



# FACT SHEET

Office of  
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National Institute of Allergy and Infectious Diseases

▪ National Institutes of Health

## The Evidence That HIV Causes AIDS

The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 and has since become a major worldwide epidemic. AIDS is caused by the human immunodeficiency virus (HIV). By leading to the destruction and/or functional impairment of cells of the immune system, notably CD4+ T cells, HIV progressively destroys the body's ability to fight infections and certain cancers.

Between June 1981 and December 31, 1994, physicians reported 441,528 cases of AIDS, including 270,870 AIDS-related deaths, to the U.S. Centers for Disease Control and Prevention (CDC). AIDS is now the leading cause of death among adults aged 25 to 44 in the United States.

This document summarizes the abundant evidence that HIV causes AIDS. Questions and answers at the end of this document address the specific claims of those who assert that HIV is not the cause of AIDS.

### Definition of AIDS

The CDC currently defines AIDS in an adult or adolescent age 13 years or older as the presence of one of 25 conditions indicative of severe immunosuppression associated with HIV infection, such as *Pneumocystis carinii* pneumonia (PCP), or HIV infection in an individual with a CD4+ T cell count less than 200/cells per cubic millimeter (mm<sup>3</sup>) of blood. 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.

*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, and leading to progressively severe symptoms and, ultimately, profound immunodeficiency and opportunistic infections and cancers.

## Evidence That HIV Causes AIDS

**Before the appearance of HIV, AIDS-like syndromes were rare; today, they are common in HIV-infected individuals.**

Prior to the appearance of HIV, AIDS-related conditions such as *Pneumocystis carinii* pneumonia (PCP), Kaposi's sarcoma (KS) and disseminated infection with the *Mycobacterium avium* complex (MAC) were extraordinarily rare in the United States. In a 1967 survey, only 107 cases of PCP in this country had been described in the medical literature, virtually all among individuals with underlying immunosuppressive conditions. Before the AIDS epidemic, the annual incidence of Kaposi's sarcoma in the United States was 0.021 to 0.061 per 100,000, and only 32 individuals with disseminated MAC disease had been described in the medical literature.

By December 31, 1994, physicians had reported to the CDC 127,626 patients with AIDS in the United States with definitive diagnoses of PCP, 36,693 with KS and 28,954 with disseminated MAC.

**AIDS and HIV infection are invariably linked in time, place and population group.**

Historically, the occurrence of AIDS-like illnesses in populations has closely followed the appearance of HIV. The first cases of AIDS in homosexual men in San Francisco were detected in 1981, and retrospective examination of frozen blood samples from a cohort of gay men showed the presence of HIV antibodies as early as 1978 but not before then. Subsequently, in every country and city where AIDS has appeared, evidence of HIV infection has preceded AIDS by just a few years. In Thailand, for example, the explosion of AIDS cases followed a dramatic increase in HIV seroprevalence rates.

**The main risk factors for AIDS -- sexual contact between men and between men and women, transfusions, treatment for hemophilia and needle-sharing during injection-drug use -- have existed for years, increasing only in a relative sense in recent years.**

If, as argued by some, these factors were themselves immunosuppressive, one would expect to have seen a large number of AIDS-like syndromes among prostitutes (male or female), HIV-seronegative blood recipients, hemophiliacs and users of recreational drugs prior to the appearance of HIV. Reviews of the medical literature, autopsy records and tumor registries indicate that such cases were extraordinarily rare.

**Many studies agree that only a single factor, HIV, predicts whether a person will develop AIDS.**

Other viral infections, bacterial infections, sexual behavior patterns and

drug abuse patterns do not predict who develops AIDS. Individuals from diverse backgrounds, including heterosexual men and women, homosexual men and women, hemophiliacs, sexual partners of hemophiliacs and transfusion recipients, injection-drug users and infants have all developed AIDS, with the only common denominator being their infection with HIV.

