

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

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## Introduction

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.

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## 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 (mm<sup>3</sup>) 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).

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## 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) (Figure 1).

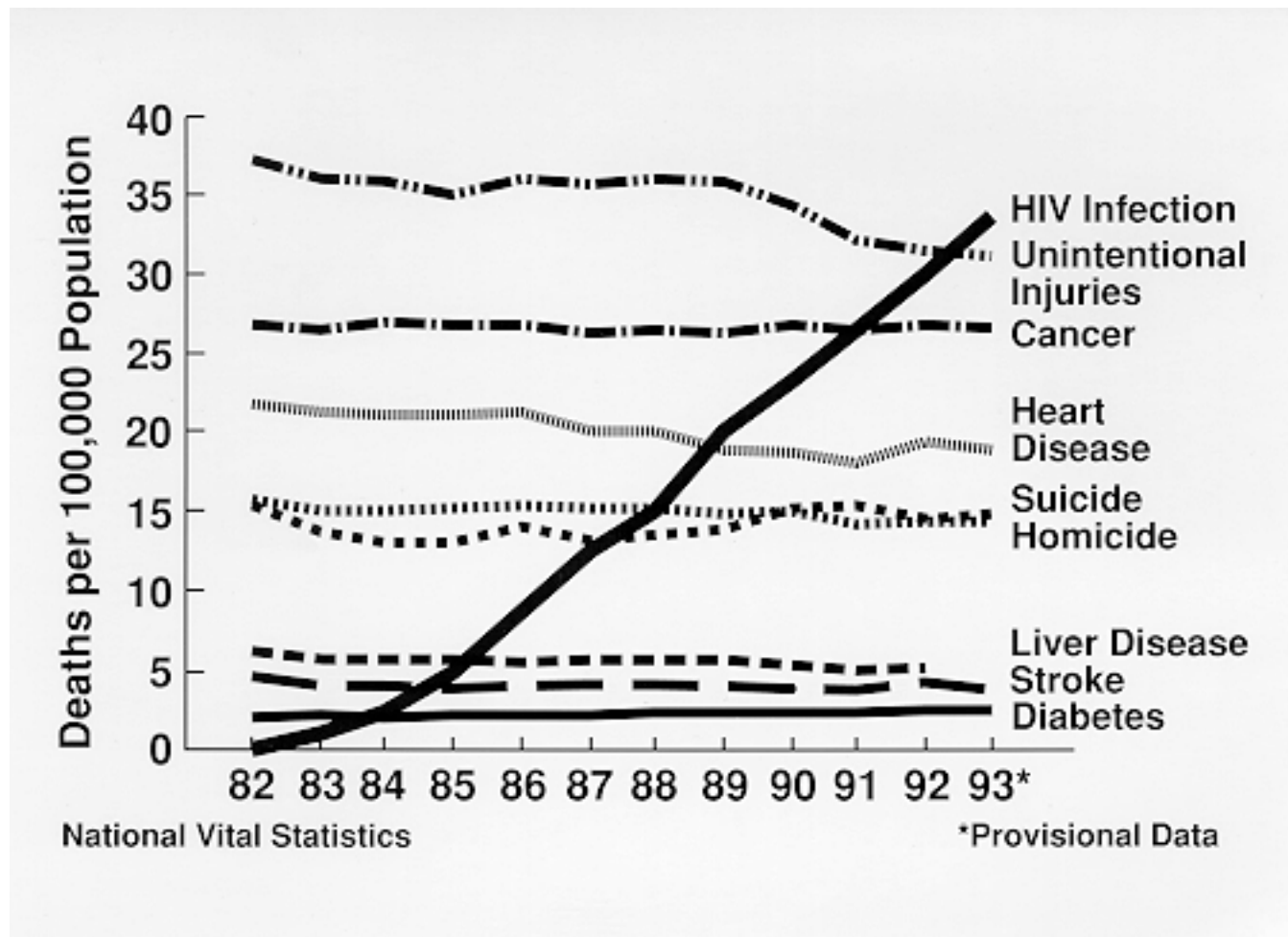
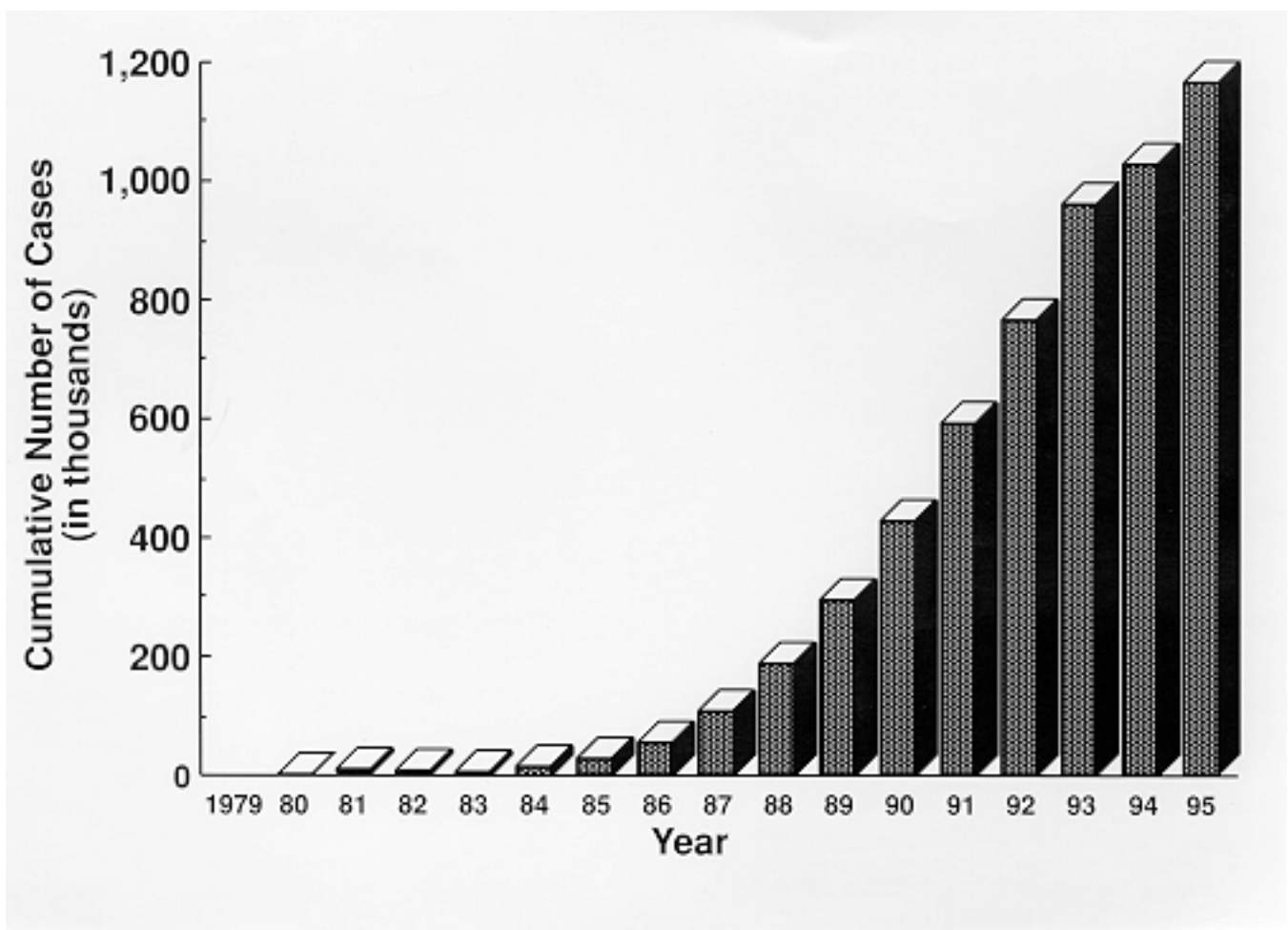


