are occurring. With recent reductions in the price of antiretroviral drugs for Africa — and with the development of the Global Fund for AIDS, Tuberculosis, and Malaria — there is renewed optimism that antiretroviral drugs may soon be made available to those afflicted with AIDS. Unfortunately, while the developed world shares in the benefits of these drugs in terms of increased survival, decreased mortality, and decreased hospitalizations, fewer than 1% of AIDS patients in Africa have access to antiretroviral therapy.

In a sense, it is a sad commentary that the conclusions and recommendations that can be made today are in fact similar to those we made in 1986. What has changed is that the epidemic is now much worse, millions more have died or have been orphaned, and the effects of the epidemic are even more profound in African communities. In retrospect, if we thought the AIDS epidemic had reached a crisis in 1986, then it is now a medical emergency of unprecedented proportions that threatens the social, economic, and cultural framework of Africa. Such an epidemic requires immediate and unprecedented international assistance to support effective interventions to prevent transmission and to provide financial resources for care of those already infected and suffering from AIDS. ■

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AIDS in Africa: An Epidemiologic Paradigm

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Cases of the acquired immune deficiency syndrome (AIDS) have been reported in countries throughout the world. Initial surveillance studies in Central Africa suggest an annual incidence of AIDS of 550 to 1000 cases per million adults. The male to female ratio of cases is 1:1, with age- and sex-specific rates greater in females less than 30 years of age and greater in males over age 40. Clinically, AIDS in Africans is often characterized by a diarrhea-wasting syndrome, opportunistic infections, such as tuberculosis, cryptococcosis, and cryptosporidiosis, or disseminated Kaposi's sarcoma. From 1 to 18% of healthy blood donors and pregnant women and as many as 27 to 88% of female prostitutes have antibodies to human immunodeficiency virus (HIV). The present annual incidence of infection is approximately 0.75% among the general population of Central and East Africa. The disease is transmitted predominately by heterosexual activity, parenteral exposure to blood transfusions and unsterilized needles, and perinatally from infected mothers to their newborns, and will continue to spread rapidly where economic and cultural factors favor these modes of transmission. Prevention and control of HIV infection through educational programs and blood bank screening should be an immediate public health priority for all African countries.

The acquired immune deficiency syndrome (AIDS) has become recognized as a global health problem. Cases have now been reported in 74 countries with more than 25,000 cases in the United States, nearly 3,000 cases in other countries of the Americas, more than 3,000 cases in Europe, and several thousand cases suspected and many more unrecognized in Africa (*1, 2*). It is estimated that at least several million people worldwide have been infected with the causative agent, referred to as human T-lymphotropic virus type III (HTLV-III)/lymphadenopathy virus (LAV), or more recently as human immunodeficiency virus (HIV) (*3*). As many as 10 to 30% of these HIV-infected individuals may develop AIDS within the next 5 to 10 years (*4–6*). With the present lack of a curative therapy or vaccine, this disease now ranks as the most serious epidemic of the past 50 years.

Although the immunopathogenesis of HIV infection is similar in most AIDS patients (*7*), the epidemiology and clinical features of the infection in different countries may vary, depending on cultural

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differences, endemic diseases, and other unidentified risk factors. In Africa, the different clinical features of AIDS and the difficulty in identifying the risk factors frequently associated with AIDS in the United States, such as homosexuality and intravenous drug use, have raised questions regarding the nature of the disease and the factors responsible for HIV dissemination in that continent (*1, 2, 4*). Here we review the epidemiologic and clinical features of AIDS in Africa and discuss the potential problems faced by public health officials in developing prevention and control strategies.

Historical Perspective

Shortly after the recognition of AIDS in the United States, cases of the disease were identified among Africans residing in Europe (*8*). Immunologically, these cases were identical to AIDS cases in the United States, with marked depression of $CD4^+$ lymphocytes (T-helper cells) and cell-mediated immunosuppression. Clinically, the African cases resembled Haitian AIDS cases with prominent gastrointestinal symptoms and opportunistic infections, such as oroesophageal candidiasis, cryptococcosis, toxoplasmosis, and mycobacterial infections (*8–10*). As of 31 March 1986, 177 cases of AIDS were reported among Africans residing in ten European countries (Table 1) (*2*). These cases originated from 24 African countries, mostly in Central Africa. In contrast to the European cases, African cases had a male to female ratio of 1.7:1, and 90% had no identifiable risk factors. Even among Europeans with AIDS and a recent history of travel to Africa, nearly 90% denied homosexuality or intravenous drug use.

These unusual epidemiologic features prompted a series of investigations in 1983 to determine the pattern of AIDS in Central Africa. During a 4-week period, 38 patients with AIDS and 20 patients with AIDS-related diseases were identified in a large general hospital in Kinshasa, Zaire (*11*). Cases were equally distributed among men and women; females with the disease were younger and more often unmarried than male AIDS patients; and clusters of AIDS cases among men and women were linked by heterosexual contact. In a simultaneous investigation of 26 cases in Kigali, Rwanda, 43% of the female patients were identified as prostitutes (*12*). The fact that there was no evidence of homosexual transmission or intravenous drug use indicated that the pattern of AIDS transmission was different, and that heterosexual contact might be an important factor in transmission.

Although the recognition of AIDS in Africa is consistent with the temporal occurrence of the disease in the United States and Haiti, several case reports and retrospective serologic surveys of banked sera have suggested that HIV infection may have occurred earlier in Africa (*13–15*). The earliest serologic response to HIV was found in serum collected from Kinshasa, Zaire, in 1959 (*14*). Sera from West and East Africa in the 1960's and early 1970's have also shown a high prevalence of weakly positive specimens (for example, seropositivity in 1.4% of 144 children from Burkina Faso in 1963, and in 50 of 75 Uganda children in 1972–1973) (*15*). However, serologic studies of HIV in Africa have been inconsistent because of problems in interpretation of the results from ELISA's (enzyme-linked immunosorbent assays) and Western blot tests of banked specimens, particularly from malaria endemic areas, and the validity of these data has been questioned (*15*, *16*).

