HIV, AIDS

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapter 182)

Definition

- HIV disease
  - An infectious disease caused by HIV, a human retrovirus
  - HIV disease should be viewed as a spectrum ranging from primary infection, with or without the acute syndrome, to an asymptomatic stage, to advanced disease characterized by profound immunodeficiency and susceptibility to opportunistic infections.
- AIDS
  - Late stage of infection with HIV
  - Current case definition
    - Any HIV-infected person with a CD4+ T-cell count <200/μL
    - Development of an AIDS-defining clinical condition (see Classification)

Epidemiology

- Prevalence worldwide
  - A global pandemic, with cases reported from virtually every country
  - ~38 million adults were living with HIV/AIDS as of the end of 2005.
    - Two-thirds of these adults are in sub-Saharan Africa.
    - ~50% are women.
  - ~2.3 million children <15 years are living with HIV/AIDS.
  - In 2005, there were ~5 million new cases worldwide.
  - Through 2005, the cumulative number of AIDS-related deaths worldwide exceeds 25 million.
    - HIV/AIDS is the second leading infectious cause of death worldwide.
- Prevalence in the U.S.
  - ~1 million people were living with HIV/AIDS as of the end of 2004.
- Incidence in the U.S.
  - The number of new infections per year is estimated to be ~40,000.
    - This number has remained stable for more than a decade.
  - Among persons newly diagnosed with HIV/AIDS from 2001–2004 in U.S. states with confidential name-based reporting:
    - ~71% are male.
      - The Centers for Disease Control and Prevention estimate that ~60% were infected through male-to-male sexual contact.
      - 16% through injection drug use
      - 5% through male-to-male sexual contact and injection drug use
      - 17% through heterosexual transmission
    - ~29% are female.
      - ~76% were infected through heterosexual transmission.
      - 21% through injection drug use

    - New diagnoses of HIV/AIDS
        - Decreased approximately 2% among all men and 15% among all women from 2001 to 2004
        - Increased among men who have sex with men, but decreased among men and women in other risk categories
- Distribution (U.S.)
    - Most cases of transmission by injection drug use and heterosexual transmission are reported from the Northeast and Southeast, particularly among minority groups.
    - HIV infection and AIDS have disproportionately affected minority groups in the U.S.
    - The estimated rates of AIDS diagnoses per 100,000 persons among adults and adolescents in 2004 were:
        - 72.1 for African Americans
        - 25.0 for Hispanics
        - 7.1 for whites
        - 9.9 for American Indians/Alaska Natives
        - 4.4 for Asian/Pacific Islanders

Risk Factors

- Sexual transmission
    - Homosexual and heterosexual contact with an infected person
    - In U.S.
        - 44% of new HIV/AIDS diagnoses in 2001–2004 were attributed to male-to-male sexual contact.
        - 34% of new HIV/AIDS diagnoses in 2001–2004 were attributed to heterosexual contact.
    - Worldwide
        - Heterosexual transmission is the most common mode of infection.
    - Male-to-female transmission is 8 times more efficient than female to male.
    - Receptive anal intercourse is a much more efficient mode of transmission than oral sex.
    - The presence of other sexually transmitted diseases significantly increases the risk of transmission, especially those with genital ulceration.
    - Lack of circumcision carries an increased risk of HIV infection.
    - The association of alcohol consumption and illicit drug use with unsafe sexual behavior leads to an increased risk of sexual transmission of HIV.
- Transmission by blood and blood products
    - Transmission by HIV-tainted blood transfusions, blood products, or transplanted tissue
    - Intravenous drug users
        - Exposed to HIV while sharing injection paraphernalia, such as needles, syringes, the water in which the drugs are mixed, or the cotton through which drugs are filtered
        - Does not require intravenous puncture
            - Subcutaneous (skin popping) or intramuscular (muscling) injections can transmit HIV.
- Occupational transmission of HIV (health care workers and laboratory personnel)
    - Risk of HIV transmission after skin puncture from a needle or a sharp object that was contaminated with blood from a person with documented HIV infection is ~0.3%, and after a mucous membrane exposure it is 0.09%.
    - Transmission after nonintact skin exposure has been documented.

    - The risk is estimated to be less than the risk for mucous membrane exposure.
    - Risk of transmission from an infected health care worker to patients is extremely low; in fact, too low to be measured accurately.
- Maternal-fetal/infant transmission
    - Can be transmitted intrapartum, perinatally (most commonly), or via breast milk
    - In the absence of prophylactic antiretroviral therapy to the mother during pregnancy, labor, and delivery, and to the fetus following birth, the probability of transmission of HIV from mother to infant/fetus ranges from:
        - 15–25% in industrialized countries
        - 25–35% in developing countries
- Transmission by other body fluids
    - Although the virus can be identified from virtually any body fluid, there is no evidence that HIV can be transmitted as a result of exposure to saliva, tears, sweat, or urine.
    - Transmission of HIV by a human bite can occur but is rare.

