

AIDS in Times of HAART

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In 2006, the AIDS epidemic enters its second quarter century. There is good news and bad news. The good news from an AHRQ press release, 1 Dec 2005:

Hospital Admissions of HIV Patients Have Fallen By More Than Half Since 1995.

“The number of hospital admissions for HIV infection in the United States declined from a high of 149,000 in 1995—just before approval of life-prolonging protease inhibitor drugs known as the “AIDS cocktail”—to 70,000 admissions in 2003, according to statistics released by HHS' Agency for Healthcare Research and Quality. During the same period, the percentage of AIDS patients who died in the hospital dropped by 32 percent—from a death rate of 12.5 percent in 1995 to 8.5 percent in 2003.

The bad news:

On the same day as the AHRQ press release, UNAIDS reported that there are 40.3 million people living with HIV/AIDS and more than 25 million people have already died. Nearly 5 million people were newly infected in 2005, the single largest increase since the beginning of the epidemic. More than 90% of people living with HIV infection do not have access to treatment. And even in the United States, the fall in AIDS associated hospitalizations has not been equal. For example, close to where we are today in Atlanta, at Grady Memorial Hospital, the number of AIDS related hospitalizations has not changed appreciably with 2758 admissions among 1516 patients in 2003 compared to 1755 admissions among 1326 patients in 1996. Many of these patients are either newly diagnosed with HIV/AIDS or are not in care and thus not benefiting from HAART. However, some are admitted as a result of complications of HAART.

A Brief History of the Pandemic

Unlike the plague of previous centuries, AIDS emerged on three continents at once and continued to expand rather than decline in each area of emergence. In 1981, physicians on both coasts of the US reported clusters of previously healthy gay men with unusual opportunistic infections and tumors. The disease, originally called Gay Related Immune Deficiency Syndrome or GRID, would gradually spread from the gay community into IV drug users, hemophiliacs and blood recipients. The current term, Acquired Immune Deficiency Syndrome (AIDS) was adopted in the summer of 1982.

Within two years of the original report, cases were identified in 15 US states, Europe and Central Africa. Epidemiologists determined that the syndrome consisted of an early phase of lymphadenopathy followed by a period of apparent latency and finally resulting in immunosuppression complicated by various opportunistic infections and specific tumors (Kaposi Sarcoma and B-cell lymphoma). The initial suspected causes included sexual practices, various known viruses, amyl nitrate “poppers” and immune overload.

The etiologic agent, a previously unknown retrovirus, was first identified in 1983 at the Pasteur Institute, France, from a lymph node of a man with lymphadenopathy syndrome. Montagnier and his colleagues called the virus LAV (lymphadenopathy associated virus). Robert Gallo isolated a virus several months later that he believed to be a third human T-cell lymphotropic virus, he called his isolate HTLV III. Eventually an international committee would adopt the term human immunodeficiency virus or HIV.

FDA approved the first HIV antibody test in 1984. Serologic testing provided an important tool for both the diagnosis and surveillance of HIV infection, but also revealed that patients with good antibody responses were unable to control the infection. With the use of serologic tests, international teams were able to estimate the true extent of the disease and the incidence rates in different populations around the globe. By the mid-80's, the virus was already wide spread in Central Africa and incidence rates were much higher than expected.

During the 2nd and 3rd decades of the epidemic, prevalence rates of HIV rose to 10%-20% of adults across much of sub-Saharan Africa. The highest incidence rates are found in girls and young women. In the southern cone of Africa, up to 30% of pregnant women carry the virus. Loss of one or both parents to AIDS has left millions of orphans. The majority of cases are transmitted through heterosexual contact. Contaminated blood (transfusions and reuse of needles) and perinatal transmission are also important.

