Acquired Immune Deficiency Syndrome (AIDS)
Updated 2007 Jun 27 08:05 AM:
Description:

- this document describes the AIDS syndrome, diagnosis and treatment of related disorders and prophylactic therapy for opportunistic infections
- see HIV infection for diagnosis and treatment of the underlying HIV infection
- AIDS is a clinical syndrome associated with chronic HIV infection
    - characterized by HIV encephalopathy, HIV wasting syndrome, or certain (indicator) diseases:
        - protozoan - Pneumocystic carinii pneumonia (PCP), Toxoplasma gondii encephalitis or dissemination, chronic cryptosproidium enteritis, chronic isospora enteritis
        - non-congenital viral - herpes simplex virus (HSV) causing mucocutaneous ulcer > 1 month or infecting lung, bronchus, or esophagus; cytomegalovirus (CMV) infection of retina, GI tract, or lung (any organ except liver or lymph nodes); progressive multifocal leukoencephalopathy (PML, caused by papovavirus)
        - bacterial - disseminated acid-fast bacilli (AFB), non-TB AFB, recurrent nontyphoidal salmonella bacteremia
        - fungal - chronic mucocutaneous, tracheal, pulmonary, esophageal or bronchial candidiasis; cryptococcal meningitis or dissemination; disseminated histoplasmosis or coccidioidiomycosis
        - malignancies - Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, primary brain lymphoma in patients < 60
        - chronic lymphoid interstitial pneumonia in patients < 13 years
    - now AIDS definition also includes HIV infection combined with CD4 count < 200 or pulmonary TB or recurrent pneumonia or invasive cervical cancer

Organs Involved:

- CD4 receptors found on lymphocytes, monocytes, macrophages, microglia, intestinal epithelium, bone marrow progenitors, endothelium; neurons also infected

Who is most affected:

- of AIDS cases in adults - 66% homo/bisexual men, 17% IV drug abusers (IVDA), 8% homosexual and IVDA, 4% heterosexual contact, 2% transfusion, 1% coagulation disorders
- of AIDS cases in children - 6% coagulation disorders, 13% transfusion, 77% from parents; for children mean age of symptoms 4 months, range 0-60 months
- epidemiology of first and second 100,000 cases in US
    - first 100,000 cases - 61% homo/bisexual men, 20% IV drug abuse, 5% heterosexual men, 9% women, 1.6% children, 27% black, 15% Hispanic

    - second 100,000 cases - 55% homo/bisexual men, 24% IV drug abuse, 7% heterosexual men, 12% women, 1.7% children, 31% black, 17% Hispanic
    - Reference - Neurologic Clinics 1993 Aug;11(3):605

Incidence/Prevalence:

- **rates of AIDS and death among HIV infections decreased substantially with introduction of highly active antiretroviral therapy**; study of 9,803 patients from 1994 to 2002 in 70 European HIV centers; incidence per 100 patient-years of follow-up from 1994-1995 to 1998-2002 decreased from 19% to 2.6% for all-cause mortality, from 14.6% to 1.5% for HIV-related mortality, and from 27.4% to 2.6% for AIDS (Lancet 2003 Jul 5;362(9377):22
- prevalence of AIDS in United States
    - 44,232 cases of AIDS in US reported to CDC in 2003 (MMWR 2004 Aug 6;53(30):687)
    - 42,745 cases of AIDS in US reported to CDC in 2002 (MMWR 2003 Aug 8;52(31):741)
    - estimated 337,731 persons living with AIDS in US at end of 2000 (MMWR 2002;51:592 in JAMA 2002 Aug 14;288(6):691)
    - cumulative total of 816,149 cases of AIDS in US reported to CDC as of December 2001 (MMWR 2003 Jun 13;52(23):540)
    - 80,000 cases in US in 1994
    - 1994 CDC mortality statistics - 9% US deaths totalling 41,930 deaths in 1994, #1 cause (23%) of deaths in men at age 25-44, #3 cause (11%) of deaths in women at age 25-44 (MMWR 1996 Feb 16;45:121 in J Watch 1996 Apr 1;16(7):55)
    - 1996 CDC statistics (first 6 months) - mortality decreased 13%, 68,473 AIDS cases reported in first 1996 (increased incidence from 1992) (MMWR 1997 Feb 28 in Am Fam Physician 1997 May 1;55(6):2347
    - #3 notifiable infectious disease in US in 1995 (MMWR 1996 Oct 18;45:883)

Causes:

- human immunodeficiency virus - HIV-1; HIV-2 in west Africa
    - a virus of Lentivirus family (type D retrovirus), also called HTLV-III
    - single-stranded diploid RNA, a nontransforming cytopathic RNA retrovirus
    - viral-encoded proteins
        - gag - p24 core protein
        - pol - reverse transcriptase
        - env - glycoproteins of envelope - gp120 for attachment, gp41 for internalization
        - tat - trans-acting protein activates transcription
- Transmission - 80% sexual, 24% IVDA, 4% transfusions (pre-1980), 1% hemophiliacs (pre-1980), perinatal (in utero transmission with 30-40% efficiency, delivery, breast feeding)

Pathogenesis:

- single cell killing, apoptosis, autoimmune mechanisms, superantigen-mediated perturbation of T cell subsets, virus-specific immune responses, anergy
- opportunistic infections and neoplasms secondary to immune deficiency

Likely risk factors:

- black, homosexual, IVDA, prostitution, other STDs (break in mucosal integrity), lack of circumcision

