

HIV IN AFRICA: EPICENTER OF THE GLOBAL PANDEMIC

The epidemiology of HIV-1 infection and the divergence of viral subtypes occurring in sub-Saharan Africa were discussed at the San Francisco course by David A. Katzenstein, MD.

There is persuasive evidence that HIV originated in primates in central Africa. Researchers have isolated viruses similar to HIV-1 from chimpanzees and to HIV-2 from sooty mangabees. Available serologic evidence indicates that HIV-1 was present in humans in central Africa in the 1960s; numerous hypotheses regarding the migration and global spread of virus thereafter have been put forward, including the role of international travel in the spread of the HIV-1 B subtype that predominates in the United States and Europe and among infected homosexual men and intravenous drug users. Figure 1 shows the estimated numbers of adults and children living with HIV-1 infection as of the end of 1998; sub-Saharan Africa accounts for nearly two-thirds of these cases and more than 5 million new infec-



Figure 1. Estimates of adults and children living with HIV infection as of end of 1998. Courtesy of UNAIDS, <http://www.unaids.org>.

tions are projected to occur this year. Figure 2 shows the proportional increase in global HIV prevalence rates between 1994 and 1997. Figure 3 shows the spread of HIV infection and increase in prevalence rates between 1982 and 1997 in sub-Saharan Africa, with cases clustering around Lake Victoria initially and spreading outward thereafter.

The impact of HIV infection in sub-Saharan Africa has been catastrophic, with more than 10 million deaths from HIV disease. Life expectancy has undergone a sharp reduction in many countries as a result of mortality from HIV in both children and adults, returning to levels present before the institution of immunization and other public health programs. Figure 4 (see page 22) shows the estimated impact of HIV-1 disease on mortality in children less than 5 years old in selected countries.

In many countries, obstetric and prenatal clinic programs have provided a great deal of epidemiologic data on HIV, which indicate that the epidemic is not increasing at equivalent rates in all countries. Seroprevalence rates among pregnant women in areas in East Africa and West Africa appear to increase more gradually than rates in the southern cone of the continent. In some of these areas, seroprevalence exceeds 30% in prenatal clinic populations. A recent finding indicating that pregnancy rates in Uganda are lower among HIV-1-infected women (14.2%) than among uninfected women (21.4%) suggests that estimates of seroprevalence in women of childbearing age may be underestimated by prenatal clinic

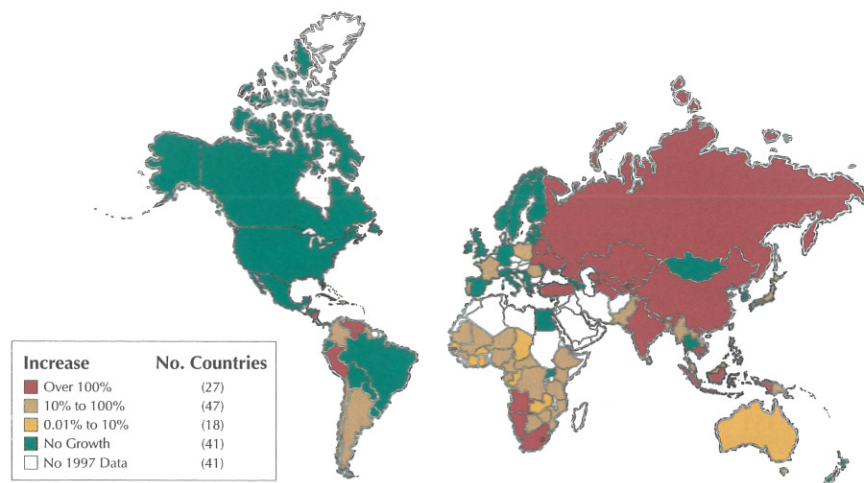


Figure 2. Proportional increase in prevalence of HIV infection between 1994 and 1997; in some locations, increase is heavily influenced by increased reporting. Courtesy of UNAIDS, <http://www.unaids.org>.