In high income countries, HIV infections continue to occur predominately in drug users and men who have sex with men (MSM). Injecting drug users in many countries have prevalence rates up to 50%. Individuals in this group are least likely to be tested early and seldom follow adequate therapy. Massive prevention and treatment campaigns among gay men reduced high risk behavior and substantially reduced AIDS mortality during the late 80's and through the 90's. But in the past 5 years, rates of sexually transmitted infections (syphilis, HIV and LGV) in gay men have spiked in groups who engage in risky sex, often in association with use crystal methamphetamine. There is also evidence that the incidence of new HIV infections is rising among young MSM of all races/ethnicities. In the United States we have the most severe epidemic among developed countries. CDC estimates that approximately 40,000 new infections occur each year and that there are over 1 million people living with HIV in America of which approximately 25% don't know that they are infected.

The epidemic in Latin America varies by location - heterosexual contact in Central America, men who have sex with men in Mexico, and injecting drug use in Brazil. Like North America and Western Europe, many Latin American countries offer testing and antiretroviral therapy. This increases the number of people living with the virus, but decreases the rates of full blown AIDS and death.

Several of the Caribbean islands have epidemics similar to sub-Saharan Africa. The majority of infections are acquired through heterosexual contact. Puerto Rico has high rates of injecting drug use. Several islands have high rates in a sub-population of men infected through sexual contact with other men. Unlike the rest of the world's regions, incidence rates in this population have stabilized in the past 2 years.

In the countries of the former Soviet Union, the epidemic began in injecting drug users but it is now spreading through heterosexual contact. The number of HIV cases in the Ukraine rose from close to zero in 1995 to 20,000 per year from 1996 onwards and HIV prevalence in Ukraine is now >1% (a number which defines a generalized epidemic).

Although prevalence rates in Asia remain low, the large populations mean high absolute numbers of cases. Although less than 10/1000 adults in India are infected, the total number of cases (~5 million) is second only to South Africa with a prevalence rate of 200/1000 adults. Experts predict that China will have 10 million infections by 2010. The major routes of transmission are through heterosexual contact, often with commercial sex workers, and injecting drug use. In addition, in rural China there has been an epidemic of HIV among plasma donors who probably became infected at the time of donation by the use and reuse of contaminated equipment.

The Changing Face of HIV Infection in the US

There are an estimated 1.3 million people living with HIV infection in the US; more than 550,000 have died since the epidemic began. Although all states and territories report cases, ten states account for 71% of all reported cases (top 5, total # of cases: NY, CA, FL, TX, NJ). Washington DC has the highest case rate (170/100,000) followed by New York (34.8). The Northeast has the highest number of HIV infections, but the Southeast has the largest number of people with full-blown AIDS.

Transmission patterns and affected populations have shifted over time. In 1985, 65% of cases were reported in men who have sex with men (MSM), 19% in injecting drug users, and 3% heterosexual. By 2003, MSM accounted for only 42%, IDU rose to 22%, with the most dramatic increase in heterosexual transmission which is now 31%.

Over the past 10 years, HIV and AIDS have disproportionately impacted minority populations, both male and female. African Americans represent 13% of the population and 40% of all AIDS cases; 67% of new cases in females and 65% of new cases in teens are in African Americans. Because this group is less likely to be tested until late in the disease and have less access to good care, they have higher death rates and shorter survival than other groups. Latinos represent 15% of the US population and 19% of all AIDS cases.

The CDC estimates that 28% of HIV-positive people are over the age of 50. Sexually active adults in retirement communities are unaware of their risks, as are many of their physicians. Some researchers refer to nursing homes as the “new breeding grounds” for AIDS.

The Impact of Antiretroviral Therapy

Zidovudine (AZT) was produced by Burroughs Wellcome Laboratories and used for the first AIDS clinical trials in February 1986. By September, the drug showed such effectiveness that trials were stopped and in the spring of 1987 Retrovir (brand name for AZT) was on the market. Despite the early therapeutic hopes of AZT, patients on monotherapy rapidly developed drug resistance. Adequate therapy has required the development of additional nucleoside reverse transcriptase inhibitors (NRTI) as well as new classes of antiretroviral drugs including the nonnucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and fusion

inhibitors. Twenty drugs have been approved by the FDA to treat HIV infection (See Table 1) and many more are on the pipeline of drug discovery.