Complications:

- opportunistic infections, malignancies with viral cofactors
- **incidence of AIDS-defining illnesses decreasing, attributed to use of highly active antiretroviral therapy (HAART)**; prospective study of > 7,300 AIDS patients in Europe, incidence of AIDS-defining illnesses per 100 patient-years was 30.7 in 1994 and 2.5 in 1998 (Lancet 2000 Jul 22;356(9226):291
- **incidence of AIDS-defining events substantially lower after starting HAART**; cohort of 12,574 antiretroviral-naive patients who started HAART followed for up to 3 years (22,958 person-years of follow-up); incidence of any AIDS event per 1,000 person-years decreased from 129.3 in first 3 months to 13.1 in third year after starting HAART; 928 AIDS-defining events included 25.3% viral, 24.6% bacterial, 20.7% fungal, 8.1% protozoal, and 21.2% other causes; rate of decline in incidence was highest for viral causes (87% per year) and lowest for fungal causes (54% per year) (Arch Intern Med 2005 Feb 28;165(4):416), correction can be found in Arch Intern Med 2005 May 23;165(10):1200
- most frequent causes of AIDS-defining illnesses in Singapore similar to in the West
    - retrospective study of 1,504 adults seen at national HIV referral center in Singapore 1985-2001, 834 experienced 1,742 AIDS-defining illnesses
    - most frequent causes of initial AIDS-defining illness were Pneumocystis carinii pneumonia (36%), Mycobacterium tuberculosis (23%) and herpes simplex (7.4%)
    - most frequent causes of all AIDS-defining illness were Pneumocystis carinii pneumonia (25%), Mycobacterium tuberculosis (16%) and cytomegalovirus retinitis (9.5%)
    - Reference - BMC Infectious Diseases 2004 Nov 12;4:47
- incidence of infections in HIV-infected children in HAART era
    - prospective study of 2,767 HIV-infected children ages 6-13 years (median 8.2 years) followed for median 3.4 years, 90% acquired HIV perinatally
    - 395 (14%) patients dveloped 553 first episodes of a specific infection
    - incidence per 100 person-years of 4 most common first-time infections
        - 123 bacterial pneumonia
        - 77 herpes zoster
        - 57 dermatophyte infections
        - 52 oral candidiasis
    - incidence < 0.5 per 100 person-years for each of
        - bacteremia
        - *Pneumocystis jeroveci* pneumonia

        - disseminated *Mycobacterium avium* complex
        - lymphoid interstitial pneumonitis
        - systemic fungal infection
        - cytomegalovirus retinitis
        - tuberculosis
    - Reference - JAMA 2006 Jul 19;296(3):292, editorial can be found in JAMA 2006 Jul 19;296(3):330
- AIDS associated with increased risk for cancer
    - **AIDS associated with increased risk for cancer, especially Hodgkin's disease**, based on study of AIDS and cancer registries (JAMA 2001 Apr 4;285(13):1736), commentary can be found in JAMA 2001 Jun 27;285(24):3090
    - **AIDS associated with greatly increased risk for cancer, even in children**; study of 4,954 children with AIDS, 124 (2.5%) had cancer, expected number with cancer without AIDS would be < 1 child; cancers included non-Hodgkin lymphoma (100 cases), Kaposi sarcoma (8), leiomyosarcoma (4), Hodgkin disease (2) (JAMA 2000 Jul 12;284(2):205), commentary can be found in JAMA 2000 Nov 22-29;284(20):2593
    - **invasive cervical cancer** present in 2.5% of 23,054 women aged 20-49 years diagnosed with AIDS in 15 European countries in 1993-1999 (AIDS 2002 Mar 29;16(5):781)
    - **no randomized trials found for treating AIDS-associated Hodgkin's disease in treatment-naive adults with AIDS**
        - based on Cochrane review
        - Reference - systematic review last updated 2007 Feb 19 (Cochrane Library 2007 Issue 2:CD006149)
    - **no randomized trials found for treating conjunctival squamous cell carcinoma in HIV-infected individuals**
        - based on Cochrane review
        - Reference - systematic review last updated 2007 Feb 19 (Cochrane Library 2007 Issue 2:CD005643)
- American Academy of Periodontology practice parameter on periodontitis associated with systemic conditions can be found in J Periodontol 2000 May;71(5 Suppl):876 but withdrawn from National Guideline Clearinghouse 2000 Nov 6:2333
- skin lesions - Kaposi's sarcoma (KS, in homosexuals; involves head, neck, trunk, GI tract), seborrheic dermatitis, telangiectasias, hemangiomas
    - New York State Department of Health guidelines on dermatologic manifestations can be found at National Guideline Clearinghouse 2005 Mar 14:5972
- upper GI tract - HSV and candidal esophagitis, KS, oral hairy leukoplakia (EBV; 2.5 times more common in men with HIV than women with HIV (Arch Intern Med 1996 Oct 28;156(19):2249)
- enteropathy - HIV (stomach and small intestine), lymphoma, Cryptosporidium, Giardia, Salmonella, Shigella, CMV
- American Gastroenterological Association recommendations for gastrointestinal complications can be found at National Guideline Clearinghouse 1998 Nov 24:837

