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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

HIV update 2005: Origins, issues, prospects, and complications

ABSTRACT

Morbidity and mortality rates of human immunodeficiency virus (HIV) have plummeted where highly active antiretroviral therapy (HAART) is available. However, therapy is out of reach for most people who need it in developing nations, where the infrastructure to deliver care and resources for medications is lacking. Worldwide, the epidemic is increasing at alarming rates.

KEY POINTS

The origin of HIV from chimpanzee viruses is now well established. Related viruses in many other primate species have also been identified, underlining the danger that new strains may emerge in humans.

About 70% of HIV cases are in sub-Saharan Africa. In the United States, African Americans have the highest rate of new infection, 2.5 times higher than Hispanics and 9 times higher than Caucasians.

Vaccine efforts to date have largely failed. Basic understanding of protective immunity is still needed. Microbicides have potential for prevention, but are still in early phases of development.

Significant side effects of long-term HAART are now being seen in the United States, including fat redistribution, insulin resistance, a worsened lipid profile, and increased risk of myocardial infarction.

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THE EPIDEMIC of human immunodeficiency virus (HIV) continues to grow unabated, especially in African nations, which are unable to adequately address prevention and treatment needs. Prevention through vaccines and microbicides will not be a viable option for years. Where highly active antiretroviral therapy (HAART) is available, it has brought considerable benefit, although cardiovascular risk increases with long-term use.

This article provides an update on several important issues in the HIV epidemic, including:

- Current thinking on the origins of the disease
- Global epidemiology and health care needs
- At-risk populations in the United States
- Vaccine and microbicide development
- Complications of HAART.

CLASSIFYING HIV

HIV is a retrovirus that comes in two forms: HIV-1, which is responsible for most of the worldwide epidemic, and HIV-2, which is largely in western Africa and in pocket areas where immigrants from this region reside.

HIV-1 can be subdivided into three groups:

- Group M (main), which can be further subdivided into subtypes known as clades A through K
- Group O (outlier)
- Group N (non-M, non-O).

ORIGINS OF THE EPIDEMIC

HIV arose from simian immunodeficiency virus (SIV) in nonhuman primates: HIV-1 from SIV_{CPZ} from the chimpanzee *Pan*

troglodytes, and HIV-2 from SIV_{SM} from the sooty mangabey monkey *Cercocebus atys*.

More than 30 primate species have been identified as having SIV subtypes, and within each species, 16% to more than 20% of animals harbor the virus. Some of these primates have extremely high levels of viremia, but very little immune activation and no clinical illness. Many of these viruses have been shown to be capable of productive infection in human lymphocytes.

Chimpanzees and monkeys are hunted for food and kept as pets in Africa, leading to frequent human contact with their bodily fluids. Evidence indicates that transmissions have occurred repeatedly through the years; the earliest one recorded happened sometime between 1920 and 1940.

Why do we have an epidemic now if primates and humans have lived together for centuries? Modern social factors may be responsible, including the opening of interior areas with urbanization and logging, "bush meat" becoming a commercial enterprise rather than being eaten at home for subsistence, prostitution, and the advent of "modern" medicine, which can efficiently transmit a virus to many people via a single dirty needle.

New transmission events leading to new strains of HIV are all but inevitable. Detecting new epidemics is important: treatment differs for HIV-1 and HIV-2, and new strains will likely need to be treated differently as well.[1]

In Africa, 4.1 million people need HIV treatment, but < 2% are getting it

ATTACKING THE GLOBAL PROBLEM

HIV and acquired immunodeficiency syndrome (AIDS) continue to increase at an alarming rate around the world. An estimated 40 million people now live with HIV; 5 million new infections and 3 million deaths occurred in 2003, with 500,000 of those deaths in children. Sub-Saharan Africa has the majority of cases, with 28 million people infected, but there are also epidemics of concern in China, India, the Caribbean, Southeast Asia, and Russia.

