

**THE RELATIONSHIP BETWEEN THE HUMAN IMMUNODEFICIENCY VIRUS
AND
THE ACQUIRED IMMUNODEFICIENCY SYNDROME**

From NIH on the Web, downloaded 11/27/95

From:
The National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Contents:

The Definition of AIDS	2
The Designation AIDS Is a Surveillance Tool	2
Quantifying the Epidemic	2
A Brief History of the Emergence of AIDS	2
Initial Theories	3
Retrovirus Hypothesis	4
Seroprevalence Surveys	5
HIV and Other Lentiviruses	6
Course of HIV Infection	6
Immunologic Profile of People With AIDS	8
Mechanisms of CD4+ T Cell Depletion	9
Koch's Postulates Fulfilled	10
Evidence From Animal and Laboratory Models	11
Geographic Considerations	11
Evidence From Blood Donor-Recipient Pairs	12
Impact of HIV Infection on Mortality of Hemophiliacs	13
Pediatric AIDS	13
Single Source Outbreak of Pediatric AIDS	14
Answering the Skeptics: the "Risk-AIDS" or "Behavioral" Hypothesis	14
AIDS and Injection Drug Users	15
Sex and the AIDS Epidemic	16
Drug Use in the Pre-AIDS Era	17
AZT and AIDS	18
Disease Progression Despite Antibodies	19
Risks Associated With Transfusion	19
Exposure to Factor VIII	20
Distribution of AIDS Cases	21
AIDS in Africa	21
Conclusion	22
References	22

The acquired immunodeficiency syndrome (AIDS) is characterized by the progressive loss of the CD4+ helper/inducer subset of T lymphocytes, leading to severe immunosuppression and constitutional disease, neurological complications, and opportunistic infections and neoplasms that rarely occur in persons with intact immune function. Although the precise mechanisms leading to the destruction of the immune system have not been fully delineated, abundant epidemiologic, virologic and immunologic data support the conclusion that infection with the human immunodeficiency virus (HIV) is the underlying cause of AIDS.

The evidence for HIV's primary role in the pathogenesis of AIDS is reviewed elsewhere (Ho et al., 1987; Fauci, 1988, 1993a; Greene, 1993; Levy, 1993; Weiss, 1993). In addition, many scientists (Blattner et al., 1988a,b; Ginsberg, 1988; Evans, 1989a,b, 1992; Weiss and Jaffe, 1990; Gallo, 1991; Goudsmit, 1992; Groopman, 1992; Kurth, 1990; Ascher et al., 1993a,b; Schechter et al., 1993a,b; Lowenstein, 1994; Nicoll and Brown, 1994; Harris, 1995) have responded to specific arguments from individuals who assert that AIDS is not caused by HIV. The present discussion reviews the AIDS epidemic and summarizes the evidence supporting HIV as the cause of AIDS.

The Definition of AIDS

The term AIDS first appeared in the Morbidity and Mortality Weekly Report (MMWR) of the Centers for Disease Control (CDC) in 1982 to describe "... a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring with no known cause for diminished resistance to that disease" (CDC, 1982b). The initial CDC list of AIDS-defining conditions, which included Kaposi's sarcoma (KS), Pneumocystis carinii pneumonia (PCP), Mycobacterium avium complex (MAC) and other conditions, has been updated on several occasions, with significant revisions (CDC, 1985a, 1987a, 1992a).

For surveillance purposes, the CDC currently defines AIDS in an adult or adolescent age 13 years or older as the presence of one of 25 AIDS-indicator conditions, such as KS, PCP or disseminated MAC. In children younger than 13 years, the definition of AIDS is similar to that in adolescents and adults, except that lymphoid interstitial pneumonitis and recurrent bacterial infections are included in the list of AIDS-defining conditions (CDC, 1987b). The case definition in adults and adolescents was expanded in 1993 to include HIV infection in an individual with a CD4+ T cell count less than 200 cells per cubic millimeter (mm³) of blood (CDC, 1992a). The current surveillance definition replaced criteria published in 1987 that were based on clinical conditions and evidence of HIV infection but not on CD4+ T cell determinations (CDC, 1987a).

In many developing countries, where diagnostic facilities may be minimal, epidemiologists employ a case definition based on the presence of various clinical symptoms associated with immune deficiency and the exclusion of other known causes of immunosuppression, such as cancer or malnutrition (Ryder and Mugewrwa, 1994a; Davachi, 1994).

The Designation AIDS Is a Surveillance Tool

Surveillance definitions of AIDS have proven useful epidemiologically to track and quantify the recent epidemic of HIV-mediated immunosuppression and its manifestations. However, AIDS represents only the end stage of a continuous, progressive pathogenic process, beginning with primary infection with HIV, continuing with a chronic phase that is usually asymptomatic, leading to progressively severe symptoms and, ultimately, profound immunodeficiency and opportunistic infections and neoplasms (Fauci, 1993a). In clinical practice, symptomatology and measurements of immune function, notably levels of CD4+ T lymphocytes, are used to guide the treatment of HIV-infected persons rather than an all-or-nothing paradigm of AIDS/non-AIDS (CDC, 1992a; Sande et al., 1993; Volberding and Graham, 1994).

Quantifying the Epidemic

Between June 1981 and Dec. 31, 1994, 441,528 cases of AIDS in the United States, including 270,870 AIDS-related deaths, were reported to the CDC (CDC, 1995a). AIDS is now the leading cause of death among adults aged 25 to 44 in the United States (CDC, 1995b).

Worldwide, 1,025,073 cases of AIDS were reported to the World Health Organization (WHO) through December 1994, an increase of 20 percent since December 1993 (WHO, 1995a). Allowing for under-diagnosis, incomplete reporting and reporting delay, and based on the available data on HIV infections around the world, the WHO estimates that over 4.5 million AIDS cumulative cases had occurred worldwide by late 1994 and that 19.5 million people worldwide had been infected with HIV since the beginning of the epidemic (WHO, 1995a). By the year 2000, the WHO estimates that 30 to 40 million people will have been infected with HIV and that 10 million people will have developed AIDS (WHO, 1994). The Global AIDS Policy Coalition has developed a considerably higher estimate--perhaps up to 110 million HIV infections and 25 million AIDS cases by the turn of the century (Mann et al., 1992a).

A Brief History of the Emergence of AIDS

In 1981, clinical investigators in New York and California observed among young, previously healthy, homosexual men an unusual clustering of cases of rare diseases, notably Kaposi's sarcoma (KS) and oppor-

tunistic infections such as *Pneumocystis carinii* pneumonia (PCP), as well as cases of unexplained, persistent lymphadenopathy (CDC, 1981a,b, 1982a; Masur et al., 1981; Gottlieb et al., 1981; Friedman-Kien, 1981). It soon became evident that these men had a common immunologic deficit, an impairment in cell-mediated immunity resulting from a significant loss of "T-helper" cells, which bear the CD4 marker (Gottlieb et al., 1981; Masur et al., 1981; Siegal et al., 1981; Ammann et al., 1983a).

The widespread occurrence of KS and PCP in young people with no underlying disease or history of immunosuppressive therapy was unprecedented. Searches of the medical literature, autopsy records and tumor registries revealed that these diseases previously had occurred at very low levels in the United States (CDC, 1981b; CDC, 1982f).

KS, a very rare skin neoplasm, had affected mostly older men of Mediterranean origin or cancer or transplant patients undergoing immunosuppressive therapy (Gange and Jones, 1978; Safai and Good, 1981). Before the AIDS epidemic, the annual incidence of Kaposi's sarcoma in the United States was 0.02 to 0.06 per 100,000 population (Rothman, 1962a; Oettle, 1962). In addition, a more aggressive form of KS that generally occurred in younger individuals was seen in certain parts of Africa (Rothman, 1962b; Safai, 1984a). By 1984, never-married men in San Francisco were found to be 2,000 times more likely to develop KS than during the years 1973 to 1979 (Williams et al., 1994). As of Dec. 31, 1994, 36,693 patients with AIDS in the United States with a definitive diagnosis of KS had been reported to the CDC (CDC, 1995b).

PCP, a lung infection caused by a pathogen to which most individuals are exposed with no undue consequences, was extremely rare prior to 1981 in individuals other than those receiving immunosuppressive therapy or among the chronically malnourished, such as certain Eastern European children following World War II (Walzer, 1990). A 1967 survey, for example, found only 107 U.S. cases of PCP reported in the medical literature up to that point, virtually all among individuals with underlying immunosuppressive conditions or who had undergone immunosuppressive therapy (Le Clair, 1969). In that year, CDC became the sole supplier in the United States of pentamidine isethionate, then the only recommended PCP therapy, and began collecting data on each PCP case diagnosed and treated in this country. After reviewing requests for pentamidine in the period 1967 to 1970, researchers found only one case of confirmed PCP without a known underlying condition (Walzer et al., 1974). In the period immediately prior to the recognition of AIDS, January 1976 to June 1980, CDC received only one request for pentamidine isethionate to treat an adult in the United States who had PCP and no underlying disease (CDC, 1982f). In 1981 alone, 42 requests for pentamidine were received to treat patients with PCP and no known underlying disorders (CDC, 1982f). By Dec. 31, 1994, 127,626 individuals with AIDS in the United States with definitive diagnoses of PCP had been reported to the CDC (CDC, 1995b).

Another rare opportunistic disease, disseminated infection with the *Mycobacterium avium* complex (MAC), also was seen frequently in the first AIDS patients (Zakowski et al., 1982; Greene et al., 1982). Prior to 1981, only 32 individuals with disseminated MAC disease had been described in the medical literature (Masur, 1982a). By Dec. 31, 1994, the CDC had received reports of 28,954 U.S. AIDS patients with definitive diagnoses of disseminated MAC (CDC, 1995b).

Initial Theories

The fact that homosexual men constituted the initial population in which AIDS occurred in the United States led some to surmise that a homosexual lifestyle was specifically related to the disease (Goedert et al., 1982; Hurtenbach and Shearer, 1982; Sonnabend et al., 1983; Durack, 1981; Mavligit et al., 1984). These early suggestions that AIDS resulted from behavior specific to the homosexual population were largely dismissed when the syndrome was observed in distinctly different groups in the United States: in male and female injection drug users; in hemophiliacs and blood transfusion recipients; among female sex partners of bisexual men, recipients of blood or blood products, or injection drug users; and among infants born to mothers with AIDS or with a history of injection drug use (CDC, 1982b,c,d,f, 1983a; Poon et al., 1983; Elliot et al., 1983; Masur et al., 1982b; Davis et al., 1983; Harris et al., 1983; Rubinstein et al., 1983; Oleske et al., 1983; Ammann et al., 1983b). In 1983, for example, a study found that hemophiliacs with no history of any of the proposed causes of AIDS

in homosexual men had developed the syndrome, and some of the men had apparently transmitted the infection to their wives (deShazo et al., 1983).

Many public health experts concluded that the clustering of AIDS cases (Auerbach et al., 1984; Gazzard et al., 1984) and the occurrence of cases in diverse risk groups could be explained only if AIDS were caused by an infectious microorganism transmitted in the manner of hepatitis B virus (HBV): by sexual contact, by inoculation with blood or blood products, and from mother to newborn infant (Francis et al., 1983; Curran et al., 1984; AMA, 1984; CDC, 1982f, 1983a,b).

Early suspects for the cause of AIDS were cytomegalovirus (CMV), because of its association with immunosuppression, and Epstein-Barr virus (EBV), which has an affinity for lymphocytes (Gottlieb et al., 1981; Hymes et al., 1981; CDC, 1982f). However, AIDS was a new phenomenon, and these viruses already had a worldwide distribution. Comparative seroprevalence studies showed no convincing evidence to assign these viruses or other known agents a primary role in the syndrome (Rogers et al., 1983). Also lacking was evidence that these viruses, when isolated from patients with AIDS, differed significantly from strains found in healthy individuals or from strains found in the years preceding the emergence of AIDS (AMA, 1984).

Retrovirus Hypothesis

By 1983, several research groups had focused on retroviruses for clues to the cause of AIDS (Gallo and Montagnier, 1987). Two recently recognized retroviruses, HTLV- I and HTLV-II, were the only viruses then known to preferentially infect helper T lymphocytes, the cells depleted in people with AIDS (Gallo and Reitz, 1982; Popovic et al., 1984). The pattern of HTLV transmission was similar to that seen among AIDS patients: HTLV was transmitted by sexual contact, from mother to child or by exposure to infected blood (Essex, 1982; Gallo and Reitz, 1982). In addition, HTLV-I was known to cause mild immunosuppression, and a related retrovirus, the lymphotropic feline leukemia virus (FeLV), caused lethal immunosuppression in cats (Essex et al., 1975).

In May 1983, the first report providing experimental evidence for an association between a retrovirus and AIDS was published (Barre-Sinoussi et al., 1983). After finding antibodies cross-reactive with HTLV-I in a homosexual patient with lymphadenopathy, a group led by Dr. Luc Montagnier isolated a previously unrecognized virus containing reverse transcriptase that was cytopathic for cord- blood lymphocytes (Barre-Sinoussi et al., 1983). This virus later became known as lymphadenopathy-associated virus (LAV). The French group subsequently reported that LAV was tropic for T-helper cells, in which it grew to substantial titers and caused cell death (Klatzmann et al., 1984a; Montagnier et al., 1984).

In 1984, a considerable amount of new data added to the evidence for a retroviral etiology for AIDS. Researchers at the National Institutes of Health reported the isolation of a cytopathic T-lymphotropic virus from 48 different people, including 18 of 21 with pre-AIDS, three of four clinically normal mothers of children with AIDS, 26 of 72 children and adults with AIDS, and one (who later developed AIDS) of 22 healthy homosexuals (Gallo et al., 1984). The virus, named HTLV-III, could not be found in 115 healthy heterosexual subjects.

Antibodies reactive with HTLV-III antigens were found in serum samples of 88 percent of 48 patients with AIDS, 79 percent of 14 homosexuals with pre-AIDS, and fewer than 1 percent of hundreds of healthy heterosexuals (Sarngadharan et al., 1984).

Shortly thereafter, the researchers found that 100 percent (34 of 34) of AIDS patients tested were positive for HTLV-III antibodies in a study in which none of 14 controls had antibodies (Safai et al., 1984b).

In a study in the United Kingdom reported later that year, investigators found that 30 of 31 AIDS patients tested were seropositive for HTLV-III antibodies, as were 110 of 124 individuals with persistent generalized lymphadenopathy (Cheingsong- Popov et al., 1984). None of more than 1,000 blood donors selected randomly had antibodies to HTLV-III in this study.

During the same time period, HTLV-III was isolated from the semen of patients with AIDS (Zagury et al.,

1984, Ho et al., 1984), findings consistent with the epidemiologic data demonstrating AIDS transmission via sexual contact.

Researchers in San Francisco subsequently reported the isolation of a retrovirus they named the AIDS-associated retrovirus (ARV) from AIDS patients in different risk groups, as well as from asymptomatic people from AIDS risk groups (Levy et al., 1984). The researchers isolated ARV from 27 of 55 patients with AIDS or lymphadenopathy syndrome; they detected antibodies to ARV in 90 percent of 113 individuals with the same conditions. Like HTLV-III and LAV, ARV grew substantially in peripheral blood mononuclear cells and killed CD4+ T cells. The same group subsequently isolated ARV from genital secretions of women with antibodies to the virus, data consistent with the observation that men could contract AIDS following contact with a woman infected with the virus (Wofsy et al., 1986).

During the same period, HTLV-III and ARV were isolated from the brains of children and adults with AIDS-associated encephalopathy, which suggested a role for these viruses in the central nervous system disorders seen in many patients with AIDS (Levy et al., 1985; Ho et al., 1985).

By 1985, analyses of the nucleotide sequences of HTLV-III, LAV and ARV demonstrated that the three viruses belonged to the same retroviral family and were strikingly similar (Wain-Hobson et al., 1985; Ratner et al., 1985; Sanchez-Pescador et al., 1985). In 1986, the International Committee of Viral Taxonomy renamed the viruses the human immunodeficiency virus (HIV) (Coffin et al., 1986).

Seroprevalence Surveys

Serologic tests for antibodies to HIV, developed in 1984 (Sarngadharan et al., 1984; Popovic et al., 1984; reviewed in Brookmeyer and Gail, 1994), have enabled researchers to conduct hundreds of seroprevalence surveys throughout the world. Using these tests, investigators have repeatedly demonstrated that the occurrence of AIDS-like illnesses in different populations has closely followed the appearance of HIV antibodies (U.S. Bureau of the Census, 1994). For example, retrospective examination of sera collected in the late 1970s in association with hepatitis B studies in New York, San Francisco and Los Angeles suggests that HIV entered the U.S. population sometime in the late 1970s (Jaffe et al., 1985a). In 1978, 4.5 percent of men in the San Francisco cohort had antibodies to HIV (Jaffe et al., 1985a). The first cases of AIDS in homosexual men in San Francisco were reported in 1981, and by 1984, more than two-thirds of the San Francisco cohort had HIV antibodies and almost one-third had developed AIDS-related conditions (Jaffe et al., 1985a). By the end of 1992, approximately 70 percent of 539 men in the San Francisco cohort with a well-documented date of HIV seroconversion before 1983 had developed an AIDS-defining condition or had a CD4+ T cell count of less than 200/mm³; another 11 percent had CD4+ T cell counts between 200 and 500/mm³ (Buchbinder et al., 1994).

Retrospective tests of the U.S. blood supply have shown that, in 1978, at least one batch of Factor VIII was contaminated with HIV (Evatt et al., 1985; Aronson, 1993). Factor VIII was given to some 2,300 males in the United States that year. In July 1982, the first cases of AIDS in hemophiliacs were reported (CDC, 1982c). Through Dec. 31, 1994, 3,863 individuals in the United States with hemophilia or other coagulation disorders had been diagnosed with AIDS (CDC, 1995a).

Elsewhere in the world, a similar chronological association between HIV and AIDS has been noted. The appearance of HIV in the blood supply has preceded or coincided with the occurrence of AIDS cases in every country and region where cases of AIDS have been reported (Institute of Medicine, 1986; Chin and Mann, 1988; Curran et al., 1988; Piot et al., 1988; Mann, 1992; Mann et al., 1992; U.S. Bureau of the Census, 1994). For example, a review of serosurveys associated with dengue fever in the Caribbean found that the earliest evidence of HIV infection in Haiti appeared in samples from 1979 (Pape et al., 1983, 1993); the first cases of AIDS in Haiti and in Haitians in the United States were reported in the early 1980s (CDC, 1982e; Pape et al., 1983, 1993).

In Africa between 1981 and 1983, clinical epidemics of chronic, life-threatening enteropathic diseases ("slim disease"), cryptococcal meningitis, progressive KS and esophageal candidiasis were recognized in Rwanda, Tanzania, Uganda, Zaire and Zambia, and in 1983 the first AIDS cases among Africans were reported

ed (Quinn et al., 1986; Essex, 1994). The earliest blood sample from Africa from which HIV has been recovered is from a possible AIDS patient in Zaire, tested in connection with a 1976 Ebola virus outbreak (Getchell et al., 1987; Myers et al., 1992).

Serologic data have suggested the presence of HIV infection as early as 1959 in Zaire (Nahmias et al., 1986). Other investigators have found evidence of HIV proviral DNA in tissues of a sailor who died in Manchester, England, in 1959 (Corbitt et al., 1990). In the latter case, this finding may have represented a contamination with a virus isolated at a much later date (Zhu and Ho, 1995).

HIV did not become epidemic until 20 to 30 years later, perhaps because of the migration of poor and young sexually active individuals from rural areas to urban centers in developing countries, with subsequent return migration and, internationally, due to civil wars, tourism, business travel and the drug trade (Quinn, 1994).

HIV and Other Lentiviruses

As a retrovirus, HIV is an RNA virus that codes for the enzyme reverse transcriptase, which transcribes the viral genomic RNA into a DNA copy that ultimately integrates into the host cell genome (Fauci, 1988). Within the retrovirus family, HIV is classified as a lentivirus, having genetic and morphologic similarities to animal lentiviruses such as those infecting cats (feline immunodeficiency virus), sheep (visna virus), goats (caprine arthritis-encephalitis virus), and non-human primates (simian immunodeficiency virus) (Stowring et al., 1979; Gonda et al., 1985; Haase, 1986; Temin, 1988, 1989). Like HIV in humans, these animal viruses primarily infect cells of the immune system, including T lymphocytes and macrophages (Haase, 1986, 1990; Levy, 1993).

Lentiviruses often cause immunodeficiency in their hosts in addition to slow, progressive wasting disorders, neurodegeneration and death (Haase, 1986, 1990). SIV, for example, infects several subspecies of macaque monkeys, causing diarrhea, wasting, CD4+ T cell depletion, opportunistic infections and death (Desrosiers, 1990; Fultz, 1993). HIV is closely related to SIV, as evidenced by viral protein cross-reactivity and genetic sequence similarities (Franchini et al., 1987; Hirsch et al., 1989; Desrosiers, 1990; Myers, 1992).