- diarrhea common in HIV patients, intestinal infections diagnosed in < 50% diarrheal episodes, endoscopic evaluation did not improve diagnostic yield compared with stool examination except for diagnosis of cytomegalovirus enteritis and leishmaniasis; prospective study of 1933 participants in Swiss HIV Cohort Study followed up for median 25.5 months, 560 diarrheal episodes evaluated by standardized stool exam, endoscopy performed in 25% of patients with chronic diarrhea; incidence of diarrhea was 14.2 per 100 person-years; among patients with CD4 cell counts < 500, probability to develop diarrhea within 1, 2 and 3 years was 48.5%, 74.3% and 95.6%; risk to develop diarrhea was increased among patients with severe immunodeficiency, homosexual men and patients taking antiretroviral therapy; diarrhea was an independent negative predictor of survival; enteric pathogens were detected in 16.5% of 212 acute diarrheal episodes and 46% of 348 chronic diarrheal episodes, diagnosis of intestinal cytomegalovirus infection and leishmaniasis required invasive evaluation (Arch Intern Med 1999 Jul 12;159(13):1473)
- 1.4% incidence of tuberculosis (and 4.5% incidence of M. avium isolation) in prospective cohort study of 286 patients with HIV infection followed for 6 months (BMC Infectious Diseases 2001 Nov 8;1(1):21)
- lungs
    - PCP, pneumococcus, cryptococcus, tuberculosis, CMV
    - tuberculosis -- 222,234 AIDS cases were reported to state or local health departments from 1981-1991. 11,299 (5.1%) were matched with a reported TB case. Five states (New York, New Jersey, Florida, Texas, and California) reported > 75% of the matched TB-AIDS cases. Individuals with active TB were much more likely than the rest of the population to have AIDS (relative risk of 204). AIDS patients were significantly more likely to have TB (relative risk of 59) compared with the general population. All HIV patients should be given tuberculin skin tests early in their disease and should receive prophylaxis for an induration > 5 mm after active TB has been excluded. CDC recommends HIV testing for all individuals with active TB. (Arch Intern Med 1995 Jun 26;155(12):1281)
    - most pulmonary complications in hospitalized HIV patients are due to PCP or mycobacteria; in series of 1,225 hospital admissions among 599 HIV patients, pulmonary complications included Pneumocystis carinii pneumonia (85), Mycobacterium avium complex (51), Mycobacterium tuberculosis (40), Mycobacterium gordonae (11), Mycobacterium kansasii (10), Cytomegalovirus (10), Nocardia asteroides (3), fungus ball (2), respiratory syncytial virus (1), herpes simplex virus (1), Histoplasma capsulatum (1), lymphoma (3), bronchogenic carcinoma (2), and Kaposi sarcoma (1) (BMC Pulmonary Medicine 2001 Sep 19;1(1):1)
    - incidence of pneumococcal bacteremia in HIV-infected patients reported to decrease from 24.1 episodes per 1,000 patient-years in 1986-1996 to 8.2 per 1,000 patient-years in 1997-2002, attributed to highly active antriretroviral therapy and vaccination (Arch Intern Med 2005 Jul 11;165(13):1533)
- cardiomyopathy
    - review of cardiac manifestations of AIDS can be found in Arch Intern Med 2000 Mar 13;160(5):602, commentary can be found in Arch Intern Med 2000 Aug 14-28;160(15):2397

- articular - 1/3 arthralgias, 5% homosexuals have Reiter's syndrome, rarely psoriatic arthritis, AIDS-associated arthritis
- skeletal - decreased bone mineral density
- muscular - myalgias common early, 2% polymyositis (also AZT side effect)
- hematologic
    - immune thrombocytopenia, anemia of chronic disease, neutropenia, immunoglobulin disorders, lymphoma (high risk for development of aggressive non-Hodgkin's lymphoma with high-grade malignancy, B-cell phenotype, unusual extranodal involvement and poor prognosis; see review in Mayo Clin Proc 1995 Jul;70(7):665)
    - **insufficient evidence regarding treatment of anemia in HIV-infected patients**
        - based on Cochrane review
        - systematic review of 4 randomized trials of treatments for anemia in people diagnosed with HIV infection
        - 1 trial dropped due to high dropout rate
        - 2 randomized trials compared recombinant human erythropoietin (rHuEPO) to placebo
            - 1 trial with 63 adults did not find significant differences overall, but reported significant reduction in transfusion requirement in subgroup of 48 patients with low endogenous erythropoietin levels
            - 1 trial with 21 children did not have any transfusions needed, but reported improved quality of life scores with erythropoietin compared to placebo
        - 1 trial with 285 adults comparing 2 rHuEPO dosing regimens found no significant differences
        - Reference - systematic review last updated 2006 Nov 15 (Cochrane Library 2007 Issue 1:CD004776)
- **women with HIV infection have increased risk for vulvovaginal and perianal condyloma acuminata and intraepithelial neoplasia**; prospective study of 925 women (481 HIV-1-positive and 437 HIV-1-negative) who had gynecological exam including colposcopy and human papillomavirus (HPV) DNA testing of cervicovaginal lavage twice yearly for median 3.2 years; 6% vs. 1% had vulvovaginal and perianal condylomata acuminata or intraepithelial neoplasia; in analysis of women without lesions at baseline, 33 (9%) of 385 HIV-1-positive and 2 (1%) of 341 HIV-1-negative women developed vulvovaginal or perianal lesions, incidence 2.6 vs. 0.16 cases per 100 person-years (relative risk 16, 95% CI 12.9-20.5); risk factors for incident lesions included HIV-1 infection, HPV infection, lower CD4 T lymphocyte count, and history of frequent injection of drugs (Lancet 2002 Jan 12;359(9301):108 commentary can be found in Lancet 2002 Jun 8;359(9322):2040
    - **CD4 count < 500 cells/mcL associated with higher risk of cervical squamous intraepithelial lesions (SILs)**; cohort of 855 HIV-positive and 343 HIV-negative women followed with semi-annual Pap smears for median 7 years; among women with negative HPV status, 2-year rates of any SIL were 3% for HIV-negative women, 4% for HIV-positive women with CD4 counts > 500 cells/mcL, 9% with CD4 counts 200-500

cells/mcL and 9% with CD4 counts < 200 cells/mcL (JAMA 2005 Mar 23/30;293(12):1471)