BEHAVIORAL FACTORS ASSOCIATED WITH RAPID HETEROSEXUAL SPREAD OF HIV IN AFRICA

TRANSPORT AND WORK PATTERNS

Drivers often purchase sex along overland truck routes through East Africa. Large numbers of men, separated from their families and working in mines and factories, may be housed adjacent to their work place in "single men's hotels" encouraging concomitant (sexual) partnerships with a small group of commercial sex workers.

MIGRATION

Movement from rural to urban areas because of employment opportunities or agricultural disaster has led to loss of traditional structures of monogamy and polygamy and enforcement of sexual taboos. Incursions of armies and guerillas and mass migration of civilian populations in civil war contribute to a breakdown in traditional sexual relationships.

DEMOGRAPHICS

The majority of the population in Africa is under the age of 15. Large numbers of women entering adolescence may seek (or be sought by) older male sexual partners (who have a high prevalence of HIV infection). The average age of first pregnancy in most African countries is 17 to 18, suggesting many young women are sexually active.

SEXUALLY TRANSMITTED DISEASES

Acquisition of gonorrhea, syphilis, chancroid, and herpesvirus are associated with risk for HIV infection.

SEXUAL NETWORKS

Sexual networks map the numbers of concomitant or serial sexual relationships within a community or group. The example of the small number of commercial sex workers who supply sexual services to a large community of men working in mines and factories has been examined as a model that may lead to high prevalence of HIV among sex workers and their male partners.

surveys. Other data indicate that more than 25% of men and women in their 20s are infected in Zimbabwe, Malawi, Rwanda, Burundi, parts of South Africa, Zambia, and Botswana. Among sexually transmitted disease patients, commercial sex workers, the military, and the police, infection rates of greater than 50% are common.

It remains unclear to what degree the rapid spread of the epidemic in Africa is associated with ecologic factors—the environmental and behavioral dynamics in societies—and with biologic factors—the pathogenetic and genetic factors in both host and virus. Ecologic factors include transport routes, migration, changes in demographics, and influence of sexually transmitted diseases and sexual networks (see sidebar). Biologic factors include human and viral genetic variation and diversity of immune response. However, it is known that a large diversity of viral subtypes has emerged, and it is becoming increasingly clear that such factors as cellular tropism, viral regulatory genes, and

the contribution of other infections to viral shedding and susceptibility to infection may play a role in the dynamics of HIV infection in Africa.

Currently, there are 10 known subtypes of HIV-1, designated as A through J, in the major (M) group. These subtypes differ from each other by more than 10% in nucleoside sequences for the viral envelope, the key region for cellular receptor binding. They are more closely related to each other, however, than they are to the outlier subtypes O and N of HIV-1 and the more distantly related HIV-2. Many of these major subtypes are present in Africa. Whereas most infected homosexual men in North and South America, Europe, and Australia are infected with the subtype B virus, this subtype is relatively infrequent in Africa. Heterosexual transmission of infection has been predominantly associated with subtypes A, C, D, and E. Most of the isolates from infected individuals in Uganda, Kenya, and equatorial West Africa are subtypes A or D, with subtype C consti-