One feature that distinguishes lentiviruses from other retroviruses is the remarkable complexity of their viral genomes. Most retroviruses that are capable of replication contain only three genes--env, gag and pol (Varmus, 1988). HIV contains not only these essential genes but also the complex regulatory genes tat, rev, nef, and auxiliary genes vif, vpr and vpu (Greene, 1991). The actions of these additional genes probably contribute to the profound pathogenicity that differentiates HIV from many other retroviruses.

CD4+ T cells, the cells depleted in AIDS patients, are primary targets of HIV because of the affinity of the gp120 glycoprotein component of the viral envelope for the CD4 molecule (Dalglish et al., 1984; Klatzmann et al., 1984b; McDougal et al., 1985a, 1986). These so-called T-helper cells coordinate a number of critical immunologic functions. The loss of these cells results in the progressive impairment of the immune system and is associated with a deteriorating clinical course (Pantaleo et al., 1993a). In advanced HIV disease, abnormalities of virtually every component of the immune system are evident (Fauci, 1993a; Pantaleo et al., 1993a).

Course of HIV Infection

Primary HIV infection is associated with a burst of HIV viremia and often a concomitant abrupt decline of CD4+ T cells in the peripheral blood (Cooper et al., 1985; Daar et al., 1991; Tindall and Cooper, 1991; Clark et al., 1991; Pantaleo et al., 1993a, 1994). The decrease in circulating CD4+ T cells during primary infection is probably due both to HIV-mediated cell killing and to re-trafficking of cells to the lymphoid tissues and other organs (Fauci, 1993a).

The median period of time between infection with HIV and the onset of clinically apparent disease is approximately 10 years in western countries, according to prospective studies of homosexual men in which dates of seroconversion are known (Lemp et al., 1990; Pantaleo et al., 1993a; Hessel et al., 1994). Similar estimates of

asymptomatic periods have been made for HIV-infected blood-transfusion recipients, injection drug users and adult hemophiliacs (reviewed in Alcabes et al., 1993a).

HIV disease, however, is not uniformly expressed in all individuals. A small proportion of persons infected with the virus develop AIDS and die within months following primary infection, while approximately 5 percent of HIV-infected individuals exhibit no signs of disease progression even after 12 or more years (Pantaleo et al., 1995a; Cao et al., 1995). Host factors such as age or genetic differences among individuals, the level of virulence of the individual strain of virus, as well as influences such as co-infection with other microbes may determine the rate and severity of HIV disease expression in different people (Fauci, 1993a; Pantaleo et al., 1993a). Such variables have been termed "clinical illness promotion factors" or co-factors and appear to influence the onset of clinical disease among those infected with any pathogen (Evans, 1982). Most people infected with hepatitis B, for example, show no symptoms or only jaundice and clear their infection, while others suffer disease ranging from chronic liver inflammation to cirrhosis and hepatocellular carcinoma (Robinson, 1990). Co-factors probably also determine why some smokers develop lung cancer, while others do not.

As disease progresses, increasing amounts of infectious virus, viral antigens and HIV-specific nucleic acids in the body correlate with a worsening clinical course (Allain et al., 1987; Nicholson et al., 1989; Ho et al., 1989; Schnittman et al., 1989, 1990a, 1991; Mathez et al., 1990; Genesca et al., 1990; Hufert et al., 1991; Saag et al., 1991; Aoki-Sei et al., 1992; Yerly et al., 1992; Bagnarelli et al., 1992; Ferre et al., 1992; Michael et al., 1992; Pantaleo et al., 1993b; Gupta et al., 1993; Connor et al., 1993; Saksela et al., 1994; Dickover et al., 1994; Daar et al., 1995; Furtado et al., 1995).

Cross-sectional studies in adults and children have shown that levels of infectious HIV or proviral DNA in the blood are substantially higher in patients with AIDS than in asymptomatic patients (Ho et al., 1989; Coombs et al., 1989; Saag et al., 1991; Srugo et al., 1991; Michael et al., 1992; Aoki-Sei et al., 1992). In both blood and lymph tissues from HIV-infected individuals, researchers at the National Institutes of Health found viral burden and replication to be substantially higher in patients with AIDS than in early-stage patients (Pantaleo et al., 1993b). This group also found deterioration of the architecture and microenvironment of the lymphoid tissue to a greater extent in late-stage patients than in asymptomatic individuals. The dissolution of the follicular dendritic cell network of the lymph node germinal center and the progressive loss of antigen-presenting capacity are likely critical factors that contribute to the immune deficiency seen in individuals with AIDS (Pantaleo et al., 1993b).

More recently, the same group studied 15 long-term non-progressors, defined as individuals infected for more than seven years (usually more than 10 years) who received no antiretroviral therapy and showed no decline in CD4+ T cells. They found that viral burden and viral replication in the peripheral blood and in lymph nodes, measured by DNA and RNA PCR, respectively, were at least 10 times lower than in 18 HIV-infected individuals whose disease progression was more typical. In addition, the lymph node architecture in long-term non-progressors remained intact (Pantaleo et al., 1995a).

Longitudinal studies also have quantified viral burden and replication in the blood and their relationship to disease progression (Schnittman et al., 1990a; Connor et al., 1993; Saksela et al., 1994; Daar et al., 1995; Furtado et al., 1995). In a study of asymptomatic HIV-infected individuals who ultimately developed rapidly progressive disease, the number of CD4+ T cells in which HIV DNA could be found increased over time, whereas this did not occur in patients with stable disease (Schnittman et al., 1990a). Using serial blood samples from HIV-infected individuals who had a precipitous drop in CD4+ T cells followed by a rapid progression to AIDS, other groups found a significant increase in the levels of HIV DNA concurrent with or prior to CD4+ T cell decline (Connor et al., 1993; Daar et al., 1995). Increased expression of HIV mRNA in peripheral blood mononuclear cells has also been shown to precede clinically defined progression of disease (Saksela et al., 1994).

In the longitudinal Multicenter AIDS Cohort Study (MACS), homosexual and bisexual men for whom the time of seroconversion had been documented had increasing levels of both plasma HIV RNA and intracellular RNA as disease progressed and had CD4+ T cell numbers that declined (Gupta et al., 1993; Mellors et

al., 1995). Men who remained asymptomatic with stable CD4+ T cell numbers maintained extremely low levels of viral RNA. These findings suggest that plasma HIV RNA levels are a strong, CD4-independent predictor of rapid progression to AIDS. Another longitudinal study found that increasing plasma RNA levels were highly predictive of the development of zidovudine (AZT) resistance and death in patients on long-term therapy with that drug (Vahey et al., 1994).

Other evidence suggests that changes in viral load due to changes in therapy can predict clinical benefit in patients. It was recently found that the amount of HIV RNA in the peripheral blood decreased in patients who switched to didanosine (ddI) after taking AZT and increased in patients who continued to take AZT (NTIS, 1994; Welles et al., 1995). Decreases in HIV RNA were associated with fewer progressions to new, previously undiagnosed AIDS-defining diseases or death. This study provided the first evidence that a therapy-induced reduction of HIV viral load is associated with clinical outcome. Similarly, studies of blood samples collected serially from HIV-infected patients found that a decrease in HIV RNA copy number in the first months following treatment with AZT strongly correlated with improved clinical outcome (O'Brien et al., 1994; Jurriaans et al., 1995).

The emergence of HIV variants that are more cytopathic and replicate in a wider range of susceptible cells *in vitro* has also been shown to correlate with disease progression in HIV-infected individuals (Fenyo et al., 1988; Tersmette et al., 1988, 1989a,b; Richman and Bozzette, 1994; Connor et al., 1993, Connor and Ho, 1994a,b). Similar results have been seen *in vivo* with macaques infected with molecularly cloned SIV (Kodama et al., 1993). It has also been reported that HIV isolates from patients who progress to AIDS have a higher rate of replication compared with HIV isolates from individuals who remain asymptomatic (Fenyo et al., 1988; Tersmette et al., 1989a), and that rapidly replicating variants of HIV emerge during the asymptomatic stage of infection prior to disease progression (Tersmette et al., 1989b; Connor and Ho, 1994b).

Immunologic Profile of People With AIDS

It is well established that a number of viral, rickettsial, fungal, protozoal and bacterial infections can cause transient T cell decreases (Chandra, 1983). Immune deficiencies due to tumors, autoimmune diseases, rare congenital disorders, chemotherapy and other factors have been shown to render certain individuals susceptible to opportunistic infections (Ammann, 1991). As mentioned above, chronic malnutrition following World War II resulted in PCP in Eastern European children (Walzer, 1990). Transplant recipients treated with immunosuppressive drugs such as cyclosporin and glucocorticoids often suffer recurrent diseases due to pathogens such as varicella zoster virus and cytomegalovirus that also cause disease in HIV-infected individuals (Chandra, 1983; Ammann, 1991).

However, the specific immunologic profile that typifies AIDS--a progressive reduction of CD4+ T cells resulting in persistent CD4+ T lymphocytopenia and profound deficits in cellular immunity--is extraordinarily rare in the absence of HIV infection or other known causes of immunosuppression. This was recently demonstrated in several surveys that sought to determine the frequency of idiopathic CD4+ T-cell lymphocytopenia (ICL), which is characterized by CD4+ T cell counts lower than 300 cells per cubic millimeter (mm³) of blood in the absence of HIV antibodies or conditions or therapies associated with depressed levels of CD4+ T cells (reviewed in Fauci, 1993b; Laurence, 1993).

In a CDC survey, only 47 (.02 percent) of 230,179 individuals diagnosed with AIDS were both HIV-seronegative and had persistently low CD4+ T cell counts (<300/mm³) in the absence of conditions or therapies associated with immunosuppression (Smith et al., 1993).

In the MACS, 22,643 CD4+ T cell determinations in 2,713 HIV-seronegative homosexual men revealed only one individual with a CD4+ T cell count persistently lower than 300 cells/mm³, and this individual was receiving immunosuppressive therapy (Vermund et al., 1993a). A similar review of another cohort of homosexual and bisexual men found no case of persistently lowered CD4+ T cell counts among 756 HIV-seronegative men who had no other cause of immunosuppression (Smith et al., 1993). Analogous results were reported from the San Francisco Men's Health Study, a population-based cohort recruited in 1984. Among 206 HIV-

seronegative heterosexual and 526 HIV-seronegative homosexual or bisexual men, only one had consistently low CD4+ T cell counts (Sheppard et al., 1993). This individual also had low CD8+ T cell counts, suggesting that he had general lymphopenia rather than a selective loss of CD4+ T cells. No AIDS-defining clinical condition was observed among these HIV-seronegative men.

Studies of blood donors, recipients of blood and blood products, and household and sexual contacts of transfusion recipients also suggest that persistently low CD4+ T cell counts are extremely rare in the absence of HIV infection (Aledort et al., 1993; Busch et al., 1994). Longitudinal studies of injection-drug users have demonstrated that unexplained CD4+ T lymphocytopenia is almost never seen among HIV-seronegative individuals in this population, despite a high risk of exposure to hepatitis B, cytomegalovirus and other blood-borne pathogens (Des Jarlais et al., 1993; Weiss et al., 1992).

Mechanisms of CD4+ T Cell Depletion

HIV infects and kills CD4+ T lymphocytes in vitro, although scientists have developed immortalized T-cell lines in order to propagate HIV in the laboratory (Popovic et al., 1984; Zagury et al., 1986; Garry, 1989; Clark et al., 1991). Several mechanisms of CD4+ T cell killing have been observed in lentivirus systems in vitro and may explain the progressive loss of these cells in HIV-infected individuals (reviewed in Garry, 1989; Fauci, 1993a; Pantaleo et al., 1993a). These mechanisms include disruption of the cell membrane as HIV buds from the surface (Leonard et al., 1988) or the intracellular accumulation of heterodisperse RNAs and unintegrated DNA (Pauza et al., 1990; Koga et al., 1988). Evidence also suggests that intracellular complexing of CD4 and viral envelope products can result in cell killing (Hoxie et al., 1986).

In addition to these direct mechanisms of CD4+ T cell depletion, indirect mechanisms may result in the death of uninfected CD4+ T cells (reviewed in Fauci, 1993a; Pantaleo et al., 1993a). Uninfected cells often fuse with infected cells, resulting in giant cells called syncytia that have been associated with the cytopathic effect of HIV in vitro (Sodroski et al., 1986; Lifson et al., 1986). Uninfected cells also may be killed when free gp120, the envelope protein of HIV, binds to their surfaces, marking them for destruction by antibody-dependent cellular cytotoxicity responses (Lyerly et al., 1987). Other autoimmune phenomena may also contribute to CD4+ T cell death since HIV envelope proteins share some degree of homology with certain major histocompatibility complex type II (MHC-II) molecules (Golding et al., 1989; Koenig et al., 1988).

A number of investigators have suggested that superantigens, either encoded by HIV or derived from unrelated agents, may trigger massive stimulation and expansion of CD4+ T cells, ultimately leading to depletion or anergy of these cells (Janeway, 1991; Hugin et al., 1991). The untimely induction of a form of programmed cell death called apoptosis has been proposed as an additional mechanism for CD4+ T cell loss in HIV infection (Ameisen and Capron, 1991; Terai et al., 1991; Laurent-Crawford et al., 1991). Recent reports indicate that apoptosis occurs to a greater extent in HIV-infected individuals than in non-infected persons, both in the peripheral blood and lymph nodes (Finkel et al., 1995; Pantaleo and Fauci, 1995b; Muro-Cacho et al., 1995).

It has also been observed that HIV infects precursors of CD4+ T cells in the bone marrow and thymus and damages the microenvironment of these organs necessary for the optimal sustenance and maturation of progenitor cells (Schnittman et al., 1990b; Stanley et al., 1992). These findings may help explain the lack of regeneration of the CD4+ T cell pool in patients with AIDS (Fauci, 1993a).

Recent studies have demonstrated a substantial viral burden and active viral replication in both the peripheral blood and lymphoid tissues even early in HIV infection (Fox et al., 1989; Coombs et al., 1989; Ho et al., 1989; Michael et al., 1992; Bagnarelli et al., 1992; Pantaleo et al., 1993b; Embretson et al., 1993; Piatak et al., 1993). One group has reported that 25 percent of CD4+ T cells in the lymph nodes of HIV-infected individuals harbor HIV DNA early in the course of disease (Embretson et al., 1993). Other data suggest that HIV infection is sustained by a dynamic process involving continuous rounds of new viral infection and the destruction and replacement of over 1 billion CD4+ T cells per day (Wei et al., 1995; Ho et al., 1995).

Taken together, these studies strongly suggest that HIV has a central role in the pathogenesis of AIDS, either directly or indirectly by triggering a series of pathogenic events that contribute to progressive immunosuppression.

Koch's Postulates Fulfilled

Recent developments in HIV research provide some of the strongest evidence for the causative role of HIV in AIDS and fulfill the classical postulates for disease causation developed by Henle and Koch in the 19th century (Koch's postulates reviewed in Evans, 1976, 1989a; Harden, 1992). Koch's postulates have been variously interpreted by many scientists over the years. One scientist who asserts that HIV does not cause AIDS has set forth the following interpretation of the postulates for proving the causal relationship between a microorganism and a specific disease (Duesberg, 1987):

- 1) The microorganism must be found in all cases of the disease.
- 2) It must be isolated from the host and grown in pure culture.
- 3) It must reproduce the original disease when introduced into a susceptible host.
- 4) It must be found in the experimental host so infected.

Recent developments in HIV/AIDS research have shown that HIV fulfills these criteria as the cause of AIDS.

1) The development of DNA PCR has enabled researchers to document the presence of cell-associated proviral HIV in virtually all patients with AIDS, as well as in individuals in earlier stages of HIV disease (Kwok et al., 1987; Wages et al., 1991; Bagasra et al., 1992; Bruisten et al., 1992; Petru et al., 1992; Hammer et al., 1993). RNA PCR has been used to detect cell-free and/or cell-associated viral RNA in patients at all stages of HIV disease (Ottmann et al., 1991; Schnittman et al., 1991; Aoki-Sei, 1992; Michael et al., 1992; Piatak et al., 1993).

2) Improvements in co-culture techniques have allowed the isolation of HIV in virtually all AIDS patients, as well as in almost all seropositive individuals with both early- and late-stage disease (Coombs et al., 1989; Schnittman et al., 1989; Ho et al., 1989; Jackson et al., 1990).

1-4) All four postulates have been fulfilled in three laboratory workers with no other risk factors who have developed AIDS or severe immunosuppression after accidental exposure to concentrated HIV-1 in the laboratory (Blattner et al., 1993; Reitz et al., 1994; Cohen, 1994c). Two patients were infected in 1985 and one in 1991. All three have shown marked CD4+ T cell depletion, and two have CD4+ T cell counts that have dropped below 200/mm³ of blood. One of these latter individuals developed PCP, an AIDS indicator disease, 68 months after showing evidence of infection and did not receive antiretroviral drugs until 83 months after the infection. In all three cases, HIV-1 was isolated from the infected individual, sequenced, and shown to be the original infecting strain of virus.

In addition, as of Dec. 31, 1994, CDC had received reports of 42 health care workers in the United States with documented, occupationally acquired HIV infection, of whom 17 have developed AIDS in the absence of other risk factors (CDC, 1995a). These individuals all had evidence of HIV seroconversion following a discrete percutaneous or mucocutaneous exposure to blood, body fluids or other clinical laboratory specimens containing HIV.

The development of AIDS following known HIV seroconversion also has been repeatedly observed in pediatric and adult blood transfusion cases (Ward et al., 1989; Ashton et al., 1994), in mother-to-child transmission (European Collaborative Study, 1991, 1992; Turner et al., 1993; Blanche et al., 1994), and in studies of hemophilia, injection drug use, and sexual transmission in which the time of seroconversion can be docu-

mented using serial blood samples (Goedert et al., 1989; Rezza et al., 1989; Biggar, 1990; Alcabes et al., 1993a,b; Giesecke et al., 1990; Buchbinder et al., 1994; Sabin et al., 1993).

In many such cases, infection is followed by an acute retroviral syndrome, which further strengthens the chronological association between HIV and AIDS (Pedersen et al., 1989, 1993; Schechter et al., 1990; Tindall and Cooper, 1991; Keet et al., 1993; Sinicco et al., 1993; Bachmeyer et al., 1993; Lindback et al., 1994).

Evidence From Animal and Laboratory Models

A recent study demonstrated that an HIV variant that causes AIDS in humans--HIV-2--also causes a similar syndrome when injected into baboons (Barnett et al., 1994). Over the course of two years, HIV-2-infected animals exhibited a significant decline in immune function, as well as lymphocytic interstitial pneumonia (which often afflicts children with AIDS), the development of lesions similar to those seen in Kaposi's sarcoma, and severe weight loss akin to the wasting syndrome that occurs in human AIDS patients. Other studies suggest that pigtailed macaques also develop AIDS-associated diseases subsequent to HIV-2 infection (Morton et al., 1994).

Asian monkeys infected with clones of the simian immunodeficiency virus (SIV), a lentivirus closely related to HIV, also develop AIDS-like syndromes (reviewed in Desrosiers, 1990; Fultz, 1993). In macaque species, various cloned SIV isolates induce syndromes that parallel HIV infection and AIDS in humans, including early lymphadenopathy and the occurrence of opportunistic infections such as pulmonary *Pneumocystis carinii* infection, cytomegalovirus, cryptosporidium, candida and disseminated MAC (Letvin et al., 1985; Kestler et al., 1990; Dewhurst et al., 1990; Kodama et al., 1993).

In cell culture experiments, molecular clones of HIV are tropic for the same cells as clinical HIV isolates and laboratory strains of the virus and show the same pattern of cell killing (Hays et al., 1992), providing further evidence that HIV is responsible for the immune defects of AIDS. Moreover, in severe combined immunodeficiency (SCID) mice with human thymus/liver implants, molecular clones of HIV produce the same patterns of cell killing and pathogenesis as seen with clinical isolates (Bonyhadi et al., 1993; Aldrovandi et al., 1993).

Geographic Considerations

Convincing evidence that HIV causes AIDS also comes from the geographic correlation between rates of HIV antibody positivity and incidence of disease. Numerous studies have shown that AIDS is common only in populations with a high seroprevalence of HIV antibodies. Conversely, in populations in which HIV antibody seroprevalence is low, AIDS is extremely rare (U.S. Bureau of the Census, 1994).