In Africa, 4.1 million people need treatment now, as defined by a CD4 count of less than 200 cells per mL, a standard far stricter than is used in the United States. Only 70,000 to 100,000 of these patients, or fewer than 2%, are actually receiving therapy.

When plans were first considered to provide HAART in developing countries, experts expressed concern that adherence would be poor and resistance would flourish because of widespread illiteracy, lack of refrigeration, and the difficulty of keeping a strict time schedule in societies where few people wear watches.

Such concerns have not been borne out. Studies of adherence in Africa show rates as high as and in some cases better than rates in San Francisco and San Diego. The real barriers in developing countries are lack of infrastructure and money to purchase medications and laboratory tests.

Brazil offers a successful model. At the beginning of the AIDS epidemic in Brazil, the government decided to provide free antiretroviral treatment to every infected person, even in remote areas of the country. Generic drug supplies were aggressively pursued. Over the years, this policy has resulted in a net cost savings with greater avoided expenditures than antiretroviral costs.

Current initiatives

The World Health Organization (WHO) has proposed the "3 by 5 Initiative" to provide lifelong treatment to 3 million people by 2005. This comprehensive plan includes providing infrastructure as well as monitoring and delivery systems. An estimated additional $200 million is needed for the current operating budget to meet this goal.

The cost of medications and laboratory tests remains a major barrier. Pharmaceutical companies are under pressure to provide drugs at a reduced cost or to release patents so that generic companies can provide them. Progress has been made: all companies now offer drugs at lower prices in developing countries, and recently GlaxoSmithKline granted licenses to generic companies to produce drugs in India and South Africa for only 5% royalties.

The WHO has also established a prequalification program to more swiftly evaluate generic drugs for safety and efficacy. Unfortunately, the United States has refused to pay for medications that are not under patent and has proposed a separate evaluation system that is even more stringent than the one used by the US Food and Drug Administration; it would require clinical trials of each drug separately, which is

no longer ethical. Currently, this policy is being reevaluated.

The Clinton Foundation has been instrumental in negotiating lower prices with manufacturers of drugs and laboratory tests. They recently negotiated lower costs for a generic three-drug combination pill (not available in the United States) that provides complete antiretroviral therapy. The cost is $132 per person per year vs $562 when the components are bought individually at developing-country prices.

The Global Fund to Fight AIDS, Tuberculosis, and Malaria, started in January 2002 and spearheaded by Kofi Annan, finances initiatives in eligible countries in both the private and public sectors, and especially encourages grass roots organizations to submit proposals for local programs.

This program was designed to be funded by donations of 0.7% of each country's gross national product. It is, in fact, extremely underfunded, with only $4.7 billion committed through 2008. The United States, which should contribute $1.2 billion per year, only allocated $305 million in 2004 and $200 million for 2005.

Ongoing challenges

Problems with testing are a major barrier to the success of public health efforts. For example, identifying 3 million patients with the threshold CD4 counts for the WHO 3 by 5 Initiative requires that 100 million people be tested.

Rates of access to and utilization of voluntary counseling and testing sites are very low. Encouraging people to be tested is especially difficult if treatment is not available.

Even in Uganda, which has the most advanced HIV and AIDS treatment program in Africa, only 1.2% of adults aged 15 to 49 visited testing centers. The estimated cost to increase testing in Africa from current levels to 6% per year is $1 million.

Prevention campaigns. Initial prevention campaigns were simple and catchy: eg, "Avoiding AIDS is as easy as ABC: Abstain, Be faithful, use Condoms."

Unfortunately, we now realize the situation is not so simple. Women between the ages of 15 and 25 are infected at twice the rate of men. Many of these women are married and believe they are in a monogamous relationship.

Maternal-child transmission. Optimism soared when early studies found that a single dose of nevirapine (Viramune) given to an HIV-infected mother at labor and a second dose given to the baby reduced HIV transmission from over 30% to 12%.