While it is difficult to determine precisely when and where the first cases of AIDS or HIV infection occurred in Africa, retrospective studies on the frequency of certain clinical diseases as sentinel markers of AIDS indicate that there was a marked increase in cases in Africa during the late 1970's and early 1980's. Epidemic increases in chronic, life-threatening enteropathic illnesses were noted in the late 1970's in Kinshasa and in the early 1980's in Uganda and Tanzania, where this was referred to as "slim disease" (*17*). In Rwanda, a marked increase in esophageal candidiasis was first noted in 1983 in a hospital where approximately 300 esophagoscopies had been performed annually since 1979 (*12*). In Kinshasa, the annual number of cases of Kaposi's sarcoma diagnosed in a large public hospital tripled from 1970 to 1984, and the number of aggressive Kaposi's sarcoma cases increased eight times in 1981 (*11*, *18*). Investigators in Zambia and Uganda also reported a marked increase in disseminated Kaposi's sarcoma starting in 1982 and 1983 (*19*). Finally, careful surveillance of cryptococcal meningitis in Kinshasa showed a sevenfold increase in 1978–1984 compared with the period in 1953–1977 (*20*). These studies suggested that while isolated cases of AIDS may have occurred in Africa earlier, it was probably rare until the late 1970's and early 1980's, a pattern similar to that in the United States and Haiti.

Present Magnitude of the Problem

The geographic scope and intensity of AIDS and HIV infection in Africa is difficult to assess precisely. First, infectious disease surveillance capability is often limited because of weaknesses in the health infrastructure and inadequate resources. Second, the widely used CDC/WHO definition of AIDS (*21*) requires sophisticated laboratory support for diagnosis of opportunistic infections and

Table 1. Adult AIDS cases diagnosed in 26 European countries through 31 March 1986, by risk group and geographic origin. Data from the WHO Collaborating Center on AIDS in Paris, France (*2*).

Patient risk group	Europe	Caribbean	Africa	Other*	Total
Number	2162	61	177	73	2473
Male : female ratio	16:1	1.4:1	1.7:1	16:1	10:1
Homosexual/bisexual male	73%	8%	5%	85%	67%
Intravenous drug user	11%	3%	0%	1%	10%
Homosexual male and intravenous drug user	2%	0%	1%	1%	2%
Hemophiliac	4%	0%	0%	1%	4%
Blood transfusion	2%	0%	4%	4%	2%
No known risk factor					
Male	4%	49%	50%	3%	9%
Female	2%	36%	30%	1%	4%
Unknown	2%	3%	10%	4%	2%

*Other includes patients whose major place of residence included countries of North and South America, Asia, Oceania, and the Middle East.

Table 2. Annual incidence of AIDS among adult Kinshasa residents. Incidence was calculated by extending the number of cases documented from July 1984 to February 1985 to a 1-year period. This figure was then multiplied by 0.9, since approximately 90% of cases occurred among Kinshasa residents. The 1983 statistics were used to calculate age-specific rates. Adapted from Mann *et al.* (*24*).

Age group (years)	Cases per 1 million adults	
	Men	Women
20–29	155	417
30–39	786	601
40–49	748	180
50–59	337	83
≥60	168	0
Total	365	394

Table 3. Prevalence of HIV antibody in selected populations in Nairobi, Kenya, and Kinshasa, Zaire, between 1970 and 1985. Data were collected from stored sera from previous studies (1970, 1980–1981, 1983–1984) and from ongoing prospective serosurveys (1985–1986) of selected populations in Nairobi and Kinshasa. Seropositive specimens were repeatedly reactive on two commercially available ELISA's and were confirmed by Western blot. STD sexually transmitted diseases; NA, not available.

Sera from	Year of study				Reference
	Number of positives/number tested (%)				
	1970	1980–1981	1983–1984	1985–1986	
		Nairobi, Kenya			
Female prostitutes	NA	5/116 (4%)	66/130 (51%)	126/215 (59%)	(*31, 33*)
Men attending STD clinic	NA	2/188 (1%)	13/93 (14%)	19/107 (18%)	(*33*)
Pregnant women	NA	0/111 (0%)	NA	15/735 (2%)	(*33*)
		Kinshasa, Zaire			
Pregnant women	1/500 (0.2%)	15/500 (3%)	NA	36/449 (8%)	(*32, 34*)

malignancies and exclusion of other known causes of immunodeficiency, and is not applicable to developing countries. Third, diagnostic services for opportunistic infections and for serodiagnosis of HIV infection are not yet generally available. Furthermore, serodiagnosis is complicated by the need for confirmatory testing because of the presence of possible cross-reacting antibodies (*16, 22*). However, African countries in collaboration with international investigators are now attempting to address these issues so that a clear picture of the descriptive epidemiology of AIDS in Africa is gradually emerging.

On the basis of available information, it appears that Central Africa and, to a lesser degree, adjacent countries in East and Southern Africa, are most severely affected by HIV infection (*18, 23*). HIV is being increasingly detected in areas of Africa previously thought to be free of infection, although, with few exceptions, the data are inadequate to distinguish between recent introduction of the virus and recent recognition or awareness of the problem. Investigators extrapolating from 1983 studies in Kigali, Rwanda, and Kinshasa, Zaire, estimated the annual AIDS incidence in 1983 to be 800 per million and 170 per million population, respectively (*11, 12*). AIDS surveillance has continued in Kinshasa where 332 cases were identified between July 1984 and February 1985, for an adjusted annual incidence of approximately 176 per million population (*24*). Since nearly all reported cases occurred among persons 20 years of age or older, the incidence for adult Kinshasa residents would be approximately 380 cases per million. Peak age-specific incidence of 786 per million and 601 per million were present among 30- to 39-year-old men and women, respectively (Table 2). While these surveillance data provided a preliminary estimate of the actual disease incidence in Kinshasa, a more reasonable estimate of the annual incidence based on the first 6 months of 1985 would be between 550 to 1000 cases per million adults. However, these are probably minimal estimates since the data reflect only recognized and reported cases of AIDS in several hospitals within Kinshasa.