Malawi, a country in southern Africa with 8.2 million inhabitants, reported 34,167 cases of AIDS to the WHO as of December 1994 (WHO, 1995a). This is the highest case rate in the region. The rate of HIV seroprevalence in Malawi is also high, as evidenced by serosurveys of pregnant women and blood donors (U.S. Bureau of the Census, 1994). In one survey, approximately 23 percent of more than 6,600 pregnant women in urban areas were HIV-positive (Dallabetta et al., 1993). Approximately 20 percent of 547 blood donors in a 1990 survey were HIV-positive (Kool et al., 1990).

In contrast, Madagascar, an island country off the southeast coast of Africa with a population of 11.3 million, reported only nine cases of AIDS to the WHO through December 1994 (WHO, 1995a). HIV seroprevalence is extremely low in this country; in recent surveys of 1,629 blood donors and 1,111 pregnant women, no evidence of HIV infection was found (Rasamindrakotroka et al., 1991). Yet, other sexually transmitted diseases are common in Madagascar; a 1989 seroepidemiologic study for syphilis found that 19.5 percent of 12,457 persons tested were infected (Latif, 1994; Harms et al., 1994). It is likely that due to the relative geographic isolation of this island nation, HIV was introduced late into its population. However, the high rate of other STDs such as syphilis would predict that HIV will spread in this country in the future.

Similar patterns have been noted in Asia. Thailand reported 13,246 cases of AIDS to the WHO through December 1994, up from only 14 cases through 1988 (WHO, 1995a). This rise has paralleled the spread of HIV infection in Thailand. Through 1987, fewer than .05 percent of 200,000 Thais from all risk groups were HIV-seropositive (Weniger et al., 1991). By 1993, 3.7 percent of 55,000 inductees into the Royal Thai Army tested positive for HIV antibodies, up from 0.5 percent of men recruited in 1989 (U.S. Bureau of the Census Database, December 1994). Seropositivity among brothel prostitutes in Thailand rose from 3.5 percent in June 1989 to 27.1 percent in June 1993 (Hananberg et al., 1994). By mid-1993, an estimated 740,000 people were infected with HIV in Thailand (Brown and Sittitrai, 1994). By the year 2000, researchers estimate that there may be 1.4 million cumulative HIV infections and 480,000 AIDS cases in that country (Cohen, 1994b).

By comparison, South Korea reported only 25 cases of AIDS to the WHO through Dec. 1994 (WHO, 1995a). In serosurveys in that country conducted in 1993, HIV seroprevalence was .008 percent among female prostitutes and .00007 percent among blood donors (Shin et al., 1994).

Evidence From Blood Donor-Recipient Pairs

By the end of 1994, 7,223 cumulative cases of AIDS in the United States resulting from blood transfusions or the receipt of blood components or tissue had been reported to the CDC (CDC, 1995a). Virtually all of these cases can be traced to transfusions before the screening of the blood supply for HIV commenced in 1985 (Jones et al., 1992; Selik et al., 1993).

Compelling evidence supporting a cause-and-effect relationship between HIV and AIDS has come from studies of transfusion recipients with AIDS who have received blood from at least one donor with HIV infection. In the earliest such study (before the discovery of HIV), seven patients with transfusion-acquired AIDS were shown to have received a total of 99 units of blood components. At least one donor to each patient was identified who had AIDS-like symptoms or immunosuppression (Curran et al., 1984).

With the identification of HIV and the development of serologic assays for the virus in 1984, it became possible to trace infected donors (Sarngadharan et al., 1984). The first reports of donor-recipient pairs appeared later that year (Feorino et al., 1984; Groopman et al., 1984). In one instance, HIV was isolated from both donor and recipient, and both had developed AIDS (Feorino et al., 1984); in the other, the recipient was HIV antibody-positive and had developed AIDS, and the donor had culturable virus in his blood and was in a group considered to be at high risk for AIDS (Groopman et al., 1984). Molecular analysis of HIV isolates from these donor-recipient pairs found that the viruses were slightly different but much more similar than would be expected by chance alone (Feorino et al., 1984; Groopman et al., 1984).

In a subsequent study of patients with transfusion-acquired AIDS, 28 of 28 individuals had antibodies to HIV, and each had received blood from an HIV-infected donor (Jaffe et al., 1985b). Similar results were reported from a set of 18 patients with transfusion-acquired AIDS, each of whom had received blood from an HIV-infected donor (McDougal et al., 1985b). Fifteen of the 18 donors in this study had low CD4+/CD8+ T cell ratios, an immune defect seen in pre-AIDS and AIDS patients.

Another group studied seropositive recipients of blood from 112 donors in whom AIDS later developed and from 31 donors later found to be positive for HIV antibody. Of 101 seropositive recipients followed for a median of 55 months after infection, 43 developed AIDS (Ward et al., 1989).

More recently, Australian investigators identified 25 individuals with transfusion-acquired HIV whose infection could be traced to eight individuals who donated blood between 1980 and 1985, and subsequently developed AIDS. By 1992, nine of the 25 HIV-infected blood recipients had developed AIDS, with progression to AIDS and death more rapid among the recipients who received blood from the faster-progressing donors (Ashton et al., 1994).

Impact of HIV Infection on Mortality of Hemophiliacs

As noted above, HIV has been detected in stored blood samples taken from hemophilic patients in the United States as early as 1978 (Aronson, 1993). By 1984, 55 to 78 percent of U.S. hemophilic patients were HIV-infected (Lederman et al., 1985; Andes et al., 1989). A more recent survey found 46 percent of 9,496 clotting-factor recipients to be HIV-infected, only 9 of whom had a definitive date of seroconversion subsequent to April 1987 (Fricke et al., 1992). By Dec. 31, 1994, 3,863 individuals in the United States with hemophilia or coagulation disorders had been diagnosed with AIDS (CDC, 1995a).

The impact of HIV on the life expectancy of hemophiliacs has been dramatic. In a retrospective study of mortality among 701 hemophilic patients in the United States, median life expectancy for males with hemophilia increased from 40.9 years at the beginning of the century (1900-1920) to a high of 68 years after the introduction of factor therapy (1971 to 1980). In the era of AIDS (1981 to 1990), life expectancy declined to 49 years (Jones and Ratnoff, 1991).

Another analysis found that the death rate for individuals with hemophilia A in the United States rose three-fold between the periods 1979-1981 and 1987-1989. Median age at death decreased from 57 years in 1979-1981 to 40 years in 1987-1989 (Chorba et al., 1994).

In the United Kingdom, 6,278 males diagnosed with hemophilia were living during the period 1977-91. During 1979-86, 1,227 were infected with HIV during transfusion therapy. Among 2,448 individuals with severe hemophilia, the annual death rate was stable at 8 per 1,000 during 1977-84; during 1985-92 death rates remained at 8 per 1,000 among HIV-seronegative persons with severe hemophilia but rose steeply in those who were seropositive, reaching 81 per 1,000 in 1991-92. Among 3,830 with mild or moderate hemophilia, the pattern was similar, with an initial death rate of 4 per 1,000 in 1977-84, rising to 85 per 1,000 in 1991-92 among seropositive individuals (Darby et al., 1995).

In a British cohort of hemophiliacs infected with HIV between 1979 and 1985 and followed prospectively, 50 of 111 patients had died by the end of 1994, 43 after a diagnosis of AIDS. Only eight of the 61 living patients had CD4+ T cell counts above 500/mm³ (Lee et al., 1995).

Pediatric AIDS

Newborn infants have no behavioral risk factors, yet 6,209 children in the United States have developed AIDS through Dec. 31, 1994 (CDC, 1995a).

Studies have consistently shown that of infants born to HIV-infected mothers, only the 15-40 percent of infants who become HIV-infected before or during birth go on to develop immunosuppression and AIDS, while babies who are not HIV-infected do not develop AIDS (Katz, 1989; d'Arminio et al., 1990; Prober and Gershon, 1991; European Collaborative Study, 1991; Lambert et al., 1990; Lindgren et al. 1991; Andiman et al., 1990; Johnson et al., 1989; Rogers et al., 1989; Hutto et al., 1991). Moreover, in those infants who do acquire HIV and develop AIDS, the rate of disease progression varies directly with the severity of the disease in the mother at the time of delivery (European Collaborative Study, 1992; Blanche et al., 1994).

Almost all infants born to seropositive mothers have detectable HIV antibody, which may persist for as long as 15 months. In most cases, the presence of this antibody does not represent actual infection with HIV, but is antibody from the HIV-infected mother that diffuses across the placenta. In a French study of 22 infants born to HIV-infected mothers, seven babies had antibodies to HIV after one year and all developed AIDS. In these seven infants, the presence of HIV antibodies marked actual infection with HIV, not merely antibodies acquired from the mother. The other 15 children showed a complete loss of maternally acquired HIV antibodies, were not actually infected, and remained healthy. Of the babies who developed AIDS, virus was found in four of four infants tested. HIV was not found in the 15 children who remained healthy (Douard et al., 1989; Gallo, 1991).

In the European Collaborative Study, children born to HIV-seropositive mothers are followed from birth in 10 European centers. A majority of the mothers have a history of injection drug use. A recent report showed that none of the 343 children who had lost maternally transferred HIV antibodies (i.e. they were truly HIV-negative) had developed AIDS or persistent immune deficiency. In contrast, among 64 children who were truly HIV-infected (i.e. they remained HIV antibody positive), 30 percent presented with AIDS within 6 months of age or with oral candidiasis followed rapidly by the onset of AIDS. By their first birthday, 17 percent died of HIV-related diseases (European Collaborative Study, 1991).

In a multicenter study in Bangkok, Thailand, 105 children born to HIV-infected mothers were recently evaluated at 6 months of age (Chearskul et al., 1994). Of 27 infants determined to be HIV-infected by polymerase chain reaction, 24 developed HIV-related symptoms, including six who developed CDC-defined AIDS and four who died with conditions clinically consistent with AIDS. Among 77 exposed but uninfected infants, no deaths occurred.

In a study of 481 infants in Haiti, the survival rate at 18 months was 41 percent for HIV-infected infants, 84 percent among uninfected infants born to seropositive women, and 95 percent among infants born to seronegative women (Boulos et al., 1994).

Investigators have also reported cases of HIV-infected mothers with twins discordant for HIV-infection in which the HIV-infected child developed AIDS, while the other child remained clinically and immunologically normal (Park et al., 1987; Menez-Bautista et al., 1986; Thomas et al., 1990; Young et al., 1990; Barlow and Mok, 1993; Guerrero Vazquez et al., 1993).

Single Source Outbreak of Pediatric AIDS

Other researchers have used molecular epidemiology to find a single source of HIV for an outbreak of pediatric AIDS cases in Russia. In that country between 1988 and 1990, over 250 children were infected with HIV after exposure to non-sterile needles. By June 1994, 43 of these children had died of AIDS (Irova et al., 1993). In a recent report on 22 of these children from two hospitals, 12 had developed AIDS. Molecular analysis of HIV isolates from all 22 children showed the isolates to be very closely related, confirming epidemiological data that these two outbreaks resulted from a single source: an infant born to an HIV-infected mother whose husband was infected in central Africa (Bobkov et al., 1994).

Answering the Skeptics: the "Risk-AIDS" or "Behavioral" Hypothesis

Skeptics of the role of HIV in AIDS have espoused a "risk-AIDS" or a "drug-AIDS" hypothesis (Duesberg, 1987-1994), asserting at different times that factors such as promiscuous homosexual activity; repeated venereal infections and antibiotic treatments; the use of recreational drugs such as nitrite inhalants, cocaine and heroin; immunosuppressive medical procedures; and treatment with the drug AZT are responsible for the epidemic of AIDS.

Such arguments have been repeatedly contradicted. Compelling evidence against the risk-AIDS hypothesis has come from cohort studies of high-risk groups in which all individuals with AIDS-related conditions are HIV-antibody positive, while matched, HIV-antibody negative controls do not develop AIDS or immunosuppression, despite engaging in high-risk behaviors.

In a prospectively studied cohort in Vancouver (Schechter et al., 1993a), 715 homosexual men were followed for a median of 8.6 years. Among 365 HIV-positive individuals, 136 developed AIDS. No AIDS-defining illnesses occurred among 350 HIV-negative men despite the fact that these men reported appreciable levels of nitrite use, other recreational drug use, and frequent receptive anal intercourse. The average rate of CD4+ T cell decline was 50 cells/mm³ per year in the HIV-positive men, while the HIV-negative men showed no decline. Significantly, the decline of CD4+ T cell counts in HIV-positive men and the stability of CD4+ T cell counts in HIV-negative men were apparent whether or not nitrite inhalants were used. There were 101 AIDS-related deaths among the HIV-seropositive men, including six unrelated to HIV infection. In the seronegative group, only two

deaths occurred: one heart attack and one suicide. In this study, lifetime prevalences of risk behaviors were similar in the 136 HIV-seropositive men who developed AIDS and in the 226 HIV-seropositive men who did not develop AIDS: use of nitrite inhalants, 88 percent in both groups; use of other illicit drugs, 75 percent and 80 percent, respectively; more than 25 percent of sexual encounters involving receptive anal intercourse, 78 percent and 82 percent, respectively. Among HIV-seronegative men (none of whom developed AIDS), the lifetime prevalences of these behaviors were somewhat lower, but substantial: 56 percent, 74 percent and 58 percent, respectively.

Similar results were reported from the San Francisco Men's Health Study, a cohort of single men recruited in San Francisco in 1984 without regard to sexual preference, lifestyle or serostatus (Ascher et al., 1993a). During 96 months of follow-up, 215 cases of AIDS had occurred among 445 HIV-antibody positive homosexual men, 174 of whom had died. Among 367 antibody-negative homosexual men and 214 antibody-negative heterosexual men, no AIDS cases and eight deaths unrelated to AIDS-defining conditions were observed. The authors found no overall effect of drug consumption, including nitrites, on the development of Kaposi's sarcoma or other AIDS-defining conditions, nor an effect of the extent of the participants' drug use on these conditions. A consistent loss of CD4+ T cells was limited to HIV-positive subjects, among whom there was no discernible difference in CD4+ T cell counts related to drug-taking behavior. Among HIV-seronegative men, moderate or heavy drug users had higher CD4+ T cell counts than non-users.

Observational studies of HIV-infected individuals have found that drug use does not accelerate progression to AIDS (Kaslow et al., 1989; Coates et al., 1990; Lifson et al., 1990; Robertson et al., 1990). In a Dutch cohort of HIV-seropositive homosexual men, no significant differences in sexual behavior or use of cannabis, alcohol, tobacco, nitrite inhalants, LSD or amphetamines were found between men who remained asymptomatic for long periods and those who progressed to AIDS (Keet et al., 1994). Another study, of five cohorts of homosexual men for whom dates of seroconversion were well-documented, found no association between HIV disease progression and history of sexually transmitted diseases, number of sexual partners, use of AZT, alcohol, tobacco or recreational drugs (Veugelers et al., 1994).

Similarly, in the San Francisco City Clinic Cohort, recruited in the late 1970s and early 1980s in conjunction with hepatitis B studies, no consistent differences in exposure to recreational drugs or sexually transmitted diseases were seen between HIV-infected men who progressed to AIDS and those who remained healthy (Buchbinder et al., 1994).

Because many children with AIDS are born to mothers who abuse recreational drugs (Novick and Rubinstein, 1987; European Collaborative Study, 1991), it has been postulated that the mothers' drug consumption is responsible for children developing AIDS (Duesberg, 1987-1994). This theory is contradicted by numerous reports of infants with AIDS born to women infected with HIV through heterosexual contact or transfusions who do not use drugs (CDC, 1995a). As noted above, the only factor that predicts whether a child will develop AIDS is whether he or she is infected with HIV, not maternal drug use.

AIDS and Injection Drug Users

Central to the "risk-AIDS" hypothesis is the notion that chronic injection drug use causes AIDS (Duesberg, 1992), a view that is contradicted by numerous studies.

Although some evidence suggests injection drug use can cause certain immunologic abnormalities, such as reduction in natural killer (NK) cell activity (reviewed in Kreek, 1990), the specific immune deficit that leads to AIDS--a progressive reduction of CD4+ T cells resulting in persistent CD4+ T lymphocytopenia--is rare in HIV-seronegative injection drug users in the absence of other immunosuppressive conditions (Des Jarlais et al., 1993; Weiss et al., 1992).

In a survey of 229 HIV-seronegative injection drug users in New York City, mean CD4+ T cell counts of the group were consistently over 1000/mm³ (Des Jarlais et al., 1993). Only two individuals had two CD4+ T cell measurements of fewer than 300/mm³, one of whom died with cardiac disease and non-Hodgkin's lymphoma list-

ed as the cause of death. In a study of 180 HIV-seronegative injection drug users in New Jersey, the participants' average CD4+ T cell count was 1169/mm³ (Weiss et al., 1992). Two of these individuals, both with generalized lymphocytopenia, had CD4+ T cell counts less than 300/mm³.

In the MACS, median CD4+ T cell counts of 63 HIV-seronegative injection drug users rose from 1061/mm³ to 1124/mm³ in a 15 to 21 month follow-up period (Margolick et al., 1992). In a cross-sectional study, 11 HIV-seronegative, long-term heroin addicts had mean CD4+ T cell counts of 1500/mm³, while 11 healthy controls had CD4+ T cell counts of 820 cells/mm³ (Novick et al., 1989).

Recent data also refute the notion that a certain lifetime dosage of injection drugs is sufficient to cause AIDS in HIV-seronegative individuals. In a Dutch study, investigators compared 86 HIV-seronegative individuals who had been injecting drugs for a mean of 7.6 years with 70 HIV-seropositive people who had injected drugs for a mean of 9.1 years. Upon enrollment in 1989, CD4+ T cell counts were 914/mm³ in the HIV-seronegative group, and 395/mm³ in the seropositive group. By 1994, there were 25 deaths attributable to AIDS-defining conditions in the seropositive group; among HIV-seronegative individuals, eight deaths occurred, none due to AIDS-defining diseases (Cohen, 1994a).

Excess mortality among HIV-infected injection drug users as compared to HIV-seronegative users has also been observed by other investigators. In a prospective Italian study of 2,431 injection drug users enrolled in drug treatment programs from 1985 to 1991, HIV-seropositive individuals were 4.5 times more likely to die than HIV-seronegative subjects (Zaccarelli et al., 1994). No deaths due to AIDS-defining conditions were seen among 1,661 HIV-seronegative individuals, 41 of whom died of other conditions, predominantly overdose, liver disease and accidents. Among 770 individuals who were HIV-seropositive at study entry or who seroconverted during the study period, 89 died of AIDS-related conditions and 52 of other conditions.

In HIV-seropositive individuals, a number of investigators have found no statistical association between injection drug use and decline of CD4+ T cell counts (Galli et al., 1989, 1991; Schoenbaum et al., 1989; Margolick et al., 1992, 1994; Montella et al., 1992; Alcabes et al., 1993b, 1994; Galai et al., 1995), nor a difference in disease progression between active versus former users of injection drugs (Weber et al., 1990; Galli et al., 1991; Montella et al., 1992; Italian Seroconversion Study, 1992).

Taken together, these studies suggest that any negative effects of injection drugs on CD4+ T cell levels are limited and may explain why many investigators have found that HIV-seropositive injection drug users have rates of disease progression that are similar to other HIV-infected individuals (Rezza et al., 1990; Montella et al., 1992; Galli et al., 1989; Selwyn et al., 1992; Munoz et al., 1992; Italian Seroconversion Study, 1992; MAP Workshop, 1993; Pezzotti et al., 1992; Margolick et al., 1992, 1994; Alcabes, 1993b, 1994; Galai et al., 1995).

Sex and the AIDS Epidemic

It has been asserted "... in America, only promiscuity aided by aphrodisiac and psychoactive drugs, practiced mostly by 20 to 40 year-old male homosexuals and some heterosexuals, seems to correlate with AIDS diseases" (Duesberg, 1991). Even a cursory review of history provides evidence to the contrary: such behaviors have existed for decades --in some cases centuries--and have increased only in a relative sense in recent years, if at all, whereas AIDS clearly is a new phenomenon.

If promiscuity were a cause of AIDS, one would have expected cases to have occurred among prostitutes (male or female) prior to 1978. Reports of such cases are lacking, even though prostitution has been present in most if not all cultures throughout history.

In this country, trends in gonorrheal infections suggest that extramarital sexual activity was extensive in the pre-AIDS era. Cases of gonorrhea in the United States peaked at approximately 1 million in 1978; between 250,000 and 530,000 cases were reported each year in the 1960s, approximately 250,000 cases each year in the 1950s, and between 175,000 and 380,000 cases annually in the 1940s (CDC, 1987c, 1993b). Despite the fre-

quency of sexually transmitted diseases, only a handful of documented cases of AIDS in the United States prior to 1978 have been reported.