Unfortunately, subsequent studies showed that treated mothers later demonstrated resistance to the class of drugs to which nevirapine belongs, a class that is instrumental in most fixed-dose combinations used in developing countries. Mothers exposed to nevirapine showed a subsequent therapeutic response to triple therapy at a rate of 34% to 53% after 6 months vs a 75% response rate in women who were not exposed.[2]

TRENDS IN THE US EPIDEMIC

African Americans have highest rates. In the United States, minority populations have disproportionately high rates of HIV. A 4-year, 29-state survey by the Centers for Disease Control completed in 2002 found nearly 103,000 new cases. Rates in African Americans were 2.5 times higher than in Hispanics and more than 9 times higher than in Caucasians. While African Americans make up only 12.3% of the American population, they account for nearly half of newly infected men and 72% of newly infected women.

Gay men seem to be picking partners with the same HIV status

Rates in colleges climbing. A study by Hightow et al[3] demonstrated an increasing incidence of new HIV infections in college-age men in North Carolina. The incidence increased from 4% in 2000 to 15% in 2003. An association was noted with black race, use of party drugs, use of the Internet, and bisexuality.

Risky behavior in already-infected populations. Data from San Francisco show that while the incidence of HIV has plateaued, the incidence of syphilis has risen sharply in recent years. This may be the result of men "sero-sorting" themselves (picking partners with the same HIV status). They still frequently practice unsafe sex, leading to the spread of other sexually transmitted diseases, possibly resistant HIV viruses, and more problems with treatment in time.

"Down low" culture. An emerging high-risk group is members of the so-called "down

low" culture, consisting predominantly of African American men who have steady female partners as well as casual male contacts. They engage in unprotected sex, and often do not know their HIV status, nor do they wish to be tested.[4]

Herpesvirus. The presence of active herpes simplex increases the risk of HIV infection 2 to 4 times. When both infections occur simultaneously, higher viral loads are seen both initially and in later disease states. The higher viral loads have been associated with more rapid progression to AIDS.

Prison system. Within the United States, 17% of prisoners are HIV-positive, leading to an estimated 17,000 to 25,000 infected individuals released back into the community annually. Currently, a uniform system for returning this population into the general population does not exist. In Chicago, a partnership between Rush Presbyterian Hospital and the Cook County jail is attempting to meet this need.

VACCINE DEVELOPMENT UNSUCCESSFUL TO DATE

Even a partially effective microbicide would prevent millions of HIV cases

Vaccine efforts have encompassed a variety of strategies based on various types of vectors, protein subunits, recombinant peptides, and DNA. Two large trials, the AIDS VAX B/B trial in North America and Europe and the AIDS VAX B/E trial in Thailand, demonstrated that early forms of the vaccine conferred no protection against HIV.

Animal vaccine approaches have also been unsuccessful. Basic questions about the immune correlates of protection still need to be answered. Some animals have a good antibody response but no protection against infection, while others have no response but seem to have some degree of protection.

For most people, natural immunity to HIV is ineffective. However, a very small percentage have a particularly effective response and develop high antibody levels. Through an approach called reverse vaccinology, the antigen-antibody interactions are being studied in an attempt to develop more fruitful vaccine efforts.

The true surrogates for protective immunity have also yet to be elucidated. It is uncertain whether we need cytotoxic T-cell responses, B-cell responses, or both, or how to sustain the immune response.

Individual virus variability complicates the picture. Not only is there variation between the clades, but there may be sequence variability of the glycoprotein spikes on the surface of transmembrane proteins of the HIV envelope, adding another degree of difficulty in developing effective vaccines.

An effective vaccine will likely need to provide mucosal immunity, humoral and cell-mediated responses, and effectiveness against a constantly changing virus. Considerable work still needs to be accomplished.

MICROBICIDES

Microbicide development has been ongoing since the early 1980s, and many experimental products are now in the making. Even if imperfect, microbicides have great potential to make a significant impact. The London School of Hygiene and Tropical Medicine calculated that a microbicide that is only 60% effective and used by only 20% of women worldwide could prevent several million HIV infections a year.