**Numerous serosurveys show that AIDS is common in populations where many individuals have HIV antibodies. Conversely, in populations with low seroprevalence of HIV antibodies, AIDS is extremely rare.**

For example, Malawi, an African country with high seroprevalence of HIV antibodies, had reported 34,167 cases of AIDS to the WHO as of December 31, 1994. In contrast, Madagascar, an island country off the southeast coast of Africa with a very low seroprevalence of HIV antibodies, reported only 9 cases of AIDS to the WHO through December 31, 1994.

**In cohort studies, severe immunosuppression and AIDS-defining illnesses occur exclusively in individuals who are HIV-infected.**

Conversely, matched controls, individuals with similar lifestyles but without HIV infection, virtually never suffer these symptoms.

For example, in one cohort in Vancouver, investigators followed 715 homosexual men for a median of 8.6 years. Every case of AIDS in this cohort occurred in individuals who were positive for HIV antibodies. No AIDS-defining illnesses occurred in men who remained negative for HIV antibodies, despite the fact that these men had appreciable patterns of illicit drug use and receptive anal intercourse.

**The specific immunologic profile that typifies AIDS -- a persistently low CD4+ T cell count -- is extraordinarily rare in the absence of HIV infection or other known cause of immunosuppression.**

For example, in the NIAID-supported Multicenter AIDS Cohort Study (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.

**Nearly everyone with AIDS has antibodies to HIV.**

A recent survey of 230,179 AIDS patients in the United States revealed only 299 HIV-seronegative individuals. An evaluation of 172 of these 299 patients found 131 actually to be seropositive; an additional 34 died before their serostatus could be confirmed.

**HIV can be detected in virtually everyone with AIDS.**

Recently developed sensitive testing methods, including the polymerase chain reaction (PCR) and improved culture techniques, have enabled researchers to find HIV in patients with AIDS with few exceptions. HIV has been repeatedly isolated from the blood, semen and vaginal secretions of patients with AIDS, findings consistent with the epidemiologic data demonstrating AIDS transmission via sexual activity and contact with infected blood.

### **HIV fulfills Koch's postulates as the cause of AIDS.**

Koch's postulates of disease causation stipulate that an infectious agent must be found in all cases of the disease, the agent must be isolated from the host's body, the agent must cause disease when injected into healthy hosts, and the same agent must once again be isolated from the newly diseased host.

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, cloned HIV in the laboratory. Two individuals 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 an antiretroviral drug until 83 months after the infection. In all three cases, HIV was isolated from the infected individual, sequenced and shown to be the infecting strain of virus.

In addition, through 1994 the 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. The development of AIDS following known HIV seroconversion also has been repeatedly observed in pediatric and adult blood transfusion cases, in mother-to-child transmission, and in studies of hemophilia, injection-drug use and sexual transmission in which seroconversion can be documented using serial blood samples.

### **Newborn infants have no behavioral risk factors, yet 6,209 children in the United States developed AIDS through December 31, 1994.**

Only the 15 to 40 percent of infants who become HIV-infected before or during birth go on to develop immunosuppression and AIDS. Babies who are not HIV-infected do not develop AIDS.

Because many HIV-infected mothers abuse recreational drugs, some have argued that maternal drug use itself causes pediatric AIDS. However, studies have consistently shown that babies who are not HIV-infected do not develop AIDS, regardless of their mothers' drug use.

**The HIV-infected twin develops AIDS while the uninfected twin does not.**

Researchers have documented cases of HIV-infected mothers who have given birth to twins, one of whom is HIV-infected and the other not. The HIV-infected children developed AIDS, while the other children remained clinically and immunologically normal.

**Since the appearance of HIV, mortality has increased dramatically among hemophiliacs.**

The impact of HIV on the life expectancy of hemophiliacs has been dramatic. Among those with severe factor-VIII deficiency, mortality increased six-fold from 1981 to 1990. Median life expectancy at one year of age for males with hemophilia increased from 40.9 years at the beginning of the century (1900 to 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.

**Studies of transfusion-acquired AIDS cases have repeatedly led to the discovery of HIV in the patient as well as in the blood donor.**

Numerous studies have shown an almost perfect correlation between the occurrence of AIDS in a blood recipient and donor, and evidence of homologous HIV strains in both the recipient and the donor.

