

HIV Disease and AIDS

Epidemiology, Natural History and Management

Epidemiology and transmission of HIV

There is a well-established understanding of the spread of HIV infection. Three modes account for nearly all cases: Sexual contact (either between men or heterosexual); contact with infected blood or blood-containing bodily fluids; or vertical transmission from mother to child. Cofactors for transmission have been identified such as genital ulcer disease. Recent work suggests that virulence differences between HIV strains and innate resistance to infection by the cells of some hosts may be important factors as well. The concentration of infectious virions in the blood (“viral load”) of the source patient appears to be the key determinant of transmission risk in needle stick injuries and similar associations have been shown for mother to child transmission and sexual transmission in sero-discordant couples .

The worldwide pandemic of AIDS is due to infection with HIV-1. A distantly related lentivirus termed HIV-2 is the cause of an AIDS-like illness but is less easily transmitted and is largely restricted to populations in Western Africa and Brazil. Classifying HIV-1 strains into genetically grouped subtypes or clades has revealed distinctly different patterns around the world. Subtype B is the dominant clade found in the US and Western Europe but is rarely seen in Sub-Saharan Africa or Southeast Asia where clades A and C or E predominate. There is speculation that these subtype differences account for some of the distinctive features of the HIV epidemics in these regions.

GLOBAL EPIDEMIOLOGY OF HIV INFECTION

Since the first case descriptions of AIDS and the identification of the causal role of HIV this infection has been detected throughout the world. Sixty five million people are estimated to have been infected with 45 million alive and 20 million dead. The region of sub-Saharan Africa continues to have the largest number of cases and the highest seroprevalence rates. Recently recognized but rapidly growing epidemics in the former Soviet Union, China and India are a great cause for concern especially since the population density of the latter two countries is so high. Among the many ways AIDS is impacting these hard hit countries, the estimate that 14 million children have lost one or both parents to the epidemic.

U.S. EPIDEMIOLOGY

Two distinct epidemics of HIV infection have occurred in the US. One has been concentrated among men who have sex with men (MSM) and the other among injection drug users, their heterosexual partners and children. Over the past decade the fastest growth has occurred among this latter group, especially impacting black and Latino women. In the past two years another trend has appeared with young MSM returning to high risk sexual activity and acquiring both HIV and other STDs at an increased rate.

Diagnosis of HIV infection

HIV infection is diagnosed by detecting antibodies specific for HIV with a two-stage procedure: 1. A screening test by a highly sensitive enzyme immunoassay; and 2. A confirmatory test with a highly specific Western blot if the screening test is positive. Antibodies appear 6 to 12 weeks after infection in most patients and by 6 months in almost everyone. A “window period” with false negative antibody tests can therefore persist for weeks to several months. During this period high levels of HIV viremia are present so tests that detect the virus directly are positive including HIV culture, p24 antigen and nucleic acid detection tests such as PCR or the branch chain DNA assay.

Diagnosis of AIDS

In the early 1980's the CDC created a case definition of AIDS for epidemiologic study purposes before the etiology of the syndrome was established. The name chosen for this syndrome reflected what was known about it at the time: an acquired rather than congenital syndrome of immunodeficiency. The case definition was based on indicator conditions such as Kaposi's Sarcoma and Pneumocystis pneumonia which were rare diseases in the general population only encountered in individuals such as transplant recipients known to have suppressed or deficient cellular immunity. Once the viral etiology was discovered and an antibody test for HIV became available in April, 1985 it became possible to think of HIV disease, a chronic progressive condition, rather than simply its late stage, AIDS. The CDC case-definition remains useful for tracking the epidemic and monitoring changes in the course of HIV disease. Confusion is sometimes created when the terms HIV infection and AIDS are used interchangeably. In 1993 the CDC definition was greatly amended to include asymptomatic individuals with less than 200 CD4 cells in recognition of the variable and changing course of HIV disease, especially the delay or prevention of opportunistic infections (OIs) by antimicrobial prophylaxis.

Natural history of HIV infection

HIV disease is a chronic, progressive process with a variable period of clinical latency but no microbial latency. Although HIV may be difficult to recover by culture during much of this time use of sensitive assays for HIV nucleic acid has shown that virtually all patients have evidence of active viral replication at all times. Levels of viremia are highest right after infection and are then actively suppressed by a host cellular immune response after a few months. A viral load set point is established for the concentration of HIV RNA in plasma by six months which is highly predictive of the subsequent course of HIV disease.