Fig. 1. Death rates from leading causes of death in persons aged 25-44 years, United States, 1982-1993  
 Reference: Centers for Disease Control and Prevention

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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) (Figure 2). 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).

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**Fig. 2. Cumulative AIDS cases worldwide. AIDS cases reported to the World Health Organization through December 1994.**

*Reference: WHO, 1995a*

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## 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 opportunistic 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).

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## 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).

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## 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<sup>+</sup> 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).

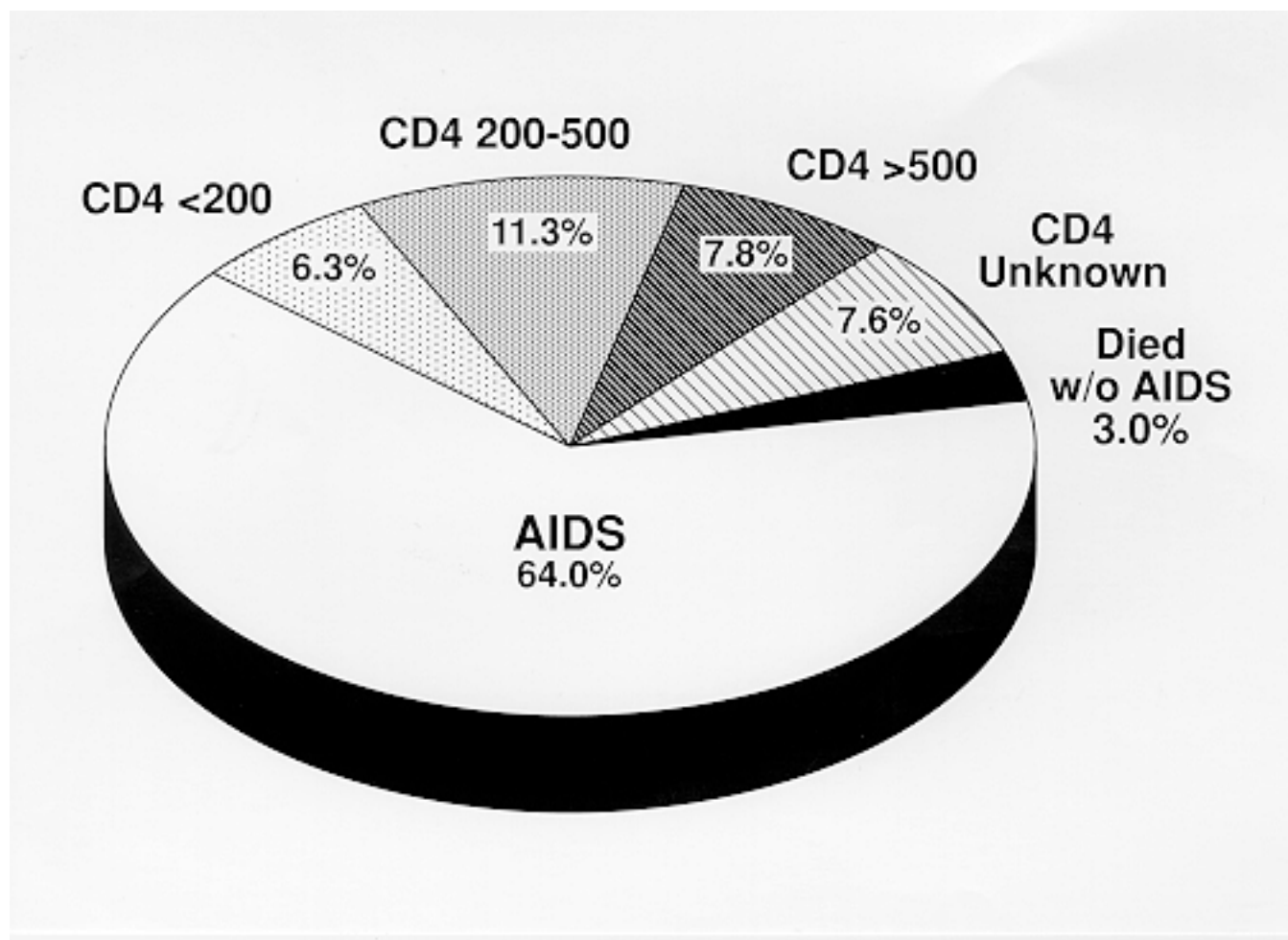
By 1985, analyses of the nucleotide sequences of HTLV-III, LAV and ARV demonstrated that the three viruses belonged to the same retroviral family and were strikingly similar (Wain-Hobson et al., 1985; Ratner et al., 1985; Sanchez-Pescador et al., 1985). In 1986, the International Committee of Viral Taxonomy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

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### 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/mm<sup>3</sup>; another 11 percent had CD4+ T cell counts between 200 and 500/mm<sup>3</sup> (Buchbinder et al., 1994) (Figure 3).