- autoimmune renal disease
- 25-40% CMV retinitis
- neurologic manifestations of HIV disease
    - HIV-related neurologic syndromes Click for Details
        - cerebral
            - acute infection - aseptic meningitis, acute encephalopathy, leukoencephalitis, seizures
            - chronic infection - recurrent meningeal pleocytosis, organic brain syndromes (dementia and- motor signs, mild cognitive impairment, organic psychiatric disorders), seizures, stroke, leukoencephalitis, cerebellar syndrome, multisystem degeneration
        - spinal cord
            - acute infection - transverse myelitis
            - chronic infection - chronic progressive myelopathy, anterior horn cell disease
        - cranial and peripheral neuropathy
            - acute infection - Bell's palsy, acute inflammatory demyelinating polyneuropathy (Guillain-Barre type), brachial plexitis, peripheral neuropathy, hearing loss, ganglioneuritis
            - chronic infection - Bell's palsy, hearing loss, chronic inflammatory demyelinating polyneuropathy, distal symmetric sensory neuropathy, mononeuritis multiplex, autonomic neuropathy
        - muscle
            - acute infection - polymyositis (proximal limb weakness, myoglobinuria)
            - chronic infection - chronic progressive myopathy
        - most common - AIDS dementia complex, acute inflammatory demyelinating neuropathy, HIV peripheral neuropathy, HIV vacuolar myelopathy
    - opportunistic infections and neoplasms Click for Details
        - leptomeninges - CMV, HSV, VZV, EBV, HBV, Cryptococcus, Histoplasma, Coccidioides, Candida, Listeria, neurosyphilis, pyogenic bacteria (Salmonella, S. aureus), atypical mycobacteria, TB, lymphoma
        - diffuse encephalopathy or encephalitis - CMV, HSV, VZV, atypical mycobacterium, Acanthamoeba, toxoplasmosis, lymphoma
        - focal cerebral syndromes (including spacy-occupying lesions) - HSV, VZV, PML, fungal abscess, Trypanosoma cruzei, Taenia solium, toxoplasmosis, primary or metastatic lymphoma, glioma, metastatic Kaposi's sarcoma
        - cerebrovascular syndromes and seizures - VZV, HSV, rarely PML, Cryptococcus, other fungi, neurosyphilis, TB, toxoplasmosis, lymphoma, lymphomatoid granulomatosis,

metastatic Kaposi's sarcoma, cerebral hemorrhage, cardiac emboli, vasculitis
        - movement disorders - CNS Whipple's disease, toxoplasmosis
        - spinal cord syndromes - VZV, CMV, HSV, Mycobacteria, pyogenic bacteria, toxoplasmosis, lymphoma
        - infectious retinitis - CMV, Candida, toxoplasmosis
        - polyneuropathy - CMV polyradiculopathy, (also due to vincristine, ddC, ddI)
        - myositis - S. aureus, mycobacteria, toxoplasmosis
    - Reference - Neurologic Clinics 1993 Aug;11(3):605
    - distal sensory polyneuropathy common in patients with immunosuppression from HIV infection; 272 HIV-infected patients followed for up to 30 months, 55% had distal sensory polyneuropathy (DSP) at baseline, 35% had symptomatic DSP at baseline, 1-year incidence of symptomatic DSP was 36% (Neurology 2002 Jun 25;58(12):1764 in JAMA 2002 Sep 11;288(10):1210)
    - review of neurologic abnormalities in HIV infection can be found in South Med J 2001 Mar;94(3):266 (Am Fam Physician 2001 Oct 15;64(8):1455)
- among 951 HIV patients in Taiwan, 49 (5.2%) had 51 episodes of invasive amebiasis (Arch Intern Med 2005 Feb 28;165(4):409)
- case report of disseminated vaccine strain varicella as AIDS-defining illness can be found in Pediatrics 2001 Aug;108(2):e39 full-text
- New York State Department of Health guidelines on pediatric malignancies in HIV infection can be found at National Guideline Clearinghouse 2005 Mar 14:5970
- incidence of AIDS-defining illnesses based on CD4 counts Click for Details
    - based on follow-up of 4,883 HIV patients in England from 1982 to 1995
    - numbers listed as incidence per 100 person-years
    - CD4 count > 2000/mm^3 - Pneumocystis carinii pneumonia (PCP) 1.35, esophageal candidiasis 1.03, Kaposi sarcoma 1.49, all others < 0.33
    - CD4 count 1000-2000/mm^3 - PCP 4.94, esophageal candidiasis 4.24, Kaposi sarcoma 3.26, Mycobacterium avium-intracellulare complex (MAI) 0.90, cytomegalovirus (CMV) retinitis 0.35, other CMV disease 1.11, pulmonary tuberculosis (TB) 1.27, all others < 0.8
    - CD4 count 500-1000/mm^3 - PCP 13.22, esophageal candidiasis 10.66, Kaposi sarcoma 10.05, MAI 2.71, CMV retinitis 1.68, other CMV disease 2.73, recurrent pneumonia 3.2, cryptosporidiosis 2.38, lymphoma 2.91, HIV wasting syndrome 2.31, toxoplasmosis 1.89, HIV encephalopathy 2, cryptococcosis 1.09, other AIDS-defining diagnoses 1.18, pulmonary TB 1.07, recurrent herpes simplex 0.2, extrapulmonary TB 0.89
    - CD4 count 250-500/mm^3 - PCP 22.11, esophageal candidiasis 15.49, Kaposi sarcoma 13.24, MAI 7.28, CMV retinitis 6.63, other CMV disease 6.95, recurrent pneumonia 12.15, cryptosporidiosis 3.5, lymphoma 3.02, HIV wasting syndrome 3.52, toxoplasmosis 3.18, HIV encephalopathy 2.49, cryptococcosis 2.89, other AIDS-defining diagnoses 1.36, pulmonary TB 1.31, recurrent herpes simplex 1.24, extrapulmonary TB 0.68