Historians, archaeologists and sociologists have documented extensive homosexual activity dating from the ancient Greeks to the well-established homosexual subculture in the United States in the 20th century (Weinberg and Williams, 1974; Gilbert, 1980-81; Saghir and Robins, 1973; Reinisch et al., 1990; Doll et al., 1990; Katz, 1992; Friedman and Downey, 1994). Depictions of anal intercourse, both male and female, can be found in the art and literature of numerous cultures on all inhabited continents (Reinisch et al., 1990). In the 1940s, Kinsey et al. reported that 37 percent of all American males surveyed had at least some overt homosexual experience to the point of orgasm between adolescence and old age and that 10 percent of men were exclusively or predominantly homosexual between the ages of 16 and 55 (Kinsey et al., 1948). More recent surveys have found that 2 to 5 percent of men are homosexual or bisexual (reviewed in Friedman and Downey, 1994; Seidman and Rieder, 1994; Laumann, 1994).

Many homosexuals had multiple sexual partners in the pre-AIDS era: a 1969 survey found that more than 40 percent of white homosexual males and one-third of black homosexual males had at least 500 partners in their lifetime, and an additional one-fourth reported between 100 and 500 partners (Bell and Weinberg, 1978). A majority of these men reported that more than half their partners had been strangers before the sexual encounters (Bell and Weinberg, 1978). Further evidence of extensive homosexual behavior in the years preceding the AIDS epidemic comes from reports of numerous cases of rectal gonorrhea and anal herpes simplex virus infections among men (Jefferiss, 1956; Scott and Stone, 1966; Pariser and Marino, 1970; Owen and Hill, 1972; British Cooperative Clinical Group, 1973; Jacobs, 1976; Judson et al., 1977; Merino and Richards, 1977; McMillan and Young, 1978).

Drug Use in the Pre-AIDS Era

A temporal association between the onset of extensive use of recreational drugs and the AIDS epidemic is also lacking. The widespread use of opiates in the United States has existed since the middle of the 19th century (Courtwright, 1982); as many as 313,000 Americans were addicted to opium and morphine prior to 1914. Heroin use spread throughout the country in the 1920s and 1930s (Courtwright, 1982), and the total number of active heroin users peaked at about 626,000 in 1971 (Greene et al., 1975; Friedland, 1989). Opiates were initially administered by oral or inhalation routes, but by the 1920s addicts began to inject heroin directly into their veins (Courtwright, 1982). In 1940, intravenous use of opiates was seen in 80 percent of men admitted to a large addiction research center in Kentucky (Friedland, 1989).

While cocaine use increased markedly during the 1970s (Kozel and Adams, 1986), the use of the drug, frequently with morphine, is well-documented in the United States since the late 19th century (Dale, 1903; Ashley, 1975; Spotts and Shontz, 1980). For example, a survey in 1902 reported that only 3 to 8 percent of the cocaine sold in New York, Boston and other cities went into the practice of medicine or dentistry (Spotts and Shontz). After a period of relative obscurity, cocaine became increasingly popular in the late 1950s and 1960s. Over 70 percent of 1,100 addicts at the addiction research center in Kentucky in 1968 and 1969 reported use or abuse of cocaine (Chambers, 1974).

The recreational use of nitrite inhalants ("poppers") also predates the AIDS epidemic. Reports of the widespread use of these drugs by young men in the 1960s were the impetus for the reinstatement by the Food and Drug Administration of the prescription requirement for amyl nitrite in 1968 (Israelstam et al., 1978; Haverkos and Dougherty, 1988). Since the early years of the AIDS epidemic, the use of nitrite inhalants has declined dramatically among homosexual men, yet the number of AIDS cases continues to increase (Ostrow et al., 1990, 1993; Lau et al., 1992).

In the general population, the number of individuals aged 25 to 44 years reporting current use of marijuana, cocaine, inhalants, hallucinogens and cigarettes declined between 1974 and 1992, while the AIDS epidemic worsened (Substance Abuse and Mental Health Services Administration, 1994).

AZT and AIDS

Although some individuals maintain that treatment with zidovudine (AZT) has compounded the AIDS epidemic (Duesberg, 1992), published reports of both placebo-controlled clinical trials and observational studies provide data to the contrary.

In patients with symptomatic HIV disease, for whom a beneficial effect is measured in months, AZT appears to slow disease progression and prolong life, according to double-blind, placebo-controlled clinical studies (reviewed in Sande et al., 1993; McLeod and Hammer, 1992; Volberding and Graham, 1994). A clinical trial known as BW 002 compared AZT with placebo in 282 patients with AIDS or advanced signs or symptoms of HIV disease. In this study, which led to the approval of AZT by the FDA, only one of 145 patients treated with AZT died compared with 19 of 137 placebo recipients in a six month period. Opportunistic infections occurred in 24 AZT recipients and 45 placebo recipients. In addition to reducing mortality, AZT was shown to have reduced the frequency and severity of AIDS-associated opportunistic infections, improved body weight, prevented deterioration in Karnofsky performance score, and increased counts of CD4+ T lymphocytes in the peripheral blood (Fischl et al., 1987; Richman et al., 1987). Continued follow-up in 229 of these patients showed that the survival benefit of AZT extended to at least 21 months after the initiation of therapy; survival in the original treatment group was 57.6 percent at that time, whereas survival among members of the original placebo group was 51.5 percent at nine months (Richman and Andrews, 1988; Fischl et al., 1989).

In another placebo-controlled study known as ACTG 016, which enrolled 711 symptomatic HIV-infected patients with CD4+ T cell counts between 200 and 500 cells/mm³, those taking AZT were less likely to experience disease progression than those on placebo during a median study period of 11 months (Fischl et al., 1990). In this study, no difference in disease progression was noted among participants who began the trial with CD4+ T cell counts greater than 500/mm³.

A Veteran's Administration study of 338 individuals with early symptoms of HIV disease and CD4+ T cell counts between 200 and 500 cells/mm³ found that immediate therapy significantly delayed disease progression compared with deferred therapy, but did not lengthen (or shorten) survival after an average study period of more than two years (Hamilton et al., 1992).

Among asymptomatic HIV-infected individuals, several placebo-controlled clinical trials suggest that AZT can delay disease progression for 12 to 24 months but ultimately does not increase survival. Significantly, long-term follow-up of persons participating in these trials, although not showing prolonged benefit of AZT, has never indicated that the drug increases disease progression or mortality (reviewed in McLeod and Hammer, 1992; Sande et al., 1993; Volberding and Graham, 1994). The lack of excess AIDS cases and death in the AZT arms of these large trials effectively rebuts the argument that AZT causes AIDS.

During a 4.5 year follow-up period (mean 2.6 years) of a trial known as ACTG 019, no differences were seen in overall survival between AZT and placebo groups among 1,565 asymptomatic patients entering the study with fewer than 500 CD4+ T cells/mm³ (Volberding et al., 1994). In that study, AZT was superior to placebo in delaying progression to AIDS or advanced ARC for approximately one year, and a more prolonged benefit was seen among a subset of patients.

The Concorde study in Europe enrolled 1,749 asymptomatic patients with CD4+ T cell counts less than 500/mm³. In that study, no statistically significant differences in progression to advanced disease were observed after three years between individuals taking AZT immediately and those who deferred AZT therapy or did not take the drug (Concorde Coordinating Committee, 1994). However, the rate of progression to death, AIDS or severe ARC was slower among the "immediate" AZT group during the first year of therapy. Although the Concorde study did not show a significant benefit over time with the early use of AZT, it clearly demonstrated that AZT was not harmful to the patients in the "immediate" AZT group as compared to the "deferred" AZT group.

A European-Australian study (EACG 020) of 993 patients with CD4+ T cell counts greater than 400/mm³

showed no differences between AZT and placebo arms of the trial during a median study period of 94 weeks, although AZT did delay progression to certain clinical and immunological endpoints for up to three years (Cooper et al., 1993). Both this study and the Concorde study reported little severe AZT-related hematologic toxicity at doses of 1,000 mg/day, which is twice the recommended daily dose in the United States.

Uncontrolled studies have found increased survival and/or reduced frequency of opportunistic infections in patients with HIV disease and AIDS who were treated with AZT or other anti-retrovirals (Creagh-Kirk et al., 1988; Moore et al., 1991a,b; Ragni et al., 1992; Schinaia et al., 1991; Koblin et al., 1992; Graham et al., 1991, 1992, 1993; Longini, 1993; Vella et al., 1992, 1994; Saah et al., 1994; Bacellar et al., 1994). In the Multicenter AIDS Cohort Study, for example, HIV-infected individuals treated with AZT had significantly reduced mortality and progression to AIDS for follow-up intervals of six, 12, 18 and 24 months compared to those not taking AZT, even after adjusting for health status, CD4+ T cell counts and PCP prophylaxis (Graham et al., 1991, 1992).

In addition, several cohort studies show that life expectancy of individuals with AIDS has increased since the use of AZT became common in 1986-87. Among 362 homosexual men in hepatitis B vaccine trial cohorts in New York City, San Francisco and Amsterdam, the time from seroconversion to death, a period not influenced by variations in diagnosing AIDS, has lengthened slightly in recent years (Hessol et al., 1994). In a Dutch study of 975 males and females with HIV infection, median survival with AIDS increased from nine months in 1982-1985, to 26 months in 1990 (Bindels et al., 1994). Even taking into consideration the benefits of improved PCP prophylaxis and treatment, if AZT were contributing to or causing disease, one would expect a decrease in survival figures, rather than an increase that parallels the use of AZT.

In an analysis from the San Francisco Men's Health Study, the investigators note that 169 (73 percent) of 233 AIDS patients had been treated with AZT at one time or another. However, 90 (53 percent of the 169) were diagnosed with clinical AIDS before beginning AZT treatment, and another 51 (30 percent of the 169) had CD4+ T cell counts lower than 200/mm³ before initiation of AZT treatment (Ascher et al., 1995). The authors conclude, "These data are not consistent with the hypothesis of a causal role for AZT in AIDS."

Disease Progression Despite Antibodies

It has been argued that HIV cannot cause AIDS because the body develops HIV-specific antibodies following primary infection (Duesberg, 1992). This reasoning ignores numerous examples of viruses other than HIV that can be pathogenic after evidence of immunity appears (Oldstone, 1989). Primary poliovirus infection is a classic example of a disease in which high titers of neutralizing antibodies develop in all infected individuals, yet a small percentage of individuals develop subsequent paralysis (Kurth, 1990). Measles virus may persist for years in brain cells, eventually causing a chronic neurological disease despite the presence of antibodies (Gershon, 1990). Viruses such as cytomegalovirus, herpes simplex and varicella zoster may be activated after years of latency even in the presence of abundant antibodies (Weiss and Jaffe, 1990). Lentiviruses with long and variable latency periods, such as visna virus in sheep, cause central nervous system damage even after the specific production of neutralizing antibodies (Haase, 1990). Furthermore, it is now well-documented that HIV can mutate rapidly to circumvent immunologic control of its replication.

Risks Associated With Transfusion

It has been argued that AIDS among transfusion recipients is due to underlying diseases that necessitated the transfusion, rather than to HIV (Duesberg, 1991). This theory is contradicted by a report by the Transfusion Safety Study Group, which compared HIV-negative and HIV-positive blood recipients who had been given transfusions for similar diseases. Approximately three years after the transfusion, the mean CD4+ T cell count in 64 HIV-negative recipients was 850/mm³, while 111 HIV-seropositive individuals had average CD4+ T cell counts of 375/mm³ (Donegan et al., 1990). By 1993, there were 37 cases of AIDS in the HIV-infected group, but not a single AIDS-defining illness in the HIV-seronegative transfusion recipients (Cohen, 1994d).

People have received blood transfusions for decades; however, as discussed above, AIDS-like symptoms were

extraordinarily rare before the appearance of HIV. Recent surveys have shown that AIDS-like symptoms remain very rare among transfusion recipients who are HIV-seronegative and their sexual contacts. In one study of transfusion safety, no AIDS-defining illnesses were seen among 807 HIV-negative recipients of blood or blood products, or 947 long-term sexual or household contacts of these individuals (Aledort et al., 1993).

In addition, through 1994, the CDC had received reports of 628 cases of AIDS in individuals whose primary risk factor was sex with an HIV-infected transfusion recipient (CDC, 1995a), a finding not explainable by the "risk-AIDS" hypothesis.

Exposure to Factor VIII

It has also been argued that cumulative exposure to foreign proteins in Factor VIII concentrates leads to CD4+ T cell depletion and AIDS in hemophiliacs (Duesberg, 1992). This view is contradicted by several large studies. Among HIV-seronegative patients with hemophilia A enrolled in the Transfusion Safety Study, no significant differences in CD4+ T cell counts were noted between 79 patients with no or minimal factor treatment and 53 patients with the largest amount of lifetime treatments (cumulative totals in the latter group ranged from 100,000 to 2,000,000 U in two years) (Hassett et al., 1993). Although the CD4+ T cell counts seen in the low- and high- groups (756/mm³ and 718/mm³, respectively) were 20 to 25 percent lower than controls, such levels are still within the normal range.

In a report from the Multicenter Hemophilia Cohort Study, the mean CD4+ T cell counts among 161 HIV-seronegative hemophiliacs was 784/mm³; among 715 HIV-seropositive hemophiliacs, the mean CD4+ T cell count was 253/mm³ (Lederman et al., 1995).

In another study, no instances of AIDS-defining illnesses were seen among 402 HIV-seronegative hemophiliacs treated with factor therapy or in 83 hemophiliacs who received no treatment subsequent to 1979 (Aledort et al., 1993; Mosely et al., 1993).

In a retrospective study of patients with severe hemophilia A, the rate of CD4+ T cell loss was 31.4 every six months for 41 HIV-seropositive individuals without AIDS and 49.7 every six months for 14 HIV-seropositive individuals with AIDS. In contrast, among 28 HIV-seronegative individuals, CD4+ T cell counts increased at a rate of 13.1 cells/six months (Becherer et al., 1990).

In a study of children and adolescents with hemophilia, the median CD4+ T cell count of 126 HIV-seronegative individuals was 895/mm³ at study entry; no individuals had CD4+ T cell counts below 200/mm³. In contrast, 26 percent of seropositive children had CD4+ T cell counts of less than 200/mm³; the mean CD4+ T cell count for seropositive children was 423/mm³ (Jason et al., 1994).

Although some reports have suggested that high-purity Factor VIII concentrates are associated with a slower rate of CD4+ T cell decline in HIV-infected hemophiliacs than products of low and intermediate purity (Hilgartner et al., 1993; Goldsmith et al., 1991; de Biasi et al., 1991), other studies have shown no such benefit (Mannucci et al., 1992; Gjerset et al., 1994). In a study of 525 HIV-infected hemophiliacs, Transfusion Safety Study investigators found that neither the purity nor the amount of Factor VIII therapy had a deleterious effect on CD4+ T cell counts (Gjerset et al., 1994). Similarly, the Multicenter Hemophilia Cohort Study found no association between the cumulative dose of plasma concentrate and incidence of AIDS among 242 HIV-infected hemophiliacs and thus "no support for cofactor hypotheses involving either antigen stimulation or inoculum size" (Goedert et al., 1989).

In addition to the evidence from the cohort studies cited above, it should be noted that 10 to 20 percent of wives and sex partners of male HIV-positive hemophiliacs in the United States are also HIV-infected (Pitchenik et al., 1984; Kreiss et al., 1985; Peterman et al., 1988; Smiley et al., 1988; Dietrich and Boone, 1990; Lusher et al., 1991). Through December 1994, the CDC had received reports of 266 cases of AIDS in those who had sex with a person with hemophilia (CDC, 1995a). These data cannot be explained by a non-infectious theory of AIDS etiology.

Distribution of AIDS Cases

Certain skeptics maintain that the distribution of AIDS cases casts doubt on HIV as the cause of the syndrome. They claim infectious microbes are not gender-specific, yet relatively few people with AIDS are women (Duesberg, 1992).

In fact, the distribution of AIDS cases, whether in the United States or elsewhere in the world, invariably mirrors the prevalence of HIV in a population (U.S. Bureau of the Census, 1994). In the United States, HIV first appeared in populations of homosexual men and injection drug users, a majority of whom are male (Curran et al., 1988). Because HIV is spread primarily through sex or by the exchange of HIV-contaminated needles during injection drug use, it is not surprising that a majority of U.S. AIDS cases have occurred in men.

Increasingly, however, women are becoming HIV-infected, usually through the exchange of HIV-contaminated needles or sex with an HIV-infected male (Vermund, 1993b; CDC, 1995a). As the number of HIV-infected women has risen, so too have the number of female AIDS cases. In the United States, the proportion of AIDS cases among women has increased from 7 percent in 1985 to 18 percent in 1994. AIDS is now the fourth leading cause of death among women aged 25 to 44 in the United States (CDC, 1994).

In Africa, HIV was first recognized in sexually active heterosexuals, and in some parts of Africa AIDS cases have occurred as frequently in women as in men (Quinn et al., 1986; Mann, 1992a). In Zambia, for example, the 29,734 AIDS cases reported to the WHO through October 20, 1993, were equally divided among males and females (WHO, 1995a,b).

AIDS in Africa

One vocal skeptic of the role of HIV in AIDS argues that, in Africa, AIDS is nothing more than a new name for old diseases (Duesberg, 1991). It is true that the diseases that have come to be associated with AIDS in Africa--wasting, diarrheal diseases and TB--have long been severe burdens there. However, high rates of mortality from these diseases, formerly confined to the elderly and malnourished, are now common among HIV-infected young and middle-aged people (Essex, 1994). In a recent study of more than 9,000 individuals in rural Uganda, people testing positive for HIV antibodies were 60 times as likely to die during the subsequent two-year observation period as were otherwise similar persons who tested negative (Mulder et al., 1994b). Large differences in mortality were also seen between HIV-seropositive and HIV-seronegative individuals in another large Ugandan cohort (Sewankambo et al., 1994).

Elsewhere in Africa findings are similar. One study of 1,400 Rwandan women tested for HIV during pregnancy found that HIV infected women were 20 times more likely to die in the two years following pregnancy than their HIV-negative counterparts (Lindan et al., 1992). In another study in Rwanda, 215 HIV-seropositive women and 216 HIV-seronegative women were followed prospectively for up to four years, during which time 21 women developed AIDS (WHO definition), all of them in the HIV-seropositive group. The mortality rate among the HIV-seropositive women was nine times higher than seen among the HIV-seronegative women (Leroy et al., 1995)

In Zaire, investigators found that families in which the mother was HIV-1 seropositive experienced a five- to 10-fold higher maternal, paternal and early childhood mortality rate than families in which the mother was HIV-seronegative (Ryder et al., 1994b). In another study in Zaire, infants with HIV infection were shown to have an 11-fold increased risk of death from diarrhea compared with uninfected children (Thea et al., 1993). In patients with pulmonary tuberculosis in Cote d'Ivoire, HIV-seropositive individuals were 17 times more likely to die than HIV-seronegative individuals (Ackah et al., 1995).

The extraordinary death rates among HIV-infected individuals confirm that the virus is an important cause of premature mortality in Africa (Dondero and Curran, 1994).

CONCLUSION

HIV and AIDS have been repeatedly linked in time, place and population group; the appearance of HIV in the blood supply has preceded or coincided with the occurrence of AIDS cases in every country and region where AIDS has been noted. Among individuals without HIV, AIDS-like symptoms are extraordinarily rare, even in populations with many AIDS cases. Individuals as different as homosexual men, elderly transfusion recipients, heterosexual women, drug-using heterosexual men and infants have all developed AIDS with only one common denominator: infection with HIV. Laboratory workers accidentally exposed to highly concentrated HIV and health care workers exposed to HIV-infected blood have developed immunosuppression and AIDS with no other risk factor for immune dysfunction. Scientists have now used PCR to find HIV in virtually every patient with AIDS and to show that HIV is present in large and increasing amounts even in the pre-AIDS stages of HIV disease. Researchers also have demonstrated a correlation between the amount of HIV in the body and progression of the aberrant immunologic processes seen in people with AIDS.

Despite this plethora of evidence, the notion that HIV does not cause AIDS continues to find a wide audience in the popular press, with potential negative impact on HIV-infected individuals and on public health efforts to control the epidemic. HIV-infected individuals may be convinced to forego anti-HIV treatments that can forestall the onset of the serious infections and malignancies of AIDS (Edelman et al., 1991). Pregnant HIV-infected women may dismiss the option of taking AZT, which can reduce the likelihood of transmission of HIV from mother to infant (Connor et al., 1994; Boyer et al., 1994).

People may be dissuaded from being tested for HIV, thereby missing the opportunity, early in the course of disease, for counselling as well as for treatment with drugs to prevent AIDS-related infections such as PCP. Such prophylactic measures prolong survival and improve the quality of life of HIV-infected individuals (CDC, 1992b).