Highly active anti-retroviral therapy (HAART) employs a combination of three or more drugs from one or more of these drug classes. In the United States, approximately one-third of known HIV-infected patients eligible for HAART are not receiving it. The CDC estimates that up to one-third of HIV-infected patients are not aware of their infection and have not been tested. MSM ages 15-22, women and minorities have the highest seroincidence rates of HIV. These groups are also the least likely to come in for testing prior to an AIDS-defining event. Men are more likely than women to be on therapy, as are whites, those with advanced education, and those in the care of physicians with experience in AIDS treatment. The lowest rates of HAART are in minorities (Hispanics > blacks) and intravenous drug users.

After the introduction of HAART, incidence of opportunistic infections and death declined by >80%. Overall hospital admissions and duration of stay also decreased. Viral suppression results in a marked increase in the numbers of CD4+ T-cells, however, studies show that increased numbers of CD4+ cells does not translate to increased immune function in all cases. Restoration of pathogen specific immunity is variable and may or may not be protective. There is poor recall antigen response and HAART treated cells do not respond well to HIV antigens.

The CDC estimates that approximately 400,000 persons are living with AIDS in the US. Although the incidence has continued to decline by 20-25% annually, so have death rates resulting in a >10% increase in AIDS prevalence (incident plus surviving cases). Many of these cases have survived five to ten years or more, resulting in an age shift in the AIDS population. Currently more than 70% of surviving persons are in the 35-64 year age groups.

The Downside of HAART

Adverse reactions to antiretroviral drugs are common and may be serious. The most frequent side effects include: hypersensitivities, dermatologic conditions, gastrointestinal complaints, headache, disorders of lipid and glucose metabolism (lipodystrophy, hyperlipidemia, impaired glucose tolerance), and hepatotoxicity. The combination of certain antiretrovirals with each other or with other medications can lead to fatal drug interactions. There may be spontaneous regression of opportunistic infections in some patients; others experience an exacerbation of these conditions during the first few months of antiretroviral therapy called immune reconstitution inflammatory syndrome or IRIS.

Antiretroviral Toxicities

Some antiretroviral drugs cause idiosyncratic reactions; for others the toxicity is dose-related or due to drug combinations and underlying medical conditions.

Hypersensitivity reactions

Nevirapine, an NNRTI, is associated with a high rate (32-48%) and severity of rash. The rash may progress to fatal Stevens-Johnson syndrome and is often associated with eosinophilia and systemic symptoms. Acute hepatitis with markedly elevated aminotransferases and jaundice are reported in HIV-infected patients and in HIV-negative patients receiving post-exposure prophylaxis. Most reactions occur within the first 3 months of therapy. Women, especially

those with a CD4 count > 250 cells/uL have 12-fold increased risk of developing adverse reactions. Particularly severe is abacavir hypersensitivity reaction. This syndrome is seen in approximately 5% of patients prescribed abacavir (which exists alone (Ziagen) or in combination with 3TC (Epzicom) or with ATZ and 3TC (Trizivir) and is characterized by fever, rash, fatigue and gastrointestinal symptoms. If the drug is not discontinued the patient progresses to multisystem organ failure and death. There is rapid improvement when the drug is discontinued but, once this diagnosis is made, the drug should never be restarted in that patient as rechallenge is uniformly fatal. The presence of HLA-B 5701 strongly predicts abacavir hypersensitivity reaction.

Dose-related toxicity

Long term toxic effects of the nucleoside analogs are due, in part, to mitochondrial damage and increased production of lactic acid and other toxic byproducts.

Myotoxicity

As early as 1988, AZT was known to cause toxicity of peripheral and cardiac muscle related to mitochondrial damage. Both non-necrotizing and necrotizing myopathy are reported in patients on long-term monotherapy. Cardiomyopathy and rhabdomyolysis are rare complications of high cumulative doses.