Surveillance data reflect some of the basic epidemiologic trends of AIDS in Africa. The sex ratio of AIDS cases in Zaire was approximately 1:1.2 (*24*). As in developed countries, AIDS in Africa primarily affects young and middle-aged persons. The mean age of AIDS patients in Kinshasa was 33.6 years (mean 32, range 1.5 to 64 years), and men were significantly older than women (mean 37.4 years versus 30.0 years). The sex and age distributions of 500 AIDS cases (see Fig. 1) reflect patterns seen with other sexually transmitted diseases both in developed and developing countries in which incidence and morbidity rates are higher among younger women (*25*). Women with AIDS were more likely than men to be unmarried (61% versus 36%), and nearly one-third of the married AIDS patients had at least one previous marriage or "union libre" (persistent cohabitation without formal marriage). One-third of AIDS patients reported having at least one sexually transmitted disease during the 3 years preceding their illness. Twenty-nine percent of patients utilized traditional medical practitioners, and 80% reported receiving medical injections. Nine percent of patients received a blood transfusion during the 3-year period before onset of illness. These data do not allow for direct assessment of the risks associated with these activities, however, since no information was provided from a control population without HIV infection.

Prevalence of HIV antibody positive individuals in Africa. Though surveillance studies have been limited in Africa, serologic studies better indicate the extent of HIV infection throughout Africa. Thus far, serologic studies have indicated the presence of HIV antibody in persons in Burundi, Botswana, Central African Republic, Congo, Gambia, Gabon, Kenya, Malawi, Rwanda, Senegal, South Africa, Tanzania, Transkei, Uganda, Zambia, Zaire, and Zimbabwe (*18, 23, 26*). Seroprevalence rates among healthy populations in these areas range from 0.7% for blood donors in the Congo to as high as 18% for blood donors in Kigali, Rwanda (*23, 26–28*). Seroprevalence rates among high-risk groups, such as female prostitutes, have been reported to range from 27 to 88%, depending on selection, socioeconomic status, and geographic location (*29, 30*).

Longitudinal data on HIV seroprevalence in different populations are available from Kenya and Zaire (Table 3) (*31–34*). The increase

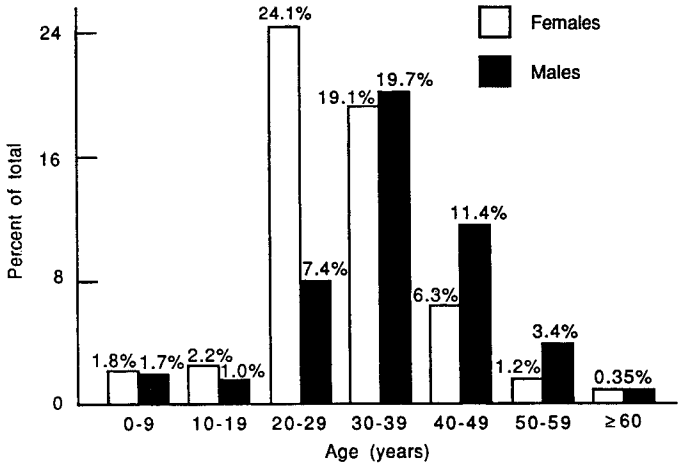

Fig. 1. Distribution by age and sex of the first 500 AIDS cases diagnosed in Kinshasa, Zaire, between August 1985 and December 1985. Female cases were significantly younger than male cases. Women accounted for the majority of AIDS cases in the age group 20 to 29, whereas men accounted for the majority of cases in the age groups 40 to 49 and 50 to 59.

in HIV seroprevalence among prostitutes in Nairobi from 4 to 59% between 1980 and 1986 demonstrates the rapid dissemination of HIV infection in a high-risk group in Africa, similar to that observed among homosexual men in San Francisco (*4, 6*). The relatively low but steady increase in seroprevalence among pregnant women in Nairobi from 0 to 2% in 5 years and in Kinshasa from 0.25 to 8% within 16 years indicates the potential spread of HIV infection to the general population in these areas (*32–34*). Consistent with this apparent rate of increase in the general population, Mann *et al.* found in a follow-up study of 579 seronegative men and women working at a general hospital in Kinshasa from 1984 to 1985 that the annual incidence of HIV antibodies was approximately 0.75% (*23*).

Data on HIV seroprevalence from 5099 healthy people (2982 men and 2117 women) in Kinshasa show a bimodal curve, with a peak prevalence under 1 year of age and among young adults aged 16 to 29 years old (Fig. 2). While other factors may be influencing this distribution of HIV infection rates, this pattern is suggestive of a sexually transmitted disease with higher prevalence among younger sexually active women (*25*). A combination of passive antibody transfer and transmission of virus from mother to infant is probably responsible for the high seroprevalence in younger children under age 2. In a preliminary evaluation of the natural history of HIV infection in Africa, 67 seropositive individuals with no signs or symptoms of disease were enrolled in a study in Kinshasa in October 1984 (*35*). Sixteen months later, one individual had developed AIDS and eight had developed generalized lymphadenopathy, giving annual progression rates of 1.3 per 100 person-years and 10.4 per 100 person-years, respectively. These data are remarkably similar to a San Francisco cohort of seropositive homosexual men in which approximately 1.3% progressed to AIDS and 5.1% developed AIDS-related conditions each year (*4, 6*). Thus, even if further HIV infections were prevented, substantial numbers of AIDS cases can be anticipated in Africa during the next decade emerging from the pool of already infected persons.