Most troubling is the prospect that individuals will discount the threat of HIV and continue to engage in risky sexual behavior and needle sharing. If public health messages on AIDS prevention are diluted by the misconception that HIV is not responsible for AIDS, otherwise preventable cases of HIV infection and AIDS may occur, adding to the global tragedy of the epidemic.

REFERENCES

Ackah AN, Coulibaly D, Digbeu H, Diallo K, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. *Lancet* 1995;345(8950):607-10.

Alcabes P, Munoz A, Vlahov D, Friedland GH. Incubation period of human immunodeficiency virus. *Epidemiol Rev* 1993a;15(2):303-18.

Alcabes P, Schoenbaum EE, Klein RS. Correlates of the rate of decline of CD4+ lymphocytes among injection drug users infected with the human immunodeficiency virus. *Am J Epidemiol* 1993b;137(9):989-1000.

Alcabes P, Munoz A, Vlahov D, Friedland G. Maturity of human immunodeficiency virus infection and incubation period of acquired immunodeficiency syndrome in injecting drug users. *Ann Epidemiol* 1994;4(1):17-26.

Aldrovandi GM, Feuer G, Gao L, Jamieson B, et al. The SCID-hu mouse as a model for HIV-1 infection. *Nature* 1993;363(6431):732-6.

Aledort LM, Operskalski EA, Dietrich SL, Koerper MA, et al. Low CD4+ counts in a study of transfusion safety. *N Engl J Med* 1993;328(6):441-2.

Allain JP, Laurian Y, Paul DA, Verroust F, et al. Long-term evaluation of HIV antigen and antibodies to p24 and gp41 in patients with hemophilia. Potential clinical importance. *N Engl J Med* 1987;317(18):1114-21.

AMA (American Medical Association), Council on Scientific Affairs. The acquired immunodeficiency syndrome (commentary). *JAMA* 1984;252(15):2037-43.

Ameisen JC, Capron A. Cell dysfunction and depletion in AIDS: the programmed cell death hypothesis. *Immunol Today* 1991;12(4):102-5.

Ammann AJ, Abrams D, Conant M, Chudwin D, et al. Acquired immune dysfunction in homosexual men: immunologic profiles. *Clin Immunol Immunopathol* 1983a;27(3):315-25.

Ammann AJ, Cowan MJ, Wara DW, Weintrub P, et al. Acquired immunodeficiency in an infant: possible transmission by means of blood products. *Lancet* 1983b;1(8331):956-8.

Ammann A. T-cell immunodeficiency disorders. In: Stites D, Terr A, eds. *Basic and Clinical Immunology*; 7th ed. Norwalk: Appleton and Lange, 1991, pp. 335-40.

Andes WA, Rangan SR, Wulff KM. Exposure of heterosexuals to human immunodeficiency virus and viremia: evidence for continuing risks in spouses of hemophiliacs. *Sex Transm Dis* 1989;16(2):68-73.

Andiman WA, Simpson BJ, Olson B, Dember L, et al. Rate of transmission of human immunodeficiency virus type 1 infection from mother to child and short-term outcome of neonatal infection. *Am J Dis Child* 1990;144:758-66.

Aoki-Sei S, Yarchoan R, Kageyama S, Hoekzema DT, et al. Plasma HIV-1 viremia in HIV-1 infected individuals assessed by polymerase chain reaction. *AIDS Res Hum Retroviruses* 1992;8(7):1263-70.

Aronson DL. Infection of hemophiliacs with HIV. *J Clin Apheresis* 1993;8(2):117-9.

Ascher MS, Sheppard HW, Winkelstein W Jr, Vittinghoff E, et al. Does drug use cause AIDS? *Nature* 1993a;362(6416):103-4.

Ascher MS, Sheppard HW, Winkelstein W Jr, Vittinghoff E. Aetiology of AIDS. *Lancet* 1993b;341(8854):1223.

Ascher MS, Sheppard HW, Winkelstein W Jr. AIDS-associated Kaposi's sarcoma (letter). *Science* 1995;267:1080.

Ashley R. *Cocaine: Its History, Uses and Effects*. New York: St. Martins Press, 1975.

Ashton LJ, Learmont J, Luo K, Wylie B, et al. HIV infection in recipients of blood products from donors with known duration of infection. *Lancet* 1994;344(8924):718-20.

Auerbach DM, Darrow WW, Jaffe HW, Curran JW. Cluster of cases of the acquired immune deficiency syndrome: patients linked by sexual contact. *Am J Med* 1984;76(3):487-92.

Bacellar H, Munoz A, Hoover DR, Phair JP, et al. Incidence of clinical AIDS conditions in a cohort of homosexual men with CD4+ cell counts < 100/mm³. *J Infect Dis* 1994;170(5):1284-7.

Bachmeyer C, Boufassa F, Sereni D, Deveau C, Buquet D. Prognostic value of acute symptomatic HIV-infection. IXth Int Conf on AIDS, (abstract no. PO-B01-0870), June 6-11, 1993.

Bagasra O, Hauptman SP, Lischner HW, Sachs M, Pomerantz RJ. Detection of human immunodeficiency virus type 1 provirus in mononuclear cells by in situ polymerase chain reaction. *N Engl J Med* 1992;326(21):1385-91.

Bagnarelli P, Menzo S, Valenza A, Manzin A, et al. Molecular profile of human immunodeficiency virus

type 1 infection in symptomless patients and in patients with AIDS. *J Virol* 1992;66(12):7328-35.

Barlow KM, Mok JY. Dizygotic twins discordant for HIV and hepatitis C virus. *Arch Dis Child* 1993;68(4):507.

Barnett SW, Murthy KK, Herndier BG, Levy JA. An AIDS-like condition induced in baboons by HIV-2. *Science* 1994;266:642-6.

Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983;220(4599):868-71.

Becherer PR, Smiley ML, Matthews TJ, Weinhold KJ, et al. Human immunodeficiency virus-1 disease progression in hemophiliacs. *Am J Hematol* 1990;34(3):204-9.

Bell AP, Weinberg MS. *Homosexualities: A Study of Diversity Among Men and Women*. New York: Simon and Schuster, 1978.

Biggar RJ. AIDS incubation in 1,891 HIV seroconverters from different exposure groups. *International Registry of Seroconverters. AIDS* 1990;4(11):1059-66.

Bindels PJ, Krol A, Mulder-Folkerts DK, van den Hoek JA, Coutinho RA. Survival of patients following the diagnosis of AIDS in the Amsterdam region, 1982-1991. *Ned Tijdschr Geneesk* 1994;138(10):513-8.

Blanche S, Mayaux MJ, Rouzioux C, Teglas JP, et al. Relation of the course of HIV infection in children to the severity of the disease in their mothers at delivery. *N Engl J Med* 1994;330(5):308-12.

Blattner W, Gallo RC, Temin HM. HIV causes AIDS. *Science* 1988a;241(4865):515-6.

Blattner W, et al. Blattner and colleagues respond to Duesberg. *Science* 1988b;241:514, 517.

Blattner W, Reitz M, Colclough G, Weiss S. HIV/AIDS in laboratory workers infected with HTLV-IIIb. *IXth Int Conf on AIDS*, (abstract no. PO-B01-0876), June 6-11, 1993.

Bobkov A, Garaev MM, Rzhaniyeva A, Kaleebu P, et al. Molecular epidemiology of HIV-1 in the former Soviet Union: analysis of env V3 sequences and their correlation with epidemiologic data. *AIDS* 1994;8(5):619-24.

Bonyhadi ML, Rabin L, Salimi S, Brown DA, et al. HIV induces thymus depletion in vivo. *Nature* 1993;363(6431):728-32.

Boulos R, Ruff A, Coberly J, McBrien M, Halsey JD. Effect of maternal HIV status on infant growth and survival. *Xth Int Conf on AIDS*, (abstract no. 054B), Aug 7-12, 1994.

Boyer PJ, Dillon M, Navaie M, Deveikis A, et al. Factors predictive of maternal-fetal transmission of HIV-1. Preliminary analysis of zidovudine given during pregnancy and/or delivery. *JAMA* 1994;271(24):1925-30.

British Cooperative Clinical Group. Homosexuality and venereal disease in the United Kingdom. *Br J Vener Dis* 1973;49:329-34.

Brookmeyer R, Gail HM. Screening and accuracy of tests for HIV. In: *AIDS Epidemiology: A Quantitative Approach*. New York: Oxford University Press, 1994.

Brown T, Sittitrai W. Estimates of HIV infection levels in the Thai population. *Xth Int Conf on AIDS*, (abstract no. 182C), Aug 7-12, 1994.

Bruisten SM, Koppelman MH, Dekker JT, Bakker M, et al. Concordance of human immunodeficiency virus detection by polymerase chain reaction and by serologic assays in a Dutch cohort of seronegative homosexual men. *J Infect Dis* 1992;166(3):620-2.

Buchbinder SP, Katz MH, Hessel NA, O'Malley PM, Holmberg SD. Long-term HIV-1 infection without immunologic progression. *AIDS* 1994;8(8):1123-8.

Busch MP, Valinsky JE, Paglieroni T, Prince HE, et al. Screening of blood donors for idiopathic CD4+ T-lymphocytopenia. *Transfusion* 1994;34(3):192-7.

Cao Y, Qin L, Zhang L, Safrit J, Ho DD. Virologic and immunologic characterization of long-term survivors of human immunodeficiency virus type 1 infection. *N Engl J Med* 1995;332(4):201-8.

CDC (Centers for Disease Control). Pneumocystis pneumonia - Los Angeles. *MMWR* 1981a;30:250-2.

CDC. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men - New York City and California. *MMWR* 1981b;30:305-8.

CDC. Persistent, generalized lymphadenopathy among homosexual males. *MMWR* 1982a;31:249-52.

CDC. Update on acquired immune deficiency syndrome (AIDS) - United States. *MMWR* 1982b;31:507-14.

CDC. Pneumocystis carinii pneumonia among persons with hemophilia A. *MMWR* 1982c;31:365-7.

CDC. Possible transfusion-associated acquired immune deficiency syndrome (AIDS) - California. *MMWR* 1982d;31:652-4.

CDC. Opportunistic infections and Kaposi's sarcoma among Haitians in the United States. *MMWR* 1982e;31:353-61.

CDC. CDC task force on Kaposi's sarcoma and opportunistic infections. *N Engl J Med* 1982f;306:248-52.

CDC. Immunodeficiency among female sex partners of males with acquired immunodeficiency syndrome (AIDS) - New York. *MMWR* 1983a;31:697-8.

CDC. Prevention of acquired immune deficiency syndrome (AIDS): report of inter-agency recommendations. *MMWR* 1983b;32:101-4.

CDC. Revision of the case definition of acquired immunodeficiency syndrome for national reporting - United States. *MMWR* 1985a;34:373-5.

CDC. Revision of the surveillance case definition of acquired immunodeficiency syndrome. *MMWR* 1987a;36:3S-15S.

CDC. Classification for human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR* 1987b;35:224-35.

CDC. Summary of notifiable diseases - United States. *MMWR* 1987c;36:1-59.

CDC. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992a;41:1-19.

CDC. Guideline for prophylaxis against Pneumocystis carinii pneumonia for persons infected with human immunodeficiency virus. *MMWR* 1992b;41:1-11.

- CDC. Summary of notifiable disease - United States, 1992. *MMWR* 1993b;41:1-73.
- CDC. Update: AIDS among women - United States, 1994. *MMWR* 1994;44:81-4.
- CDC. HIV/AIDS surveillance report, 1994 year-end edition. 1995a;6(no.2).
- CDC. Division of HIV/AIDS, Reporting and Analysis Section. Personal communication, April 12, 1995b.
- Chambers CD, Taylor WJ, Moffett AD. The incidence of cocaine use among methadone maintenance patients. *Int J Addict* 1974;7(3):427-41.
- Chandra RK, ed. Primary and secondary immunodeficiency disorders. Edinburgh: Churchill Livingstone, 1983.
- Chearskul S, Chotpitayasunondh T, Wanprapa N, Sangtaweessin V, et al. Survival among HIV-1 perinatally-infected infants, Bangkok, Thailand. Xth Int Conf on AIDS, (abstract no. 222C), Aug 7-12, 1994.
- Cheingsong-Popov R, Weiss RA, Dalgleish A, Tedder RS, et al. Prevalence of antibody to human T-lymphotropic virus type III in AIDS and AIDS-risk patients in Britain. *Lancet* 1984;2(8401):477-80.
- Chin J, Mann JM. The global patterns and prevalence of AIDS and HIV infection. *AIDS* 1988;2(suppl 1):S247-52.
- Chorba TL, Holman RC, Strine TW, Clarke MJ, Evatt BL. Changes in longevity and causes of death among persons with hemophilia A. *Am J Hematol* 1994;45(2):112-21.
- Clark SJ, Saag MS, Decker WD, Campbell-Hill S, et al. High titers of cytopathic virus in plasma of patients with symptomatic primary HIV-1 infection. *N Engl J Med* 1991;324(14):954-60.
- Coates RA, Farewell VT, Raboud J, Read SE, et al. Cofactors of progression to acquired immunodeficiency syndrome in a cohort of male sexual contacts of men with human immunodeficiency virus disease. *Am J Epidemiol* 1990;132(4):717-22.
- Coffin J, Haase A, Levy JA, Montagnier L, et al. Human immunodeficiency viruses (letter). *Science* 1986;232(4751):697.
- Cohen J. Could drugs, rather than a virus, be the cause of AIDS? *Science* 1994a;266(5191):1648-9.
- Cohen J. The epidemic in Thailand. *Science* 1994b;266(5191):1647.
- Cohen J. Fulfilling Koch's postulates. *Science* 1994c;266(5191):1647.
- Cohen J. Duesberg and critics agree: hemophilia is the best test. *Science* 1994d;266(5191):1645-6.
- Cohen J. The Duesberg phenomenon. *Science* 1994e;266(5191):1642-4.
- Concorde Coordinating Committee. MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343(8902):871-81.
- Connor RJ, Mohri H, Cao Y, Ho DD. Increased viral burden and cytopathicity correlate temporally with CD4+ T-lymphocyte decline and clinical progression in human immunodeficiency virus type 1-infected individuals. *J Virol* 1993;67(4):1772-7.
- Connor RI, Ho DD. Transmission and pathogenesis of human immunodeficiency virus type 1. *AIDS Res*

Hum Retroviruses 1994a;10(4):321-3.

Connor RI, Ho DD. Human immunodeficiency virus type 1 variants with increased replicative capacity develop during the asymptomatic stage before disease progression. *J Virol* 1994b;68(7):4400-8.

Connor EM, Sperling RS, Gelber R, Kiselev P, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994;331(18):1173-80.

Coombs RW, Collier AC, Allain JP, Nikora B, et al. Plasma viremia in human immunodeficiency virus infection. *N Engl J Med* 1989;321(24):1626-31.

Cooper DA, Gold J, Maclean P, Donovan B, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. *Lancet* 1985;1(8428):537-40.

Cooper DA, Gatell JM, Kroon S, Clumeck N, et al. Zidovudine in persons with asymptomatic HIV infection and CD4+ cell counts greater than 400 per cubic millimeter. *N Engl J Med* 1993;329(5):297-303.

Corbitt G, Bailey AS, Williams G. HIV infection in Manchester, 1959. *Lancet* 1990;336(8706):51.

Courtwright DT. *Dark Paradise: Opiate Addiction in America Before 1940*. Cambridge: Harvard University Press, 1982.

Creagh-Kirk T, Doi P, Andrews E, Nusinoff-Lehrman S, et al. Survival experience among patients with AIDS receiving zidovudine. Follow-up of patients in a compassionate plea program. *JAMA* 1988;260(20):3009-15.

Curran JW, Lawrence DN, Jaffe H, Kaplan JE, et al. Acquired immunodeficiency syndrome (AIDS) associated with transfusions. *N Engl J Med* 1984;310(2):69-75.

Curran JW, Jaffe HW, Hardy AM, Morgan WM, et al. Epidemiology of HIV infection and AIDS in the United States. *Science* 1988;239(4840):610-6.

d'Arminio Monforte A, Novati R, Galli M, Marchisio P, et al. T-cell subsets and serum immunoglobulin levels in infants born to HIV-seropositive mothers: a longitudinal evaluation. *AIDS* 1990;4(11):1141-4.

Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. *N Engl J Med* 1991;324(14):961-4.

Daar ES, Chernyavskiy T, Zhao JQ, Krogstad P, et al. Sequential determination of viral load and phenotype in human immunodeficiency virus type 1 infection. *AIDS Res Hum Retroviruses* 1995;11(1):3-9.

Dale GM. Morphine and cocaine intoxication. *JAMA* 1903;1:12, 15-6.

Dagleish AG, Beverley PC, Clapham PR, Crawford DH, et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature* 1984;312(5996):763-7.

Dallabetta GA, Miotti PG, Chipangwi JD, Saah AJ, et al. High socioeconomic status is a risk factor for human immunodeficiency virus type 1 (HIV-1) infection but not for sexually transmitted diseases in women in Malawi: implications for HIV-1 control. *J Infect Dis* 1993;167(1):36-42.

Darby SC, Ewart DW, Giangrande PLF, et al. Mortality before and after HIV infection in the UK population of haemophiliacs. *Nature* 1995;377:79-82.

Davachi F. Pediatric HIV infection in Africa. In: Essex M, et al., eds. *AIDS in Africa*. New York: Raven

Press, 1994, pp. 439-62.

Davis KC, Horsburgh CR Jr, Hasiba U, Schocket AL, Kirkpatrick CH. Acquired immunodeficiency syndrome in a patient with hemophilia. *Ann Intern Med* 1983;98(3):284-6.

de Biasi R, Rocino A, Miraglia E, Mastrullo L, Quirino AA. The impact of a very high purity factor VIII concentrate on the immune system of human immunodeficiency virus-infected hemophiliacs: a randomized, prospective, two- year comparison with an intermediate purity concentrate. *Blood* 1991;78(8):1919-22.

Des Jarlais DC, Friedman SR, Marmor M, Mildvan D, et al. CD4 lymphocytopenia among injecting drug users in New York City. *J Acquir Immune Defic Syndr* 1993;6:(7)820-2.

deShazo RD, Andes WA, Nordberg J, Newton J, et al. An immunologic evaluation of hemophiliac patients and their wives. Relationships to the acquired immunodeficiency syndrome. *Ann Intern Med* 1983;99(2):159-64.

Desrosiers RC. The simian immunodeficiency viruses. *Annu Rev Immunol* 1990;8:557-78.

Dewhurst S, Embretson JE, Anderson DC, Mullins JI, Fultz PN. Sequence analysis and acute pathogenicity of molecularly cloned SIVSMM-PBj14. *Nature* 1990;345(6276):636-40.

Dickover RE, Dillon M, Gillette SG, Deveikis A, et al. Rapid increases in load of human immunodeficiency virus correlate with early disease progression and loss of CD4 cells in vertically infected infants. *J Infect Dis* 1994;170(5):1279-84.

Dietrich SL, Boone DC. The epidemiology of HIV infection in hemophiliacs. In: Nilsson, Berntrop, eds. *Recent Advances in Hemophilia Care*. New York: Alan R. Liss, 1990, pp. 79-86.

Doll LS, Judson FN, Ostrow DG, O'Malley PM, et al. Sexual behavior before AIDS: the hepatitis B studies of homosexual and bisexual men. *AIDS* 1990;4(11):1067-73.

Dondero TJ, Curran JW. Excess deaths in Africa from HIV: confirmed and quantified (commentary). *Lancet* 1994;343(8904):989-90.

Donegan E, Stuart M, Niland JC, Sacks HS, et al. Infection with human immunodeficiency virus type 1 (HIV-1) among recipients of antibody-positive blood donations. *Ann Intern Med* 1990;113(10):733-9.

Douard D, Perel Y, Micheau M, Contraires B, et al. Perinatal HIV infection: longitudinal study of 22 children (clinical and biological follow-up) (letter). *J Acquir Immune Defic Syndr* 1989;2(2):212-3.

Duesberg PH. Retroviruses as carcinogens and pathogens: expectations and reality. *Cancer Res* 1987;47(5):1199-220.

Duesberg P. HIV is not the cause of AIDS. *Science* 1988;241(4865):514, 517.

Duesberg PH. Human immunodeficiency virus and acquired immunodeficiency syndrome: correlation but not causation. *Proc Natl Acad Sci USA* 1989;86(3):755-64.

Duesberg PH. AIDS: non-infectious deficiencies acquired by drug consumption and other risk factors. *Res Immunol* 1990;141(1):5-11.

Duesberg PH. AIDS epidemiology: inconsistencies with human immunodeficiency virus and with infectious disease. *Proc Natl Acad Sci USA* 1991;88(4):1575-9.