CD4+ T cell depletion is the hallmark of the progressive immunodeficiency of HIV disease. Natural history studies have established a series of CD4 level thresholds below which the risk of specific opportunistic infections rises greatly. This has proved enormously valuable in targeting diagnostic evaluations and using specific prophylactic regimens. The ultimate outcome of untreated HIV disease is progression to AIDS and eventual death in nearly all patients. Better clinical care, especially prophylaxis of OIs extends survival considerably and combination anti-retroviral therapy can reverse even severe immunodeficiency, reducing the risk of OIs or death dramatically.

There is substantial variability in the course of HIV disease which remains largely unexplained. The viral load setpoint mentioned above accounts for most of the variability seen in the speed of HIV disease progression. "Long-term non-progressors" are a small subgroup (5-10%) identified in several natural history studies who have relatively normal CD4 counts (>500) and no HIV-related disease for 10 years or more even without anti-retroviral therapy. The most reliable correlate identified so far is that these patients maintain much lower HIV viral loads than patients starting at the same time after infection and with the same CD4 count who have more rapidly progressive disease. A number of genetic variants termed "AIDS restriction genes" have been associated with faster or slower progression to AIDS. So far though the entire battery of almost twenty genetic markers only accounts for a minor amount of the variability observed.

Acute retroviral syndrome

In most patients the time of initial HIV infection is not known. Estimates are that only 20% of patients seek care for a clinical illness (coinciding with the appearance of antibodies several weeks to a few months after HIV infection) which is usually mild, self-limited and non-specific. Clinical features which may occur as part of this so called "acute retroviral syndrome" include fever, fatigue, sore throat, lymphadenopathy and a macular erythematous rash. The severity of these initial symptoms (or whether there is a recognized acute syndrome at all) appears to predict more rapid progression of HIV infection than in patients with few or no symptoms. It is unclear if treatment during this acute stage is beneficial since early observations suggesting short term treatment could induce better long term immunologic control of HIV have not been born out. There remains great interest in identifying acutely infected

patients for two reasons: they are extremely infectious so reducing their transmission-prone behavior is vital and there are important pathogenesis and treatment studies directed at this stage of infection.

Asymptomatic phase of HIV infection

Symptoms of acute HIV infection usually resolve fully even without treatment and the infection enters a clinically latent phase during which there is ongoing viral replication and progressive CD4 cell depletion. The average patient has a viral load set point of about 30,000 copies of HIV-1 RNA per ml and loses 50 CD4+ T cells per year. In most patients there are no symptoms of HIV infection or its complications for many years. Initial concern that cognitive function might become impaired long before other disease manifestations appear has been discarded. There are, however, three compelling reasons for early identification of HIV positive, asymptomatic patients:

1. Behavioral changes can be made to lower or eliminate the risk of further transmission of HIV;
2. Prophylactic regimens to prevent life-threatening opportunistic infections can be utilized based on CD4 cell risk staging; and
3. If antiretroviral treatment is initiated before the late stages of HIV disease immune deterioration can be halted or reversed before complications develop.

Early manifestations of HIV Disease

There is no single pattern for the clinical course of HIV disease. Many patients report no major symptoms prior to an AIDS defining event. However there are a series of manifestations which are not HIV-specific but occur much more often in HIV infected patients as prodromal events. These illnesses which are therefore important as early indicators of HIV infection include bacterial pneumonia especially due to *S. pneumoniae*, herpes zoster, new onset or major flares of psoriasis and seborrheic dermatitis, salmonella septicemia, and increasingly frequent or severe recurrences of ano-genital *Herpes simplex*. Most of these events are associated with moderately advanced immunodeficiency and are quickly followed by an AIDS-defining event if HIV infection is not recognized and prophylaxis initiated. Two exceptions are herpes zoster, which may precede AIDS by years, and tuberculosis. Kaposi sarcoma can present with a much higher CD4 count than other opportunistic processes. Any of these entities in an individual with a history of HIV risk behavior or simply in an otherwise healthy young adult should raise the possibility of HIV infection.

Prognostic markers for the course of HIV disease

The absolute value of the CD4 count (calculated by multiplying the total WBC, lymphocyte % and CD4 %) is the best established surrogate marker to predict time to AIDS, risk of specific OIs or death especially once counts have fallen from the normal range of 800-1200 to 300 or less. The CD4 % by itself, though more reproducible over time, is somewhat less accurate prognostically. Combining an HIV-1 viral load measurement with a CD4 count provides a very accurate prediction of the risk of developing AIDS 5 or more years in the future even in patients with nearly normal CD4 counts at baseline.

