Chapter 1

Overview of HIV Infection

OVERVIEW OF HIV INFECTION

Infection with Human Immunodeficiency Virus (HIV-1) leads to a chronic and, without treatment usually fatal infection characterized by progressive immunodeficiency, a long clinical latency period, and opportunistic infections. The hallmark of HIV disease is infection and viral replication within T-lymphocytes expressing the CD4 antigen (helper-inducer lymphocytes), a critical component of normal cell-mediated immunity. Qualitative defects in CD4 responsiveness and progressive depletion in CD4 cell counts increase the risk for opportunistic infections such as *Pneumocystis jirovecii (carinii)* pneumonia, and neoplasms such as lymphoma and Kaposi's sarcoma. HIV infection can also disrupt blood monocyte, tissue macrophage, and B-lymphocyte (humoral immunity) function, predisposing to infection with encapsulated bacteria. Direct attack of CD4-positive cells in the central and peripheral nervous system can cause HIV meningitis, peripheral neuropathy, and dementia.

More than 1 million people in the United States and 30 million people worldwide are infected with HIV. Without treatment, the average time from acquisition of HIV to an AIDS-defining opportunistic infection is about 10 years; survival then averages 1–2 years. There is tremendous individual variability in these time intervals, with some patients progressing from acute HIV infection to death within 1–2 years, and others not manifesting HIV-related immunosuppression for > 20 years after HIV acquisition. Antiretroviral therapy in particular and prophylaxis against opportunistic infections have markedly improved the overall prognosis of HIV disease. The approach to HIV infection is shown in Figure 1.1.

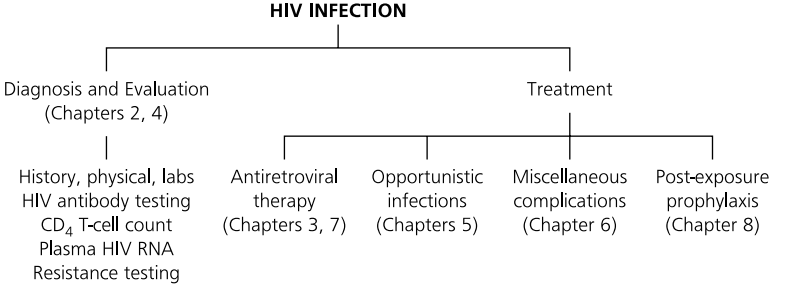

Figure 1.1. Approach to HIV Infection

STAGES OF HIV INFECTION

A. Viral Transmission. HIV infection is acquired primarily by sexual intercourse (anal, vaginal, infrequently oral), exposure to contaminated blood (through sharing of needles by injection drug users, less commonly transfusion of contaminated blood products), or maternal-fetal (perinatal) transmission. Sexual practices with the highest risk of transmission include unprotected receptive anal intercourse (especially with mucosal tearing), unprotected receptive vaginal intercourse (especially during menses), and unprotected rectal/vaginal intercourse in the presence of genital ulcers (e.g., primary syphilis, genital herpes, chancroid). Lower risk sexual practices include insertive anal/vaginal intercourse and oral-genital contact. The risk of transmission after a single encounter with an HIV source has been estimated to be 1 in 150 with needle sharing, 1 in 300 with occupational percutaneous exposure, 1 in 300–1000 with receptive anal intercourse, 1 in 500–1250 with receptive vaginal intercourse, 1 in 1000–3000 with insertive vaginal intercourse, and 1 in 3000 with insertive anal intercourse. Transmission risk increases with the number of encounters and when the source of infection has higher HIV RNA plasma levels (Lancet 2001;357:1149–53). Antiretroviral therapy reduces the risk of HIV transmission by more than 90% (N Engl J Med. 2011 Aug 11;365(6):493–505). The mode of transmission does not affect the natural history of HIV disease, though patients with active or past injection drug use may have shortened survival due to comorbid complications (AIDS 2007;21:1185–97).

B. Acute (Primary) HIV Infection (pp. 4–5). Acute HIV occurs 1–4 weeks after transmission and is accompanied by a burst of viral replication with a decline in CD4 cell count. Most patients manifest a symptomatic mononucleosis-like syndrome, which is often overlooked. Acute HIV infection is confirmed by demonstrating a high HIV RNA with either a negative HIV antibody test or a reactive ELISA with negative or indeterminate Western blot.

C. Seroconversion. Development of a positive HIV antibody test usually occurs within 4 weeks of acute infection, and invariably (with few exceptions) by 6 months.

D. Asymptomatic HIV Infection. Asymptomatic HIV lasts a variable amount of time (average 8–10 years) and is accompanied by a gradual decline in CD4 cell counts and a relatively stable HIV RNA level (sometimes referred to as the viral "set point").

E. Early Symptomatic HIV Infection. Previously referred to as "AIDS Related Complex (ARC)," findings include thrush or vaginal candidiasis (persistent, frequent, or poorly responsive to treatment), herpes zoster (recurrent episodes or involving multiple dermatomes), oral hairy leukoplakia, peripheral neuropathy, diarrhea, or constitutional symptoms (e.g., low-grade fevers, weight loss).

F. AIDS is defined by a CD4 cell count < 200/mm^3, a CD4 cell percentage of total lymphocytes < 14%, or one of several AIDS-related opportunistic infections. Common opportunistic infections include *Pneumocystis jirovecii (carinii)* pneumonia, cryptococcal meningitis, recurrent bacterial pneumonia, *Candida esophagitis*, CNS toxoplasmosis, tuberculosis, and

non-Hodgkin's lymphoma. Other AIDS indicators in HIV-infected patients include candidiasis of the bronchi, trachea, or lungs; disseminated/extrapulmonary coccidiomycosis, cryptococcosis, or histoplasmosis; chronic (> 1 month) intestinal cryptosporidiosis or isosporiasis; Kaposi's sarcoma; lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia; disseminated/extrapulmonary mycobacterial (non-tuberculous) infection; progressive multifocal leukoencephalopathy (PML); recurrent *Salmonella septicemia*; or HIV wasting syndrome.