Etiology

Human retroviruses HIV-1 and HIV-2

- Family of human retroviruses (Retroviridae)
- Subfamily of lentiviruses
- RNA viruses whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase
- HIV-1 is the most common cause of AIDS worldwide.
- HIV-2 has been identified predominantly in western Africa.
    - Small numbers of cases have also been reported in Europe, South America, Canada, and the U.S.
    - Has ~40% sequence homology with HIV-1
    - More closely related to simian immunodeficiency viruses

Transmission

- See Risk Factors.
- Sexual contact: heterosexual and homosexual
- Contact with blood, blood products, or other bodily fluids (as in drug abusers who share contaminated intravenous needles)
- Intrapartum or perinatally from mother to infant or via breast milk
- Contact with HIV-infected specimens (a definite but small occupational risk of infection for health care workers and laboratory personnel)

Pathophysiology and immunopathogenesis

- Hallmark of HIV disease is a profound immunodeficiency.
- Results from a progressive deficiency of the subset of T lymphocytes (CD4+ T cells), referred to as *helper* or *inducer T cells.*
    - The CD4 molecule serves as the primary cellular receptor for HIV.
    - A co-receptor must be present with CD4 for efficient entry of HIV-1 into target cells.
    - The 2 major co-receptors for HIV-1 are CCR5 and CXCR4.
- Although the CD4+ T lymphocyte and CD4+ monocyte lineage are the principal cellular targets of HIV, virtually any cell that expresses CD4 along with one of the co-receptors can potentially be infected by HIV.

Primary infection

- After initial transmission, the virus infects CD4+ cells, probably T lymphocytes, monocytes, or bone marrow–derived dendritic cells.
- Ultimately, lymph node architecture is completely disrupted and the efficiency of trapping virions declines, leading to equilibration of the viral burden between peripheral blood cells and lymph node cells.
- Most patients undergo a viremic stage during primary infection.
    - In some, this is associated with the "acute retroviral syndrome,"a mononucleosis-like illness.
    - Virus is disseminated to lymphoid and other organs throughout the body.
    - Infection is ultimately contained partially by the development of an HIV-specific immune response and the trapping of virions in lymphoid tissue.

Establishment of chronic and persistent infection

- Despite the robust immune response following primary infection, virus is not cleared from the body.
    - Instead, a chronic infection develops that persists for a median of 10 years before the patient becomes clinically ill.
- During this period of clinical latency
    - The number of CD4+ T cells gradually decreases.
    - Few, if any, clinical findings are evident.
    - Active viral replication can almost always be detected by measurable plasma viremia and the demonstration of virus replication in lymphoid tissue.
- Level of steady-state viremia (referred to as the *viral set point*) at approximately 1 year after infection
    - Has important prognostic implications for the progression of HIV disease
    - Persons with a low viral set point at 6 months to 1 year after infection progress to AIDS more slowly than those whose set point is very high at this time.

Advanced HIV disease

- When CD4+ T-cell counts will fall below a critical level (~200/μL), patients become highly susceptible to opportunistic disease.
- Control of plasma viremia by effective antiretroviral therapy
    - Can increase survival even in persons with extremely low CD4+ T-cell counts
    - Even though CD4+ T-cell counts may not increase significantly as a result of therapy

Symptoms & Signs

Acute HIV syndrome

- 50–70% of persons with HIV infection experience an acute clinical syndrome approximately 3–6 weeks after primary infection.
- Usually persists for 1 to several weeks
- General
    - Fever
    - Pharyngitis
    - Lymphadenopathy (70% of cases)
    - Headache/retro-orbital pain
    - Arthralgias/myalgias

    - Lethargy/malaise
    - Anorexia
    - Weight loss
    - Nausea
    - Vomiting
    - Diarrhea
- Neurologic
    - Meningitis
    - Encephalitis
    - Peripheral neuropathy
    - Myelopathy
- Dermatologic
    - Erythematous maculopapular rash
    - Mucocutaneous ulceration

Asymptomatic infection

- The length of time between infection and development of disease varies, but the median is ~10 years.
- Active viral replication continues during this asymptomatic period, and CD4+ T-cell counts decrease.
- Rate of disease progression is directly correlated with plasma HIV RNA levels.