Clinical features of AIDS

There is a consistent group of about a dozen major complicating diseases which are common among patients with advanced HIV disease. A few conditions are restricted by geographic background or HIV risk factor and therefore are not equally likely in all patients. Also, internationally there is some variation in the pattern of AIDS OIs.

PNEUMOCYSTIS PNEUMONIA (PCP)

Microbiology: Pneumocystis is a fungus which has proven difficult to propagate in vitro so there is relatively little known about its biologic or epidemiologic properties. It appears to be widely distributed in nature and antibody studies suggest most people become exposed during childhood. Recently the

taxonomy has been revised with the recognition that *P. carinii* is actually a rat pathogen while the organism implicated in human disease is designated *P. jirovecii*.

Risk factors: Pneumocystis is a prototypic opportunistic pathogen initially implicated in human disease in nursery outbreaks among malnourished infants in post-World War II Europe. Prior to AIDS it was encountered in the U.S. exclusively in congenitally immunodeficient or iatrogenically immunosuppressed transplant and cancer patients. It was therefore quickly recognized as a unique occurrence when previously healthy homosexual men began to be diagnosed with this disease in the early 1980's. Most AIDS patients with PCP have CD4 counts less than 200 though patients with higher counts (up to 350) and symptoms like oral thrush, fever, and weight loss are at high risk as well. Reinfection rather than reactivation may account for some cases but secondary cases or outbreaks have not been well documented.

Pathogenesis: Proliferation in the alveoli leading to an exudative response produces the typical disease. Hematogenous dissemination occurs in some cases and extrapulmonary involvement at numerous sites has been encountered.

Clinical features: Fever and dry cough with slowly progressive dyspnea (often over 4 weeks) are common symptoms. The chest x-ray may have a diffuse interstitial infiltrate or various localized abnormalities. Severe disease is defined by an A-a gradient >35 or $pO_2 < 70$.

Diagnosis: No culture, antigen detection or serologic diagnostic procedure is available so diagnosis rests on histologic identification of the cysts or trophozoites. Lung biopsy is definitive but alveolar contents obtained by bronchoscopic lavage also has an excellent yield.

Treatment: Trimethoprim-sulfamethoxazole (TS) or pentamidine isethionate have comparable efficacy. The high rate of drug intolerance has spurred a search for other treatments. Atovaquone, a chemically distinct agent is approved only for mild and moderate disease since its bioavailability and efficacy are quite limited. Dapsone with trimethoprim or clindamycin with primaquine are other alternatives. Patients progressing to respiratory failure have a high mortality rate and no "salvage" regimen has been found. However, early use of systemic corticosteroids in patients with severe disease (as defined by blood gases) can lower mortality by 50%.

Prevention: Prevention of PCP was one of the most important advances in care during the first decade of the AIDS epidemic. TS orally is the most effective agent (failure rate $< 5\%$). Dapsone, atovaquone or aerosolized pentamidine (given by inhalation monthly) are good but far less effective alternatives.

TOXOPLASMOSIS

Microbiology: *Toxoplasma gondii* is a protozoan parasite of members of the cat family which incidentally affects other animals including humans who ingest the fecally excreted oocysts which survive in the environment or who ingest organisms encysted in skeletal muscle of domestic animals.

Risk factors: Prior infection as indicated by serum antibodies is a reliable way to establish risk though rare cases have been reported in sero-negatives. CD4 counts are usually 100 or less when toxoplasmosis develops. IgG antibodies are a reliable indicator of prior infection and population studies show dramatically different rates between populations: in poor communities in tropical climates (such as El Salvador) seropositivity is nearly universal while U.S. born adult seroprevalence ranges from 10-20%

Pathogenesis: This appears in most cases to be reactivation of a dormant cyst. Most disease is recognized in the brain although cysts are widely distributed throughout the skeletal as well as smooth muscles.

Clinical manifestations: Most cases present as focal CNS events consistent with an expanding mass lesion. Seizures, motor defects or a "stroke" are most common.

Diagnosis: The typical clinical presentation plus focal lesions on head CT or MRI in an HIV positive patient with *T. gondii* antibodies is usually sufficient to begin therapy. Characteristically symptomatic and radiologic improvement is evident after 1-2 weeks of treatment. Diagnostic brain biopsy may be needed if there is no response.