**Fig. 3.** Clinical and immunologic outcomes in patients HIV-infected for 10-15 years in the San Francisco City Clinic; n=539.

*Modified from 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 (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).

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## 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) (Table 1).

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Table 1. Lentiviruses

Virus	Host	Primary cell type infected	Clinical disorder

Equine infectious anemia virus (EIAV)	Horse	Macrophages	Cyclical infection in the first year: hemolytic anemia and sometimes encephalopathy
Visna virus	Sheep	Macrophages	Encephalopathy
Caprine arthritis-encephalitis virus (CAEV)	Goat	Macrophages	Immune deficiency, encephalopathy
Bovine immune deficiency virus (BIV)	Cow	Macrophages	Lymphadenopathy, lymphocytosis, CNS disease (?)
Feline immunodeficiency virus (FIV)	Cat	T lymphocytes	Immune deficiency
Simian immunodeficiency (SIV)	Primate	T lymphocytes	Immune deficiency, encephalopathy
Human immunodeficiency virus (HIV)	Human	T lymphocytes	Immune deficiency, encephalopathy

*Reference: 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).

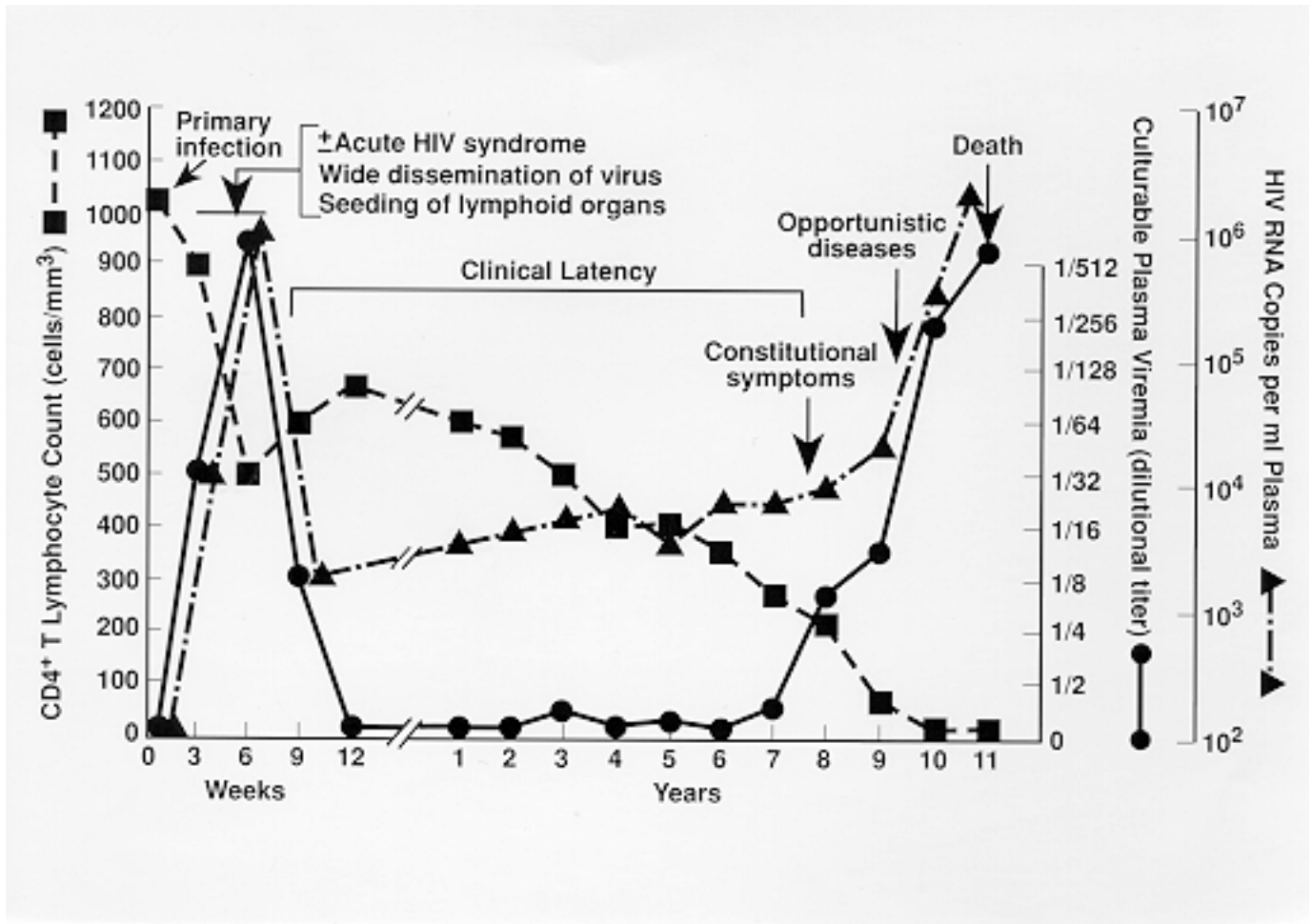
One feature that distinguishes lentiviruses from other retroviruses is the remarkable complexity of their viral genomes. Most retroviruses that are capable of replication contain only three genes--env, gag and pol (Varmus, 1988). HIV contains not only these essential genes but also the complex regulatory 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) (Figure 4). 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).



