

HIV/AIDS: Lessons from a New Disease Pandemic

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Introduction

The acquired immunodeficiency syndrome (AIDS) was first recognized about 25 years ago (Gottlieb et al., 1981; Masur et al., 1981; Siegal et al., 1981). The best available evidence suggests that HIV newly infected the human species about 50–100 years ago (Korber et al., 2000). It did not originate in Asia. It apparently moved to people from sub-human primates in Africa (Keele et al., 2006; Kanki, 1997). Because of different clinical presentations in different populations of people, and a long incubation period, it was more difficult to diagnose than SARS or avian influenza.

As a new epidemic that originated in the era of modern medicine, it taught us many lessons about the difficulties that a new infectious disease can present. Already claiming at least 60–80 million victims, AIDS seems destined to continue as a pandemic for the foreseeable future. Drugs that control HIV replication and reverse disease progression have been developed, but none eliminate the virus from the body. Sexual transmission can be prevented by abstinence or condoms, but such measures, which prevent procreation, provide only limited value.

Approaches for making a vaccine using conventional techniques have failed. Most experts believe that an effective vaccine will be made eventually, but not for at least 10–20 years. We need to learn more about the immunobiology of acute HIV infection, and about potentially protective immunopeptides, such as conformational intermediates of the virus envelope. Until a vaccine is available, there is little or no chance that HIV can be eliminated, or even drastically reduced in prevalence. AIDS has presented scientists, political leaders, and health policy experts with unprecedented challenges.

History

The first diagnosis of AIDS occurred when small groups of homosexual men in a few US cities presented with unusual diseases. The diseases observed, particularly Kaposi's sarcoma, pneumocystis pneumonia, and *Mycobacterium avium* tuberculosis,

had not been seen previously in young men, except perhaps in very rare and sporadic cases associated with other problems such as terminal cancer or immunosuppression associated with organ transplants. Of great importance for the initial identification of the AIDS epidemic, these outcomes occurred in unrelated young men who knew each other. Such a clustering in time and space is often the key clue to the etiology of a new infectious disease.

In the case of AIDS, however, infectious agents were not initially pursued as the most likely cause of the new disease. The first clusters of AIDS were among homosexual men who indulged in promiscuous recreational sex, a lifestyle associated with performance-enhancing drugs such as amyl and butyl nitrates. Early hypotheses to explain the disease often favored the use of such drugs, or autoimmune responses to antigens presented by rectal sex (Francis et al., 1983).

For most infectious disease experts who favored a microbial etiology, retroviruses were not high on the list of candidates (Rogers et al., 1983). Although retroviruses were well known as a cause of leukemia, lymphoma, and even immunosuppression in chickens, laboratory mice, and cats, the first human retroviruses had just been described in 1980 (Poiesz et al., 1980).

The clinical characterization of the AIDS complex soon revealed that it was a disease of the immune system, particularly one where CD4 T helper responses became depleted. Ultimately, the loss of CD4 cells would be one of the most reliable ways to diagnose AIDS, along with detection of HIV.

As various investigators searched for the cause of AIDS, both the Gallo group and our own hypothesized that a human retrovirus might be involved (Essex et al., 1983a; Gallo et al., 1983; Gelmann et al., 1983). The rationale for this hypothesis was based in part on the recognition that lymphotropic feline retroviruses caused immunosuppression in cats (Essex et al., 1975), and that the recently discovered human leukemia retroviruses infected the same CD4 lymphocyte population that became depleted when people developed AIDS. Additionally, patients who developed leukemia following infection with the first human lymphotropic retrovirus (HTLV-1) also experienced immunosuppression (Essex et al., 1984).

Pursuit of a Retroviral Etiology

The first attempts to link a human retrovirus to AIDS included various approaches. One approach involved the use of HTLV-1 as an antigen to search for cross-reacting antibodies in the serum of AIDS patients and people who were involved in the same epidemiological circles. Such individuals included, for example, donors who provided blood used for transfusions associated with AIDS development or blood product preparations given to hemophiliacs (Curran et al., 1984; Essex et al., 1983b). Patients from high risk categories, such as homosexual men and injection drug users, were also similarly screened when they experienced symptoms such as lymphadenopathy or oral candidiasis. A second approach to screen AIDS patients involved assays for reverse transcriptase activity using enzyme conditions that had

been developed for HTLV-1 (Barre-Sinoussi et al., 1983; Gelmann et al., 1983). A third major approach was the use of electron microscopy, to determine if particles similar to retroviruses could be found in tissues from AIDS patients (Barre-Sinoussi et al., 1983). All of these approaches yielded some degree of success, but none gave consistent positivity as an indication of complete success.