Symptomatic disease

- Symptoms can develop at any time during the course of HIV infection.
    - A spectrum of illness generally changes as the CD4+ T-cell count decreases.
    - More severe and life-threatening complications of HIV infection occur in patients with a CD4+ T-cell count <200/μL.
- Major clinical syndromes seen in the symptomatic stage of HIV infection are summarized below.
- Persistent generalized lymphadenopathy
    - Palpable adenopathy at ≥2 extrainguinal sites that persists for >3 months without explanation other than HIV infection
- Constitutional symptoms
    - Fever persisting for >1 month
    - Involuntary weight loss of >10% of baseline
    - Diarrhea for >1 month in absence of explainable cause
- Neurologic disease
    - HIV encephalopathy (AIDS dementia complex): most common
    - Opportunistic infections
    - Primary central nervous system (CNS) lymphoma
    - CNS Kaposi's sarcoma
    - Aseptic meningitis
    - Myelopathy
    - Peripheral neuropathy
    - Myopathy
- Secondary infectious diseases
    - *Pneumocystis carinii* pneumonia
    - most common opportunistic infection, occurring in ~80% of individuals during the course of their illness.
    - Cytomegalovirus (CMV) (chorioretinitis, colitis, pneumonitis, adrenalitis)

    - *Candida albicans* (oral thrush, esophagitis)
    - *Mycobacterium avium* intracellulare (localized or disseminated infection)
    - *Mycobacterium tuberculosis*
    - *Cryptococcus neoformans* (meningitis, disseminated disease)
    - *Toxoplasma gondii* (encephalitis, intracerebral mass lesion)
    - Herpes simplex virus (severe mucocutaneous lesions, esophagitis)
    - Diarrhea due to *Cryptosporidium* species or *Isospora belli*
    - Bacterial pathogens (especially in pediatric cases)
- Secondary neoplasms
    - Kaposi's sarcoma (cutaneous and visceral, more fulminant course than in non–HIV-infected patients)
    - Lymphoid neoplasms (especially B cell lymphomas of brain, marrow, GI tract)
- Organ-specific disease
    - A variety of organ-specific manifestations and complications can be seen, either as primary manifestations of the HIV infection or as complications of treatment (see Complications).

Differential Diagnosis

- Acute HIV syndrome
    - Epstein-Barr virus (mononucleosis)
    - Acute Hepatitis A or B
    - Roseola
    - Secondary syphilis
    - Cytomegalovirus
    - Toxoplasmosis
    - Other acute viral syndromes
- Symptomatic disease
    - Depends on which of many HIV complications may be causing symptoms

Diagnostic Approach

- Diagnosis of HIV infection
    - Diagnosis depends on demonstration of antibodies to HIV and/or direct detection of HIV or 1 of its components.
    - Antibodies to HIV appear 2–12 weeks after infection.
- Initial evaluation of patient with HIV infection
    - History and physical examination
    - Routine chemistry and hematology
    - CD4+ T-lymphocyte count
    - 2 plasma HIV RNA levels
    - Rapid plasma reagin test
    - Anti-*Toxoplasma* antibody titer
    - Purified protein derivative skin test
    - Mini-Mental Status Examination
    - Serologies for hepatitis A, B, and C
    - Immunization with pneumococcal polysaccharide; influenza as indicated
    - Immunization with hepatitis A and hepatitis B if seronegative
    - Counseling regarding natural history and transmission
    - Helping contact others who might be infected

- Diagnosis of AIDS
  - CD4+ T-cell count <200/μL **or**
  - AIDS-defining clinical condition(see Classification)

Laboratory Tests

Diagnosis of HIV infection

- See Figure 1 for the algorithm of serologic testing.

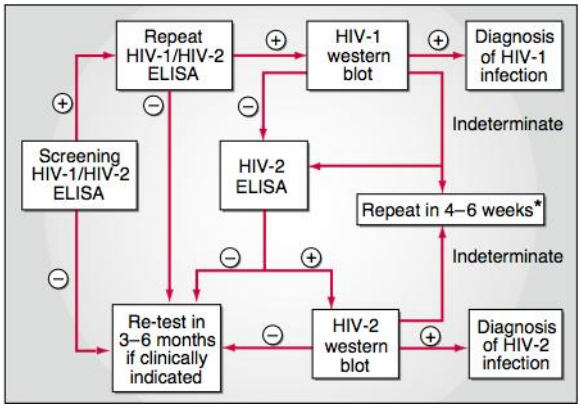

Figure 1: Algorithm for the use of serologic tests in the diagnosis of HIV-1or HIV-2 infection. *Stable indeterminate western blot 4 to 6 weeks later makes HIV infection unlikely. However, it should be repeated twice at 3-month intervals to rule out HIV infection. Alternatively, one may test for HIV-1 p24 antigen or HIV RNA.