    - CD4 count < 250/mm^3 - PCP 26.05, esophageal candidiasis 20.06, Kaposi sarcoma 1.93, MAI 17.48, CMV retinitis 19.18, other CMV disease 13.77, recurrent pneumonia 6.28, cryptosporidiosis 5.31, lymphoma 3.7, HIV wasting syndrome 4.03, toxoplasmosis 4.28, HIV encephalopathy 3.19, cryptococcosis 2.03, other AIDS-defining diagnoses 1.99, pulmonary TB 0.64, recurrent herpes simplex 1.54, extrapulmonary TB 0.71
    - Reference - Arch Intern Med 1998 Mar 9;158(5):491

History of Present Illness (HPI):

- patients often know their latest CD4 count
- bacterial infection (45%), HSV (6%), PCP (64%), MAI (10%), Candida esophagitis (11%), cryptosporidiosis (6%), cryptococcosis (1%), primary lymphoma of brain (2%)
- illnesses tend to occur at different stages of HIV infection:
    - mononucleosis-like illnesses frequent in acute stage with normal CD4 (800-1600)
    - generalized lymphadenopathy, aseptic meningitis, and skin lesions in early stage (CD4 > 500)
    - lymphadenopathy due to AIDS-related complications, candidiasis, leukoplakia and thrombocytopenia in middle stages (CD4 200-500)
    - malignancy, dementia, wasting syndrome, opportunistic infections (PCP, CMV, MAI, toxoplasmosis, cryptococcal meningitis) in advanced AIDS with CD4 count < 200

General Physical:

- percentages listed for childhood AIDS
- lymphadenopathy (90%), failure to thrive (62%)

Skin:

- chronic eczema, Kaposi's sarcoma rare

HEENT:

- oral candidiasis (48%)
- review of head and neck manifestations of AIDS can be found in Am Fam Physician 1998 Apr 15;57(8):1813)
- review of ocular manifestations of HIV infection can be found in N Engl J Med 1998 Jul 23;339(4):236

Lungs:

- Lymphoid Interstitial Pneumonitis (17%)

Abdomen:

- hepatosplenomegaly (80%)

Testing to consider:

- tuberculin skin tests (prophylaxis for induration > 5 mm after active TB excluded)
- consider lumbar puncture after CT for even mild headache to rule out cryptococcal meningitis
- stereotactic brain biopsy had high diagnostic yield in series of 26 HIV patients with brain mass lesions, procedure should be limited to patients who can tolerate specific therapy as they are the only subgroup to benefit (Arch Intern Med 1999 Nov 22;159(21):2590)

Blood tests:

- serology
  - ELISA measures Ab
  - Western blot (or PCR) confirmatory - more sensitive, more laborious; must show immunity to p24 from gag, p31 from pol, gp140/120/160 from env
  - most seroconvert within 3-6 months
- P-24 Ag negative, decreased T4/T8 ratio, CD4 count 100-400
- increased neopterin, ß2-microglobulin, acid-labile interferon, IL2 receptors (immune products)
- < 50% atypical lymphocytes, polyclonal hypergammaglobulinemia
- higher hemoglobin levels associated with better quality of life in prospective cohort of 1,406 US persons > 13 years old with AIDS (Arch Intern Med 2005 Oct 24;165(19):2229), editorial can be found in Arch Intern Med 2005 Oct 24;165(19):2187, commentary can be found in Arch Intern Med 2006 Sep 25;166(17):1923 (commentary can be found in Arch Intern Med 2007 Feb 12;167(3):309)

Imaging studies:

- American College of Radiology (ACR) Appropriateness Criteria for acute respiratory illness in HIV-positive patients can be found at National Guideline Clearinghouse 2006 Apr 10:8588

Prognosis:

- **age-adjusted mortality in persons with AIDS in New York City 1999-2004**
  - HIV-related mortality per 10,000 persons with AIDS
    - 304.6 overall
    - 233 for persons with AIDS diagnosis before 1996
    - 348.3 for persons with AIDS diagnosis 1996-1998
    - 378 for persons with AIDS diagnosis 199-2004
  - non-HIV-related mortality per 10,000 persons with AIDS
    - 100.9 overall
    - 76.4 for persons with AIDS diagnosis before 1996
    - 121.7 for persons with AIDS diagnosis 1996-1998
    - 124.8 for persons with AIDS diagnosis 199-2004