Incubation Period

In retrospect, it seems clear that two aspects of HIV/AIDS made the etiology more difficult to solve. First was the long incubation period, which ordinarily lasts 5–10 years before disease develops. This obviously made the tracking and linking of clinical AIDS cases unusually difficult and disease detectives much less likely to suspect an infectious cause. The second was the wide range of lethal clinical outcomes. While it was clear that patients died from such conditions as pneumocystis pneumonia or tuberculosis, many were reluctant to accept destruction of the immune system as a common denominator.

With most cases occurring in groups that were often marginalized by discrimination, such as homosexuals and infectious drug-users, some denied the very existence of AIDS as a new disease (Duesberg, 1988). This in turn led to a substantial delay before resources were allocated in developed countries to identify the cause and attempt measures of control. Political leaders in some developing countries also pursued a course of denialism under the mistaken impression that this would conserve financial support for health care and avoid reductions in tourism.

AIDS in Africa

The first cases of what was thought to be AIDS in Africa were reported a few years after the American cases (Clumeck et al., 1983). This happened when a few Africans sought medical treatment in Europe. The earliest epidemics within Africa were from the central and eastern regions. The most severe epidemic, which is in southern Africa, came considerably later (Essex & Mboup, 2002).

In West Africa, a modest epidemic of HIV-2 preceded the invasion of HIV-1 (Kanki, 1997). HIV-2 is less virulent than HIV-1, by both the criteria of transmission and of disease development (Kanki et al., 1994; Marlink et al., 1994). Perhaps a million people became infected with HIV-2, with the highest prevalence in Guinea-Bissau and southern Senegal. Infections were also observed in other countries in West Africa, and in sites such as Mozambique, Angola, Goa, and Cape Verde, which were apparently connected by colonial trade routes. Aside from a few diagnoses in travelers or immigrants from these regions, HIV-2 never appeared to expand elsewhere in Africa, in Europe, or in the U.S.

As of 2006, almost two-thirds of the world's infections with HIV are in Africa (UNAIDS, 2006). An even higher proportion of the deaths from AIDS are in sub-Saharan Africa, in part because treatment is less likely to be available there as compared to other regions of the world. As opposed to most other regions of the world, the vast majority of infections in Africa are due to either heterosexual transmission or transmission from infected mothers to their infants. In Asia, injection drug-users represent the most important population for transmission, at least in the early stages of the epidemic.

Viral Variation

Soon after the recognition of major differences between HIV-2 and HIV-1, it became apparent that these viruses evolved more rapidly than other viruses known to cause human diseases. Some, such as the HIV-2s of West Africa, have probably had multiple entries to people from mangabey monkeys. Some HIV-1s are very closely related to viruses of chimpanzees (Keele et al., 2006) (See Fig. 1).

HIV-related viruses in subhuman primates, designated simian immunodeficiency viruses (SIVs), were actually identified in Asian monkeys before they were identified in African monkeys or apes (Daniel et al., 1985; Kanki et al., 1985). However, in retrospect it seems clear that the viruses originated in Africa, not Asia. Many species of African monkeys have evidence of infection with SIVs, whereas wild Asian monkeys do not. It appears that captive Asian monkeys in research colonies initially became infected when injected with experimental materials. Furthermore, Asian monkeys become sick with an AIDS-like illness when injected with SIVs, whereas African monkeys or apes do not become ill when injected with SIVs and/or HIVs.

HIVs have been categorized into groups and subtypes, which differ from each other by 15–30% in nucleotide and amino acid sequences. Subtypes HIV-1A, B, C,

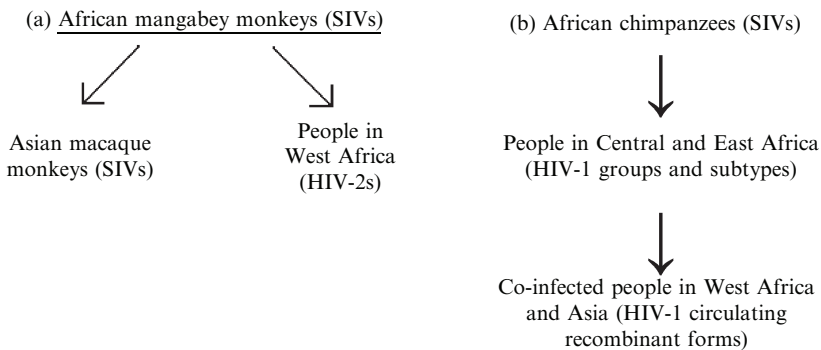


Fig. 1 Evolutionary origin of human immunodeficiency viruses

and D are particularly important because they have infected at least a million people. In the case of HIV-1C, perhaps 25 million people have become infected with the virus.