- Enzyme immunoassay (EIA) (enzyme-linked immunosorbent assay)
  - Standard screening test for HIV infection
  - The test is highly sensitive (>99.5%).
    - Most commercial EIA kits can detect antibodies to both HIV-1 and -2.
  - Test not optimally specific, therefore confirmatory test needed
    - False-positive results can occur with:
      - Antibodies to class II antigens
      - Autoantibodies
      - Hepatic disease
      - Recent influenza vaccination
      - Acute viral infections
- Western blot
  - Most commonly used confirmatory test
  - Detects antibodies to HIV antigens of specific molecular weights
  - Antibodies to HIV begin to appear within 2 weeks of infection.
  - Period of time between initial infection and development of detectable antibodies is rarely >3 months.
- Tests for direct detection of HIV
  - These tests are useful in:
    - Patients with a positive or indeterminate EIA result and an indeterminate Western blot result **or**
    - Patients in whom serologic testing may be unreliable (such as those with hypogammaglobulinemia)

    - Immune complex dissociated p24 antigen capture assay
        - Plasma p24 antigen levels increase during the first few weeks following infection, before the appearance of anti-HIV antibodies.
    - HIV RNA by polymerase chain reaction
    - HIV RNA by branched DNA
    - HIV RNA by nucleic acid sequence-based assay

Other tests at diagnosis

- Complete blood count
- Chemistry profile
- Aminotransferase measurement
- Blood urea nitrogen and creatinine measurement
- Urinalysis
- Pap smear
- Fasting blood glucose and serum lipid measurement

Monitoring HIV infection and response to therapy

- CD4+ T-cell count
    - Generally accepted indicator of immunologic competence
    - Close relationship between the CD4+ count and clinical manifestations of AIDS
        - <200/μL: high risk of infection with *Pneumocystis carinii*
        - <50/μL: high risk for CMV disease and infection with *Mycobacterium avium intracellulare*
    - Should be measured:
        - At the time of diagnosis
        - Every 3–6 months thereafter
        - Measurements may be done more frequently in patients with decreasing counts.
    - Antiretroviral therapy
        - A CD4+ T-cell count <250/μL is an indication to start therapy according to most practice guidelines.
- HIV RNA level
    - Predicts what will happen to the CD4+ T cell count in the near future and may itself be correlated with immune dysfunction
    - Should be measured:
        - At the time of HIV diagnosis
        - Every 3–4 months thereafter in the untreated patient
    - Useful in making therapeutic decisions about antiretroviral therapy
        - After initiation of therapy or any change in therapy, HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by development of a new steady-state level of HIV RNA.
        - During therapy, levels of HIV RNA should be monitored every 3–4 months to evaluate the continuing effectiveness of therapy.
- HIV resistance testing
    - Sensitivity of patient's HIV virus(es) to different antiretroviral agents can be tested by genotypic or phenotypic assays.
    - In the hands of experts, the use of resistance testing enhances the short-term ability to achieve ~0.5-log decreases in viral load compared to changing drugs merely on the basis of drug history.

- The clinical value of HIV resistance testing in selecting an initial treatment regimen is still under investigation.

Imaging

- Directed by specific HIV complications

Diagnostic Procedures

- See Diagnostic Approach and Laboratory Tests.

Classification

Clinical categories of HIV infection

Category A

- ≥1 of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection; conditions seen in B and C must not have occurred
  - Asymptomatic HIV infection
  - Persistent generalized lymphadenopathy
  - Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B (symptomatic)

- Symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet ≥1 of the following criteria:
  - Conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity **or**
  - Conditions are considered by physicians to have a clinical course or to require management complicated by HIV infection
- Examples include, but are not limited to:
  - Bacillary angiomatosis
  - Candidiasis, oropharyngeal (thrush)
  - Candidiasis, vulvovaginal: persistent, frequent, or poorly responsive to therapy
  - Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
  - Constitutional symptoms, such as fever (38.5 °C) or diarrhea lasting >1 month
  - Hairy leukoplakia, oral
  - Herpes zoster (shingles), involving ≥2 distinct episodes or >1 dermatome
  - Idiopathic thrombocytopenic purpura
  - Listeriosis
  - Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
  - Peripheral neuropathy

Category C (AIDS)

- Conditions listed in the AIDS surveillance case definition
  - Candidiasis of bronchi, trachea, or lungs
  - Candidiasis, esophageal
  - Cervical cancer, invasive

- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (loss of vision)
- Encephalopathy (HIV-related)
- Herpes simplex: chronic ulcer(s) (>1 month's duration) or bronchitis, pneumonia, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isoporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- *M. avium* complex, or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *P. carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Treatment Approach

- Principles of therapy of HIV infection
  - Ongoing HIV replication leads to immune system damage and progression to AIDS.
  - Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T-cell destruction.
  - CD4+ T-cell counts indicate the current level of competence of the immune system.
  - Rates of disease progression differ among patients, and treatment decisions should be individualized based on plasma HIV RNA levels and CD4+ T-cell counts.
  - Maximal suppression of viral replication is a goal of therapy; the greater the suppression, the less likely the appearance of drug-resistance quasispecies.
  - The most effective therapeutic strategies involve simultaneous initiation of combinations of anti-HIV drugs active against the patient's virus.
  - The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
  - The number of available drugs is limited; any decisions on antiretroviral therapy have a long-term impact on future options for the patient.
  - Women should receive optimal antiretroviral therapy regardless of pregnancy status.
  - Compliance is an important part of ensuring maximal effect from a given regimen.
    - The simpler the regimen, the easier it is for the patient to be compliant.
- Indications for initiation of antiretroviral therapy
  - Acute infection syndrome (no clear consensus)
  - Chronic infection
    - Symptomatic disease
    - Asymptomatic diseases
      - CD4+ T-cell count <250/μL or decreasing
      - HIV RNA >50,000 copies/mL or increasing
  - Postexposure prophylaxis
- Indications for changing antiretroviral regimens