    - Reference - Ann Intern Med 2006 Sep 19;145(6):397 , editorial can be found in Ann Intern Med 2006 Sep 19;145(6):463 **EBSCO*host* Full Text**, commentary can be found in Am Fam Physician 2006 Dec 1;74(11):1958
- survival after AIDS diagnosis increasing in US based on study of nearly 400,000 patients diagnosed with AIDS (JAMA 2001 Mar 14;285(10):1308); median survival steadily improved from 11 months in 1984 to 46 months in 1995, median survival could not be determined for 1996 and 1997 since > 50% those cohorts still alive at data analysis in late 1998 (J Watch 2001 May 1;21(9):75)

Treatment overview:

- when an AIDS patient develops serious illness - use CD4 count and drug history to narrow differential, look for more than one cause; note changes in pattern of fever, headache and sweats; consider common bacterial infections early, opportunistic infections in late stages; ask about patient's wishes, isolate if TB suspected, look for CMV retinitis, obtain CT before lumbar puncture
- management of common emergencies in AIDS
    - breathing difficulty
        - clinical findings - cough, dyspnea, pulmonary infiltrates, often fever
        - most frequent causes - PCP, TB, pneumococci, H. flu, fungi (Cryptococcus, Histoplasma, endemic organisms)
        - helpful tests - ABG, CXR, sputum stain (Giemsa, acid-fast, Gram), sputum culture, bronchoscopy (with lavage and biopsy)
        - stabilization
            - O2 by face mask if uncomfortable, disoriented or difficulty speaking
            - check pulse oximetry and ABG, consider intubation
            - search for readily reversible disease, e.g. bronchospasm or congestive heart failure
            - obtain chemistries, CBC, urinalysis, sputum stains; bacterial, mycobacterial and fungal cultures as indicated
        - history and physical
            - When did symptoms start? cough, dyspnea, sputum (color)? chest pain? travel or to live in place where fungal disease is prevalent? animal contact? TB exposure?
            - examine lungs, look for cyanosis, look for signs of poor dentition
            - signs of immunosuppression, e.g. weight loss, dementia, thrush, hairy leukoplakia, Kaposi's sarcoma
        - narrowing the differential
            - LDH > 220 suggests PCP if serum transaminases normal
            - CXR - diffuse interstitial infiltrate suggests PCP (but can have normal CXR in PCP), apical infiltrates and wet cough suggest TB or fungal infection, lobar infiltrates and wet cough suggest bacterial pneumonia
            - culture - every isolate of TB should be tested for susceptibilities
        - presumptive therapy

            - bacterial pneumonia - appropriate antibiotics
            - PCP
                - trimethoprim 15-20 mg/kg and sulfamethoxazole 100 mg/kg IV daily given in divided doses every 6 hours for 21 days
                - alternative - pentamidine (Pentam 300) 4 mg/kg/day IV slowly over 60 minutes for 21 days, also IM
                - steroid if PaO2 < 70 mmHg or A-a O2 gradient > 35 on room air; e.g. prednisone 40 mg twice daily for 5 days, 40 mg daily for 4 days, 20 mg daily for 11 days; methylprednisolone if IV necessary
            - pulmonary mycoses - amphotericin B (Fungizone) 0.5-0.75 mg/kg/day IV, consider fluconazole (Diflucan)
            - TB
                - for conventional TB - isoniazid (Laniazid, Teebaconin) 300 mg/day, rifampin (Rifadin, Rimactane) 600 mg/day, and either pyrazinamide 15-30 mg/kg/day or ethambutol (Myambutol) 15 mg/kg/day for 9-12 months
                - if multi-drug resistance, add quinolone (ciprofloxacin, ofloxacin) and aminoglycoside (streptomycin)
    - neurologic symptoms
        - clinical findings - seizures, focal deficit, encephalopathy, hydrocephalus, delirium, headache
        - most frequent causes - Toxoplasma gondii, cryptococcal meningitis, tuberculous meningitis, cerebral lymphoma, encephalitis (HSV, HIV)
        - helpful tests - CT head, MRI, lumbar puncture (after CT), brain biopsy
        - stabilization
            - calm patient, preferably through conversation
            - check electrolytes, BUN, creatinine, glucose and ABG
            - give glucose, oxygen, fluids, treat headache pain prn
            - consider hyperventilation, intubation and mannitol (Osmitrol) 1.5-2 mg/kg as 15-25% IV solution over 30-60 minutes, if suspecting focal lesion causing herniation
        - history and physical
            - note drug history (including any drugs recently started or discontinued), mental status, pattern of symptoms (especially headache and fever)
            - delirious? can patient follow verbal commands? can patient speak?
            - IV drugs, cocaine, alcohol?
            - signs of renal failure or liver disorder?
        - differential diagnosis
            - stroke syndrome - #1 toxoplasmosis, fungal abscesses, lymphoma, Kaposi's sarcoma, mycobacterial, vasculitis (possibly from syphilis or zoster)