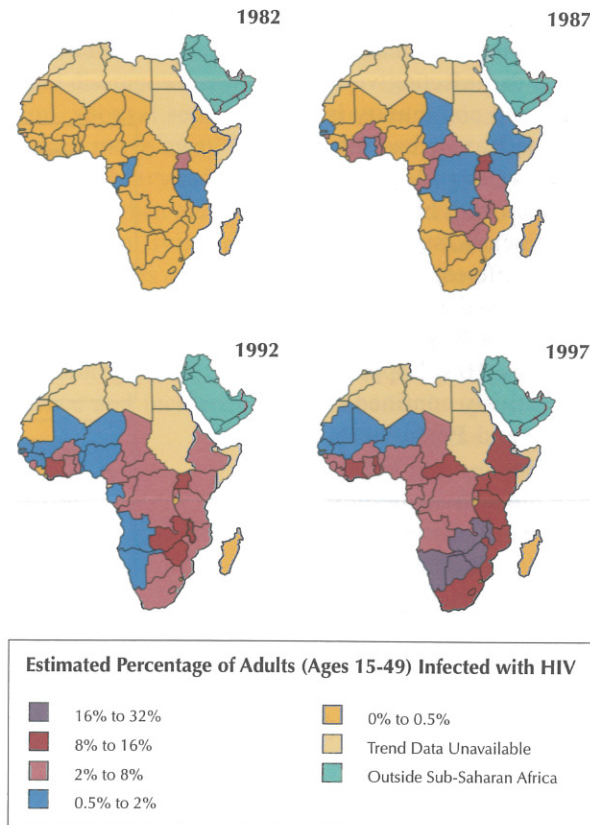


Figure 3. Spread of HIV infection and increase in prevalence rates between 1982 and 1997 in sub-Saharan Africa. Courtesy of UNAIDS, <http://www.unaids.org>.

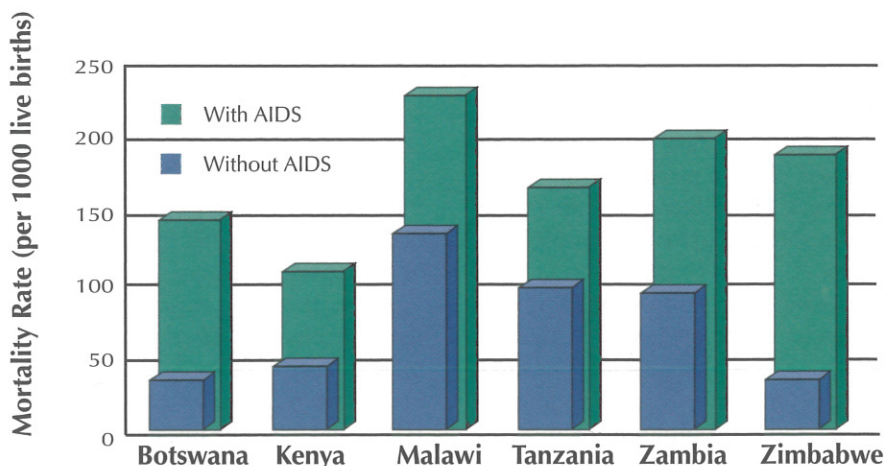


Figure 4. Estimated impact of HIV disease on mortality in children less than 5 years old by 2010. Courtesy of UNAIDS, <http://www.unaids.org>.

lead to more rapid disease progression compared with other viral subtypes. The study found that in Senegal, where subtype C virus is still a minority subtype, women infected with subtype C virus exhibited a more rapid progression to AIDS compared with women who acquired infection with other subtypes (Figure 7). It should be noted, however, that cross-sectional studies comparing prevalent infection with subtypes A, B, C, and D among Swedes and Africans in Sweden did not find a difference in disease severity. A study of the shedding of HIV in semen, conducted by Cohen and colleagues in Malawi, provides another example of a possible difference between subtype C and other subtypes. It showed that the presence of gonococcal urethritis in males is associated with higher seminal HIV virus load, with a significant decrease in viral shedding being observed after antibiotic treatment. Comparing the levels of viral RNA detected in semen in

tuting a minority. Subtype C, however, is the predominant viral subtype throughout southern Africa (Figures 5 and 6), where infection rates are increasing most rapidly, and in Ethiopia. This subtype has also recently entered India and China, where it can be expected to be the dominant virus in the coming years. Research by Van Harmelen and colleagues in South Africa has shown that the infecting virus in the white homosexual community is predominantly subtype B, whereas subtype C predominates among black and colored men and women with heterosexual risks. This phenomenon, suggesting separate epidemics for different viral subtypes, has also been observed in Thailand, with separate epidemics of B and E subtypes in separate groups. HIV-2 appears to have remained relatively confined to parts of West Africa and Portuguese-speaking African nations.