**Fig. 4.** Typical course of HIV infection. During the period following primary infection, HIV disseminates widely in the body; an abrupt decrease in CD4+ T cells in the peripheral circulation is often seen. An immune response to HIV ensures, with a decrease in detectable viremia. A period of clinical latency follows, during which CD4+ T cells counts continue to decrease, until they fall to a critical level below which there is a substantial risk of opportunistic infections.

*Adapted from Pantaleo 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).

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### 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 (mm<sup>3</sup>) 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/MM<sup>3</sup>) 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/mm<sup>3</sup>, 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) (Table 2). 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).

**Table 2. Potential Mechanisms of the Functional and Quantitative Depletion of CD4 T Lymphocytes**

Direct HIV-mediated cytopathic effects (single-cell killing)
HIV-mediated formation of syncytia
Virus-specific immune responses
HIV-specific cytolytic T lymphocytes
Antibody-dependent cellular cytotoxicity
Natural killer cells
Autoimmune mechanisms
Anergy caused by inappropriate cell signaling through gp120-CD4 interaction
Superantigen-mediated perturbation of T-cell subgroups
Programmed cell death (apoptosis)

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.

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### **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) (Table 3).

**Table 3. Assays to Detect/Measure HIV Antibody-Positive Patients**

Assay	% of antibody-positive patients	CD4+ range (cells/mm <sup>3</sup> )	Viral parameter measured
p24 antigen	20 37-95	200-500 <200	Free viral antigen in serum or plasma
ICD p24	45-70 75-100	200-500 <200	Immune-complexed viral antigen in serum or plasma
Plasma viremia	75-100	<200	Infectious cell-free virus
PBMC culture	95-100	<500	Infectious cell-associated and amplifiable virus
DNA PCR	100	<1,000	Cell-associated proviral DNA
RNA PCR	100	<1,000	Cell-free and/or cell-associated viral RNA

*Modified from Hammer 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 HIVIII B 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/mm<sup>3</sup> 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, HIVIII B 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 documented 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).

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### 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).

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### 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