G. Advanced HIV Disease corresponds with a CD4 cell count < 50/mm^3. Most AIDS-related deaths occur at this point. Common late stage opportunistic infections are caused by CMV disease (retinitis, colitis) or disseminated *Mycobacterium avium* complex (MAC).

ACUTE (PRIMARY) HIV INFECTION

A. Description. Acute clinical illness associated with primary acquisition of HIV, occurring 1–4 weeks after viral transmission (range: 6 days to 6 weeks). Symptoms develop in 50–90%, but are often mistaken for the flu, mononucleosis, or other nonspecific viral syndrome. More severe symptoms may correlate with a higher viral set point and more rapid HIV disease progression (J AIDS 2007;45:445–8). Even without therapy, most patients recover, reflecting development of a partially effective immune response and depletion of susceptible CD4 cells. Unfortunately, damage to the immune system through depletion of the gut-associated lymphoid tissue occurs rapidly (AIDS 2007;21:1–11) and may not be preventable even with effective ART.

B. Differential Diagnosis includes **EBV, CMV**, viral hepatitis, enteroviral infection, secondary syphilis, toxoplasmosis, HSV with erythema multiforme, drug reaction, Behçet's disease, acute lupus.

C. Signs and Symptoms usually reflect hematogenous dissemination of virus to lymphoreticular and neurologic sites (N Engl J Med 1998;339:33–9):

- Fever (97%).
- Pharyngitis (73%). Typically non-exudative (unlike EBV, which is usually exudative).
- Rash (77%). Maculopapular viral exanthem of the face and trunk is most common, but can involve the extremities, palms and soles.
- Arthralgia/myalgia (58%).
- Neurologic symptoms (12%). Headache is most common. Neuropathy, Bell's palsy, and meningoencephalitis are rare, but may predict worse outcome.
- Oral/genital ulcerations, thrush, nausea, vomiting, diarrhea, weight loss.

D. Laboratory Findings

1. **CBC.** Lymphopenia followed by lymphocytosis (common). Atypical lymphocytosis is variable, but usually low level (unlike EBV, where atypical lymphocytosis may be 20–30% or higher). Thrombocytopenia occurs in some.
2. **Elevated Transaminases** in some but not all patients.

3. **Depressed CD4 Cell Count.** Can rarely be low enough to induce opportunistic infections, most commonly PCP or mucosal candidiasis.
4. **HIV Antibody.** Usually negative, although persons with prolonged symptoms of acute HIV may have positive antibody tests if diagnosed late during the course of illness.

E. Confirming the Diagnosis of Acute HIV Infection

1. **Obtain HIV Antibody** to exclude prior disease.
2. **Order Viral Load Test** (HIV RNA PCR), preferably RT-PCR. HIV RNA confirms acute HIV infection prior to seroconversion when the HIV antibody test is concurrently negative. Most individuals will have very high HIV RNA (> 100,000 copies/mL). Be suspicious of a false-positive test if the HIV RNA is low (< 10,000 copies/mL) (J Infect Dis 2004;190:598–604). For any positive test, it is important to repeat HIV RNA and HIV antibody testing. p24 antigen can also be used to establish the diagnosis, but is less sensitive than HIV RNA PCR.
3. **Order Other Tests/Serologies if HIV RNA Test is Negative.** Order throat cultures for bacterial/viral respiratory pathogens, EBV VCA IgM/IgG, CMV IgM/IgG, HHV-6 IgM/IgG, and hepatitis serologies as appropriate to establish a diagnosis for patient's symptoms.

F. Management of Acute HIV Infection

1. **Initiate Antiretroviral Therapy.** Patients with acute HIV infection should be referred to an HIV specialist, who ideally will enroll the patient into a clinical study. Some treatment guidelines now recommend treatment for symptomatic acute HIV, although long term clinical studies comparing treatment with observation have not been conducted. As in chronic infection, once started, treatment should be continued without interruption. Regimens for treatment are similar to those outlined for chronic HIV infection (Table 3.3). Some clinicians elect to start with PI-based treatment given the higher risk of transmitted NNRTI than PI resistance.
2. **Obtain HIV Resistance Genotype** (Chapter 4) because of the possibility of transmission of antiretroviral therapy-resistant virus. Transmitted drug resistance is more easily detectable during acute HIV Infection than chronic disease, presumably because some of the transmitted drug mutations revert back to wild-type over time [J Acquir Immune Defic Syndr 2012 Oct 1; 61:258]. A genotype resistance test is preferred; therapy can be started pending results of the test. Again, because transmitted NNRTI resistance completely reduces the activity of initial NNRTI-based therapy, initial treatment with two NRTIs plus a boosted PI is preferred in this setting. If no NNRTI resistance is detected on genotype, therapy may be changed if indicated.
3. **Rationale for Treatment of Acute HIV Infection.** No prospective clinical studies have conclusively documented the benefits of therapy for acute HIV infection, although two randomized and one observational study strongly suggest benefits of early therapy [*N Engl J Med* 2013; 368:207; *N Engl J Med* 2013; 368:218; J Infect Dis. 2012 Jan 1;205(1):87.] These benefits include hastening symptom resolution, reducing viral transmission, lowering virologic "set point," reduction of the viral reservoir, and preserving both absolute and virus-specific CD4 responses. Eradication of HIV is not possible with currently available agents (Nat Med 2003;9:727–8), but should HIV cure strategies one day be feasible, it is likely that those treated during acute HIV infection will be the best candidates.