- Duesberg PH. The role of drugs in the origin of AIDS. *Biomed Pharmacother* 1992;46(1):3-15.
- Duesberg PH. AIDS acquired by drug consumption and other noncontagious risk factors. *Pharmacol Ther* 1992;55(3):201-77.
- Duesberg P. Infectious AIDS-stretching the germ theory beyond its limits. *Int Arch Allergy Immunol* 1994;103(2):118-27.
- Durack DT. Opportunistic infections and Kaposi's sarcoma in homosexual men. *N Engl J Med* 1981;305(24):1465-7.
- Edelman K, Horning P, Catalan J, Gazzard B. HIV does not cause AIDS--impact of T.V. programme on attitudes to zidovudine in HIV patients. VIIth Int Conf on AIDS, (abstract no. W.B.2097), June 16-21, 1991.
- Elliott JL, Hoppes WL, Platt MS, Thomas JG, et al. The acquired immunodeficiency syndrome and *Mycobacterium avium-intracellulare* bacteremia in a patient with hemophilia. *Ann Intern Med* 1983;98(3):290-3.
- Embretson J, Zapancic M, Ribas JL, Burke A, et al. Massive covert infection of helper T lymphocytes and macrophages by HIV during the incubation period of AIDS. *Nature* 1993;362(6418):359-62.
- Essex M, Hardy WJ Jr, Cotter SM, Jakowski RM, Sliski A. Naturally occurring persistent feline oncornavirus infections in the absence of disease. *Infect Immun* 1975;11(3):470-5.
- Essex M. Adult T-cell leukemia/lymphoma: role of a human retrovirus. *J Natl Cancer Inst* 1982;69:981.
- Essex M. The etiology of AIDS. In: Essex M, et al., eds. *AIDS in Africa*. New York: Raven Press, 1994, pp. 1-20.
- European Collaborative Study. Children born to women with HIV-1 infection: natural history and risk of transmission. *Lancet* 1991;337:253-60.
- European Collaborative Study. Risk factors for mother-to-child transmission of HIV- 1. *Lancet* 1992;339:1007-12.
- Evans AS. Causation and disease: the Henle-Koch postulates revisited. *Yale J Biol Med* 1976;49(2):175-95.
- Evans AS. The clinical illness promotion factor: a third ingredient. *Yale J Biol Med* 1982;55(3-4):193-9.
- Evans AS. Does HIV cause AIDS? An historical perspective. *J Acquir Immune Defic Syndr* 1989a;2(2):107-13.
- Evans AS. Does HIV cause AIDS: author's reply (letter). *J Acquir Immune Defic Syndr* 1989b;2(9):514-7.
- Evans AS. AIDS: the alternative view. *Lancet* 1992;339(8808):1547.
- Evatt BL, Gomperts ED, McDougal JS, Ramsey RB. Coincidental appearance of LAV/HTLV-III antibodies in hemophiliacs and the onset of the AIDS epidemic. *N Engl J Med* 1985;312(8):483-6.
- Fauci AS. The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. *Science* 1988;239(4840):617-22.
- Fauci AS. Multifactorial nature of human immunodeficiency virus disease: implications for therapy. *Science* 1993a;262(3136):1011-8.

Fauci AS. CD4+ T-lymphocytopenia without HIV infection—no lights, no camera, just facts. *N Engl J Med* 1993b;328(6):429-31.

Fenyo EM, Morfeldt-Manson L, Chiodi F, Lind B, et al. Distinct replicative and cytopathic characteristics of human immunodeficiency virus isolates. *J Virol* 1988;62(11):4414-9.

Feorino PM, Kalyanaraman VS, Haverkos HW, Cabradilla CD, et al. Lymphadenopathy associated virus infection of a blood donor-recipient pair with acquired immunodeficiency syndrome. *Science* 1984;225(4657):69-72.

Ferre F, Marchese A, Duffy PC, Lewis DE, et al. Quantitation of HIV viral burden by PCR in HIV seropositive Navy personnel representing Walter Reed stages 1 to 6. *AIDS Res Hum Retroviruses* 1992;8(2):269-75.

Finkel TH, Tudor-Williams G, Banda NK, et al. Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes. *Nature Medicine* 1995;1(2):129-34.

Fischl MA, Richman DD, Grieco MH, Gottlieb MS, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* 1987;317(4):185-91.

Fischl MA, Richman DD, Causey DM, Grieco MH, et al. Prolonged zidovudine therapy in patients with AIDS and advanced AIDS-related complex. AZT Collaborative Working Group. *JAMA* 1989;262(17):2405-10.

Fischl MA, Richman DD, Hansen N, Collier AC, et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection. A double-blind, placebo-controlled trial. *Ann Intern Med* 1990;112(10):727-37.

Fox CH, Kotler D, Tierney A, Wilson CS, Fauci AS. Detection of HIV-1 RNA in the lamina propria of patients with AIDS and gastrointestinal disease. *J Infect Dis* 1989;159(3):467-71.

Franchini G, Gurgo C, Guo HG, Gallo RC, et al. Sequence of simian immunodeficiency virus and its relationship to the human immunodeficiency viruses. *Nature* 1987;328(6130):539-43.

Francis DP, Curran JW, Essex M. Epidemic acquired immune deficiency syndrome: epidemiologic evidence for a transmissible agent. *J Natl Cancer Inst* 1983;71(1):1-4.

Fricke W, Augustyniak L, Lawrence D, Brownstein A, et al. Human immunodeficiency virus infection due to clotting factor concentrates: results of the Seroconversion Surveillance Project. *Transfusion* 1992;32(8):707-9.

Friedland G. Parenteral drug users. In: Kaslow RA, Francis DP, eds. *The Epidemiology of AIDS*. New York: Oxford University Press, 1989, pp. 153-78.

Friedman RC, Downey JI. Homosexuality. *N Engl J Med* 1994;331(14):923-30.

Friedman-Kien AE. Disseminated Kaposi's sarcoma syndrome in young homosexual men. *J Am Acad Dermatol* 1981;5(4):468-71.

Fultz PN. The pathobiology of SIV infection of macaques. In: Montagnier L, Gougeon ML, eds. *New Concepts in AIDS Pathogenesis*. New York: Marcel Dekker, 1993, pp. 59-73.

Furtado MR, Kingsley LA, Wolinsky SM. Changes in the viral mRNA expression pattern correlate with a rapid rate of CD4+ T-cell number decline in human immunodeficiency virus type 1-infected individuals. *J*

Virol 1995 Apr;69(4):2092- 2100.

Galai N, et al. Changes in markers of disease progression in HIV-1 seroconverters: a comparison between cohorts of injecting drug users and homosexual men. *J Acquir Immune Defic Syndr* 1995;8:66-74.

Galli M, Lazzarin A, Saracco A, Balotta C, et al. Clinical and immunological aspects of HIV infection in drug addicts. *Clin Immunol Immunopathol* 1989;50 (1 pt 2):S166- 76.

Galli M, Musicco M, Gervasoni C, Ridolfo AL, et al. No evidence for a role of continuing intravenous drug injection in accelerating disease progression in HIV-1 positive subjects. VIIth Int Conf on AIDS, (abstract no. TH.C.48), June 16-21, 1991.

Gallo RC, Reitz MS Jr. Human retroviruses and adult T-cell leukemia-lymphoma. *J Natl Cancer Inst* 1982;69(6):1209-14.

Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984;224(4648):500-3.

Gallo RC, Montagnier L. The chronology of AIDS research. *Nature* 1987;326(6112):435-6.

Gallo RC. *Virus Hunting. AIDS, Cancer, and the Human Retrovirus: A Story of Scientific Discovery.* New York: Harper Collins, 1991.

Gange RW, Jones EW. Kaposi's sarcoma and immunosuppressive therapy: an appraisal. *Clin Exp Dermatol* 1978;3(2):135-46.

Garry RF. Potential mechanisms for the cytopathic properties of HIV. *AIDS* 1989;3(11):683-94.

Gazzard BG, Shanson DC, Farthing C, Lawrence AG, et al. Clinical findings and serological evidence of HTLV-III infection in homosexual contacts of patients with AIDS and persistent generalised lymphadenopathy in London. *Lancet* 1984;2(8401):480-3.

Genesca J, Wang RY, Alter HJ, Shih JW. Clinical correlation and genetic polymorphism of the human immunodeficiency virus proviral DNA obtained after polymerase chain reaction amplification. *J Infect Dis* 1990;162(5):1025-30.

Gershon AA. Measles virus (rubeola). In: Mandell GL, et al., eds. *Principles and Practices of Infectious Diseases*; 3rd ed. New York: Churchill Livingstone, 1990, pp. 1279-84.

Getchell JP, Hicks DR, Svinivasan A, Heath JL, et al. Human immunodeficiency virus isolated from a serum sample collected in 1976 in Central Africa. *J Infect Dis* 1987;156(5):833-7.

Giesecke J, Scalia-Tomba G, Hakansson C, Karlsson A, Lidman K. Incubation time of AIDS: progression of disease in a cohort of HIV-infected homo- and bisexual men with known dates of infection. *Scand J Infect Dis* 1990;22(4):407-11.

Gilbert AN. Conceptions of homosexuality and sodomy in Western history. *J Homosex* 1980-81;6(1-2):57-68.

Ginsberg HS (moderator). Scientific forum on AIDS: a summary. Does HIV cause AIDS? *J Acquir Immune Defic Syndr* 1988;1(2):165-72.

Gjerset GF, Pike MC, Mosley JW, Hassett J, et al. Effect of low- and intermediate- purity clotting factor therapy on progression of human immunodeficiency virus infection in congenital clotting disorders. *Blood*

1994;84(5):1666-71.

Goedert JJ, Neuland CY, Wallen WC, Greene MH, et al. Amyl nitrite may alter T lymphocytes in homosexual men. *Lancet* 1982;1(8269):412-6.

Goedert JJ, Kessler CM, Aledort LM, Biggar RJ, et al. A prospective study of human immunodeficiency virus type 1 infection and the development of AIDS in subjects with hemophilia. *N Engl J Med* 1989;321(17):1141-8.

Golding H, Shearer GM, Hillman K, Lucas P, et al. Common epitope in human immunodeficiency virus I (HIV) I-GP41 and HLA class II elicits immunosuppressive antibodies capable of contributing to immune dysfunction in HIV-infected individuals. *J Clin Invest* 1989;83(4):1430-5.

Goldsmith JM, Deutsche J, Tang M, Green D. CD4 cells in HIV-1 infected hemophiliacs: effect of factor VIII concentrates. *Thromb Haemost* 1991;66(4):415-9.

Gonda MA, Wong-Staal F, Gallo RC, Clements JE, et al. Sequence homology and morphologic similarity of HTLV-III and visna virus, a pathogenic lentivirus. *Science* 1985;227(4683):173-7.

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981;305(24):1425-31.

Goudsmit J. Alternative view on AIDS. *Lancet* 1992;339(8804):1289-90.

Graham NM, Zeger SL, Kuo V, Jacobson LP, et al. Zidovudine use in AIDS-free HIV-1-seropositive homosexual men in the Multicenter AIDS Cohort Study (MACS), 1987-1989. *J Acquir Immune Defic Syndr* 1991;4(3):267-76.

Graham NM, Piantadosi S, Park LP, Phair JP, et al. CD4+ lymphocyte response to zidovudine as a predictor of AIDS-free time and survival time. *J Acquir Immune Defic Syndr* 1993;6(11):1258-66.

Graham NM, Zeger SL, Park LP, Vermund SH, et al. The effects on survival of early treatment of human immunodeficiency virus infection. *N Engl J Med* 1992;326(16):1037-42.

Greene JB, Sidhu GS, Lewin S, Levine JF, et al. Mycobacterium-avium- intracellulare: a cause of disseminated life-threatening infection in homosexuals and drug abusers. *Ann Intern Med* 1982;97(4):539-46.

Greene MH, Nightingale SL, DuPont RL. Evolving patterns of drug abuse. *Ann Intern Med* 1975;83(3):402-11.

Greene WC. AIDS and the immune system. *Sci Am* 1993;269(3):98-105.

Greene WC. The molecular biology of human immunodeficiency virus type 1 infection. *N Engl J Med* 1991;324(5):308-17.

Groopman JE. A dangerous delusion about AIDS. *New York Times*, September 10, 1992; A19.

Groopman JE, Salahuddin SZ, Sarngadharan MG, Mullins JI, et al. Virologic studies in a case of transfusion-associated AIDS. *N Engl J Med* 1984;311(22):1419-22.

Guerrero Vazquez J, de Paz Aparicio P, Olmedo Sanlaureano S, Omenaca Teres F, et al. Discordant acquired immunodeficiency syndrome in dizygotic twins. *An Esp Pediatr* 1993;39(5):445-7.

Gupta P, Kingsley L, Armstrong J, Ding M, et al. Enhanced expression of human immunodeficiency virus type 1 correlates with development of AIDS. *Virology* 1993;196(2):586-95.

Haase AT. Lentiviruses. In: Mandell GL, et al., eds. *Principles and Practices of Infectious Diseases*; 3rd ed. New York: Churchill Livingstone, 1990, pp. 1341-4.

Haase AT. Pathogenesis of lentivirus infections. *Nature* 1986;322(6075):130-6.

Hamilton JD, Hartigan PM, Simberkoff MS, Day PL, et al. A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection. Results of the Veterans Affairs Cooperative Study. *N Engl J Med* 1992;326(7):437-43.

Hammer S, Crumpacker C, D'Aquila R, Jackson B, et al. Use of virologic assays for detection of human immunodeficiency virus in clinical trials: recommendations of the AIDS Clinical Trials Group Virology Committee. *J Clin Microbiol* 1993;31(10):2557-64.

Hanenberg RS, Rojanapithayakorn W, Kunasol P, Sokal DC. Impact of Thailand's HIV-control programme as indicated by the decline of sexually transmitted diseases. *Lancet* 1994;344(8917):243-5.

Harden VA. Koch's postulates and the etiology of AIDS: an historical perspective. *Hist Phil Life Sci* 1992;14(2):249-69.

Harms G, Kirsch T, Rahelimiarana N, Hof U, et al. HIV and syphilis in Madagascar (letter). *AIDS* 1994;8(2):279-88.

Harris C, Small CB, Klein RS, Friedland GH, et al. Immunodeficiency in female sexual partners of men with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;308(20):1181-4.

Harris SB. The AIDS heresies: a case study of skepticism taken too far. *Skeptical* 1995; 3(2):42-79.

Hassett J, Gjerset GF, Mosley JW, Fletcher MA, et al. Effect on lymphocyte subsets of clotting factor therapy in human immunodeficiency virus-1-negative congenital clotting disorders. *Blood* 1993;82(4):1351-7.

Haverkos HW, Dougherty JA, eds. *Health Hazards of Nitrite Inhalants*. NIDA research monograph 83, U.S. Department of Health and Human Services, PHS, ADAMHA. U.S. Government Printing Office, 1988.

Hays EF, Uittenbogaart CH, Brewer JC, Vollger LW, Zack JA. In vitro studies of HIV-1 expression in thymocytes from infants and children. *AIDS* 1992;6(3):265-72.

Hessol NA, Koblin BA, van Griensven GJ, Bacchetti P, et al. Progression of human immunodeficiency virus type 1 (HIV-1) infection among homosexual men in hepatitis B vaccine trial cohorts in Amsterdam, New York City and San Francisco, 1978-1991. *Am J Epidemiol* 1994;139(11):1077-87.

Hilgartner MW, Buckley JD, Operskalski EA, Pike MC, Mosley JW. Purity of factor VIII concentrates and serial CD4 counts. *Lancet* 1993;341(8857):1373-4.

Hirsch VM, Olmsted RA, Murphey-Corb M, Purcell RH, Johnson PR. An African primate lentivirus (SIVsm) closely related to HIV-2. *Nature* 1989;339(6223):389-92.

Ho DD, Moudgil T, Alam M. Quantitation of human immunodeficiency virus type 1 in the blood of infected persons. *N Engl J Med* 1989;321(24):1621-5.

Ho DD, Pomerantz RJ, Kaplan JC. Pathogenesis of infection with human immunodeficiency virus. *N Engl J Med* 1987;317(5):278-86.

Ho DD, Schooley RT, Rota TR, Kaplan JC, et al. HTLV-III in the semen and blood of a healthy homosexual man. *Science* 1984;226(4673):451-3.

Ho DD, Rota TR, Schooley RT, Kaplan JC, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med* 1985;313(24):1493-7.

Ho DD, Neumann AU, Perelson AS, Chen W, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995;373:123-6.

Hoxie JA, Alpers JD, Rackowski JL, Huebner K, et al. Alterations in T4 (CD4) protein and mRNA synthesis in cells infected with HIV. *Science* 1986;234(4780):1123-7.

Hufert FT, von Laer D, Fenner TE, Schwander S, et al. Progression of HIV-1 infection. Monitoring of HIV-1 DNA in peripheral blood mononuclear cells by PCR. *Arch Virol* 1991;120(3-4):233-40.

Hugin AW, Vacchio MS, Morse HC III. A virus-encoded superantigen in a retrovirus-induced immunodeficiency syndrome of mice. *Science* 1991;252(5004):424-7.

Hurtenbach U, Shearer GM. Germ cell-induced immune suppression in mice. Effect of inoculation of syngeneic spermatazoa on cell-mediated immune responses. *J Exp Med* 1982;155(6):1719-29.

Hutto C, Parks WP, Lai SH, Mastrucci MT, et al. A hospital-based prospective study of perinatal infection with human immunodeficiency virus type 1. *J Pediatr* 1991;118(3):347-53.

Hymes KB, Cheung T, Greene JB, Prose NS, et al. Kaposi's sarcoma in homosexual men--a report of eight cases. *Lancet* 1981;2(8247):598-600.

Institute of Medicine, National Academy of Sciences. *Confronting AIDS. Directions for Public Health, Health Care and Research.* Washington, D.C: National Academy Press, 1986.

Irova T, Serebrovskaya L, Pokrovsky VV. The life of HIV+ children infected in nosocomial foci. IXth Int Conf on AIDS, (abstract no. PO-C04-2626), June 6-11, 1993.

Israelstam S, Lambert S, Oki G. Use of isobutyl nitrite as a recreational drug. *Br J Addict Alcohol Other Drugs* 1978;73(3):319-20.

Italian Seroconversion Study. Disease progression and early predictors of AIDS in HIV-seroconverted injecting drug users. *AIDS* 1992;6(4):421-6.

Jackson JB, Kwok SY, Sninsky JJ, Hopsicker JS, et al. Human immunodeficiency virus type 1 detected in all seropositive symptomatic and asymptomatic individuals. *J Clin Microbiol* 1990;28(1):16-9.

Jacobs E. Anal infections caused by herpes simplex virus. *Dis Colon Rectum* 1976;19(2):151-7.

Jaffe HW, Darrow WW, Echenberg DF, O'Malley PM, et al. The acquired immunodeficiency syndrome in a cohort of homosexual men. A six-year follow-up study. *Ann Intern Med* 1985a;103(2):210-4.

Jaffe HW, Sarngadharan MG, DeVico AL, Bruch L, et al. Infection with HTLV-III/LAV and transfusion-associated acquired immunodeficiency syndrome. Serologic evidence of an association. *JAMA* 1985b;254(6):770-3.

Janeway C. Immune recognition. Mls: makes little sense. *Nature* 1991;349(6309):459-61.

Jason J, Murphy J, Sleeper LA, Donfield SM, et al. Immune and serologic profiles of HIV-infected and noninfected hemophilic children and adolescents. *Am J Hematol* 1994;46(1):29-35.

Jefferiss FJG. Venereal disease and the homosexual. *Br J Vener Dis* 1956;32:17-20.

Johnson JP, Nair P, Hines SE, Seiden SW, et al. Natural history and serologic diagnosis of infants born to human immunodeficiency virus-infected women. *Am J Dis Child* 1989;143(10):1147-53.

Jones PK, Ratnoff OD. The changing prognosis of classic hemophilia (factor VIII deficiency). *Ann Intern Med* 1991;114(8):641-8.

Jones DS, Byers RH, Bush TJ, Oxtoby MJ, Rogers MF. Epidemiology of transfusion-associated acquired immunodeficiency syndrome in children in the United States, 1981-1989. *Pediatrics* 1992;89(1):123-7.

Judson FN, Miller KG, Schaffnit TR. Screening for gonorrhea and syphilis in the gay baths--Denver, Colorado. *Am J Public Health* 1977;67(8):740-2.

Jurriaans S, Weverling GJ, Goudsmit J, et al. Distinct changes in HIV type 1 RNA versus p24 antigen levels in serum during short-term zidovudine therapy in asymptomatic individuals with and without progression to AIDS. *AIDS Res Hum Retroviruses* 1995;11(4):473-9.

Kaslow RA, Blackwelder WC, Ostrow DG, Yerg D, et al. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals. A report from the Multi-center AIDS Cohort Study. *JAMA* 1989;261(23):3424-9.

