



Human Immunodeficiency Virus (HIV)

Commander Richard Joralmon, DC, USN, and Captain Robert Sherman, DC, USN

Introduction

The ever-expanding HIV epidemic continues to test both the scientific and political foundations of the world community. Since 1981, the number of cumulative AIDS cases in the US has exceeded 733,374 with over 430,441 reported deaths (1). In addition, an estimated 650,000 to 900,000 individuals are infected with HIV. The purpose of this clinical update is to review and update the pathogenesis, testing, treatment modalities, and drug interactions of concern to Navy dentists when treating HIV infected patients.

Pathogenesis

HIV is a long-term progressive disease featuring immune dysfunction. AIDS is considered to be a late stage of the disease. The usual routes of transmission remain sexual contact, exposure to infected blood/blood products (IV needle sharing, occupational exposure), breast milk and perinatal transmission. The advent of sensitive detection tests has significantly reduced the risk of transfusion-associated HIV. The primary target of HIV is the CD4+ helper lymphocyte, as well as monocytes, macrophages, and nerve cells. The CD4+ cells are important components of both the humoral and cell-mediated immune system. HIV is an RNA virus containing *reverse transcriptase*, an enzyme that transcribes viral RNA into DNA. The resulting proviral DNA integrates into the host cellular genome and begins replication (2). HIV replication is accompanied by a rapid turnover of CD4+ cells; however, the rate of replenishment does not offset the rate of destruction, and immunologic decline occurs. Replication is a continual process in the body with ten billion virions existing at any given time with a plasma half-life of 6 hours (3).

Testing

The ELISA (enzyme-linked immunosorbant assay) is the primary screening test used to detect serum antibodies to HIV. A reactive ELISA is duplicated. If positive on repeat testing, it is further confirmed by the Western blot, which detects antibodies to specific HIV antigens (4). Three assays are currently available for measurement of viral load: polymerase chain reaction, branched DNA, and nucleic acid sequence-based amplification. These tests detect plasma levels of viral RNA and nucleic acids (copies/ml) (4). Viral load testing plays a role in four strategic management issues: assessing the risk of disease progression, determining when to initiate antiretroviral therapy, evaluating the effectiveness of an antiretroviral regimen and determining when a drug regimen is failing. The CD4+ cell count and HIV RNA level are usually inversely

correlated and together provide complementary information regarding viral replication and the effectiveness of therapy.

Clinical manifestations

Acute HIV infection (4-6 weeks post infection) may feature lymphadenopathy, fever, pharyngitis, oropharyngeal ulcers, constitutional complaints, GI upset, and CNS or peripheral nervous system symptoms (5). In most cases, an antibody response is usually detectable within 2 –3 months post-infection. After the acute stage, patients enter a clinical “latent” stage of variable duration. “Latency” is a misnomer however, because viral replication continues and an ever increasing number of CD4+ cells are infected and destroyed. As the disease progresses, fatigue, wasting and dementia may develop.

Opportunistic infection

When the CD4+ count falls below 400 cells/ml (normal > 1000), the risk for opportunistic infections increases dramatically. *Pneumocystis carinii*, cytomegalovirus, mycobacteria avium, histoplasmosis, coccidioidomycosis, cryptococcus meningitis, toxoplasmosis and drug resistant tuberculosis may be noted in advanced disease and may be difficult to treat (5).

Oral manifestations

Oral manifestations* are often the first sign of HIV disease and may indicate disease progression. They include fungal, viral, bacterial infections, periodontal disease, soft tissue lesions, and cancers (6). Oral manifestations may include:

- Candidiasis: pseudomembranous, erythematous, angular cheilitis
- Hairy leukoplakia (Epstein-Barr virus)
- Linear gingival erythema
- Necrotizing gingivitis (NUG)
- Necrotizing periodontitis (NUP)
- Kaposi’s sarcoma
- Oral non-Hodgkin’s lymphoma
- Aphthous Ulcers (major, herpetiform)
- Palatal and pharyngeal ulcers

Management / treatment

The advent of new antiretroviral agents has essentially transformed HIV infection into a chronic, potentially manageable disease. *Highly active antiretroviral therapy (HAART)* (7) is the practice of administering a protease inhibitor or non-nucleoside analogue in combination with two reverse transcriptase inhibitors. HAART is designed to interfere with viral replication at multiple points in the HIV lifecycle and to mini-

mize viral resistance that may occur in monotherapy. HAART is monitored by viral load assays usually 6-8 weeks after initiating therapy and every 3-6 months thereafter (7,8). Strict patient compliance to complex multi-daily dosing antiretroviral regimens is crucial for long-term virologic, immunologic, and clinical success and to minimize the development of HIV drug resistance. The goal of successful antiretroviral regimens is to reduce and maintain plasma HIV RNA levels below detectable levels of the most sensitive assays available (< 500 copies/ml) (8). HAART is initiated when the CD4+ count is less than 500 cells/ml or the initial viral load is higher than 10,000 copies per mm³ (8, 9). A threefold increase in viral load or persistent decline in CD4+ cells may indicate treatment failure. If a change in therapy is deemed necessary, the new regimen usually includes a combination of at least two new drugs (8).

Nucleoside analogue reverse transcriptase inhibitors are structurally similar to the building blocks of nucleic acids and compete with those same building blocks to act as chain terminators in the synthesis of proviral DNA.

- zidovudine (Retrovir, ZDV, AZT)
- zalcitabine (Hivid, ddC)
- didanosine (Videx, ddI)
- stavudine (Zerit, d4T)
- lamivudine (Epivir, 3TC)
- abacavir (Ziagen, ABC)

Nonnucleoside reverse transcriptase inhibitors bind directly to the enzyme reverse transcriptase and block DNA polymerase activity.

- nevirapine (Viramune)
- delavirdine (Rescriptor)
- efavirenz (Sustiva)

Protease inhibitors. HIV protease is an enzyme that cleaves large polypeptide chains into smaller functional proteins which allows maturation of the HIV virion during the final stage of the HIV life cycle. Protease inhibitors inhibit the protease enzyme, which results in the release of structurally disorganized and noninfectious viral particles.

- saquinavir (Invirase)
- ritonavir (Norvir)
- indinavir (Crixivan)
- nelfinavir (Viracept)
- amprenavir (Agenerase)

Adverse effects of these drugs may include: oral ulcerations, xerostomia, thrombocytopenia, granulocytopenia, headache, peripheral neuropathy, gastrointestinal symptoms, anemia, insomnia, rash and fatigue. Drug interactions of note to the dentist are noted in Table 1.

Table 1

HIV Drug	Interacting Drug	Effects
Zidovudine (AZT)	Acetaminophen Aspirin	Increased toxicity of AZT
Zalcitabine	Aminoglycoside	Increased peripheral neuropathy
Didanosine	Tetracycline (TCN) Ketoconazole Itraconazole	Decreased absorption of TCN Decreased effect (give 2 hrs prior)
Saquinavir	Dexamethasone Carbamazepine	Decreased effect of saquinavir
Indinavir	Ketoconazole Clarithromycin Erythromycin	Decreased effect of ketoconazole Increased toxicity of indinavir
Nelfinavir	Midazolam Triazolam	Increased sedation
Efavirenz	Midazolam Triazolam	Increased sedation

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Commander Joralmon is the Department Head, Oral Diagnosis Department, Naval Dental Center, Great Lakes. Captain Sherman is the Program Director of the oral medicine residency, Naval Postgraduate Dental School, and Navy Specialty Leader for Oral Medicine.

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* See the April 1995 Clinical Update for detailed description of HIV-associated oral lesions and their management.