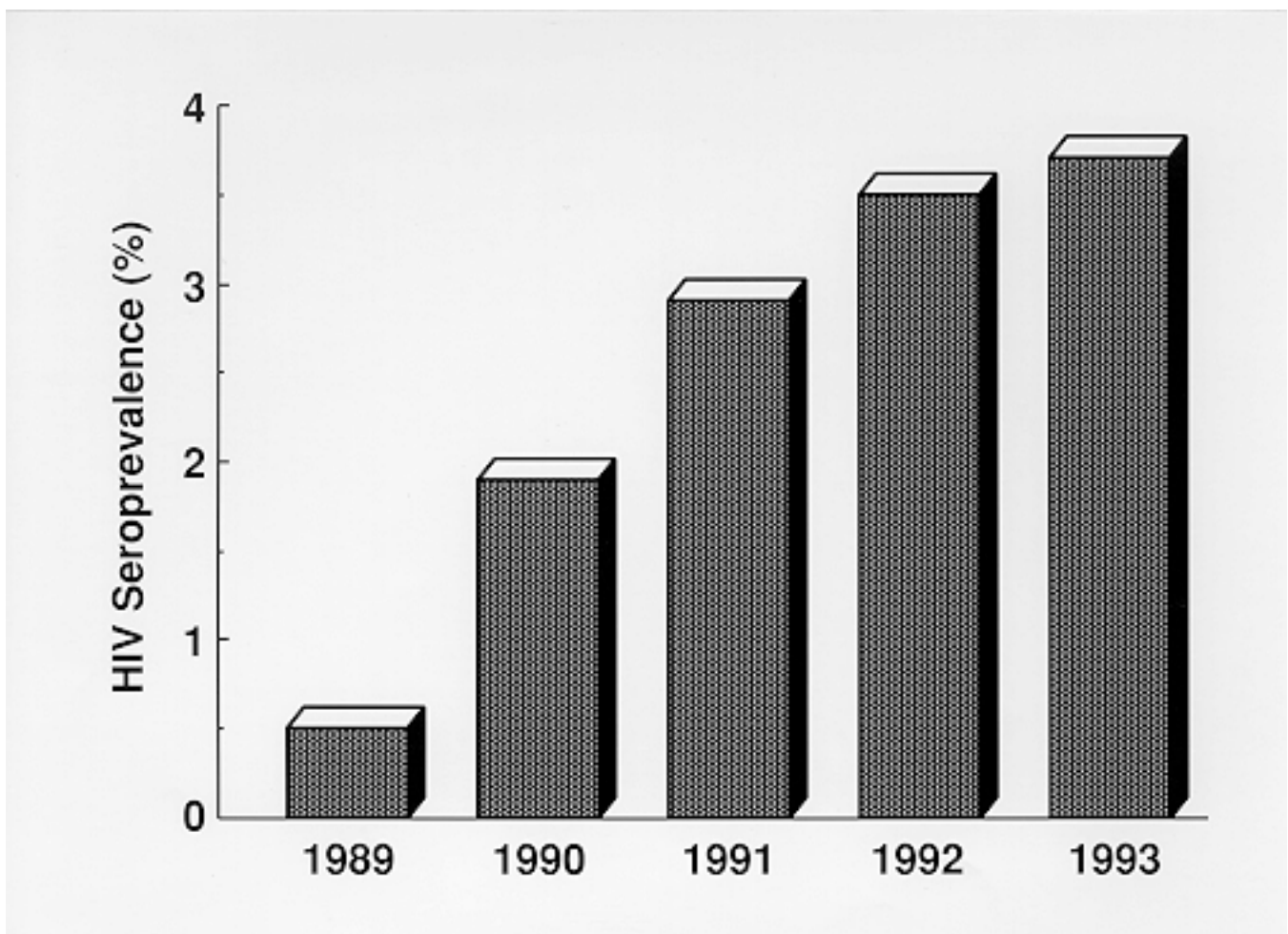
HIV antibody seroprevalence is low, AIDS is extremely rare (U.S. Bureau of the Census, 1994).

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) (Figure 5). 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 (Hansen 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).

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**Fig. 5. Cumulative AIDS cases in Thailand, 1979-1994**

*References: WHO, 1995a*

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<sup>+</sup>/CD8<sup>+</sup> 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).