Treatment: A combination of pyrimethamine and sulfadiazine is standard and reliably effective but often not tolerated for long term use. Clindamycin can substitute for sulfa drugs. Long term suppression with one of these combinations is needed.

Prevention: Evidence from PCP prophylaxis trials shows that TS lowers the risk of toxoplasmosis compared to dapsone or aerosolized pentamidine. Therefore individuals with *T. gondii* antibodies and CD4 counts less than 100 should have pyrimethamine added to dapsone or pentamidine PCP prophylaxis if they are unable to tolerate TS.

TUBERCULOSIS

Risk Factors: Globally TB is the greatest cause of HIV-associated mortality. Past infection (indicated by a + PPD or x-ray abnormality) or recent infection are both important contributors to the high rate of TB in HIV patients.

Pathogenesis: HIV is the most powerful accelerant known to promote the activation of latent TB infection. Reinfection with new strains clearly occurs in AIDS patients and increased susceptibility to primary infection is likely as well. Lacking effective cell-mediated immunity, patients with advanced HIV disease experience reactivation of dormant TB infection at a high rate but do not develop the immune responses which produce the characteristic lung cavities and productive sputum seen in HIV uninfected patients. In addition the PPD reaction may be absent making diagnosis especially difficult.

Clinical manifestations: TB can occur in HIV patients at any CD4 count but the frequency and severity rise and the manifestations change as the CD4 count falls. Pulmonary disease is most common but the typical pattern of an apical cavity on x ray with a productive cough and an AFB positive sputum smear becomes less common at very low CD4 counts. Hilar adenopathy and lower lobe infiltrates in these patients may reflect either atypical reactivation, primary infection or reinfection. The proportion of TB cases with disseminated or extrapulmonary disease is increased in advanced HIV infection.

Diagnosis: TB infection is defined by a reactive PPD (≥ 5 mm) in an HIV infected patient but many patients with advanced HIV disease are anergic. Typical cases of active pulmonary disease are easy to detect but many outbreaks have been started when atypical presentations were missed. Sputum AFB smears are only positive in 50% of cases and an aggressive, invasive approach may be needed to detect extrapulmonary sites. Culture still takes several weeks. Rapid tests like PCR are helpful if positive but false negative results may occur.

Treatment: For sensitive isolates standard therapy appears to work as well or nearly so as in HIV negatives. Currently 6-9 months of treatment is recommended. Drug resistant TB epidemics have been centered in AIDS treatment facilities in several countries and are characterized by very high early mortality rates. Therapy for resistant TB is best guided by sensitivity test results but may have to be started empirically especially in settings where multi-drug resistant strains have been encountered.

Prevention: Strict adherence to isolation protocols is vital in avoiding nosocomial infection. INH prophylaxis (for 9 rather than 6 months) is effective in PPD+ /HIV+ patients. Clear guidelines do not exist however for the anergic patient or for preventing multi-drug resistant disease. Ironically TB appears to be the single OI which is curable and doesn't require lifelong suppression.

CRYPTOCOCCAL DISEASE

Microbiology: *Cryptococcus neoformans* is a widely distributed soil fungus associated with pigeon and other bird droppings. The polysaccharide capsule is antiphagocytic and a major virulence factor.

Risk Factors: Cryptococcal infection usually begins as a subclinical pulmonary infection leading to silent hematogenous dissemination. Most AIDS patients with cryptococcosis have severe immunodeficiency (CD4 = 100 or less).

Pathogenesis: Reactivation of foci seeded during primary infection occurs when immunity is compromised although unlike other OIs reactivation cryptococcal disease can occur in apparently normal, HIV negative people as well.

Clinical Manifestations: Meningitis is the most common cryptococcal syndrome in AIDS patients. Mild headache and low grade fever may be the only features. Stiff neck and major mental status compromise are uncommon. Widespread dissemination throughout the body is probably frequent involving lungs, pleura, mediastinal nodes and skin. Blood cultures are often positive. Except for the skin these other sites are rarely recognized because meningitis is easily confirmed and further diagnostic efforts are not made.

Diagnosis: Cerebrospinal fluid (CSF) is usually only mildly abnormal (lymphocytic pleocytosis and elevated protein) but the test for cryptococcal antigen is almost always positive as is CSF culture.

Treatment: Intravenous Amphotericin B is the mainstay of acute therapy. Addition of 5 fluorocytosine may be helpful. Long term suppression with oral fluconazole is highly effective.