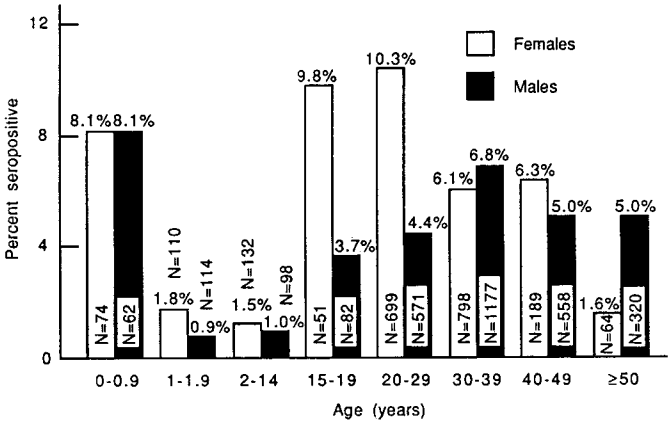

Fig. 2. HIV seroprevalence rates among 5099 healthy persons by age in Kinshasa, Zaire, 1984–1985. Sample population consisted of 2982 men and 2117 women. Positive patients had sera that were repeatedly reactive on a commercially available ELISA and were Western blot–positive. In age groups 16 to 19 years and 20 to 29 years, seroprevalence rates were significantly higher in women (10.3%) than men (4.3%). For 50 to 59 years of age, seroprevalence rates were significantly higher in men (5.0%) than women (1.6%).

Modes of Transmission

In North America and Europe, transmission of HIV infection has been documented to occur through one or more of four modes: sexual contact, exposure to blood-contaminated needles, administration of infected blood or blood products, and passage of the virus from infected mothers to their newborns (*4*). In contrast to North American and European AIDS patients, African AIDS patients rarely report a history of homosexual activity or intravenous drug abuse (*1, 2, 4*). While it may be difficult to ascertain homosexual and drug history because of cultural differences, it is evident from the multiple studies performed in Africa by both national and international experts in sexually transmitted diseases that these two risk factors do not play a major role in HIV transmission in Africa. Available data suggest that heterosexual activity, blood transfusions, vertical transmission from mother to infant, and probably frequent exposure to unsterilized needles account for the spread of HIV infection and AIDS in Africa.

Heterosexual transmission. Several lines of evidence support the concept that HIV infection is transmitted heterosexually in Africa. In addition to the 1:1 male to female ratio among cases and the younger age and single marital status for female cases, case-control studies have also shown that AIDS patients have a significantly higher number of heterosexual partners than controls (mean of 32 versus 3), that male patients have had sex significantly more often with female prostitutes (81 versus 34%), and that the risk of seropositivity increases significantly with the number of different sexual partners per year and with a history of other sexually transmitted diseases (*29–31*). In Africa, prostitutes show the highest infection rate (27 to 88%) and may have played an important role in the dissemination of HIV infection in Nairobi, since HIV antibody prevalence was initially higher in prostitutes in that city than in men with sexually transmitted diseases who frequented prostitutes (Table 3) (*31, 33*).

Whereas male-to-female transmission of HIV has been increasingly documented in the United States and Europe (*1, 2, 36*), evidence of female-to-male transmission has been limited in the United States because of the relatively low number of infected women (*36, 37*). In Africa, however, there is sufficient evidence to support bidirectional transmission of HIV. First, it may be possible for HIV to be transmitted bidirectionally among heterosexual contacts, since the virus can be isolated from semen as well as from cervical-vaginal secretions (*38, 39*). Second, African male AIDS patients, as well as expatriate males with AIDS who previously lived in Africa, frequently report a history of sex with prostitutes, and the prevalence of HIV in male heterosexuals attending clinics for sexually transmitted diseases is increasing, suggesting female-to-male transmission (*12, 29–31, 33, 40*). Further evidence for such transmission comes from a household study of AIDS patients in Zaire in which HIV antibody was significantly higher among spouses and infants of infected mothers than in other household members or controls (*41*). In this study, 11 (3 men, 8 women) (61%) of 18 spouses of 3 female and 15 male AIDS cases were HIV antibody–positive compared to only 1 (3.7%) of 27 spouses of seronegative control patients, a statistically significant difference. Finally, several clusters of African AIDS cases have been identified in whom the chronology of events suggested both female-to-male and male-to-female transmission of HIV (*11, 42*).

Risk factors associated with HIV infection in heterosexuals include number of sexual partners, sex with prostitutes, being a prostitute, and being a sexual partner of an infected person (*29–31, 33, 40*). Specific sexual activities, including anal intercourse reported by only 4 to 8% of female AIDS patients, were not associated with HIV infection in surveys in Kenya, Zaire, and Rwanda (*26, 29–31*). In studies among Nairobi prostitutes, HIV seropositivity was significantly associated with current sexually transmitted diseases such as gonorrhea, genital ulcers, and syphilis (*31*). In another study

in Zambia (*33*), seropositivity in men was also correlated with the presence of genital ulcers. These observations suggest that disruption of genital epithelial integrity caused by sexually transmitted diseases that are common in Africa may facilitate transmission of HIV during vaginal intercourse. Alternatively, the presence of these sexually transmitted diseases may be indicative of high-risk activities for HIV infection or of exposure to unsterilized needles for treatment of sexually transmitted diseases, and may not be directly related to transmissibility. However, in two studies of female prostitutes in Nairobi and Kinshasa, HIV seropositivity was directly associated with number of sexual exposures, independent of the frequency of needle exposures which was not associated with HIV seropositivity (*30, 31*). The potential for HIV transmission by unsterilized needles, however, should not be underestimated, and further studies should be undertaken to assess risk associated with these factors and to develop effective means of prevention.