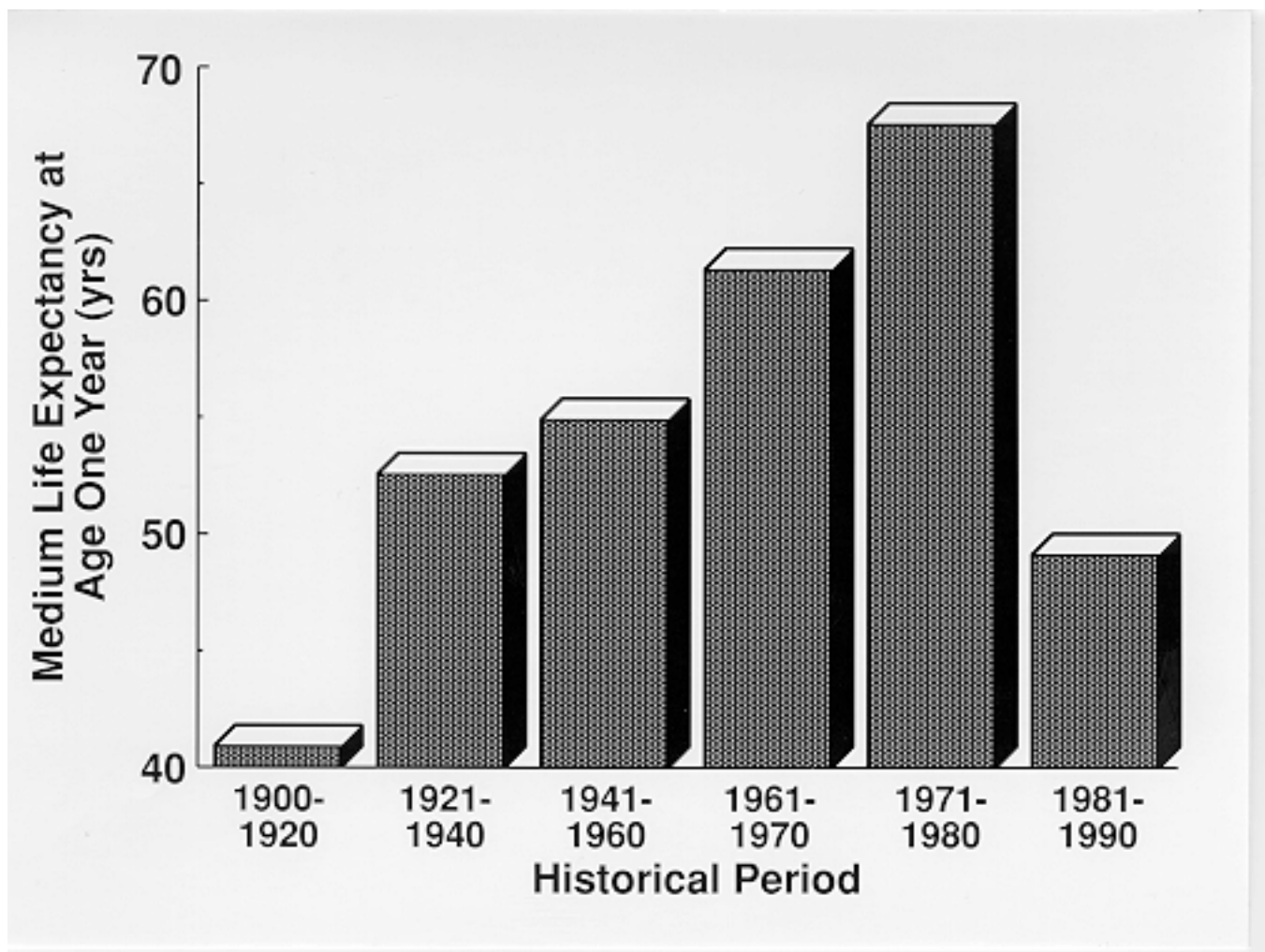
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### Impact of HIV Infection on Mortality of Hemophiliacs

As noted above, HIV has been detected in stored blood samples taken from hemophiliac 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) (Figure 6).

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**Fig. 6. The changing prognosis of classic hemophilia. After improvement in survival from 1971-1980 (corresponding to widespread treatment with lyophilized concentrates of Factor VIII), mortality among individuals with Factor VIII deficiency is now increasing, due in large measure to AIDS among people who became HIV-infected during transfusions between 1978 and 1985**

*Reference: 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/mm<sup>3</sup> (Lee et al., 1995).

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## **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).

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## 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).

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### 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/mm<sup>3</sup> 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.

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## 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/mm<sup>3</sup> (Des Jarlais et al., 1993). Only two individuals had two CD4+ T cell measurements of fewer than 300/mm<sup>3</sup>, one of whom died with cardiac disease and non-Hodgkin's lymphoma listed 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/mm<sup>3</sup> (Weiss et al., 1992). Two of these individuals, both with generalized lymphocytopenia, had CD4+ T cell counts less than 300/mm<sup>3</sup>.