Zimbabwe has the second-highest prevalence of HIV-1 infection in the world, after Botswana, both involving infection with subtype C virus. In Zimbabwe, among a population of 10 to 12 million, seroprevalence studies indicate infection rates of 1.0% and 0.3% in 17- to 20-year-old female and male blood donors, 18% to more than 30% in prenatal women, 15% to 30% in factory workers, 90% in commercial sex workers, 60% to 75% in sexually transmitted disease patients in city clinics, and 66% to 80% in tuberculosis inpatients.

Differences in HIV prevalence

within Africa may be explained by behavioral or biological factors. A recent study by Kanki and colleagues provides evidence that subtype C virus infection may

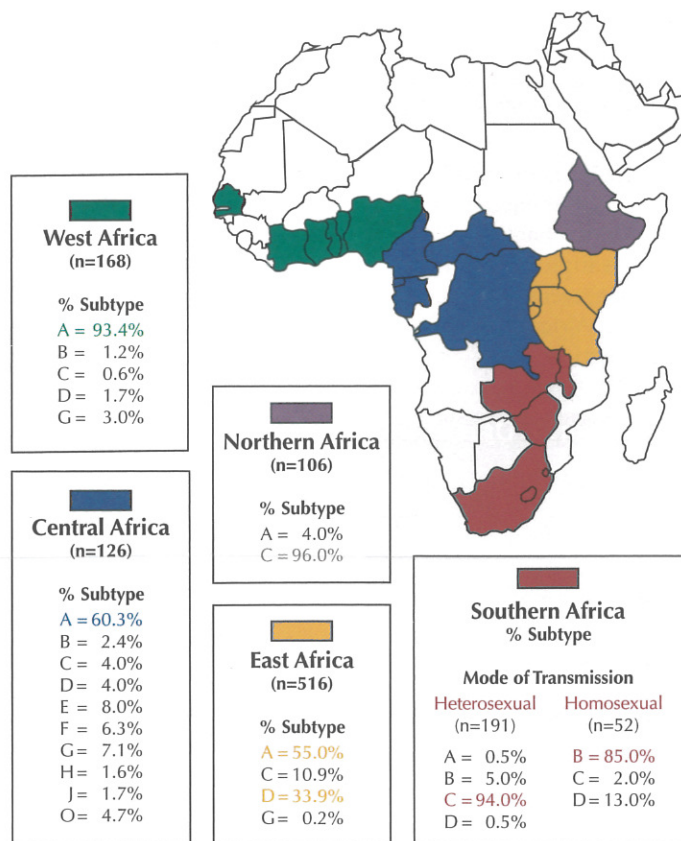


Figure 5. Distributions of subtypes by region in serologic studies. Adapted from Janssens W, et al. The puzzle of HIV-1 subtypes in Africa. AIDS. 1997; 11:705-712.

men in Malawi before and after treatment, it was further observed that seminal viral load in those with subtype C virus is strikingly higher than that observed in subtype B infection, although these comparisons are made across studies in Africa and Europe.

A distinct feature of subtype C viruses has been identified in the structure of the regulatory region of the long-terminal repeat, which may explain the increased levels of genital virus in association with sexually transmitted disease in subtype C infection. Studies of subtype C isolates from Ethiopia, Zimbabwe, and Botswana demonstrate repeated NF- κ B binding sites in a pattern that is distinct from other subtypes. Subtype C virus have 3 or sometimes 4 κ -B binding sites in the long-terminal repeats. In vitro, these result in increased transcription in response to cellular activation by tumor necrosis factor- α and other inflammatory cytokines that increase cellular NF- κ B activity.