Perinatal transmission. As a result of heterosexual transmission, African women of child-bearing age are exposed to HIV. In 1985, the proportion of seropositive pregnant women was 2% in one maternity hospital in Nairobi and 8% in Kinshasa (*33, 34*). As in U.S. studies (*43*), maternal HIV infection appears to be strongly associated with seropositivity among infants in Africa. In an ongoing study of 44 seropositive children between the ages of 1 and 24 months in Kinshasa, 27 (61%) had seropositive mothers (*34*). Until prospective studies are performed, it will be unclear what percentage of these children acquired maternal HIV antibody passively as opposed to acquiring the virus perinatally. Nevertheless, it is clear from the high seropositivity among pregnant women that a substantial number of newborn children are being infected with HIV. The impact that this high seropositivity rate will have on the general health of these children and on the safety and efficacy of childhood vaccinations is unknown.

Injections. The use of unsterilized needles or other skin-piercing instruments for medical or ritual purposes (for example, scarification, tattooing, ear piercing, male or female circumcision, blood-brotherhood ceremonies) has potential for HIV transmission. In a seroprevalence study of 2384 hospital workers in Kinshasa, significantly more HIV seropositive than seronegative workers reported receiving medical injections during the previous 3 years; among those reporting injections, seroprevalence was nearly twice as high for those with five or more injections compared with those receiving fewer than five injections (*44*). In a study of hospitalized seropositive children aged 1 to 24 months in Kinshasa who had similar medical problems, 16 born to seronegative mothers received significantly more injections compared with 222 seronegative children born to seronegative mothers (Table 4) (*34*). In addition, among adult patients with tuberculosis, HIV seropositives reported significantly more injections than seronegatives during the 5-year period prior to hospitalization (*45*). Similarly, a history of scarification in the previous year was significantly more common among 40 seropositive hospitalized children of 2 to 14 years old (25%) compared with 92 seronegative children of the same age and sex (25 versus 6.6%) (*46*).

These data suggest that injections and scarifications are associated with HIV infection, but it is difficult to distinguish whether the association is truly causal, that is, provides a means of exposure to HIV, or secondary due to treatment for early symptoms of HIV infection or other illnesses, such as sexually transmitted diseases. The potential importance of HIV transmission by needles reflects several cultural factors in Africa that merit emphasis. Patients often express a strong preference for parenteral rather than oral therapy. For example, in survey of 50 mothers in Kinshasa, 84% expressed the belief that parenteral medication is more effective than oral medication (*47*). Injections as well as scarifications may be administered in clinics or nonmedical sites by personnel inadequately trained in aseptic techniques. Financial and other practical constraints also lead to reuse of disposable equipment and to insufficient sterilization or use of contaminated needles and instruments. In contrast, the lack of association between HIV seropositivity and childhood vaccinations (Table 4) probably reflects the wider use of properly sterilized injection equipment in immunization programs, relatively small numbers of vaccinations received per child, and the general absence of traditional healers in vaccination programs.

Table 4. Risk factors for exposure to HIV among 238 hospitalized children between the ages of 1 and 24 months. Seropositive children born to seronegative mothers were compared to seronegative children of seronegative mothers to determine the attributable risks of HIV infection in children other than being born to infected mothers. Seropositive blood specimens were repeatedly reactive by a commercially available ELISA and were confirmed by Western blot. Adapted from Mann *et al.* (*34*).

Demographic feature or risk factor	Seronegative mother, seropositive child (n = 16)	Seronegative mother, seronegative child (n = 222)
Mean age	10.6 months	11.4 months
Lifetime medical injections (mean)	44*	23
Prior hospitalization	8 (50%)†	29 (13%)
Previous blood transfusion	5 (31%)‡	15 (7%)
Vaccinations received (mean)	2.8	3.2
Prior surgery	9 (60%)	89 (40%)
Scarifications	1 (6%)	33 (15%)

*$P<0.001$, Wilcoxon rank sum test. †$P = 0.0009$, Fisher's exact test. ‡$P = 0.006$, Fisher's exact test.

Transfusions. The seroprevalence rate among blood donors in Uganda, Rwanda, and Zaire has ranged from 8 to 18%, suggesting that the risk to transfusion recipients in these areas is very high (*23, 26–28*). In Kinshasa, 9% of 295 AIDS patients reported receiving at least one blood transfusion during the 3 to 5 years prior to onset of illness (*24*). Among 2384 hospital workers in Kinshasa, 9.3% of seropositives and 4.8% of seronegatives reported transfusions within the past 10 years, a significant difference (*44*). Among 368 hospitalized children between 2 and 14 years of age in Zaire, 60% of 40 seropositive children compared with 32.7% of 328 seronegative children and 14.3% of 92 healthy outpatient control children had a history of prior blood transfusions (*47*). Similarly, 31% of 16 seropositive children born to seronegative mothers had a history of blood transfusion compared to 7% of 222 seronegative control children, a significant difference (Table 4) (*34*). Seventeen percent of 50 patients with sickle cell anemia in Zaire had confirmed antibody to HIV; the majority of these had also received multiple blood transfusions (*27*).

As with injections, patient expectations and medical overuse of blood transfusions may contribute to the potential spread of HIV through transfusions. In a recent review of transfusion practices in a large public hospital in Central Africa, over 90% of transfusions to adult patients involved only a single unit of blood (*27*). However, in a more careful analysis of indications for blood transfusions in children, over 70% of transfusions in one large hospital were for severe anemia associated with acute malaria. This may be a particularly difficult problem in some areas of Africa where malaria is highly endemic and frequently causes severe anemia in children. Studies are needed to assess the present indications for blood transfusion in Africa and the risks of HIV transmission via transfusions. While practices for collecting and transfusing blood vary throughout the continent, screening of donors is not performed for hepatitis B and HIV in many areas, and storage and processing facilities are rudimentary. Furthermore, efforts to identify and exclude high-risk

donors in Africa on epidemiological or clinical grounds have thus far been unsuccessful.

Other modes of transmission. The concordance of African data with data from studies in the United States and Europe (*41, 44, 48, 49*) strongly suggest that HIV is not more readily transmitted by casual contact in Africa, despite important socioeconomic and environmental differences in household and occupational settings. Among nonspousal household members of 46 AIDS cases and 43 seronegative controls in Kinshasa, seropositivity in 9 (4.8%) of 186 case-household members did not differ significantly compared to 2 (1.5%) of the 128 control household members (*41*). The absence of documented HIV infection or AIDS among expatriates without known risk factors (*2*) is evidence that frequent casual contacts with merchants, colleagues, or domestic workers do not result in viral transmission.