It is still not clear whether certain subtypes of HIV-1 entered people independently from subhuman primates, or diverged to form distinct subtypes after they already existed in people. In the case of HIV-1B and HIV-1D, it is most likely that they diverged in people, as these viruses are more similar than either is to other subtypes. In the case of HIV-1C and HIV-1A, it seems possible that they entered separately into the human population.

The HIV retroviruses also replicate through the use of a diploid genome that contains two complete copies of all viral genes. As a result, when a single human cell happens to get infected with two different HIVs, recombinants are created. These recombinants retain block segments from each parental virus. When the two parental viruses represent different clades or subtypes, intersubtype recombinants develop. Some of the new recombinants, or chimeras, represent circulating recombinant forms (CRFs) that themselves infect large populations of people.

In places such as Tanzania, where high rates of multiple subtypes such as A, C, and D are already present, up to one-third of the infectious viruses found in infants infected from their mothers were new intersubtype recombinants (Renjifo et al., 1999). The virus that caused the first major epidemic in Asia is CRF01_AE, which apparently originated in the region of the Central African Republic (Gao et al., 1996). Although HIV-1B, from the west, was the first virus detected in injection drug-users in Bangkok, it was rapidly overtaken by CRF01_AE, which now predominates in Thailand, Myanmar, and the Kunming region of China. Another recombinant, CRF02_AG, is the second most common virus in the world, predominating in the countries of West and West Central Africa (Essex & Mboup, 2002). The viruses that are most important in China at present are CRFs made as recombinants of HIV-1B and HIV-1C. The two that are most common are designated CRF07_BC and CRF08_BC (Piyasirisilp et al., 2000; Su et al., 2000; Qiu et al., 2005). Unlike CRF01_AE, these viruses have not been reported outside Asia and so they presumably originated from B and C parental viruses that were already present in the region.

Clinical Significance of Genomic Variation

The elevated mutation rates characteristic of HIVs are responsible for the rapid emergence of drug resistance, especially in HIV-infected people treated with only one or two drugs rather than the three-drug combinations often called highly active antiretroviral therapy (HAART). The use of only one or two drugs happened more often in earlier stages of the epidemic, when fewer drugs were available, but it is also widely practiced when chemoprophylaxis is used to reduce the transmission of HIV from infected mothers to their infants.

Antiretroviral drugs have been very effective for treating clinical AIDS and for chemoprophylaxis in all parts of the world. However, when drug resistance develops, fewer options may be available for switching to new drug combinations in the developing world. The first drugs available were nucleoside analogue reverse transcriptase inhibitors, such as zidovudine, or non-nucleoside reverse transcriptase inhibitors, such as nevirapine. Such drugs have become less expensive and more readily available in developing countries. However, the drug resistance mutations they elicit are often shared by other drugs of their class. Newer drugs that do not share the same patterns of drug resistance, such as the protease inhibitors, the fusion inhibitors, and the integrase inhibitors, are much more expensive and less likely to be available as back-up regimens for patients who become resistant to the first-line drugs in developing countries. For this reason, monitoring for adherence or compliance during therapy is extremely important, particularly in sites where limited drug regimens and highly experienced therapy specialists may not be available.

Some drug resistance mutations may develop more readily with certain viruses. This has been observed, for example, as (1) higher rates of resistance in HIV-1C-infected people, such as pregnant women given nevirapine during labor (Eshleman et al., 2005), (2) faster development of resistance to tenofovir through K65R when selected in vitro in HIV-1C-infected cell cultures (Brenner et al., 2006), and (3) faster development of the resistance mutation D30N when HIV-1C AIDS patients were given nelfinavir (Doualla-Bell et al., 2006).

The high rates of genetic variation observed with HIVs also provide the largest hurdle to the development of vaccines. Antibodies directed at the V3 (i.e., 3rd variable region) of the outer envelope glycoprotein (gp120) can be quite effective for neutralizing the virus. However, with rapid mutation and selection, variant viruses that are not neutralized by the same antibodies soon occur in the same individual. This pattern of immunoselection and immune evasion also occurs with immunodominant epitope targets used by the cytolytic T-cell response, and probably represents the single greatest impediment to the development of an effective vaccine. Current approaches to overcoming this problem involve the targeting of immune responses, through immunogen design, to selected conserved regions. These include structural determinants in gp120 that are exposed as conformational epitopes when the virus unfolds to attach to a co-receptor, and cytolytic T-cell epitopes that contain highly conserved residues for virus survival.