Subtype C isolates are also different in their nearly exclusive use of CCR5 as a coreceptor as the predominant second receptor with CD4 for viral entry. In several studies of subtype C, including patients with advanced HIV disease, nearly all subtype C isolates were CCR5-tropic (X5 viruses), while in advanced disease it is common in subtypes A, B, and D infection to find a phenotypic switch to CXC4 (X4) tropism.

In addition to potential viral factors underlying the establishment of subtype C infection in a population of more than 100 million people south of the equator, there

are a number of other factors that may explain the rapid spread of HIV-1 infection. These include frequency of multiple sexual partners; attitudes, practices, and beliefs regarding condom use; and the role of patriarchy and disempowerment of women. In addition, spousal separation may be involved; men move away from their families to work for heavy industries and mining operations in urban areas, and the concentration of men living apart from their families encourages casual sexual partnerships and commercial sex provided by a relatively small number of women. Additional biologic risk factors include the prevalence and incidence of

sexually transmitted diseases and genital ulcers; circumcision practices; prevalence of bacterial vaginosis; and the use of intravaginal agents and practice of "dry" vaginal intercourse.

Effective prevention of HIV-1 infection in Africa depends on education, counseling, testing, provision of condoms, and the treatment of other sexually transmitted diseases. The institution of programs for prevention depends largely on local initiatives and conditions. In some countries, programs targeting sex workers or other segments of the population have resulted in demonstrable benefits in reducing transmission rates. However, the only real hope for widespread prevention in the foreseeable future is the development of an effective vaccine; this endeavor is itself fraught with formidable obstacles, including the genetic variability of HIV-1. Overall, there are enormous challenges inherent to providing prevention and treatment services in countries that are among the poorest in the world. The HIV pandemic is likely to prove the severest test of global cohesion and cooperation across economic and social divides in the coming century.

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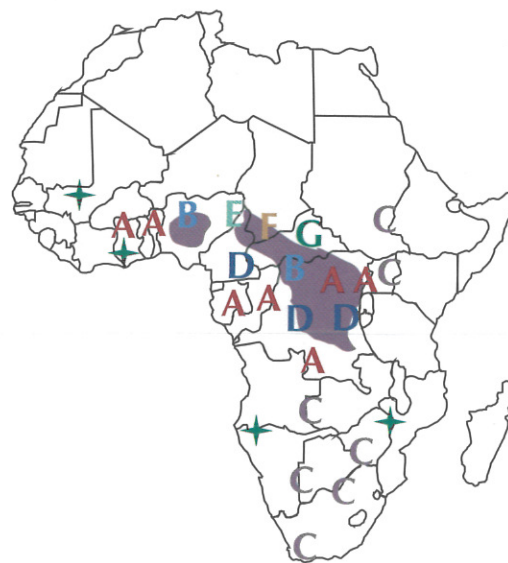


Figure 6. Dominant HIV-1 subtypes in sub-Saharan countries. Green stars show areas of HIV-2 infection. Courtesy of DA Katzenstein, MD.

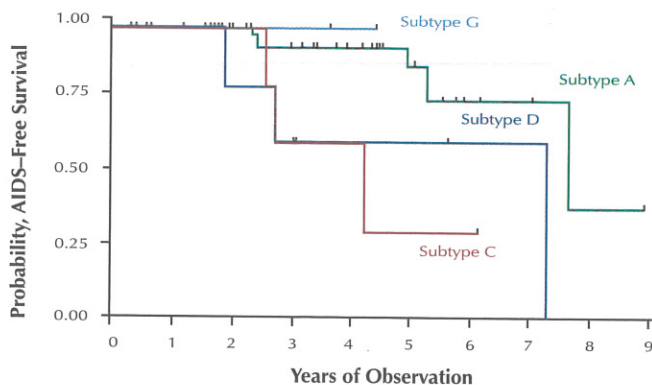


Figure 7. Probability of AIDS-free survival by viral subtype in infected female sex workers from Senegal. Adapted from Kanki PJ, et al. *J Infect Dis.* 1999.

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