None	Injection site reactions	

bid, twice daily; sq, subcutaneous; tid, three times daily.

resistance, to all drugs in this class. Another major issue with nonnucleoside analog reverse transcriptase inhibitors is the potential for drug interactions with other HIV agents, especially the protease inhibitors, and many non-HIV agents are metabolized by the hepatic p450 system. All nonnucleoside analog reverse transcriptase inhibitors are metabolized by the CYP3A4 enzyme of the hepatic p450 system. Additionally, nevirapine and efavirenz induce CYP3A4, and delavirdine inhibits CYP3A4, making drug interactions difficult to generalize. All the nonnucleoside analog reverse transcriptase inhibitors are associated with rash, including the Stevens-Johnson syndrome. The occurrence of a serious skin manifestation with one nonnucleoside analog reverse transcriptase inhibitor would preclude use of other drugs in this class (24). Hepatotoxicity is also common with this class, especially with nevirapine. Efavirenz is associated with central nervous system manifestations, such as drowsiness, dizziness, abnormal dreams, and rarely, hallucinations (24). These symptoms usually improve after 2–4 weeks.

Protease inhibitors are a potent class of antiretrovirals that are active against both HIV-1 and HIV-2, and inhibit the HIV protease by binding to the active site of the enzyme, preventing the cleavage of precursor polyproteins at a late stage of viral replication, resulting in the formation of noninfectious virions. Similarly to nonnucleoside analog reverse transcriptase inhibitors, protease inhibitors are metabolized by the CYP3A4 isoenzyme of the hepatic p450 system and also inhibit CYP3A4 to varying degrees. Ritonavir is one of the most potent inhibitors of CYP3A4 and is commonly used at low doses to increase the levels of other protease inhibitors. Many potential drug interactions exist between protease inhibitors and other nonnucleoside analog reverse transcriptase inhibitors and many non-HIV agents; therefore, it is prudent to check for contraindications or dose-adjustment requirements prior to prescribing a new medication. Gastrointestinal intolerance, including nausea, vomiting, and diarrhea and liver enzyme elevations, are common with protease inhibitors. The development of hyperlipidemia, including increased total cholesterol, low-density lipoprotein, and triglycerides, insulin resistance, and visceral adiposity, is also an increasingly recognized adverse effect of protease inhibitors.

Enfuvirtide is the only approved fusion inhibitor. Enfuvirtide binds to the gp41 transmembrane glycoprotein of HIV and prevents virus–cell fusion. It can only be given by subcutaneous injection and its major adverse effect is the development of injection

site reactions, which range from pruritic indurations to painful nodules. Enfuvirtide is usually reserved for salvage regimens.

Combination antiretroviral therapy has dramatically transformed the management and course of HIV infection. Suppression of viral replication results in prolongation of life, and improvement in quality of life, of the HIV-infected patient, and of reduction in the transmission of HIV (89). Therapy is recommended for all patients with symptomatic HIV disease and for asymptomatic HIV disease with CD4 cell counts of  $\leq 200$  cells/mm<sup>3</sup> (141). Antiretroviral therapy should be considered in patients with CD4 cells counts between 200 and 350/mm<sup>3</sup>. Initiation of antiretroviral therapy at this stage may decrease potentially life-threatening conditions, such as tuberculosis and lymphoma, which are more common in patients with moderately advanced immunodeficiency (141), and there is some evidence that patients treated with CD4 counts between 200 and 350/mm<sup>3</sup> had lower mortality than those treated with CD4 counts of  $< 200$ /mm<sup>3</sup> (90). Antiretroviral therapy is generally not recommended for patients with  $> 350$  cells/mm<sup>3</sup> because of significant drug toxicity and concerns about the long-term safety of antiretroviral therapy, including the development of metabolic disorders, potential cardiovascular consequences, and changes in body morphometry; however, antiretroviral therapy may be considered in patients with a high plasma viral load or a rapid decline in CD4 cell count. Although antiretroviral therapy initiated during primary HIV infection appears to have short-term immunological and virological efficacy as compared with no therapy, there is currently no evidence to suggest that therapy at this stage can alter future disease progression or reduce clinical progression compared with treatment effected at a later stage (120).

There are several initial treatment regimens that are generally preferable to others, based upon clinical trial data; however, treatment must be individualized with consideration of the patient's comorbid conditions, concomitant regimens, and ability to adhere to a treatment regimen. The nonnucleoside analog reverse transcriptase inhibitor-based regimen, recommended by the expert panel of the U.S. Department of Health and Human Services, consists of efavirenz + (zidovudine or tenofovir) + (lamivudine or emtricitabine), and the protease inhibitor-based regimen consists of lopinavir/ritonavir + zidovudine + (lamivudine or emtricitabine) (24). The recommended nonnucleoside analog reverse transcriptase inhibitor regimen has a lower pill burden

(two to three pills per day) and can be taken once daily, but has a lower genetic barrier for the development of resistance. The preferred protease inhibitor-based regimen has a higher pill burden (eight to nine pills) and is taken twice daily, has more significant metabolic complications, including dyslipidemias and insulin resistance, but has a higher genetic barrier for the development of resistance. Alternative regimens, with different side-effect profiles and including once-daily protease inhibitor-based regimens, are also considerations, especially in patients with comorbid illnesses.

Viral load reductions to below the limits of assay detection (<50 copies/ml for the Amplicor assay) in treatment-naïve patients usually occur within the first 16–24 weeks of therapy. In patients with an inadequate virologic response, adherence, drug–drug interactions, intolerance of the antiretroviral regimen, and resistance are primary considerations. HIV drug resistance is an increasing problem. Because of high viral turnover and the inherent error rate of the HIV reverse transcriptase, genetic variants of HIV are continuously produced. The survival of the resulting viral mutants depends upon the replication competence of the mutants and the selective pressures of drugs. Resistant mutations that exist before drug exposure may emerge quickly after it is introduced; therefore, drugs that develop high-level resistance with a single mutation are at highest risk.

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