    - <1-log decrease in plasma HIV RNA by 4 weeks after initiation of therapy
    - A reproducible significant increase (defined as 3-fold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test method
    - Persistently decreasing CD4+ T-cell count
    - Clinical deterioration
    - Side effects
- Treatment prophylaxis considerations based on CD4+ count
    - <200/μL
        - *P. carinii* prophylaxis
    - <50/μL
        - Primary prophylaxis for *M. avium* infection

Specific Treatments

Antiretroviral therapy

- Combination highly active antiretroviral therapy is the cornerstone of management of patients with HIV infection
    - Marked decrease in incidence of most AIDS-defining conditions since initiation of widespread use of highly active antiretroviral therapy in the U.S. in 1995–1996
- Primary goals of treatment
    - Reduce HIV-related morbidity and mortality.
    - Improve quality of life.
    - Restore and preserve immunologic function.
    - Maximally and durably suppress viral load.
- Indications for treatment
    - All patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4+ T-cell count.
    - Asymptomatic patients with <250 CD4+ T cells/μL
    - For asymptomatic patients with a CD4+ T-cell count >250 cells/μL and plasma HIV RNA level >100,000 copies/mL, most experienced clinicians defer therapy, but some clinicians may consider initiating treatment.
    - Therapy should be deferred for patients with CD4+ T-cell counts >350 cells/μL and plasma HIV RNA level <100,000 copies/mL.
    - Treatment for acute and recent HIV infection is considered optional.
        - Long-term virologic, immunologic, or clinical benefit is unknown.
- Antiretroviral drugs
    - Nucleoside/nucleotide reverse transcriptase inhibitors
        - Zidovudine (Retrovir)
        - Didanosine (Videx, Videx EC)
        - Zalcitabine (HIVID)
        - Stavudine (Zerit)
        - Lamivudine (Epivir)
        - Emtricitabine (FTC, Emtriva)
        - Abacavir (Ziagen)
        - Tenofovir (Viread)
    - Non-nucleoside reverse transcriptase inhibitors
        - Efavirenz (Sustiva)
        - Nevirapine (Viramune)
        - Delavirdine (Rescriptor)

    - Protease inhibitors
        - Lopinavir/ritonavir (Kaletra)
        - Atazanavir (Reyataz)
        - Fosamprenavir (Lexiva)
        - Saquinavir mesylate (Invirase—hard gel capsule; Fortovase—soft gel capsule)
        - Ritonavir (Norvir)
        - Indinavir sulfate (Crixivan)
        - Nelfinavir mesylate (Viracept)
        - Amprenavir (Agenerase)
    - Fusion inhibitor
        - Enfuvirtide (Fuzeon)
- Preferred regimens for treatment-naïve patients (optimal regimen remains in flux)
    - Non-nucleoside reverse transcriptase inhibitor based
        - Efavirenz **plus** (lamivudine or emtricitabine) **plus** (zidovudine or tenofovir DF)
        - Except during first trimester of pregnancy or in women with high pregnancy potential
    - Protease inhibitor based
        - Atazanavir **or** lopinavir/ritonavir (coformulation) **plus** (lamivudine or emtricitabine) **plus** (zidovudine or tenofovir DF)
    - For more details and alternative regimens, see the U.S Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.
- Adverse effects and drug–drug interactions are common and must be taken into consideration when using these medications.
    - One of the main problems has been a syndrome of hyperlipidemia and fat redistribution referred to as *lipodystrophy syndrome.*

Virologic failure during treatment

- Virologic failure is currently defined as:
    - HIV RNA level >400 copies/mL after 24 weeks
    - >50 copies/mL after 48 weeks
    - Repeated HIV RNA level >400 copies/mL after prior suppression of viremia to <400 copies/mL
- Evaluation of antiretroviral treatment failure should include:
    - Assessing the severity of HIV disease
    - Antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity
    - Results of prior drug resistance testing
- Drug resistance testing
    - Should be done while the patient is taking the failing antiretroviral regimen (or as soon as possible within 4 weeks of treatment discontinuation)
- Managing virologic failure
    - Use the treatment history and past and current resistance test results to identify active agents (preferably at least two fully active agents) to design a new regimen.
        - A fully active agent is one likely to demonstrate antiretroviral activity on the basis of both the treatment history and susceptibility on drug-resistance testing.
    - If at least 2 fully active agents cannot be identified:
        - Consider pharmacokinetic enhancement of protease inhibitors (with the exception of nelfinavir) with ritonavir **and/or**
        - Reuse other prior antiretroviral agents to provide partial antiretroviral activity.