            - nonfocal processes - bacteremia, sepsis, focal infection, CNS infection, CMV disease, herpes simplex, syphilis
            - cryptococcal meningitis - 75% headache, 65% fever, 25% meningismus and photophobia
        - narrowing the differential
            - immediate CT head (best with contrast), lumbar puncture if no mass effect
            - cryptococcal meningitis - CSF opening pressure > 200 mm H_2O, protein > 55, glucose < 40, > 50% budding yeast forms stained with India ink
            - toxoplasmosis - CT shows multiple low density, ring-enhancing lesions; 50% headache, 60% lateralizing neurologic deficits and altered mentation
            - herpes simplex - CT shows abnormal temporal lobe if delirious, RBCs in spinal fluid, confirmed by brain biopsy
            - syphilis - consider in any patient with ischemic neurologic abnormalities, 5% false negative fluorescent treponemal Ab titer with neurosyphilis
        - treatment - *
    - systemic symptoms
        - clinical findings - fever, rigors, night sweats
        - most frequent causes - cryptococcal infection, mycobacterial infection (disseminated), sinusitis, PCP, CMV, endocarditis, Salmonella, neutropenia with sepsis
        - helpful tests - CBC, blood cultures (viruses, bacteria, fungi, mycobacteria), CT head, lumbar puncture (after CT), CXR
        - stabilization - *
        - initial workup - *
        - differential diagnosis - *
        - treatment - *
    - gastrointestinal symptoms
        - clinical findings - diarrhea, dehydration
        - most frequent causes - Cryptosporidium, Shigella, Salmonella, Campylobacter jejuni, Entamoeba histolytica
        - helpful tests - stool culture, microscopic exam for parasites (O+P)
        - first considerations - *
        - diarrhea - *
        - bleeding - *
        - nausea - *
        - abdominal pain - *
    - inability to eat or swallow - *
    - hematologic problems
        - clinical findings - bleeding, purpura
        - most frequent causes - thrombocytopenia, Kaposi's sarcoma (intestinal or pulmonary, rare)
        - helpful tests - CBC, platelet count, endoscopy
    - changes in visual acuity - *
    - * under construction from Patient Care 1993 Jan 15;140
- things that prolong survival
    - antiretroviral therapy

- PCP prophylaxis
- MAC prophylaxis
- physician experience with AIDS improves patient survival (N Engl J Med 1996 Mar 14;334(11):701 in J Watch 1996 May 1;16(9);70)

Diet:

- **vitamins C, E and B complex may protect against wasting in HIV-infected women (level 3 [lacking direct] evidence)**
  - 1,078 HIV-infected women in Tanzania randomized to multivitamins (B complex, C and E) vs. vitamin A plus beta-carotene vs. both vs. placebo
  - median follow-up 5.3 years
  - multivitamins reduced risk of first episode of midupper arm circumference < 22 cm ($p = 0.02$)
  - Reference - Am J Clin Nutr 2005 Oct;82(4):857

Medications:

- see HIV infection for HIV-directed treatment
- see Opportunistic Infections - Prophylaxis and Treatment in HIV infection for prophylaxis and treatment recommendations
- routine immunization for influenza, pneumococcal pneumonia and hepatitis B recommended (Am Fam Physician 1997 May 1;55(6):2327)
- testosterone treatment
  - testosterone 400 mg IM every 2 weeks produced subjective improvement in mood, sexual interest, appetite and energy in 81 HIV-infected men with low serum testosterone levels; no controlled trials for wasting syndrome although it has been used (The Medical Letter 1996 May 24;38(975):50)
  - testosterone well tolerated and effective in short-term treatment of men with AIDS and hypogonadal symptoms (diminished libido, low energy); 74 such patients randomized to testosterone vs. placebo injections biweekly for 6 weeks, 70 completed the study, 74% vs. 19% had improved libido ($p < 0.001$, NNT 2), 59% vs. 25% had improved energy ($p < 0.001$, NNT 3) for 62 with fatigue (Arch Gen Psychiatry 2000 Feb;57(2):141 in JAMA 2000 May 24-31;283(20):2638), editorial can be found in Arch Gen Psychiatry 2000 Feb;57(2):155
  - **testosterone improved muscle strength in low-weight women (level 2 [mid-level] evidence)**; 57 HIV-infected women with free testosterone levels less than median for reference range and weight < 90% ideal body weight or weight loss > 10% were randomized to transdermal testosterone 4 mg/patch vs. placebo twice weekly for 6 months; muscle mass tended to increase (1.4 kg vs. 0.3 kg, $p = 0.08$), testosterone significantly increased muscle strength for shoulder flexion, elbow flexion, knee extension and knee flexion (Arch Intern Med 2004 Apr 26;164(8):897)
- psychostimulants (methylphenidate or pemoline) effective for treating AIDS-unrelated fatigue in HIV patients based on randomized trial, 109 of 144 patients completed 6 week-trial, 4 or 5 patients need to be treated for 1 to benefit (Arch Intern Med 2001 Feb 12;161(3):411)