Possible microbicide candidates include physical barriers, agents that disrupt the virus via a detergent-type mechanism, and those that block fusion and insertion of the virus with CD4 cells. Therapeutic drugs may also work as microbicides. Cervical rings, for example, may be impregnated with medications against HIV to fight the virus at that site.

The development of microbicides presents a formidable challenge. It is unlikely that the first products will be available for 6 to 10 years. They must:

- Be effective against different cell types involved in transmission—in the vagina, endocervix, exocervix, rectum, uterus, and possibly the oral cavity
- Allow the target environment to maintain a normal pH and microflora to preserve natural protection
- Protect against all HIV phenotypes and clades
- Function in different physiologic fluids, including mucus, blood, and semen.

CLINICAL CONSIDERATIONS OF HAART

About 400,000 to 500,000 people in the United States are on HAART. Although patients are frequently seen by subspecialists, all physicians should have a working knowledge of HIV diagnosis and treatment.

The advent of HAART in the mid 1990s brought about a plummeting of morbidity and mortality. However, new complications have arisen as a result of therapy (TABLE 1).

Lipodystrophy

About half of patients on chronic therapy develop lipodystrophy,[5] the selective loss of subcutaneous fat. There is a characteristic loss of fat in the face and distal extremities as well as occasional central fat accumulation. "Buffalo-hump" fat, scapular fat pads, and subcutaneous lipomas are also seen.

Those at higher risk for developing lipodystrophy are women, patients older than 40 years, and those who have been on therapy longer.[6,7] Nucleoside analogues such as stavudine (d4T, Zerit) are more likely to cause it than nucleoside reverse transcriptase inhibitors such as abacavir (Ziagen) and zidovudine (AZT, Retrovir). Switching drugs may modestly reverse the condition.[8]

Lipodystrophy is associated with a variety of metabolic factors that are significant for vascular disease, such as insulin resistance, dyslipidemia, and hypertension. It is also disfiguring, making patients less likely to adhere to therapy.

Insulin resistance

Up to half of patients on protease inhibitors develop insulin resistance, and up to 10% have frank diabetes, more than twice the expected rate.[9] Patients on indinavir (Crixivan) appear to be especially at risk. Experimentally, rats administered only a single dose of indinavir appear to develop perturbations of glucose-insulin homeostasis.[10] Patients starting therapy should have baseline glucose measured, and should undergo glucose tolerance testing if other risk factors for diabetes are present.

Dyslipidemia

Lipid abnormalities were noted in treated patients even before the advent of HAART.

TABLE 1

Major complications of HAART

- Lipodystrophy
- Insulin resistance and diabetes mellitus
- Dyslipidemia
- Atherosclerosis and coronary artery disease
- Lactic acidosis
- Osteopenia
- Mitochondrial dysfunction leading to neuropathy

HAART causes elevated triglyceride levels and increased LDL while HDL remains low, creating an especially high-risk pattern. The United States HIV/AIDS Consensus Panels recommend that all patients newly diagnosed with HIV have baseline fasting lipid profiles and that lipids be aggressively managed with traditional lipid-lowering therapy.

Cardiovascular disease

Other indicators of accelerated vascular disease due to HAART include increased C-reactive protein levels, poorer immune activation profiles, age-inappropriate carotid artery intimal thickness, and increased lesions within coronary arteries as shown by electron beam computed tomography.[11,12]

Several studies have demonstrated small but significant increases in risk for myocardial infarction in HIV patients on HAART therapy.[13–15] More definitive evidence was provided by the European Cooperative Study, which prospectively observed more than 23,000 patients in 11 centers over 1.6 years and found that risk of myocardial infarction was proportional to years of exposure to HAART, with a 26% increased risk per year over the first 4 to 6 years.[16]

The benefits of antiretroviral therapy far outweigh the increased risk of mortality from heart disease. However, heart disease is expected to become a formidable problem as patients are now expected to live for decades on HAART. Doctors should recognize the increased risk, use medications as appropriate, and apply National Cholesterol Education Program guidelines.

The benefits of HAART far outweigh the risks of heart disease

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