Prevention: Use of fluconazole to prevent fungal disease in HIV + patients with low CD4 counts is effective at lowering the incidence of cryptococcal and candida disease but not mortality. Due to this lack of a mortality effect and concern about fluconazole-resistant candidiasis routine use of this prophylactic regimen is not recommended.

MYCOBACTERIUM AVIUM COMPLEX DISEASE

Microbiology: The atypical mycobacteria *M. avium* and *M. intracellulare* are soil and water organisms widely distributed throughout the world. Because they are difficult to distinguish they are usually referred to as *M. avium* complex or MAC. They are commonly isolated as saprophytes from sputum and other clinical isolates submitted to rule out tuberculosis in immunologically intact hosts.

Risk Factors: Exposure to these ubiquitous organisms is probably more intense in certain regions such as the Southeastern US judging by epidemiologic studies using special skin test reagents. HIV infected patients with very advanced disease (CD4 count <50) are at risk for the development of disseminated MAC infection.

Pathogenesis: Reactivation of a dormant MAC focus was felt to be the usual pattern of disease. Newer data suggest that recent re-infection via the GI route may be common. Loss of immune control, specifically deficient interferon gamma production, may be a mechanism accounting for the occurrence of disseminated MAC in AIDS, a syndrome virtually never seen in other comparably immunodeficient HIV-negative patients.

Clinical Manifestations: Disseminated MAC usually presents in an indolent, non-specific fashion in patients who are already chronically ill with advanced HIV disease. Fever, weight loss, anemia and diarrhea are common features. A characteristic syndrome with hepatosplenomegaly reflects massive infiltration of the reticuloendothelial viscera by MAC. Skin, lungs and brain are rarely major sites of involvement.

Diagnosis: Biopsy with acid-fast staining of affected organs is a reliable means of diagnosis but blood culture on appropriate media is usually sufficient since there is high level mycobacteremia in most patients.

Treatment: Since MAC organisms are resistant to standard anti- mycobacterial drugs, the macrolides clarithromycin and azithromycin are the main therapeutic agents. Current treatment calls for one of these drugs in combination with at least one additional agent (usually ethambutol or rifabutin) to prevent resistance. Treatment is lifelong as even this regimen is only suppressive and relapses are common unless immune recovery can be induced with antiretrovirals.

Prevention: Three drugs (rifabutin, clarithromycin and azithromycin) have been approved for preventing MAC. The major concern is development of resistance (about 50% of patients with breakthrough mycobacteremia while on clarithromycin will have resistant organisms) which then removes the best agent for treating MAC disease.

CYTOMEGALOVIRUS (CMV) DISEASE

Microbiology: CMV is a herpes group DNA virus which establishes a latent infection with intermittent asymptomatic shedding and is commonly acquired through sexual or other exposure to infectious oral or urogenital secretions. About half of normal adults are seropositive.

Risk Factors: Along with disseminated MAC, CMV syndromes occur in the most advanced stages of HIV disease and are therefore rarely the first HIV-related complications a patient experiences. The mean CD4 count at the time of CMV disease in one study was 29. As with other OIs there is growing evidence that recent re-infection may account for a portion of CMV episodes.

Pathogenesis: CMV disseminates throughout the body and persists in a proviral state so reactivation can occur anywhere. Loss of cellular immune control allows replication of the latent virus. A complex interaction between the virus and host appears to contribute to the distinct patterns of CMV disease that are associated with different kinds of immunodeficiency. For instance CMV pneumonia is common in organ transplant patients but not in AIDS where retinitis and GI tract involvement are most common. CMV hepatitis is especially common in liver transplant recipients.

Clinical Manifestations: Retinitis with visual impairment and eventual blindness is the major morbidity in AIDS patients. The GI tract can be involved at any site: manifestations include oral and esophageal ulcers, gastritis and enteritis, colitis and intestinal perforation. Increasingly CNS CMV disease is recognized in the form of polyradiculopathy, encephalitis and ventriculitis.

Diagnosis: Retinitis is diagnosed by the characteristic pattern of hemorrhage and exudate on ocular fundus exam. GI or other sites require biopsy confirmation since secretions are often positive due to asymptomatic shedding of CMV in AIDS and other immunocompromised patients and therefore are not specific for the diagnosis of active CMV disease. PCR of serum allows detection of CMV viremia.