There is no direct evidence yet for arthropod transmission of HIV in Africa, nor in the United States, where HIV infection occurs in some areas of substantial arthropod densities (*50*). Recently, it was shown that HIV could be cultured from bedbugs (*Cimex lectularius*) 60 minutes after they had engorged on blood containing tissue culture supernatants from HIV-infected cells (*51*). Becker *et al.* (*52*), using HIV molecular probes, also demonstrated genomic material of HIV within several insects from HIV-endemic areas of Africa. However, HIV could not be isolated from these insects, and, as with hepatitis B virus, it appears that prolonged survival and transmission of HIV by insects is unlikely. In fact, the sex- and age-specific HIV seroprevalence data in Kinshasa are not suggestive of a vector-borne disease, there being very low prevalence rates in children between 1 and 15 years of age (Fig. 2). Malaria, a vector-borne disease, is particularly common in children between 1 and 24 months old in Kinshasa, but among 44 HIV-seropositive children in this city, 43 (98%) had other, known, risk factors for AIDS, including birth to an HIV seropositive mother, a history of blood transfusion, and frequent exposure to unsterilized needles (Table 4) (*34*). In addition, the lack of evidence for increased exposure to HIV among nonspousal household contacts of AIDS cases suggests that insect transmission does not occur over short distances (for example, by bedbugs, lice, or mosquitoes with interrupted feeding). Because of the low titer of HIV in the blood of infected persons and the small amount of blood ingested by an insect, mechanical transmission of HIV by insect vectors seems unlikely, particularly in view of the fact that hepatitis B virus, which is more readily parenterally transmitted, has not been found to be transmitted by arthropods (*50*).

Clinical Spectrum of Disease

The clinical manifestations associated with HIV infection vary in different populations according to the relative frequency of other endemic opportunistic infections. In tropical areas, such as Central Africa and Haiti, gastrointestinal and dermatologic manifestations are commonly observed, while generalized lymphadenopathy and pulmonary symptoms are frequently seen in AIDS patients in the United States (*8, 9, 53, 54*). In a recent review of 196 AIDS patients in Kinshasa, Zaire, the mean duration of symptoms prior to diagnosis was 11.8 months (range, 1 to 78 months; median, 8 months) (*54*). Symptoms consisted of profound weight loss (mean, 29% of body weight; 99% of the patients), fever (81% of the patients), diarrhea (68%), cough (37%), dysphasia (35%), pruritus (30%), and dyspnea (23%). On physical examination, oral candidiasis was present in 47% of the patients, of whom 61% had dysphagia. A generalized pruritic maculopapular eruption, frequently referred to as "prurigo," was seen in 22%, and generalized lymphadenopathy was seen in 11% of patients (*54*). In Europe, where extensive diagnostic procedures have been performed in African AIDS patients, the most commonly observed opportunistic infections included oroesophageal candidiasis, central nervous system cryptococcosis, toxoplasmosis, tuberculosis, and cryptosporidiosis in approximately equal frequency (14 to 25%) (*8, 10*). In contrast to American and European AIDS cases where approximately 63% of all AIDS patients eventually develop *Pneumocystis carinii* pneumonia (*1*), this opportunistic infection was found in only 14% of African patients diagnosed in Europe. In Africa, where the diagnostic procedures are limited, oral candidiasis, cryptococcal meningitis, probable cytomegalovirus chorioretinitis, cryptosporidiosis, mucocutaneous herpes virus infection, and Kaposi's sarcoma are most commonly observed (*54–56*).

Other infections that are seen include disseminated histoplasmosis, salmonellosis, disseminated strongyloidiasis, and mycobacterial disease (*8, 10, 55, 57*). In Zaire, 53 (33%) of 159 confirmed pulmonary patients hospitalized at a tuberculosis sanitarium were HIV-seropositive, including 10 (67%) of 15 patients with extrapulmonary tuberculosis (*45*). Seropositivity was significantly associated with ages 20 to 59 years, anergy to intradermally injected tuberculin, and a blood transfusion during the previous 5 years. Among patients with tuberculosis, there was no significant association between HIV infection and extent of radiographic lesions, duration of disease, or initial response to treatment. Thus, HIV infections may substantially complicate both the management of individual patients with tuberculosis and strategies for tuberculosis control in countries where HIV infection occurs. It is possible that patients living in tropical areas and immunosuppressed as a result of HIV will manifest other infections endemic in these areas, such as leishmaniasis, leprosy, malaria, filariasis, and other parasitic and bacterial infections.

What is referred to as slim disease in Uganda and Tanzania (*17*) is essentially identical to enteropathic AIDS with the major symptoms of weight loss and unexplained diarrhea occurring in 99 and 80% of cases, respectively. Seroprevalence studies among these patients demonstrated HIV antibody in all of the patients who presented with clinical diarrhea and a weight loss of 10 kilograms or more. While the etiology of these gastrointestinal symptoms remains unknown in the majority of patients, the persistence of these symptoms is highly predictive of HIV infection. In Zaire, the positive predictive value of chronic diarrhea, weight loss, and oral candidiasis for HIV infection in a hospitalized patient was 97% (*57*). Consequently, the World Health Organization has developed a provisional clinical case definition for AIDS in Africa where sophisticated diagnostic equipment may not be available (Table 5). In a survey of 178 hospitalized patients in Kinshasa, this definition was found to be highly specific (93%) with a positive predictive value of 82% for seropositivity to HIV (*58*). The sensitivity was only 54%, but was improved to 75% by including moderate to severe asthenia as a major clinical sign. As more clinical data become available, development of clinical definitions that maximize both sensitivity and specificity for HIV disease should be encouraged for surveillance and epidemiologic purposes, and eventually for treatment regimens.