Lactic acidosis and hepatic steatosis

This rare but serious side effect of antiretroviral drugs is caused by damage to the mitochondria of the hepatocytes. Patients present with severe nausea, vomiting and abdominal pain followed by tachypnea. This problem has been reported with zidovudine, didanosine and especially stavudine. Severe cases are rare and since the availability of nucleosides in 1986 there have been less than 100 cases reported to the FDA. However, mild lactic acidosis is much more common with up to 10% of patients having mild elevations in serum lactate. When lactic acidosis is suspected serum lactate should be measured and frequently a liver biopsy is obtained. In addition to this syndrome there are other hepatic abnormalities in patients with HIV/AIDS and the liver is now one of the most important organs to consider when treating HIV-infected patients because of the rising rates of morbidity and mortality associated with Hepatitis C liver disease in this population. There are several patterns of liver injury: hepatocellular, cholestatic, and mixed. Massive mitochondrial injury due to nucleoside analogues leads to swelling and lysis of the hepatocyte (necrosis). Lesser degrees of injury (intracellular stress) due to metabolic or cytokine damage cause cell shrinkage and apoptosis.

Drug metabolites can also damage endothelium and bile duct epithelium. Biliary damage produces cholestasis. Stavudine has higher rates of steatosis; nevirapine has higher rates of fibrosis. Periodic monitoring of lactate in patients-at-risk (especially obese women who are taking stavudine) is recommended.

Antiretroviral drugs may cause direct hepatotoxicity but liver damage is often related to the interaction of HIV and HBV/HCV in response to HAART. The overall rate for severe hepatotoxicity is approximately 10% and can cause morbidity, mortality and result in discontinuation of antiretroviral therapy. Co-infection with HCV or HBV and alcohol use are

both associated with increased severity of hepatic lesions. Women are at higher risk for fatty liver as are patients with decreased creatinine clearance.

PIs can cause both hepatocellular and cholestatic disease; a pattern of ballooning degeneration with pericellular fibrosis is associated with administration of ritonavir. Combination therapy may cause even greater hepatotoxicity. Indinavir and Atazanavir inhibit hepatic enzymes and can cause asymptomatic, reversible hyperbilirubinemia similar to Gilbert syndrome.

Metabolic dysfunction and morphologic abnormalities

Lipid and glucose abnormalities are also associated with mitochondrial dysfunction. Three forms of morphologic changes are seen in patients on antiretroviral therapy: lipodystrophy, lipoatrophy, and lipohypertrophy. In lipodystrophy fat accumulation is usually truncal with buffalo hump between the shoulders or increased abdominal girth, but has also manifested as gynecomastia and multiple lipomas. Lipoatrophy is peripheral and includes diffuse or focal fat loss in the limbs or the face. Patients with lipodystrophy were more likely to have truncal adiposity, impaired glucose tolerance, diabetes, hypertriglycerides and decreased HDL. Cardiovascular disease risk factors are markedly elevated in patients with fat redistribution. Breast lipodystrophy and gynecomastia increased in men on HAART.

Cardiovascular disease can be a result of lipid and glucose abnormalities or from toxic effects of lactic acid. Myocyte necrosis, cardiomyopathy and arteriosclerosis all contribute in the cardiovascular disease in this population. Age, smoking history and genetic risk factors increase the rates of cardiovascular pathology. Early studies show dramatic increases in carotid artery intima-media thickness. This can be reversed with lipid-lowering agents. The true impact of HAART on coronary artery atherosclerosis and subsequent myocardial infarctions will probably increase with duration of therapy, especially in those with known cardiac risk factors of smoking and hypertension.

Osteonecrosis and osteopenia

Osteonecrosis with avascular necrosis is increased in patients on antiretroviral therapy. Suggested mechanisms include: antiphospholipid antibodies, hyperlipidemia (PIs may contribute to lipid abnormalities, but are not the sole factor). Patients on tenofovir appear to have increased loss of bone mineral density. Hips and shoulders are the most common sites. It occurs in all known risk groups and is not associated with T-cell counts or viral load. Pain and radiologic evidence of fractures or lytic lesions may lead to request for a bone biopsy to rule out infection or malignancy. Histology reveals osteopenia, osteonecrosis with microsequeae, fibrosis, and osteoblastic activity.