Treatment: Three agents have been approved for treating CMV disease in AIDS: ganciclovir, foscarnet and cidofovir. While ganciclovir is now available in a well absorbed valine ester form (Valcyte) the other two agents require intravenous administration both for induction and long term suppression and all three have substantial toxicity potential. While these drugs can delay the progression of CMV retinitis they do not stop it. Reinduction is often needed and loss of vision may occur despite aggressive treatment. Another therapeutic modality is an intra-ocular implant which releases ganciclovir and is highly effective in the treated eye but gives no protection to the other eye or systemically.

Prevention. Prophylaxis has not been routinely used because of the toxicity and expense of the agents. New strategies are in development to use PCR detection of CMV in blood to identify patients for early presumptive therapy before disease is evident.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

In some patients who only begin antiretroviral treatment at an advanced stage of disease there may be a major illness provoked when the recovering immune system encounters a pathogen to which there was previously little response. This can produce the paradox of a patient with mild or no symptoms at the time antiretroviral treatment is started who become ill after several weeks to months due to an improving immune system. Many of these reactions have been associated with MAC infection which is transformed from a clinically indolent process to a highly inflammatory one. Usually continuation of HIV treatment along with management of the opportunistic infection is successful in these cases. In some instances such as the intracranial processes of toxoplasmosis and cryptococcal meningitis it seems prudent to delay anti-HIV treatment for several weeks or longer until the OI has been well controlled in order to avoid paradoxical worsening with immune reconstitution.

OTHER MANIFESTATIONS OF HIV DISEASE

In addition to the major OIs discussed above there are a wide range of other less common HIV-related complications.

Cryptosporidiosis and other infectious diarrheas. Diarrhea is an extremely common complaint especially in patients in the advanced stages of HIV disease. *Cryptosporidium parvum* causes self-limited if sometimes severe diarrhea in normal hosts. In AIDS patients it can cause a chronic, watery diarrhea that can be as severe as cholera and other secretory processes leading to hypovolemia, acidosis and death. Many other intestinal pathogens are associated with increased frequency or severity of diarrhea in AIDS patients. Two late stage OI's (MAC and CMV) also may present with diarrhea as the dominant symptom. In the majority of diarrheal episodes among AIDS patients no specific etiology can be found and management is symptomatic.

Regional mycoses. Disseminated histoplasmosis and coccidioidomycosis are important AIDS OIs in endemic areas (the Midwest, Caribbean and Central America in the case of Histo and the Southwest and west for Cocci). Histoplasmosis can present in a variety of disseminated forms including a fulminant, septic syndrome.

Neuropsychiatric processes. The nervous system is involved frequently and in a wide variety of ways in AIDS patients. A painful peripheral neuropathy and subcortical dementia are two prominent complications. Progressive multifocal leukoencephalopathy (PML) is an opportunistic, JC virus-induced white matter disease usually presenting as behavioral change or dementia in advanced AIDS patients. Depression, suicidality, pain control and substance abuse are other frequent issues in AIDS care.

Malignancies. Kaposi's sarcoma (KS), Non-Hodgkins lymphoma (NHL) and cervical cancer occur at increased frequency in AIDS. KS is strongly linked to a particular risk factor (male to male sex) and is caused by a recently identified human herpes virus (HHV 8). Lymphoma incidence is increased in advanced HIV disease especially primary CNS lymphoma. Early detection of cervical dysplasia through frequent pap smears seems an effective control strategy. Current therapy for KS and NHL is essentially palliative with chemo or radiotherapy. As with several other untreatable or poorly responsive complications of AIDS the best therapy now appears to be restoration of immune control by effective anti-retroviral therapy.

Wasting syndrome and nutrition issues. Weight loss is a common feature of AIDS, often attributable to chronic systemic infections and/or GI tract infiltrative, ulcerative or diarrheal disease. Weight restoration often occurs with successful treatment of the OI or with initiation of anti-retroviral therapy. Nutritional supplements and dietary counseling may be helpful for some patients. Severe unexplained weight loss in an HIV infected patient ("wasting syndrome" or "slim disease" in Africa) is an AIDS defining event. Neither the pathogenesis or treatment are clear but there is interest in therapy with growth hormone, testosterone, anabolic steroids and anti-tumor necrosis factor agents. In the era of antiretroviral treatment a new set of issues has arisen including obesity, even in previously wasted patients, hyperlipidemia and glucose intolerance driven both by excessive weight gain and the adverse effects of some of the antiretroviral drugs.