Katz BZ. Natural history and clinical management of the infant born to a mother infected with human immunodeficiency virus. *Semin Perinatol* 1989;13(1):27-34.

Katz JN. *Gay American history. Lesbian and Gay Men in the USA: A Documentary*. New York: Meridian, 1992.

Keet IP, Krijnen P, Koot M, Lange JM, et al. Predictors of rapid progression to AIDS in HIV-1 seroconverters. *AIDS* 1993;7(1):51-7.

Keet IP, Krol A, Klein MR, Veugelers P, et al. Characteristics of long-term asymptomatic infection with human immunodeficiency virus type 1 in men with normal and low CD4+ cell counts. *J Infect Dis* 1994;169(6):1236-43.

Kestler H, Kodama T, Ringler D, Marthas M, et al. Induction of AIDS in rhesus monkeys by molecularly cloned simian immunodeficiency virus. *Science* 1990;248(4959):1109-12.

Kinsey AC, et al. *Sexual Behavior in the Human Male*. Philadelphia: Saunders, 1948.

Klatzmann D, Barre-Sinoussi F, Nugeyre MT, Danquet C, et al. Selective tropism of lymphadenopathy associated virus (LAV) for helper-inducer T lymphocytes. *Science* 1984a;225(4657):59-63.

Klatzmann D, Champagne E, Chamaret S, Gruest J, et al. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature* 1984b;312(5996):767-8.

Koblin BA, Taylor PE, Rubinstein P, Stevens CE. Effect of zidovudine on survival in HIV-1 infection: observational data from a cohort study of gay men. VIIIth Int Conf on AIDS, (abstract no. PoC 4349), July 19-24, 1992.

Kodama T, Mori K, Kawahara T, Ringler DJ, Desrosiers RC. Analysis of simian immunodeficiency virus

sequence variation in tissues of rhesus macaques with simian AIDS. *J Virol* 1993;67(11):6522-34.

Koenig S, Earl P, Powell D, Pantaleo G, et al. Group-specific, major histocompatibility complex class-I restricted cytotoxic responses to human immunodeficiency virus I (HIV-1) envelope proteins by cloned peripheral blood T cells from an HIV-1 infected individual. *Proc Natl Acad Sci USA* 1988;85(22):8638-42.

Koga Y, Lindstrom E, Fenyo EM, Wigzell H, Mak TW. High levels of heterodisperse RNAs accumulate in T cells infected with human immunodeficiency virus and in normal thymocytes. *Proc Natl Acad Sci USA* 1988;85(12):4521-5.

Kool HE, Bloemkolk D, Reeve PA, Danner SA. HIV seropositivity and tuberculosis in a large general hospital in Malawi. *Trop Geogr Med* 1990;42(2):128-32.

Kozel NJ, Adams EH. Epidemiology of drug abuse: an overview. *Science* 1986;234(4779):970-4.

Kreek MJ. Immune function in heroin addicts and former heroin addicts in treatment: pre- and post-AIDS epidemic. In: Pham PTK, Rice K, eds. *Drugs of Abuse: Chemistry, Pharmacology, Immunology, and AIDS*. NIDA Research Monograph 96, 1990, pp. 192-219.

Kreiss JK, Kitchen LW, Prince HE, Kasper CK, Essex M. Antibody to human T-lymphotropic virus type III in wives of hemophiliacs. Evidence for heterosexual transmission. *Ann Intern Med* 1985;102(5):623-6.

Kurth R. Does HIV cause AIDS? An updated response to Duesberg's theories. *Intervirology* 1990;31(6):301-14.

Kwok S, Mack DH, Mullis KB, Poiesz B, et al. Identification of human immunodeficiency virus sequences by using in vitro enzymatic amplification and oligomer cleavage detection. *J Virol* 1987;61(5):1690-4.

Lambert JS. Maternal and perinatal issues regarding HIV infection. *Pediatr Ann* 1990;19(8):468-72.

Latif AS. HIV and AIDS in southern Africa and the island countries. In: Essex M, et al., eds. *AIDS in Africa*. New York: Raven Press, 1994, pp. 691-711.

Lau RK, Jenkins P, Caun K, Forster SM, et al. Trends in sexual behaviour in a cohort of homosexual men: a 7 year prospective study. *Int J STD AIDS* 1992;3(4):267-72.

Laumann, et al. *The Social Organization of Sexuality*. Chicago: University of Chicago Press, 1994.

Laurence J. T-cell subsets in health, infectious disease, and idiopathic CD4+ T lymphocytopenia. *Ann Intern Med* 1993;119(1):55-62.

Laurent-Crawford AG, Krust B, Muller S, Riviere Y, et al. The cytopathic effect of HIV is associated with apoptosis. *Virology* 1991;185(2):829-39.

Le Clair RA. Descriptive epidemiology of interstitial pneumocystic pneumonia. An analysis of 107 cases from the United States, 1955-1967. *Am Rev Respir Dis* 1969;99(4):542-7.

Lederman MM, Ratnoff OD, Evatt BL, McDougal JS. Acquisition of antibody to lymphadenopathy-associated virus in patients with classic hemophilia (factor VIII deficiency). *Ann Intern Med* 1985;102(6):753-7.

Lederman MM, Jackson JB, Kroner BL, White, GC, et al. Human immunodeficiency virus (HIV) type 1 infection status and in vitro susceptibility to HIV infection among high-risk HIV-1-seronegative hemophiliacs. *J Infect Dis* 1995;172(1):228-31.

Lee CA, Sabin CA, Phillips AN, Elford J, Pasi J. Morbidity and mortality from transfusion-transmitted disease in haemophilia. *Lancet* 1995;345:1309.

Lemp GF, Payne SF, Rutherford GW, Hessol NA, et al. Projections of AIDS morbidity and mortality in San Francisco. *JAMA* 1990;263(11):1497-1501.

Leonard R, Zagury D, Desportes I, Bernard J, et al. Cytopathic effect of human immunodeficiency virus in T4 cells is linked to the last stage of virus infection. *Proc Natl Acad Sci USA* 1988;85(10):3570-4.

Leroy V, Msellati P, Lepage P, Batungwanayo J, et al. Four years of natural history of HIV-1 infection in African women: a prospective cohort study in Kigali (Rwanda), 1988-1993. *J Acquir Immune Defic Syndr* 1995;9(4):415-421.

Letvin NL, Daniel MD, Sehgal PK, Desrosiers RC, et al. Induction of AIDS-like disease in macaque monkeys with T-cell tropic retrovirus STLV-III. *Science* 1985;230(4721):71-3.

Levy JA, Hoffman AD, Kramer SM, Landis JA, et al. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science* 1984;225(4664):840-2.

Levy JA, Shimabukuro J, Hollander H, Mills J, Kaminsky L. Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. *Lancet* 1985;2(8455):586-8.

Levy JA. Pathogenesis of human immunodeficiency virus infection. *Microbiol Rev* 1993;57(1):183-289.

Lifson JD, Reyes GR, McGrath MS, Stein BS, Engleman EG. AIDS retrovirus induced cytopathology: giant cell formation and involvement of CD4 antigen. *Science* 1986;232(4754):1123-7.

Lifson AR, Darrow WW, Hessol NA, O'Malley PM, et al. Kaposi's sarcoma in a cohort of homosexual and bisexual men. Epidemiology and analysis for cofactors. *Am J Epidemiol* 1990;131(2):221-31.

Lindan CP, Allen S, Serufilira A, Lifson AR, et al. Predictors of mortality among HIV-infected women in Kigali, Rwanda. *Ann Intern Med* 1992;116(4):320-8.

Lindback S, Brostrom C, Karlsson A, Gaines H. Does symptomatic primary HIV-1 infection accelerate progression to CDC stage IV disease, CD4 count below 200 x 10⁶/l, AIDS, and death from AIDS? *Br Med J* 1994;309(6968):1535-7.

Lindgren S, Anzen B, Bohlin AB, Lidman K. HIV and child-bearing: clinical outcome and aspects of mother-to-infant transmission. *AIDS* 1991;5(9):1111-6.

Longini IM Jr, Clark WS, Karon JM. Effect of routine use of therapy in slowing the clinical course of human immunodeficiency virus (HIV) infection in a population-based cohort. *Am J Epidemiol* 1993;137(11):1229-40.

Lowenstein JM. Is AIDS a myth? *California Academy of Sciences: Pacific Discovery Magazine*. Fall, 1994.

Lusher JM, Operskalski EA, Aledort LM, Dietrich SL, et al. Risk of human immunodeficiency virus type 1 infection among sexual and nonsexual household contacts of persons with congenital clotting disorders. *Pediatrics* 1991;88(2):242-9.

Lyerly HK, Matthews TJ, Langlois AJ, Bolognesi DP, Weinhold KJ. Human T-cell lymphotropic virus IIIB glycoprotein (gp120) bound to CD4 determinants on normal lymphocytes and expressed by infected cells serves as target for immune attack. *Proc Natl Acad Sci USA* 1987;84(13):4601-5.

- Mann JM, et al., eds. AIDS in the World. Cambridge: Harvard University Press, 1992.
- Mann JM. AIDS--the second decade: a global perspective. *J Infect Dis* 1992;165(2):245-50.
- Mannucci PM, Gringeri A, de Biasi R, Baudo F, et al. Immune status of asymptomatic HIV-infected hemophiliacs: randomized, prospective, two-year comparison of treatment with a high-purity or an intermediate-purity factor VIII concentrate. *Thromb Haemost* 1992;67(3):310-3.
- Mannucci PM, Gringeri A, Savidge G, Gatenby P, et al. Randomized double-blind, placebo-controlled trial of twice-daily zidovudine in asymptomatic haemophiliacs infected with the human immunodeficiency virus type 1. *Br J Haematol* 1994;86(1):174-9.
- MAP Workshop (Multi-cohort Analysis Project). Extending public health surveillance of HIV infection: information from a five cohort workshop. *Stat Med* 1993;12(22):2065-85.
- Margolick JB, Munoz A, Vlahov D, Solomon L, et al. Changes in T-lymphocyte subsets in intravenous drug users with HIV-1 infection. *JAMA* 1992;267(12):1631-6.
- Margolick JB, Munoz A, Vlahov D, Astemborski J, et al. Direct comparison of the relationship between clinical outcome and change in CD4+ lymphocytes in human immunodeficiency virus-positive homosexual men and injecting drug users. *Arch Intern Med* 1994;154(8):869-75.
- Masur H, Michelis MA, Greene JB, Onorato I, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med* 1981;305(24):1431-8.
- Masur H. *Mycobacterium avium*-intracellulare: another scourge for individuals with the acquired immunodeficiency syndrome. *JAMA* 1982a;248(22):3013.
- Masur H, Michelis MA, Wormser GP, Lewin S, et al. Opportunistic infection in previously healthy women. Initial manifestations of a community-acquired cellular immunodeficiency. *Ann Intern Med* 1982b;7(4):533-9.
- Mathez D, Paul D, de Belilovsky C, Sultan Y, et al. Productive human immunodeficiency virus infection levels correlate with AIDS-related manifestations in the patient. *Proc Natl Acad Sci USA* 1990;87(19):7438-42.
- Mavligit GM, Talpaz M, Hsia FT, Wong W, et al. Chronic immune stimulation by sperm alloantigens: support for the hypothesis that spermatozoa induce immune dysregulation in homosexual males. *JAMA* 1984;251(2):237-41.
- McDougal JS, Mawle A, Cort SP, Nicholson JK, et al. Cellular tropism of the human retrovirus HTLV-III/LAV. Role of T cell activation and expression of the T4 antigen. *J Immunol* 1985a;135(5):3151-62.
- McDougal JS, Jaffe HW, Cabridilla CD, Sarngadharan MG, et al. Screening tests for blood donors presumed to have transmitted the acquired immunodeficiency syndrome. *Blood* 1985b;65(3):772-5.
- McDougal JS, Kennedy MS, Sligh JM, Cort SP, et al. Binding of HTLV-III/LAV to T4+ T cells by a complex of the 110K viral protein and the T4 molecule. *Science* 1986;231(4736):382-5.
- McLeod GX, Hammer SM. Zidovudine: five years later. *Ann Int Med* 1992;117(6):487-501.
- McMillan A, Young H. Gonorrhoea in the homosexual man: frequency of infection by culture site. *Sex Transm Dis* 1978;5(4):146-50.
- Mellors JW, Kingsley LA, Rinaldo CR, Todd JA, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med* 1995;122(8):573-7.

Menez-Bautista R, Fikrig SM, Pahwa S, Sarngadharan MG, Stoneburner RL. Monozygotic twins discordant for the acquired immunodeficiency syndrome. *Am J Dis Child* 1986;140(7):678-9.

Merigan TC, Amato DA, Balsley J, Power M, et al. Placebo-controlled trial to evaluate zidovudine in treatment of human immunodeficiency virus infection in asymptomatic patients with hemophilia. *Blood* 1991;78(4):900-6.

Merino HI, Richards JB. An innovative program of venereal disease casefinding, treatment and education for a population of gay men. *Sex Transm Dis* 1977;4(2):50-2.

Michael NL, Vahey M, Burke DS, Redfield RR. Viral DNA and mRNA correlate with the stage of human immunodeficiency virus (HIV) type 1 infection in humans: evidence for viral replication in all stages of HIV disease. *J Virol* 1992;66(1):310-6.

Montagnier L, et al. A new lymphotropic retrovirus: characterization and possible role in lymphadenopathy and acquired immune deficiency syndromes. In: Gallo RC, et al., eds. *Human T-cell Leukemia/Lymphoma Virus*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1984, pp. 363-79.

Montella F, Di Sora F, Perucci CA, Abeni DD, Recchia O. T-lymphocyte subsets in intravenous drug users with HIV-1 infection. *JAMA* 1992;268(18):2516-7.

Moore RD, Creagh-Kirk T, Keruly J, Link G, et al. Long-term safety and efficacy of zidovudine in patients with advanced human immunodeficiency virus disease. *Arch Intern Med* 1991a;151(5):981-6.

Moore RD, Hidalgo J, Sugland BW, Chaisson RE. Zidovudine and the natural history of the acquired immunodeficiency syndrome. *N Engl J Med* 1991b;324(20):1412-6.

Morton WR, et al. Infection of *Macaca nemestrina* by HIV-1/HIV-2: development of infection and disease models. Laboratory of Tumor Cell Biology Annual Meeting, Aug 22-28, 1993. *AIDS Res Hum Retroviruses* 1994;10(suppl 1):S1-125.

Mosley JW. Low CD4+ counts in a study of transfusion safety: correction. *N Engl J Med* 1993;328(15):1129.

Mulder JW, Cooper DA, Mathiesen L, Sandstrom E, et al. Zidovudine twice daily in asymptomatic subjects with HIV infection and a high risk of progression to AIDS: a randomized, double-blind placebo-controlled study. *AIDS* 1994a;8(3):313-21.

Mulder DW, Nunn AJ, Kamali A, Nakiyingi J, et al. Two-year HIV-1-associated mortality in a Ugandan rural population. *Lancet* 1994b;343(8904):1021-3.

Munoz A, Vlahov D, Solomon L, Margolick JB, et al. Prognostic indicators for development of AIDS among intravenous drug users. *J Acquir Immune Defic Syndr* 1992;5(7):694-700.

Muro-Cacho CA, Pantaleo G, Fauci AS. Analysis of apoptosis in lymph nodes of HIV-infected persons. Intensity of apoptosis correlates with the general state of activation of the lymphoid tissue and not with stage of disease or viral burden. *J Immunol* 1995;154(10):5555-66.

Myers G, MacInnes K, Korber B. The emergence of simian/human immunodeficiency viruses. *AIDS Res Hum Retroviruses* 1992;8(3):373-86.

Nahmias AJ, Weiss J, Yao X, Lee F, et al. Evidence for human infection with an HTLV III/LAV-like virus in Central Africa, 1959 (letter). *Lancet* 1986;31,1(8492):1279-80.

Nicholson JK, Spira TJ, Aloisio CH, Jones BM, et al. Serial determinations of HIV-1 titers in HIV-infected

homosexual men: association of rising titers with CD4 T cell depletion and progression to AIDS. *AIDS Res Hum Retroviruses* 1989;5(2):205-15.

Nicoll A, Brown P. HIV: beyond reasonable doubt. *New Scientist* Jan. 15, 1994:24-8.

Novick BE, Rubinstein A. AIDS--the paediatric perspective. *AIDS* 1987;1(1):3-7.

Novick DM, Ochshorn M, Ghali V, Croxson TS, et al. Natural killer cell activity and lymphocyte subsets in parenteral heroin abusers and long-term methadone maintenance patients. *J Pharmacol Exp Ther* 1989;250(2):606-10.

NTIS (National Technical Information Service). ACTG Protocol 116b/117: Viral load analysis for study investigators, 1994. Springfield, VA.

O'Brien WA, Hartigan PM, McCreedy B, Hamilton JD. Plasma HIV RNA and beta 2 microglobulin as surrogate markers. *Xth Int Conf on AIDS*, (abstract no. 254B), Aug 7-12, 1994.

Oettle AG. Geographical and racial differences in the frequencies of Kaposi's sarcoma as evidence of environmental or genetic causes. *Acta Unio Int Contra Cancrum* 1962;18:330-63.

Oldstone MB. Viral persistence. *Cell* 1989;56(4):517-20.

Oleske J, Minnefor A, Cooper R Jr, Thomas K, et al. Immune deficiency syndrome in children. *JAMA* 1983;249(17):2345-9.

Ostrow D, Vanhaden MJ, Fox R, Kingsley LA, et al. Recreational drug use and sexual behavior in a cohort of homosexual men. *AIDS* 1990;4(8):759-65.

Ostrow DG, Beltran ED, Joseph JG, DiFranceisco W, et al. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. *J Subst Abuse* 1993;5(4):311-25.

Ottmann N, Innocenti P, Thenadey M, Micoud M, et al. The polymerase chain reaction for the detection of HIV-1 genomic RNA in plasma from infected individuals. *J Virol Methods* 1991;31(2-3):273-83.

Owen RL, Hill JL. Rectal and pharyngeal gonorrhoea in homosexual men. *JAMA* 1972;220(10):1315-8.

Pantaleo G, Graziosi C, Fauci AS. The immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med* 1993a;328(5):327-35.

Pantaleo G, Graziosi C, Demarest JF, Butini L, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature* 1993b;362(6418):355-8.

Pantaleo G, Demarest JF, Soudeyns H, Graziosi C, et al. Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV. *Nature* 1994;370(6489):463-7. Pantaleo G, Menzo S, Vaccarezza M, Graziosi C, et al. Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. *N Engl J Med* 1995a;332:209-16.

Pantaleo G, Fauci AS. Apoptosis in HIV infection. *Nature Medicine* 1995b;1(2):118-20.

Pape JW, Liautaud B, Thomas F, Mathurin JR, et al. Characteristics of the acquired immunodeficiency syndrome (AIDS) in Haiti. *N Engl J Med* 1983;309(16):945-50.

Pape J, Johnson WD Jr. AIDS in Haiti: 1982-1992. *Clin Infect Dis* 1993;17(suppl 2):S341-5.