**Sex partners of HIV-infected hemophiliacs and transfusion recipients acquire the virus and develop AIDS without other risk factors.**

Ten to 20 percent of wives and sex partners of male HIV-positive hemophiliacs in the United States are also HIV-infected. Through December 31, 1994, the CDC had received reports of 266 cases of AIDS in those whose only risk factor was sex with an HIV-infected person with hemophilia. The CDC had also received reports of 628 cases of AIDS in individuals whose primary risk factor was sex with an HIV-infected transfusion recipient.

**HIV infects and is responsible for the death of CD4+ T lymphocytes *in vitro* and *in vivo*.**

CD4+ T cells are the cells depleted in people with AIDS. Although the loss of CD4+ T cells is not the only immune defect seen in people with AIDS, the observation that HIV also infects and damages these cells *in vitro* establishes an obvious link between HIV and AIDS. Recent *in vivo* studies suggest that during HIV infection, more than 1 billion CD4+ T cells are destroyed every day, eventually overwhelming the immune system's regenerative capacity.

**HIV damages the body's sources of CD4+ T cells and centers of**

## **immune activity.**

HIV destroys precursor cells and the structures in the bone marrow and thymus that are needed for the development of mature immune cells. This damage may help explain why the immune systems of people with AIDS do not successfully regenerate their CD4+ T cells. The virus also progressively destroys the lymph nodes, the centers of immune activity in the body. Significantly, in the approximately 5 percent of HIV-infected people whose disease does not progress, the lymph node architecture appears to remain intact.

### **Studies of HIV-infected people show that increasing amounts of HIV in the body correlate with the progression of the immunologic processes that lead to AIDS.**

As levels of viral replication and the amount of virus in the body increase, so too do the various immunologic processes associated with AIDS. Recent studies have shown that a rise in expression of HIV RNA in peripheral blood mononuclear cells **precedes** clinically defined progression of disease in people with HIV.

In the approximately 5 percent of HIV-infected individuals whose disease progresses very slowly, the amount of virus in the blood and lymph nodes is significantly lower than that in HIV-infected people whose disease progression is more typical.

### **HIV is similar in genetic structure and morphology to other lentiviruses that often cause immunodeficiency in their animal hosts in addition to slow, progressive wasting disorders, neurodegeneration and death.**

Like HIV in humans, animal viruses such as feline immunodeficiency virus (FIV) in cats, visna virus in sheep and simian immunodeficiency virus (SIV) in monkeys primarily infect cells of the immune system such as T cells and macrophages. For example, visna virus infects macrophages and causes a slowly progressive neurologic disease.

### **Baboons develop AIDS after inoculation with clones of an HIV variant that also causes AIDS in humans.**

Over the course of two years, baboons infected with HIV-2 exhibited a significant decline in immune function, as well as AIDS-like symptoms.

### **Asian monkeys develop AIDS after infection with the simian immunodeficiency virus (SIV), a virus closely related to HIV.**

In macaque species, various cloned SIV isolates induce syndromes that parallel HIV infection and AIDS in humans, including swollen lymph nodes early in infection, CD4+ T cell depletion, opportunistic infections such as PCP and MAC, and death.

## Answering the skeptics:

### Responses to arguments that HIV does not cause AIDS

**Myth:** *HIV cannot be the cause of AIDS because researchers are unable to explain precisely how HIV destroys the immune system.*

**Fact:** A great deal is known about the pathogenesis of HIV disease, even though important details remain to be elucidated. However, a complete understanding of the pathogenesis of a disease is not a prerequisite to knowing its cause. Most infectious agents have been associated with the disease they cause long before their pathogenic mechanisms have been discovered. Because research in pathogenesis is difficult when precise animal models are unavailable, the disease-causing mechanisms in many diseases, including tuberculosis and hepatitis B are poorly understood. The critics' reasoning would lead to the conclusion that *M. tuberculosis* is not the cause of tuberculosis or that hepatitis B virus is not a cause of liver disease.