In the MACS, median CD4+ T cell counts of 63 HIV-seronegative injection drug users rose from

1061/mm<sup>3</sup> to 1124/mm<sup>3</sup> 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/mm<sup>3</sup>, while 11 healthy controls had CD4+ T cell counts of 820 cells/mm<sup>3</sup> (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/mm<sup>3</sup> in the HIV-seronegative group, and 395/mm<sup>3</sup> 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).

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## 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 frequency 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 gonorrheal 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).

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### 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 (Table 4).

**Table 4. Major placebo-controlled trials of zidovudine (AZT) monotherapy in HIV-infected patients without AIDS**

<b>Early symptomatic HIV infection</b>						
<b>Study</b>	<b>Reference</b>	<b>CD4+ T cell count at study entry (cells/mm<sup>3</sup>)</b>	<b>Daily dose zidovudine (milligrams)</b>	<b>Avg. Duration of follow-up (months)</b>	<b>Number in analysis ZDV/imm/P/def</b>	<b>No. progressing to AIDS or death ZDV/imm/P/def</b>
ACTG 016	Fischl, 1990	200-800	1200	11	360/351	7/21
VA 298	Hamilton, 1992	200-500	1500	28	170/168	38/48
<b>Asymptomatic HIV infection</b>						
<b>Study</b>	<b>Reference</b>	<b>CD4+ T cell count at study entry (cells/mm<sup>3</sup>)</b>	<b>Daily dose zidovudine (milligrams)</b>	<b>Avg. Duration of follow-up (months)</b>	<b>Number in analysis ZDV/imm/P/def</b>	<b>No. progressing to AIDS or death ZDV/imm/P/def</b>
ACTG 019‡	Volberding, 1990	<500	1500 500	13	457,453/428	14,11/33
-	Volberding, 1994¶ (extended follow-up)	<500	1500 500	31	530,542/493	75,79/78
EACG 020	Cooper, 1993	<400	1000	21	495/489	6/9

ACTG 036	Merigan, 1991	<=500	1500	10	92/101	3/6
EA hemophilia	Mannucci, 1994	100-400†	1000	21	69/71	5/4
EACG 017	Mulder, 1994	200-400†	1000	14	167/162	11/12
Concorde	Concorde, 1994	any	1000	36	877/872	176/171

The Concorde trial and VA 298 compared immediate (imm) and deferred (def) use of zidovudine (ZDV); the other trials compared zidovudine (ZDV) and placebo (P).

† Or p24 antigenemia.

‡ In ACTG 019, original treatment group included placebo, 500 mg. ZDV/day or 1500 mg. ZDV/day.

¶ After the unblinding of the original randomized trial in 1989, subjects in each original arm were offered a daily dose of 500 mg. open-label zidovudine.

*Modified from Concorde Coordinating Committee, 1994.*

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/mm<sup>3</sup>, 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/mm<sup>3</sup>.

A Veteran's Administration study of 338 individuals with early symptoms of HIV disease and CD4+ T cell counts between 200 and 500 cells/mm<sup>3</sup> 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/mm<sup>3</sup> (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/mm<sup>3</sup>. 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/mm<sup>3</sup> 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/mm<sup>3</sup> 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."

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### 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.

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### 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/mm<sup>3</sup>, while 111 HIV-seropositive individuals had average CD4+ T cell counts of 375/mm<sup>3</sup> (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.

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### 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/mm<sup>3</sup> and 718/mm<sup>3</sup>, 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/mm<sup>3</sup>; among 715 HIV-seropositive hemophiliacs, the mean CD4+ T cell count was 253/mm<sup>3</sup> (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/mm<sup>3</sup> at study entry; no individuals had CD4+ T cell counts below 200/mm<sup>3</sup>. In contrast, 26 percent of seropositive children had CD4+ T cell counts of less than 200/mm<sup>3</sup>; the mean CD4+ T cell count for seropositive children was 423/mm<sup>3</sup> (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.

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### 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).

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## 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).

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## 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.

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