- Pariser H, Marino AF. Gonorrhea: frequently unrecognized reservoirs. *South Med J* 1970;63(2):198-201.
- Park CL, Streicher H, Rothberg R. Transmission of human immunodeficiency virus from parents to only one dizygotic twin. *J Clin Microbiol* 1987;25(6):1119-21.
- Pauza CD, Galindo JE, Richman DD. Reinfection results in accumulation of unintegrated viral DNA in cytopathic and persistent human immunodeficiency virus type 1 infection of CEM cells. *J Exp Med* 1990;172(4):1035-42.
- Pedersen C, Lindhardt BO, Jensen BL, Lauritzen E, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. *Br Med J* 1989;299(6692):154-7.
- Pedersen C, Gerstoft J, Lundgren J, Jensen BL, et al. Development of AIDS and low CD4 cell counts in a cohort of 180 seroconverters. IXth Int Conf on AIDS, (abstract no. PO-Bo1-0862), June 6-11, 1993.
- Peterman TA, Stoneburner RL, Allen JR, Jaffe HW, Curran JW. Risk of human immunodeficiency virus transmission from heterosexual adults with transfusion-associated infections. *JAMA* 1988;259(1):55-8.
- Petru A, Dunphy MG, Azimi P, Janner D, et al. Reliability of polymerase chain reaction in the detection of human immunodeficiency virus infection in children. *Pediatr Infect Dis J* 1992;11(1):30-3.
- Pezzotti P, Rezza G, Lazzarin A, Angarano G, et al. Influence of gender, age, and transmission category on the progression from HIV seroconversion to AIDS. *J Acquir Immune Defic Syndr* 1992;5(7):745-7.
- Piatak M Jr, Saag MS, Yang LC, Clark SJ, et al. High levels of HIV-1 in plasma during all stages of infection determined by competitive PCR. *Science* 1993;259(5102):1749-54.
- Piot P, Plummer FA, Mhalu FS, Lamboray JL, et al. AIDS: an international perspective. *Science* 1988;239(4840):573-9.
- Pitchenik AE, Shafron RD, Glasser RM, Spira TJ. The acquired immunodeficiency syndrome in the wife of a hemophiliac. *Ann Intern Med* 1984;100(1):62-5.
- Poon MC, Landay A, Prasthofer EF, Stagno S. Acquired immunodeficiency syndrome with *Pneumocystis carinii* pneumonia and *Mycobacterium avium*-intracellulare infection in a previously healthy patient with classic hemophilia. Clinical, immunologic, and virologic findings. *Ann Intern Med* 1983;98(3):287-90.
- Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science* 1984;224(4648):497-500.
- Prober CG, Gershon AA. Medical management of newborns and infants born to human immunodeficiency virus-seropositive mothers. *Pediatr Infect Dis J* 1991;10(9):684-95.
- Quinn TC, Mann JM, Curran JW, Piot P. AIDS in Africa: an epidemiologic paradigm. *Science* 1986;234(4779):955-63.
- Quinn TC. Population migration and the spread of types 1 and 2 human immunodeficiency viruses. *Proc Natl Acad Sci USA* 1994;91(7):2407-14.
- Ragni MV, Kingsley LA, Zhou SJ. The effect of antiviral therapy on the natural history of human immunodeficiency virus infection in a cohort of hemophiliacs. *J Acquir Immune Defic Syndr* 1992;5(2):120-6.
- Rasamindrakotroka AJ, et al. Seroprevalence of HIV-1, hepatitis B and syphilis in a population of blood donors in Antananavivo, Madagascar. VIth Int Conf on AIDS in Africa, Dakar, Senegal, (poster TA101), Dec 16-19, 1991.

Ratner L, Gallo RC, Wong-Staal F. HTLV-III, LAV, ARV are variants of same AIDS virus. *Nature* 1985;313(6004):636.

Reitz MS Jr, Hall L, Robert-Guroff M, Lautenberger J, et al. Viral variability and serum antibody response in a laboratory worker infected with HIV type 1 (HTLV type IIIB). *AIDS Res Hum Retroviruses* 1994;10(9):1143-55.

Reinisch JM, et al. Sexual behavior and AIDS: lessons from art and sex research. In: Veoller B, et al., eds. *AIDS and Sex: An Integrated Biomedical and Biobehavioral Approach*. New York: Oxford University Press, 1990, pp. 37-80.

Rezza G, Lazzarin A, Angarano G, Sinicco A, et al. The natural history of HIV infection in intravenous drug users: risk of disease progression in a cohort of seroconverters. *AIDS* 1989;3(2):87-90.

Rezza G, Lazzarin A, Angarano G, Zerboni R, et al. Risk of AIDS in HIV seroconverters: a comparison between intravenous drug users and homosexual males. *Eur J Epidemiol* 1990;6(1):99-101.

Richman DD, Fischl MA, Grieco MH, Gottlieb MS, et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *N Engl J Med* 1987;317(4):192-7.

Richman DD, Andrews J. Results of continued monitoring of participants in the placebo-controlled trials of zidovudine for serious human immunodeficiency virus infection. *Am J Med* 1988;85:208-13.

Richman DD, Bozzette SA. The impact of the syncytium-inducing phenotype of human immunodeficiency virus on disease progression. *J Infect Dis* 1994;169(5):968-74.

Robertson JR, Skidmore CA, Roberts JJ, Elton RA. Progression to AIDS in intravenous drug users, cofactors and survival. VIth Int Conf on AIDS, (abstract no. Th.C.649), June 20-23, 1990.

Robinson WS. Hepatitis B virus and hepatitis delta virus. In: Mandell GL, et al., eds. *Principles and Practices of Infectious Diseases*; 3rd ed. New York: Churchill Livingstone, 1990.

Rogers MF, Morens DM, Stewart JA, Kaminski RM, et al. National case-control study of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia in homosexual men: part 2. Laboratory results. *Ann Intern Med* 1983;99(2):151-7.

Rogers MF, Ou CY, Rayfield M, Thomas PA, et al. Use of the polymerase chain reaction for early detection of the proviral sequences of human immunodeficiency virus in infants born to seropositive mothers. *N Engl J Med* 1989;320(25):1649-54.

Rothman S. Remarks on sex, age and racial distribution of Kaposi's sarcoma and on possible pathogenic factors. *Acat Unio Int Contra Cancrum* 1962a;18:326.

Rothman S. Medical research in Africa. *Arch Dermatol* 1962b;85:311-24.

Rubinstein A, Sicklick M, Gupta A, Bernstein L, et al. Acquired immunodeficiency with reversed T4/T8 ratios in infants born to promiscuous and drug-addicted mothers. *JAMA* 1983;249:2350-6.

Ryder RW, Mugewrwa RW. The clinical definition and diagnosis of AIDS in African adults. In: Essex M, et al., eds. *AIDS in Africa*. New York: Raven Press, 1994a, pp. 269-81.

Ryder RW, Nsuami M, Nsa W, Kamenga M, et al. Mortality in HIV-1-seropositive women, their spouses and their newly born children during 36 months of follow-up in Kinshasa, Zaire. *AIDS* 1994b;8(5):667-72.

Saag MS, Crain MJ, Decker WD, Campbell-Hill S, et al. High level viremia in adults and children infected with human immunodeficiency virus: relation to disease stage and CD4+ lymphocyte levels. *J Infect Dis* 1991;164(1):72-80.

Saah AJ, Hoover DR, He Y, Kingsley LA, Phair JP. Factors influencing survival after AIDS: report from the Multicenter AIDS Cohort Study (MACS). *J Acquir Immune Defic Syndr* 1994;7(3):287-95.

Sabin C, Phillips A, Elford J, Griffiths P, et al. The progression of HIV disease in a hemophilic cohort followed for 12 years. *Br J Haematol* 1993;83(2):330-3.

Safai B, Good RA. Kaposi's sarcoma: a review and recent developments. *CA Cancer J Clin* 1981;31:1-12.

Safai B. Kaposi's sarcoma: a review of classical and epidemic forms. *Ann NY Acad Sci* 1984a;437:373-82.

Safai B, Sarngadharan MG, Groopman JE, Arnett K, et al. Seroepidemiological studies of human T-lymphotropic retrovirus type III in acquired immunodeficiency syndrome. *Lancet* 1984b;1(8392):1438-40.

Saghir MT, Robins E. *Male and Female Homosexuality: A Comprehensive Investigation*. Baltimore: Williams and Wilkins, 1973.

Saksela K, Stevens C, Rubinstein P, Baltimore D. Human immunodeficiency virus type 1 mRNA expression in peripheral blood cells predicts disease progression independently of the numbers of CD4+ lymphocytes. *Proc Natl Acad Sci USA* 1994;91(3):1104-8.

Sanchez-Pescador R, Power MD, Barr PJ, Steimer KS, et al. Nucleotide sequence and expression of an AIDS-associated retrovirus (ARV-2). *Science* 1985;227(4686):484-92.

Sande MA, Carpenter CC, Cobbs CG, Holmes KK, Sanford JP. Antiretroviral therapy for adult HIV-infected patients: recommendations for a state-of-the-art conference. *JAMA* 1993;270(21):2583-9.

Sarngadharan MG, Popovic M, Bruch L, Schupbach J, Gallo RC. Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. *Science* 1984;224(4648):506-8.

Schechter MT, Craib KJ, Le TN, Montaner JS, et al. Susceptibility to AIDS progression appears early in HIV infection. *AIDS* 1990;4(3):185-90.

Schechter MT, Craib KJ, Gelman KA, Montaner JS, et al. HIV-1 and the aetiology of AIDS. *Lancet* 1993a;341:658-9.

Schechter MT, Craib KJ, Montaner JS, Lee TN, et al. Aetiology of AIDS. *Lancet* 1993b;341(8854):1222-3.

Schinaia N, Ghirardini A, Chiarotti F, Gringeri A, Mannucci PM. Progression to AIDS among Italian HIV-seropositive haemophiliacs. *AIDS* 1991;5(4):385-91.

Schnittman SM, Psallidopoulos MC, Lane HC, Thompson L, et al. The reservoir for HIV-1 in human peripheral blood is a T cell that maintains expression of CD4. *Science* 1989;245(4915):305-8.

Schnittman SM, Greenhouse JJ, Psallidopoulos MC, Baseler M, et al. Increasing viral burden in CD4+ T cells from patients with human immunodeficiency virus infection reflects rapidly progressive immunosuppression and clinical disease. *Ann Intern Med* 1990a;113(6):438-43.

Schnittman SM, Denning SM, Greenhouse JJ, Justement JS, et al. Evidence for susceptibility of intrathymic T-cell precursors and their progeny carrying T-cell antigen receptor phenotypes TCR alpha beta + and TCR gamma delta + to human immunodeficiency virus infection: a mechanism for CD4+ (T4) lymphocyte depletion. *Proc*

Natl Acad Sci USA 1990b;87(19):7727-31.

Schnittman SM, Greenhouse JJ, Lane HC, Pierce PF, Fauci AS. Frequent detection of HIV-1 specific mRNAs in infected individuals suggests ongoing active viral expression in all stages of disease. *AIDS Res Hum Retroviruses* 1991;7(4):361-7.

Schoenbaum EE, Hartel D, Selwyn PA, Davenny K, et al. Lack of association of T- cell subsets with continuing intravenous drug use and high risk heterosexual sex, independent of HIV infection and disease. Program and Abstracts of the Vth Int Conf on AIDS (Montreal). Ottawa: International Development Research Center, 1989.

Scott J, Stone AH. Some observations on the diagnosis of rectal gonorrhoea in both sexes using a selective culture medium. *Br J Vener Dis* 1966;42(27):103-6.

Seidman SN, Rieder RO. A review of sexual behavior in the United States. *Am J Psychiatry* 1994;151(3):330-41.

Selik RM, Ward JW, Buehler JW. Trends in transfusion-associated acquired immune deficiency syndrome in the United States, 1982-1991. *Transfusion* 1993;33(11):890-3.

Selwyn PA, Alcabes P, Hartel D, Buono D, et al. Clinical manifestations and predictors of disease progression in drug users with human immunodeficiency virus infection. *N Engl J Med* 1992;327(24):1697-703.

Sewankambo NK, Wawer MJ, Gray RH, Serwadda D, et al. Demographic impact of HIV infection in rural Rakai District, Uganda: results of a population-based cohort study. *AIDS* 1994;8:1707-13.

Sheppard HW, Winkelstein W, Lang W, Charlebois E. CD4+ T-lymphocytopenia without HIV infection. *N Engl J Med* 1993;28(25):1847-8.

Shin YO, Hur SJ, Kim SS, Kee MK. Human immunodeficiency virus (HIV) epidemiological trends among risk groups in Korea. Xth Int Conf on AIDS, (abstract no. 041C), Aug 7-12, 1994.

Siegel FP, Lopez C, Hammer GS, Brown AE, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* 1981;305(24):1439-44.

Sinicco A, Fora R, Sciandra M, Lucchini A, et al. Risk of developing AIDS after primary acute HIV-1 infection. *J Acquir Immune Defic Syndr* 1993;6(6):575-81.

Smiley ML, White GC, Becherer P, Macik G, et al. Transmission of human immunodeficiency virus to sexual partners of hemophiliacs. *Am J Hematol* 1988;28(1):27-32.

Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. *N Engl J Med* 1993;328(6):373-9.

Sodroski J, Goh WC, Rosen C, Campbell K, Haseltine WA. Role of the HTLV- III/LAV envelope in syncytium formation and cytopathicity. *Nature* 1986;322(6078):470-4.

Sonnabend J, Witkin SS, Purtilo DT. Acquired immunodeficiency syndrome, opportunistic infections, and malignancies in male homosexuals. A hypothesis of etiologic factors in pathogenesis. *JAMA* 1983;249(17):2370-4.

Spotts JV, Shontz FC. *Cocaine Users: A Representative Case Approach*. New York: The Free Press, 1980.

Srugo I, Brunell PA, Chelyapov NV, Ho DD, et al. Virus burden in human immunodeficiency virus type 1-

infected children: relationship to disease status and effect of antiviral therapy. *Pediatrics* 1991;87(6):921-5.

Stanley SK, Kessler SW, Justement JS, Schnittman SM, et al. CD34+ bone marrow cells are infected with HIV in a subset of seropositive individuals. *J Immunol* 1992;149(2):689-97.

Stowring L, Haase AT, Charman HP. Serological definition of the lentivirus group of retroviruses. *J Virol* 1979;29(2):523-8.

Substance Abuse and Mental Health Services Administration. National Household Survey on Drug Abuse: Population Estimates, 1993. Rockville, MD, 1994.

Temin HM. Mechanisms of cell killing/cytopathic effects by nonhuman retroviruses. *Rev Infect Dis* 1988;10(2):399-405.

Temin HM. Is HIV unique or merely different? *J Acquir Immune Defic Syndr* 1989;2(1):1-9.

Terai C, Kornbluth RS, Pauza CD, Richman DD, Carson DA. Apoptosis as a mechanism of cell death in cultured T lymphoblasts acutely infected with HIV-1. *J Clin Invest* 1991;87(5):1710-5.

Tersmette M, de Goede RE, Al BJ, Winkel IN, et al. Differential syncytium-inducing capacity of human immunodeficiency virus isolates: frequent detection of syncytium-inducing isolates in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. *J Virol* 1988;62(6):2026-32.

Tersmette M, Lange JM, de Goede RE, de Wolf F, et al. Association between biological properties of human immunodeficiency virus variants and risk for AIDS and AIDS mortality. *Lancet* 1989a;1(8645):983-5.

Tersmette M, Gruters RA, de Wolf F, de Goede RE, et al. Evidence for a role of virulent human immunodeficiency virus variants in the pathogenesis of acquired immunodeficiency syndrome: studies on sequential HIV isolates. *J Virol* 1989b;63(5):2118-25.

Thea DM, St Louis ME, Atido U, Kanjinga K, et al. A prospective study of diarrhea and HIV-1 infection among 429 Zairian infants. *N Engl J Med* 1993;329(23):1696-702.

Thomas PA, Ralston SJ, Bernard M, Williams R, O'Donnell R. Pediatric immunodeficiency syndrome: an unusually high incidence of twinning. *Pediatrics* 1990;86(5):774-7.

Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. *AIDS* 1991;5(1):1-14.

Turner BJ, Denison M, Eppes SC, Houchens R, et al. Survival experience of 789 children with the acquired immunodeficiency syndrome. *Pediatr Infect Dis J* 1993;12(4):310-20.

United States Bureau of the Census, Center for International Research, Washington, D.C. HIV/AIDS Surveillance Database, 1994.

Vahey MT, Mayers DL, Wagner KF, Chung RC, et al. Plasma HIV RNA predicts clinical outcome on AZT therapy. Xth Int Conf on AIDS, (abstract no. 253B), Aug 7- 12, 1994.

Varmus H. Retroviruses. *Science* 1988;240(4858):1427-35.

Vella S, Giuliano M, Pezzotti P, Agresti MG, et al. Survival of zidovudine-treated patients with AIDS compared with that of contemporary untreated patients. Italian Zidovudine Evaluation Group. *JAMA* 1992;267(9):1232-6.

Vella S, Giuliano M, Dally LG, Agresti MG, et al. Long-term follow-up of zidovudine therapy in asymptomatic HIV infection: results of a multicenter cohort study. *J Acquir Immune Defic Syndr* 1994;7(1):31-8.

Vermund SH, Hoover DR, Chen K. CD4+ counts in seronegative homosexual men. *N Engl J Med* 1993a;328(6):442.

Vermund SH. Rising HIV-related mortality in young Americans. *JAMA* 1993b;16,269(23):3034-5.

Veugelers PJ, Page KA, Tindall B, Schechter MT, et al. Determinants of HIV disease progression among homosexual men registered in the Tricontinental Seroconverter Study. *Am J Epidemiol* 1994;15,140(8):747-58.

Volberding PA, Lagakos SW, Koch MA, Pettinelli C, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med* 1990;322(14):941-9.

Volberding PA, Lagakos SW, Grimes JM, Stein DS, et al. The duration of zidovudine benefit in persons with asymptomatic HIV infection. Prolonged evaluation of protocol 019 of the AIDS Clinical Trials Group. *JAMA* 1994;272(6):437-42.

Volberding PS, Graham NM. Initiation of antiretroviral therapy in HIV infection: a review of interstudy consistencies. *J Acquir Immune Defic Syndr* 1994;7(suppl 2):S12-22.

Wages JM Jr, Hamdallah M, Calabro MA, Fowler AK, et al. Clinical performance of a polymerase chain reaction testing algorithm for diagnosis of HIV-1 infection in peripheral blood mononuclear cells. *J Med Virol* 1991;33(1):58-63.

Wain-Hobson S, Sonigo P, Danos O, Cole S, Alizon M. Nucleotide sequence of the AIDS virus, LAV. *Cell* 1985;40(1):9-17.

Walzer PD, Perl DP, Krogstad DG, Rawson PG, Schultz MG. Pneumocystis carinii pneumonia in the United States. Epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974;80(1):83-93.

Walzer PD. Pneumocystis carinii. In: Mandell GL, et al., eds. *Principles and Practices of Infectious Diseases*; 3rd ed. New York: Churchill Livingstone, 1990, pp. 2103-10.

Ward JW, Bush TJ, Perkins HA, Lieb LE, et al. The natural history of transfusion-associated infections with the human immunodeficiency virus. *N Engl J Med* 1989;321(14):947.

Weber R, Ledergerber B, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. *Br Med J* 1990;301(6765):1362-5.

Wei X, Ghosh SK, Taylor ME, Johnson VA, et al. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 1995;373:117-22.

Weinberg MS, Williams CJ. *Male Homosexuals*. London: Oxford University, 1974.

Weiss RA. How does HIV cause AIDS? *Science* 1993;260(5112):1273-9.

Weiss RA, Jaffe HW. Duesberg, HIV and AIDS (commentary). *Nature* 1990;345:659-60.

Weiss SH, Klein CW, Mayur RK, Besra J, Denny TN. Idiopathic CD4+ T-lymphocytopenia. *Lancet* 1992;340:608-9.

Welles SL, et al. Prognostic capacity of plasma HIV-1 RNA copy number in ACTG 116A. Second National Conference on Human Retroviruses and Related Infections, Washington, D.C. Jan 29-Feb 2, 1995.

Weniger BG, Limpakarnjanarat K, Ungchusak K, Thanprasertsuk S, et al. The epidemiology of HIV infection and AIDS in Thailand. *AIDS* 1991;5(suppl 2):S71-85.

WHO (World Health Organization). *AIDS: images of the epidemic*. 1994.

WHO. The current global situation of the HIV/AIDS pandemic. Jan 3, 1995a.

WHO. Surveillance, Evaluation and Forecasting Unit, Division of Technical Cooperation, Global Programme on AIDS. Personal communication. June 1, 1995b.

Williams CKO, et al. AIDS-associated cancers. In: Essex M, et al., eds. *AIDS in Africa*. New York: Raven Press, 1994, pp. 325-71.

Wofsy CB, Cohen JB, Hauer LB, Padian NS, et al. Isolation of AIDS-associated retrovirus from genital secretions of women with antibodies to the virus. *Lancet* 1986;8,1(8480):527-9.

Yerly S, Chamot E, Hirschel B, Perrin LH. Quantitation of human immunodeficiency virus provirus and circulating virus: relationship with immunologic parameters. *J Infect Dis* 1992;166(2):269-76.

Young KY, Nelson RP, Good RA. Discordant human immunodeficiency virus infection in dizygotic twins detected by polymerase chain reaction. *Pediatr Infect Dis J* 1990;9(6):454-6.

Zaccarelli M, Gattari P, Rezza G, Conti S, et al. Impact of HIV infection on non-AIDS mortality among Italian injecting drug users. *AIDS* 1994;8(3):345-50.

Zagury D, Bernard J, Leibowitch J, Safai B, et al. HTLV-III in cells cultured from semen of two patients with AIDS. *Science* 1984;226(4673):449-51.

Zagury D, Bernard J, Leonard R, Cheymier R, et al. Long-term cultures of HTLV-III infected T cells: a model of cytopathology of T-cell depletion in AIDS. *Science* 1986;231(4740):850-3.

Zakowski P, Fligiel S, Berlin GW, Johnson L. Disseminated *Mycobacterium avium*-intracellulare infection in homosexual men dying of acquired immunodeficiency. *JAMA* 1982;248(22):2980-2.

Zhu T, Ho DD. Was HIV present in 1959? *Nature* 1995;374:503-4.

September 1995.