Immune Restoration Syndrome

Following the initiation of highly active antiretroviral therapy (HAART) some patients develop exaggerated local and systemic inflammatory reactions. The immune restoration disease (IRD), also known as immune restoration inflammatory syndrome (IRIS) usually occurs within the first 6 months of initiating therapy and coincides with a rapid increase in CD4+ T-lymphocytes and the resulting immune reconstitution. The reaction is thought to be due to increased hypersensitivity to the antigens. IRD reflects dysregulated immune responses against pre-existing infections with different immunopathological mechanisms for different pathogens.

These paradoxical reactions have been reported most commonly in cases of tuberculosis and MAC disease involving lymph nodes as well as surrounding soft tissue. CNS conditions include retinitis, uveitis and vitritis due to CMV, symptomatic cryptococcal meningitis, toxoplasmosis and exacerbation of progressive multifocal encephalopathy, HIV encephalitis and Parvo B19 focal encephalitis. Other reported conditions include granulomatous PCP, acute viral hepatitis B and/or C, HPV-associated oral warts, recurrent herpes zoster, erosive HSV, sarcoidosis, Grave's disease, Guillian-Barre syndrome, and aggressive KS. Reactions in the gastrointestinal tract can mimic appendicitis, ulcerative colitis, or Crohn disease clinically. Abdominal adenopathy has been diagnosed as lymphoma on CT scan and often causes abdominal pain.

Histologic features include reactive lymphadenopathy, edema and granulomatous reactions, often with few or no organisms identified. Atypical lymphoid or histiocytic lesions are sometimes misinterpreted as malignancies. CD8 lymphocytes are often increased in these reactions. CD8 lymphocytosis is manifestation of IRIS in the CNS related to PML and HIVE.

A marked inflammatory response in the absence of an easily identifiable etiology should suggest this condition in an HIV-infected patient. Clinical history or recent initiation of therapy or other immune modulation (including IL-2 or interferon therapy) is important in making the differential diagnosis.

Treatment Failure

Not all individuals on HAART have equal benefits. Some of the factors that portend a poor outcome include: advanced disease at the initiation of therapy, infection with multidrug resistant strains of the virus, poor compliance, and inability to tolerate therapy. In addition, many patients with HIV infection who are well controlled on HAART are now dying from liver failure as a result of advanced Hepatitis C.

Current Trends in the Surgical Pathology of HIV and AIDS

The following are predictions that I made in 1996 USCAP course regarding the surgical pathology of HIV and AIDS:

1. For those patients who have never taken or are no longer on HAART, we can expect to see the same AIDS-indicator conditions that have been prevalent in specific geographic areas in the past.
2. HIV/AIDS patients have many of the same diseases as others in their age cohort (non-AIDS related diseases). This is important to consider since the median age of this population is increasing. The most common co-morbid conditions in the >50 age group are cardiovascular diseases, chronic pulmonary diseases, liver diseases, diabetes and tumors.
3. HAART may not decrease the incidence or severity of viral-induced tumors.
4. There will be many more cases of AIDS in women (increased rates of HPV-induced dysplasia?).
5. Tuberculosis, bacterial pneumonia and drug-related conditions are more frequent in minorities and injecting drug users.
6. HAART and prophylactic medicines are toxic. There will probably be a significant number of adverse drug reactions in these patients.

In the years since I made those predictions, HAART has changed HIV infection from a uniformly fatal disease to a chronic illness, but the benefits are still limited to a small percentage of the 40+ million infected worldwide. As the epidemic expands, many international agencies are focused on narrowing the treatment gaps. Until that time, individuals who are not tested early and do not receive prophylaxis and antiretroviral therapy will continue to die from opportunistic infections and AIDS-related tumors.

The undiagnosed and untreated in the US are most likely to be women, minorities, injecting drug users, young gay men and senior citizens. HIV-related conditions and other co-morbidities vary widely among these subpopulations. Drug-resistance and treatment failure (for any reason) may result in similar end-stage outcomes.

There are several trends already evident that are directly influenced by the changing demographics of the epidemic and to the marked increase in years of survival for those on effective therapy.