- Significant antiretroviral activity can be obtained by adding to an optimized background antiretroviral regimen.
  - A drug with activity against drug-resistant virus (e.g., a potent ritonavir-boosted PI)
  - A drug with a new mechanism of action (e.g., HIV entry inhibitor)
- One active drug should not be added to a failing regimen because drug resistance is likely to develop quickly.
  - However, in patients with advanced HIV disease (e.g. CD4+ T-cell count <100/μL) and high risk of clinical progression, adding 1 active agent (with an optimized background regimen) may provide clinical benefits and should be considered.

Prevention of opportunistic infections

Primary and secondary prophylaxis

- *P. carinii*
  - Indications
    - CD4 count <200/μL **or**
    - Oropharyngeal candidiasis **or**
    - Unexplained fever >2 weeks **or**
    - Prior bout of *P. carinii* pneumonia
    - May stop prophylaxis if CD4+ T-cell count >200/μL for 6 months
  - First choice
    - Trimethoprim–sulfamethoxazole, 1 double-strength tablet qd
- *M. tuberculosis*
  - Indications
    - Skin test >5 mm **or**
    - Prior positive test without treatment **or**
    - Close contact with case of active tuberculosis
  - First choices
    - Isoniazid, 300 mg PO qd **plus** pyridoxine, 50 mg PO qd for 9 months
    - Isoniazid, 900 mg PO **plus** pyridoxine, 100 mg PO twice weekly for 9 months
  - If drug resistance is suspected, check with local public health authorities.
- *M. avium* complex
  - Indications
    - CD4 count <50/μL
    - Prior documented disseminated disease
    - May stop prophylaxis if CD4+ T-cell count >100/μL for 6 months
  - First choice
    - Azithromycin: 1,200 mg PO weekly

Immunizations recommended

- Hepatitis B virus
  - Indications
    - All susceptible (anti–hepatitis B core antigen and anti–hepatitis B surface antigen negative) patients

- Hepatitis A virus
  - Indications
    - All susceptible (anti–hepatitis A virus negative) patients at increased risk for hepatitis A
- Influenza virus
  - Indications
    - All patients annually
- *Streptococcus pneumoniae*
  - Indications
    - All patients

Recommendations for prevention of severe and frequent recurrences

- Herpes simplex
  - Indications
    - Frequent/severe recurrences
  - First choices
    - Acyclovir: 200 mg PO tid
    - Acyclovir: 400 mg PO bid
    - Famciclovir: 250 mg PO bid
- *Candida*
  - Indications
    - Frequent/severe recurrences
  - First choice
    - Fluconazole: 100–200 mg PO qd

Monitoring

- CD4+ T-cell counts
  - Measure every 3–6 months after diagnosis.
    - Measurements may be done more frequently in patients with decreasing counts.
  - <200/μL: high risk for infection with *P. carinii*
  - <50/μL: at high risk of infection with CMV, *M. avium* complex
- Plasma HIV RNA levels
  - Useful in making decisions about antiretroviral therapy
  - In untreated patients
    - Measure every 3–6 months after diagnosis.
  - After initiation or any change in therapy
    - Monitor about every 4 weeks until effectiveness is determined by development of new steady-state level of HIV RNA.
  - During chronic therapy
    - Monitor every 3–4 months to evaluate the continuing effectiveness of therapy.

Complications

General

- For details, see U.S. Health and Human Services Treating Opportunistic Infections Among HIV-Infected Adults and Adolescents.

Diseases of the respiratory system

- Acute bronchitis
- Sinusitis
- Pneumonia
    - Bacterial
    - Tuberculosis
    - Atypical mycobacterial infections
    - *Rhodococcus equi* infection
- Fungal infections of the lung
    - Coccidioidomycosis
    - Aspergillus infection
    - Histoplasmosis
- Idiopathic interstitial pneumonia

Diseases of the cardiovascular system

- HIV-associated cardiomyopathy
- Drug-induced cardiomyopathy
- Cardiomyopathy due to:
    - Kaposi's sarcoma
    - Cryptococcosis
    - Chagas' disease
    - Toxoplasmosis
- Pericardial effusions
- Pericarditis
- Nonbacterial thrombotic endocarditis
- Ischemic heart disease/myocardial infarction

Diseases of the oropharynx and GI system

- Most frequently due to secondary infections
- Thrush
- Hairy leukoplakia
- Aphthous ulcers
- Esophagitis
    - Candida
    - CMV
    - Herpes simplex virus
- Infections of the small and large intestines
    - Bacterial (Salmonella , Shigella , Campylobacter)
    - Fungal (histoplasmosis, coccidioidomycosis, penicilliosis)
    - Protozoal (cryptosporidia, microsporidia, *Isospora belli*)
- Peritonitis
- CMV colitis
- AIDS enteropathy
- Rectal lesions
    - Herpes simplex virus
    - Condylomata acuminata
    - Kaposi's sarcoma
    - Intraepithelial neoplasia