Few studies have characterized the clinical features of HIV infection in children in Africa. Among 368 hospitalized children in Kinshasa, Zaire, aged 2 to 14 years, seropositivity in 40 (11%) children was significantly associated with the diagnosis of malnutrition, pneumonia, and anemia, compared to seronegative hospitalized children (*47*). In patients with both malnutrition and pneumonia, 31% were seropositive, and the in-hospital mortality rate of seropositive children was over three times greater than that for seronegative children. In Bangui, Central African Republic, 21 (12.3%) of 175 children with malnutrition and 25 (24.8%) of 101

mothers were HIV-seropositive, whereas only 3 (3.1%) of 96 healthy children were seropositive (*59*). Pneumonitis, diarrhea, lymphadenopathy, oral thrush, and dermatitis were each more frequently seen in the seropositive children than in seronegative malnourished children. Thus, while pediatric HIV disease in Africa resembles HIV infections in children in the United States (*43*), it is difficult to distinguish HIV-associated disease in Africa on clinical grounds, where failure to thrive, malnutrition, and pulmonary disease are common pediatric problems.

Kaposi's sarcoma. A chronic variety of Kaposi's sarcoma has been recognized in some areas of Central Africa for at least the last 40 years (*57*). This form typically affects men, the male to female ratio being 14:1, and it is not associated with persistent immunosuppression or HIV infection (*58*). The lesions are generally nodular, distributed on the lower extremities, and are generally nonprogressive. A sporadic, aggressive lymphadenopathic form of Kaposi's sarcoma was also described in Africa before the recognition of AIDS (*60*). It is most frequently seen in children and younger adults, including pregnant women. While this form has a more progressive course, affected patients usually lack evidence of HIV infection. A third form of Kaposi's sarcoma, which is highly aggressive and similar to that observed in AIDS patients in the United States, has recently been identified in Africa (*19, 61, 62*). This form was rarely seen in Central Africa until 1982 when investigators in Zambia and Uganda noted a marked increased in its occurrence (*19*). While these three varieties of Kaposi's sarcoma are histologically similar, the last, epidemic form frequently involves other parts of the skin including arms, trunk, and face and spreads rapidly to internal organs, eventually resulting in death. It occurs almost exclusively in HIV-seropositive individuals (*61*). Patients with this form appear to have a more profound immunosuppression with anergy and reversed T-helper to T-suppressor lymphocyte ratios due to depressed T-helper lymphocytes (*61*).

HIV and Other Retroviruses in Africa

In one study, HIV was isolated from 27 (77%) of 35 African patients with AIDS and from 5 of 9 patients with AIDS-related complex (*63*). These viral isolates were consistent with the classification of HIV by reverse transcriptase production, electron microscopic visualization, and restriction map analysis. In comparing three isolates from Zairian patients with eight isolates from North American and European patients, several conserved genomic restriction sites were common to all viral isolates, such as the Hind III sites in the long terminal repeats, the Hind II site at 2.5 kb, the Kpn I site at 3.8 kb, and the Bgl II site at 7.0 kb, which collectively could be considered the "signature" of the AIDS virus (*64*). However, this study (*61*) and others (*65*) have indicated that the African isolates, as a group, are more heterogeneous than isolates from North America and Europe, having more unique sites and 40% fewer conserved restriction sites.

Two recent studies have reported the isolation of retroviruses from individuals residing in West Africa that appear to be different from HIV by protein analysis (*66, 67*) (Table 6). Viral isolates referred to as HTLV-IV have been recovered from prostitutes in Senegal which appear to cross-react serologically with HIV and more strongly with STLV-III$_{AGM}$, a recently described retrovirus isolated from healthy, wild-caught African Green monkeys (*Cercopithecus sp.*) (*66*). This virus appears to be noncytolytic in vitro, and has not been associated with any disease manifestations such as AIDS among infected individuals. Another virus, referred to as LAV-2 (*67*), has been isolated from patients with AIDS from Guinea-Bissau and Cape Verde whose sera cross-reacted more strongly with STLV-III$_{MAC}$, a primate retrovirus isolated from captive macaques (*68*). Unlike HTLV-IV, LAV-2 appears to be more cytopathic in vitro and to be associated with clinical AIDS in infected individuals. In contrast to HIV, neither HTLV-IV or LAV-2 induced antibody to the gp41 commonly seen in HIV-infected individuals. Instead, antibodies to a 32-kD and a 36-kD glycoprotein were present in HTLV-IV– and LAV-2–infected individuals, respectively, and were found to cross-react with STLV-III but not HIV. Although genomic comparisons of HTLV-IV, LAV-2, and HIV have not been published, protein analysis suggests further divergence among these isolates within the exterior glycoprotein portion of the envelope gene (*66, 67*). More studies on the origin of this group of viruses, including genomic and protein comparisons, pathogenicity in vitro, and relationship to human disease, would facilitate vaccine studies.

Equally important in the study of these retroviruses is the potential for cross-reactivity in the ELISA's for HIV antibody (*16, 69*). Although the prototype ELISA's had a low specificity in low prevalence areas of Africa because of cross-reactivity with autoantibodies to antigens in the cell line used to grow the virus (*16, 22*), several new commercially available ELISA's appear to be highly specific for HIV antibodies, even in malarious areas of Africa (*70, 71*). In an examination of 400 AIDS patients and 100 healthy controls in Zaire, the sensitivity and specificity of a commercially available ELISA for HIV infection was 99 and 98%, respectively (*70*). Ninety-eight percent of the sera repeatedly positive by the ELISA were found by Western blot to have protein bands characteristic of HIV infection. However, with the possibility of other related retroviruses present in certain populations in West Africa, confirmatory testing of clinically suspect patients, whether initially ELISA-

Table 5. Provisional WHO clinical case definition for AIDS where diagnostic resources are limited. Definition developed at WHO Workshop on AIDS in Bangui, Central African Republic. Adapted from (*21*).