As mortality rates decrease and long-term survival rates increase, those on HAART are more likely to die of non-AIDS causes such as drug-overdose, suicide, hepatic and cardiovascular disease, and non-AIDS malignancies. Mortality rates are higher in women, individuals over 50 years of age, IDUs, and patients with viral hepatitis. Smoking contributes to 2/3 of cancer deaths and alcohol to more than half of deaths due to liver disease. Approximately 1% die of complications of HAART.

End-stage liver disease has become the leading cause of death in some HIV-cohorts. Risk factors include co-infection with hepatitis B or C, ethanol abuse, use of hepatotoxic drugs other than ART and length of ART exposure. Cholestasis may be poor prognostic marker. Alcoholic

and non-alcoholic steatohepatitis progress to fibrosis and cirrhosis at higher rates and in shorter time in patients with HIV-Hep C coinfections.

A VA cohort study found that ethanol abuse was common and often missed among HIV patients. This was related to poor adherence to HAART, increased liver disease, and higher rates of unprotected sex.

Kaposi sarcoma is the only HIV-related cancer that has decreased with HAART. Both non-Hodgkin and Hodgkin lymphomas occur at much higher rates in HIV-infected patients despite HAART. This may be due to longer survival rates and lower death rates from opportunistic infections in chronically immunosuppressed individuals.

HPV-related anogenital neoplasias have increased progressively since the beginning of the HIV epidemic. HIV-infection is associated with higher HPV prevalence, higher rates of oncogenic-risk types, persistent infection and neoplasia. Although the highest rates are in men who have sex with men, anal intraepithelial neoplasia occurs in both men and women who have no history of anal receptive intercourse. Cytology is adequate for cervical disease, but has low specificity for anal lesions.

The number of aggressive squamous cell carcinomas is greater than before in other sites such as lung, larynx, esophagus (so called aerodigestive squamous cancers) and skin. Lung cancer occurs at a young age (median 45 yrs) in HIV-infected smokers even in the absence of severe immunodeficiency. Prognosis is poor because of extensive disease at diagnosis and poor response to therapy. Several studies show the incidence of lung cancer in patients on HAART, is directly related to the number of years with HIV infection.

Renal disease, hypertension, and diabetes are important non-AIDS diseases in inner city African American women with HIV. They are also more likely to have metabolic syndrome, rash and lactic acidosis. HAART often exacerbates, rather than improving these conditions.

Hopefully, in 2016, I will be able to give a presentation on HIV-infection and AIDS that includes data on an effective vaccine, a declining epidemic and universal access to therapy. Despite the progress in therapy and increased hope for longer and better quality life for those living with HIV in the industrialized world, *HAART is not available to 92% of those living with HIV in developing countries.* Yet there is some cause for optimism. Unprecedented multilateral and bilateral initiatives are poised to make comprehensive HIV/AIDS care the world's best-funded public health initiative but many challenges lie ahead. It is now critical to sustain these efforts to remediate the gross inequalities in access to treatment that have existed for over a decade.

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Table 1 Antiretroviral Drugs

| Antiretroviral Class/Drug Names |
|---|
| Fusion Inhibitors |
| Enfuvirtide (Fuzeon, T-20) |
| Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) |
| Delavirdine (Rescriptor) |
| Efavirenz (Sustiva) |
| Nevirapine (Viramune) |
| Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) |
| Abacavir (Ziagen) |
| Abacavir + Lamivudine + Zidovudine (Trizivir) |
| Didanosine (Videz, ddI) |
| Lamivudine (Epivir, 3TC) |
| Lamivudine + Zidovudine (Combivir) |
| Stavudine (Zerit, d4T) |
| Tenofovir DF (Viread) |
| Zalcitabine (Hivid, ddC) |
| Zidovudine (Retrovir, AZT, ZDV) |
| Protease Inhibitors (PIs) |
| Amprenavir (Agenerase) |
| Atazanavir (Revataz) |
| Emtricitabine (Emtriva, FTC) |
| Fosamprenavir (Lexiva, 908) |
| Indinivir (Crixivan) |
| Lopinavir + Ritonavir (Kaletra) |
| Nelfinavir (Viracept) |
| Ritonavir (Norvir) |
| Saquinavir (Fortovase, Invirase) |