Hepatobiliary disease

- Hepatitis B
- Hepatitis C
- Granulomatous hepatitis
- Hepatic masses
- Biliary tract disease
    - Papillary stenosis
    - Sclerosing cholangitis
- Liver injury due to drug toxicity
- Pancreatic injury due to drug toxicity

Diseases of the kidney and genitourinary tract

- HIV-associated nephropathy
- Drug-induced renal damage
- Genitourinary tract infections
- Infections with *Treponema pallidum*
- Vulvovaginal candidiasis
- Vaginitis

Diseases of the endocrine system and metabolic disorders

- Lipodystrophy
    - Elevated triglyceride level
    - Elevated total cholesterol level
    - Elevated lipoprotein B level
    - Hyperinsulinemia
    - Hyperglycemia
- Avascular necrosis of the hips and shoulders
- Lactic acidosis
- Hyponatremia
    - Syndrome of inappropriate antidiuretic hormone secretion
    - Adrenal insufficiency
- Hypothyroidism
- Hypogonadism

Rheumatologic diseases

- Immune reactivation syndromes
    - After initiation of antiretroviral therapy, an exaggerated immune response to opportunistic infections
- Drug allergies
- Diffuse infiltrative lymphocytosis syndrome
- Reactive arthritis
- Psoriatic arthritis
- AIDS-associated arthropathy
- Painful articular syndrome
- Fibromyalgia
- Leukocytoclastic vasculitis
- CNS angiitis

- Polymyositis
- Septic arthritis

Diseases of the hepatopoietic system

- Lymphadenopathy
- Anemia
- Leukopenia
- Neutropenia
- Thrombocytopenia
- Persistent generalized lymphadenopathy

Dermatologic diseases

- Seborrheic dermatitis
- Eosinophilic pustular folliculitis
- Norwegian scabies
- Psoriasis
- Ichthyosis
- Reactivation herpes zoster (shingles)
- Herpes simplex virus
- Herpetic whitlow
- Diffuse skin eruptions due to *Molluscum contagiosum*
- *Condyloma acuminatum* lesions
- Erythroderma
- Stevens–Johnson syndrome

Neurologic diseases

- Opportunistic infections
    - Toxoplasmosis
    - Cryptococcosis
    - Progressive multifocal leukoencephalopathy
    - Cytomegalovirus
    - *Mycobacterium tuberculosis*
- Co-infections
    - Syphilis
    - Human T-lymphotropic virus 1 infection
- Neoplasms
    - Primary CNS lymphoma
    - Kaposi's sarcoma
- Result of HIV-1 infection
    - Aseptic meningitis
    - HIV encephalopathy (AIDS dementia complex)
- Myelopathy
    - Vacuolar myelopathy
    - Pure sensory ataxia
    - Paresthesia/dysesthesia
- Peripheral neuropathy
    - Acute inflammatory demyelinating polyneuropathy (Guillain–Barré syndrome)
    - Mononeuritis multiplex
    - Distal symmetric polyneuropathy

- Myopathy
- Seizures
- Focal neurologic deficits
- Progressive multifocal leukoencephalopathy
    - JC virus

Ophthalmologic disease

- Cotton-wool spots
- CMV retinitis
- Progressive outer retinal necrosis syndrome
- *P. carinii*
- Toxoplasmosis

Additional disseminated infections and wasting syndrome

- Bacillary angiomatosis
- Histoplasmosis
- *Penicillum marneffei* infection
- Visceral leishmaniasis
- Generalized wasting
- CNS Chagas' disease

Neoplastic diseases

- Kaposi's sarcoma
- Non-Hodgkin lymphoma
- Primary CNS lymphoma
- Cervical, brain, testicular, oral, lung, and anal cancers

Prognosis

- The median time from primary HIV infection to the development of AIDS in untreated persons in the developed world is ~10 years.
    - This period has been markedly extended by the wide availability of combinations of antiretroviral drugs.
- Mortality
    - In 2003, HIV infection was the sixth leading cause of death among Americans 25–44 years of age in the U.S.
    - The annual number of AIDS-related deaths in the U.S. decreased ~70% from 1995 to 2003.
    - Currently, ~5 deaths annually per 100,000 persons
- Approximately 60% of deaths among patients with AIDS are a direct result of an infection other than HIV, primarily:
    - Viral hepatitis
    - Other non-AIDS-defining bacterial infections