- potential treatments in AIDS wasting syndrome
  - exercise appears as effective as weekly testosterone injections in 4-arm randomized trial of 61 HIV-infected men with weight loss and low serum testosterone levels (JAMA 2000 Feb 9;283(6):763 in J Watch 2000 Mar 1;20(5);42), commentary can be found in JAMA 2000 Jul 12;284(2):175
  - **anabolic steroids associated with small increases in lean body mass and body weight in HIV-infected adults with weight loss (level 3 [lacking direct] evidence)**
    - systematic review and meta-analysis of 13 randomized placebo-controlled trials of anabolic steroids for treatment of weight loss in adults with HIV infection
    - trials were mostly high quality, but meta-analysis limited by heterogeneity
    - change from baseline in lean body mass analyzed in 532 patients, mean difference 1.3 kg (95% CI 0.6-2 kg)
    - body weight analyzed in 629 patients, mean difference 1.1 kg (95% CI 0.3-2 kg)
    - no differences in mortality (4 anabolic steroid and 4 placebo patients) or study withdrawals due to adverse events
    - Reference - systematic review last updated 2005 Aug 16 (Cochrane Library 2005 Issue 4:CD005483)
  - more on anabolic steroids
    - megestrol acetate 625 mg/5 mL (Megace ES) FDA approved for anorexia, cachexia or unexplained significant weight loss in AIDS patients (Monthly Prescribing Reference 2005 Aug:A-19)
    - testosterone helpful in men with advanced immune deficiency, high viral loads, wasting and testosterone deficiency based on randomized trial; 52 men with HIV infection, decreased free testosterone levels and wasting (body weight < 90% ideal or unintentional loss > 10% baseline weight) randomized to testosterone enanthate 300 mg IM vs. placebo every 3 weeks for 6 months; 1.9 vs. 0 kg gain in lean body mass, 1.6 vs. 0.3 kg overall weight gain (not statistically significant); testosterone group reported feeling better with improved quality of life, appearance and benefit from treatment; study had multiple exclusions (Ann Intern Med 1998 Jul 1;129(1):18 in J Watch 1998 Aug 1;18(15):122); classic definition of 10% weight loss felt to be much too demanding, testosterone and anabolic steroids may also help treat or prevent lipodystrophy associated with protease inhibitors (JAMA 1998 Dec 9;280(22):1959)
    - oxandrolone in supraphysiologic doses (20 mg/day) in addition to physiologic testosterone replacement (100 mg/week) substantially increased lean tissue accrual and strength gains in 8-week randomized trial of 24 eugonadal men with HIV-associated weight loss (JAMA 1999 Apr 14;281(14):1282), editorial can be found in JAMA 1999 Apr 14;281(14):1326, commentary can be found in JAMA 2000 Jul 12;284(2):176
    - oxandrolone (Oxandrin) 2.5 mg and 10 mg FDA approved to promote weight gain after weight loss after extensive surgery,

chronic infections, severe trauma or other reasons (PDR Monthly Prescribing Guide 2002 Dec:1(12):16)
        - nandrolone decanoate therapy associated with increased weight gain (4.6 kg vs. 3.5 kg) in 12-week randomized placebo-controlled trial of 38 HIV-infected women with weight loss (Arch Intern Med 2005 Mar 14;165(5):578)
    - recombinant human growth hormone (Serostim) approved for AIDS wasting syndrome or cachexia, dosage based on weight (Monthly Prescribing Reference 1996 Dec;A-15)
        - warning regarding a counterfeit Serostim product (FDA 2001 Jan 22)
    - recombinant human growth hormone (rhGH) has inconsistent and modest benefits (J Watch 1997 Jan 1;17(1):2)
        - study of 60 patients with AIDS wasting syndrome given rhGH 1.4 mg once daily, recombinant human insulin-like growth factor 1 (rhIGF-1) 5 mg twice daily, both or placebo; rhGH produced weight gain (about 2 kg) at 6 weeks but not sustained at 12 weeks, rhIGF-1 not associated with weight gain, increases in lean body mass sustained in combination group only; no apparent effect on quality of life (Ann Intern Med 1996 Dec 1;125(11):865
        - study of 178 HIV-infected patients with unintentional weight loss to rhGH 0.1 mg/kg/day (about 6 mg/day) or placebo; 1.6 kg increase in weight and 3 kg increase in lean body mass at 12 weeks, increase in treadmill work output; little change in placebo group; no apparent effect on quality of life (Ann Intern Med 1996 Dec 1;125(11):873
    - review of growth hormone therapy can be found in N Engl J Med 1999 Oct 14;341(16):1206 (author may have conflict of interest [N Engl J Med 2000 Feb 24;342(8):586]), commentary can be found in N Engl J Med 2000 Feb 3;342(5):359
    - American Association of Clinical Endocrinologists (AACE) clinical practice guidelines for growth hormone use in adults and children can be found in Endocr Pract 2003 Jan-Feb;9(1):64
    - improvement has been reported with thalidomide in some patients with AIDS wasting syndrome (The Medical Letter 1996 Feb 16;38(968):15)
    - review can be found in N Engl J Med 1999 Jun 3;340(22):1740, correction can be found in N Engl J Med 1999 Sep 2;341(10):776
    - review of evaluation and treatment of weight loss in adults with HIV can be found in Am Fam Physician 1999 Sep 1;60(3):843
    - treatment guidelines for HIV-associated wasting can be found in Mayo Clin Proc 2000 Apr;75(4):386
- **insufficient evidence to support herbal therapies in HIV infection and AIDS**; systematic review of 9 randomized trials of 8 herbal preparations in 499 patients with HIV infection or AIDS; systematic review last updated 2005 Apr 21 (Cochrane Library 2005 Issue 3:CD003937)

Prevention:

- decrease number of sexual partners, avoid high risk partners, use condoms; drug counseling and prevention, don't share needles; HIV Ab screening of high risk mothers; use heat-inactivated factor VIII; screen donated blood, autologous transfusion; infection control measures in hospital; pneumococcal vaccination
- reduction in perinatal transmission in mothers and infants taking zidovudine (AZT), 2/3 reduction with AIDS Clinical Trial Group (ACTG) protocol 076
- see HIV infection for further details
- among HIV-infected patients, potent antiretroviral therapy protects against AIDS and opportunistic infections (JAMA 1998 Jul 1;280(1):72)