Infection Rates in Asia

According to UNAIDS (2006), infection rates in Asia range from less than one per thousand, for countries such as Japan or Korea, to almost 2% for countries such as Papua New Guinea or Cambodia (See Table 1). Thailand has an estimated rate of 1.4%, and India 0.4% (UNAIDS, 2007). Because it is a very large country, this translates to a total number of about 2,500,000 HIV-infected people in India (UNAIDS, 2007). This is the largest number of total infections for any country in Asia, although

Table 1 Estimated rates of HIV infection in adults in selected countries (UNAIDS, 2006,2007)

Country	HIV in adults		
	Rates	Numbers	Ratio of infection (men/women)
<i>Asia</i>	0.2	4,875,000	2
Australia	0.1	16,000	15.0
Cambodia	1.6	130,000	1.2
China	0.1	650,000	2.6
India	0.4	2,500,000	2.5
Indonesia	0.1	170,000	4.9
Japan	<0.1	17,000	0.7
Myanmar	1.3	350,000	2.2
Papua New Guinea	1.8	57,000	0.7
Thailand	1.4	560,000	1.5
<i>Europe</i>	0.3	760,000	2.3
France	0.4	130,000	1.9
Germany	0.1	49,000	2.3
Spain	0.6	140,000	3.4
<i>North America</i>	0.6	1,300,000	2.6
United States	0.6	1,200,000	3.0
<i>Sub-Saharan Africa</i>	5.0	22,500,000	0.6
Nigeria	3.9	2,600,000	0.6
Senegal	0.9	56,000	0.7
South Africa	18.8	5,300,000	0.7
Swaziland	33.4	210,000	0.8
Uganda	6.7	900,000	0.7

South Africa has a larger number of total infections (5,100,000) with a very small fraction of the population. China has an estimated rate of one per thousand, but because it is such a large country, this comes to about 560,000 people.

In western countries, such as the United States, France, or Spain, rates of infection (0.4–0.6%) are similar to those in India. Some countries, such as Germany or Poland, are estimated to be as low as China. However, the epidemic in the west appears to have plateaued, while it probably has not plateaued in China. In most places in Asia, the HIV epidemic began a decade or more later than it began in the West or in Africa.

In sub-Saharan Africa, HIV infection rates are about 20-fold higher than in Asia, although in southern Africa, which has the most severe epidemic, rates are about 60-fold higher. In Swaziland, for example, it was estimated that about one-third of all adults are infected.

Another major difference between the epidemics of the world is the ratio of infection in men versus women. In Asia, as in the US and Europe, substantially more men are infected than women. In Africa, women are infected significantly more often than men. Considerable variation may occur in selected countries in Asia, however, and Papua New Guinea has a sex ratio that is similar to that of sub-Saharan Africa. Higher ratios in men are generally indicative of transmission by homosexual sex and/or injection drug use, whereas higher rates in women, as in Africa, are generally indicative of an epidemic spread by heterosexual contact.

Conclusions: Lessons from the Newly Emerging Epidemics of HIV/AIDS

One key lesson from HIV/AIDS that seems very common to other infectious disease threats such as SARS and avian influenza is that new human pathogens often enter from other animal species. In the case of HIV/AIDS, this probably occurred when people butchered subhuman primates and, covered with infected blood, perhaps exposed their arms through open wounds. As with other diseases, such cross-species transmissions were rare events rapidly amplified by urbanization and travel. HIV is not spread by inhalation or ingestion, and was harder to identify as compared with the etiologic agents of other new epidemics because of the very long incubation period before disease development.

Another lesson from HIV is that the ability of the organism to rapidly evolve may pose major complications for treatment, vaccination, and even detection. For HIV, as with influenza, genetic change occurs both through the accumulation of mutations and by the exchange of entire genes (recombination in the case of HIV, reassortment in the case of influenza). With both viruses, large genetic changes occur most rapidly when individuals are co-infected with two different parental viruses.

In conclusion, many infectious disease agents have entered the human population from lower animals and we should expect such events to continue to occur in the future. With the numerous opportunities to spread rapidly in people due to modern travel, an increased surveillance of infections in both animals and people may be important.

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