Adults

AIDS in an adult is defined by the existence of at least two of the major signs associated with at least one minor sign, in the absence of known causes of immunosuppression such as cancer or severe malnutrition or other recognized etiologies.

Major signs
- (a) Weight loss >10% of body weight
- (b) Chronic diarrhea >1 month
- (c) Prolonged fever >1 month (intermittent or constant)

Minor signs
- (a) Persistent cough for >1 month
- (b) Generalized pruritic dermatitis
- (c) Recurrent herpes zoster
- (d) Oropharyngeal candidiasis
- (e) Chronic progressive and disseminated herpes simplex infection
- (f) Generalized lymphadenopathy

The presence of generalized Kaposi's sarcoma or cryptococcal meningitis are sufficient by themselves for the diagnosis of AIDS.

Children

Pediatric AIDS is suspected in an infant or child presenting with at least two major signs associated with at least two minor signs in the absence of known cases of immunosuppression.

Major signs
- (a) Weight loss or abnormally slow growth
- (b) Chronic diarrhea >1 month
- (c) Prolonged fever >1 month

Minor signs
- (a) Generalized lymphadenopathy
- (b) Oropharyngeal candidiasis
- (c) Repeated common infections (otitis, pharyngitis, and so forth)
- (d) Persistent cough >1 month
- (e) Generalized dermatitis
- (f) Confirmed maternal LAV/HTLV-III infection

Table 6. A comparison of human and nonhuman primate retroviruses in Africa.

Features	STLV-III$_{AGM}$	HTLV-IV	LAV-2	HIV
Natural host	African Green monkey	Man	Man	Man
Location	Africa	West Africa	West Africa	Ubiquitous
Virulence	No disease	No AIDS	AIDS	AIDS
Experimental infection	Macaque	Unknown	Unknown	Chimpanzee
Target cell	$T4^+$ cells	$T4^+$ cells	$T4^+$ cells	$T4^+$ cells, macrophages
In vitro pathogenicity				
Syncytia formation	+	+	+	+
Cytolysis	+	−	+	+
Immunogenic proteins				
Common *gag**	Reactive	Reactive	Reactive	Reactive
env	gp160, gp120, and gp32	gp160, gp120, and gp32	gp140 and gp36	gp160, gp120, and gp41
pol	p53 and p64	p53 and p64	p53 and p64	p53 and p64

**Gag* or core antigens of these viruses show common epitopes. Sera from infected individuals and infected African Green monkeys cross-react predominately among the *gag* proteins, although molecular weight designations may vary among different laboratories.

positive specimens or ELISA-negative, is critically important. The establishment of reference centers for confirmatory testing and the development of second- and third-generation diagnostic assays are needed for the detection of HIV infection in remote areas of Africa and in many other developing countries.

The Future, and Prospects for Control

With estimates of several million HIV-infected people in Africa, it is evident that the virus has created a major health problem in that continent. Nearly 25% of adult and 10% of pediatric inpatients in several hospitals in Central Africa are now HIV-seropositive, and the high prevalence rates of other infectious diseases endemic in Africa may potentiate expression of the virus through T-cell activation and result in further exacerbation of HIV disease (*72*). In addition, the morbidity and mortality caused by other infectious diseases may increase as a result of the underlying immunosuppression induced by HIV infection.

The recent rapid increase in urbanization in many parts of Africa has resulted in economic and sociological changes that have influenced behavior and severely affected the health infrastructure (*73*). Consequently, one cannot expect public health officials to upgrade blood transfusion services to prevent HIV infection when the proposed intervention is likely to cost, per person, approximately 30 times the annual per capita public health budget. In the United States, approximately $60 million was spent on blood-bank screening for HIV infection in 1985, a budget many times greater than the entire health budgets of many African countries. Similarly, one cannot hope to prevent reuse of disposable injection equipment when many hospital budgets are insufficient for the purchase of antibiotics. The costs of caring for ten AIDS patients in the United States (approximately $450,000) is greater than the entire budget of a large hospital in Zaire, where up to 25% of the pediatric and adult hospital admissions have HIV infection.

Nevertheless, in response to recent data on the AIDS epidemic, representatives from 45 African countries have developed, under the auspices of the African Regional Office of the World Health Organization, a plan of action for the prevention and control of AIDS (*74*). In November 1986, these representatives will reconvene in Brazzaville to discuss the following strategies. Each country will (i) establish a national AIDS committee that includes representatives from the health and social services and from communications, education, and other relevant governmental and nongovernmental sectors; (ii) conduct an epidemiologic assessment of the burden of HIV infection and associated risk factors; and (iii) institute a surveillance system for AIDS and HIV infection that includes serological surveys of selected populations, such as prostitutes or blood donors. Concomitantly, appropriate levels of laboratory capability for the serological diagnosis of HIV infection will be established either in each country or through collaborative regional agreements. In addition, increased numbers of health care personnel will be educated in the recognition and management of HIV-associated disease in hospitals and communities, with consideration being given to patient confidentiality, counseling, and ethical issues.

These strategies are expected to lead rapidly to the development of programs to halt the spread of the AIDS virus. For example, creative educational approaches are needed to prevent virus transmission through reductions in the number of sexual partners or through use of condoms. Changes in medical practices, including traditional practices are required to reduce transmission rates associated with injections, scarification, and blood transfusions. The screening of women of child-bearing age and counseling regarding contraception for HIV-seropositive women are necessary in order to interrupt perinatal HIV transmission.

To be successful, these programs will have to be integrated into existing health and educational programs and will require full support by the appropriate governmental agencies. However, many countries may lack the financial and other resources that will be required to build and sustain these activities on a long-term basis. Controlling the spread of the AIDS virus will thus require a major international commitment, not only in terms of providing financial help but also in providing scientific, educational, and technical assistance. With 74 countries of the world affected by the disease and several million people carrying the virus, worldwide cooperation is now a necessity.

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