Prevention

- Cornerstones of prevention
    - Education

    - Counseling
    - Behavior modification
        - Abstinence or practicing safer sex (condoms together with the spermatocide nonoxynol-9)
        - Stopping the use of injectable drugs or using sterilized needles and no sharing of drug paraphernalia
- Screening of blood products
    - Risk of transmission by transfusion has reduced to 1 in 725,000 to 1 in 835,000.
    - Autologous blood donation is a better choice, if possible.
    - Screening of all blood donors for HIV infection by assays for both HIV antibody and p24 antigen and self-deferral of persons at risk for HIV infection.
    - Clotting factor concentrates are heat treated, essentially eliminating the risk to hemophiliacs who require these products.
- Screening of donors for:
    - Artificial insemination
    - Tissues used in organ transplantation
- Use of universal precautions by all health care workers when caring for all patients
- Current recommendations to reduce perinatal transmission of HIV include:
    - Universal voluntary HIV testing and counseling of pregnant women
    - Antiretroviral prophylaxis with ≥1 drugs in cases in which the mother does not require therapy for her HIV infection
    - Combination therapy for women who do require therapy
    - Obstetric management to minimize exposure of the infant to maternal blood and genital secretions
    - Avoidance of breast-feeding
- Vaccines
    - Development of a safe and effective HIV vaccine is the object of active investigation.
    - Extensive animal work is ongoing, and clinical trials of candidate vaccines are under way in humans.

ICD-9-CM

- 042 Human immunodeficiency virus [HIV] disease
- V08 Asymptomatic human immunodeficiency virus [HIV] infection status (includes HIV positive, not otherwise specified)

See Also

- Anal Cancer
- Approach to Weight Loss
- Candidiasis
- CNS Lymphoma
- Cryptococcosis
- Cryptosporidiosis
- Cytomegalovirus Infections
- Disorders of Smell
- Herpes Simplex Virus Infections
- Microsporidiosis
- Myocarditis
- Nontuberculous Mycobacterial Infections
- Non-Hodgkin Lymphomas
- Pneumocystis Infections

- Sclerosing Cholangitis
- Toxoplasmosis
- Tuberculosis Associated with HIV/AIDS

Internet Sites

- Professionals
  - AIDS Info
    U.S. Department of Health and Human Services
- Patients
  - AIDS
    MedlinePlus
  - AIDS and Infections
    MedlinePlus

General Bibliography

- Benson CA et al: Treating opportunistic infections among HIV-exposed and infected children: Recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 53(RR-15):1, 2004
- Centers for Disease Control and Prevention (CDC): Trends in HIV/AIDS diagnoses--33 states, 2001-2004. *MMWR Morb Mortal Wkly Rep* 54:1149, 2005 [PMID:16292247]
- Chun TW, Fauci AS: Latent reservoirs of HIV: obstacles to the eradication of virus. *Proc Natl Acad Sci U S A* 96:10958, 1999 [PMID:10500107]
- Davey RT et al: HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. *Proc Natl Acad Sci U S A* 96:15109, 1999 [PMID:10611346]
- Dybul M et al: Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. Recommendations of the Panel on Clinical Practices for Treatment of HIV. MMWR Recomm Rep 51(RR-7):1, 2002. Updates available at *http://www.aidsinfo.nih.gov*
- Fauci AS: Host factors and the pathogenesis of HIV-induced disease. *Nature* 384:529, 1996 [PMID:8955267]
- Fauci AS: The AIDS epidemic--considerations for the 21st century. *N Engl J Med* 341:1046, 1999 [PMID:10502595]
- Grinspoon S, Carr A: Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 352:48, 2005 [PMID:15635112]
- Haase AT: Perils at mucosal front lines for HIV and SIV and their hosts. *Nat Rev Immunol* 5:783, 2005 [PMID:16200081]
- Hammer SM: Clinical practice. Management of newly diagnosed HIV infection. *N Engl J Med* 353:1702, 2005 [PMID:16236741]
- Kaplan JE et al: Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep 51(RR-8):1, 2003. Updates available at http://www.aidsinfo.nih.gov
- Lopez Bernaldo de Quiros JC et al: A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. *N Engl J Med* 344:159, 2001 [PMID:11172138]
- Mofenson LM et al: U.S. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. MMWR Recomm Rep 51 (RR-18):1, 2002. Updates available at http://www.aidsinfo.nih.gov

- Nabel GJ: Challenges and opportunities for development of an AIDS vaccine. *Nature* 410:1002, 2001 [PMID:11309631]
- Panel on Clinical Practices for Treatment of HIV: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, October 6, 2005. Available at http://AIDSinfo.nih.gov.
- Pantaleo G, Koup RA: Correlates of immune protection in HIV-1 infection: what we know, what we don't know, what we should know. *Nat Med* 10:806, 2004 [PMID:15286782]
- Quinn TC et al: Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 342:921, 2000 [PMID:10738050]
- Stevenson M: HIV-1 pathogenesis. *Nat Med* 9:853, 2003 [PMID:12835705]
- U.S. Public Health Service: Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR Recomm Rep 50(RR-11):1, 2001. Updates available at http://www.aidsinfo.nih.gov
- UNAIDS: AIDS epidemic update: December 2005. Available at http://www.unaids.org