**Myth:** *Behavioral factors such as recreational drug use and multiple sexual partners account for AIDS.*

**Fact:** The proposed behavioral causes of AIDS, such as multiple sexual partners and long-term recreational drug use, have existed for many years. The epidemic of AIDS, characterized by the occurrence of formerly rare opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP) did not occur in this country until a previously unknown human retrovirus -- HIV -- spread through certain communities.

Compelling evidence against the hypothesis that behavioral factors cause AIDS comes from recent studies that have followed cohorts of homosexual men for long periods of time and found that only HIV-seropositive men develop AIDS.

For example, in a prospectively studied cohort in Vancouver, 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 seronegative men despite the fact that these men reported appreciable use of inhalable nitrites ("poppers") and other recreational drugs, and frequent receptive anal intercourse.

Other studies show that among homosexual men and injection drug users, the specific immune deficit that leads to AIDS -- a progressive and sustained loss of CD4+ T cells -- is extremely rare in the absence of other immunosuppressive conditions. In the Multicenter AIDS Cohort Study, more than 22,000 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.

In a survey of 229 HIV-seronegative injection drug users in New York City, mean CD4+ T cell counts of the group were consistently more than 1000 cells/mm<sup>3</sup>. Only two individuals had two CD4+ T cell measurements of less 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 another study, HIV-seronegative, long-term heroin addicts had mean CD4+ T cell counts of 1500/mm<sup>3</sup>, while eleven healthy controls had CD4+ counts of 820 cells/mm<sup>3</sup>.

**Myth:** *The AIDS epidemic has been compounded by immunosuppressive effects of the medication AZT.*

**Fact:** Placebo-controlled trials have found that AZT and related anti-HIV drugs can benefit patients by prolonging, for a year or two, the onset of new AIDS-related illnesses in HIV-infected individuals. Significantly, long-term follow-up of these trials, although not showing prolonged benefit of AZT, has never indicated that the drug increases disease progression or mortality. The lack of excess AIDS cases and death in the AZT arms of these trials effectively rebuts the argument that AZT causes AIDS.

In addition, many individuals who have never taken AZT or related drugs have developed AIDS, including people in the United States prior to the availability of AZT, and in Africa today where very few people receive AZT.

Several studies suggest that life expectancy of individuals with HIV disease has increased since the use of AZT became common. One cohort study found that the time from seroconversion to death, a period not influenced by variations in diagnosing AIDS, has lengthened slightly in recent years. Even taking into account 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 coincides with the use of AZT.

**Myth:** *AIDS among transfusion recipients is due to underlying diseases that necessitated the transfusion, rather than to HIV.*

**Fact:** This notion is contradicted by a report by the Transfusion Safety Study Group (TSSG), which compared HIV-negative and HIV-positive blood recipients who had been given transfusions for similar diseases. Approximately 3 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 count of 375/mm<sup>3</sup>. 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.

**Myth:** *Cumulative exposure to contaminants in Factor VIII leads to*

### *CD4+ depletion and AIDS in hemophiliacs.*

**Fact:** This view is contradicted by several large studies. For example, 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 52 with the largest amount of lifetime treatments. Patients in both groups had CD4+ T cell counts within the normal range. In another report from the Transfusion Safety Study, no instances of AIDS-defining illnesses were seen among 402 HIV-seronegative hemophiliacs who had received factor therapy.

**Myth:** *The distribution of AIDS cases casts doubt on HIV as the cause. Viruses are not gender-specific, yet fewer than 10 percent of people with AIDS are women.*

**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. In the United States, HIV first appeared in populations of homosexual men and injection drug users, a majority of whom are male. 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 in this country are becoming HIV-infected, usually through the exchange of HIV-contaminated needles or sex with an HIV-infected male. As the number of HIV-infected women has risen, so too has the number of female AIDS patients in the United States. AIDS is now the leading cause of death among adults aged 25 to 44 in the United States, and the fourth leading cause of death of women in that age group.

In Africa, HIV was first recognized in sexually active heterosexuals, and AIDS cases in Africa have occurred at least as frequently in women as in men. Overall, the worldwide distribution of HIV infection and AIDS between men and women is approximately 1 to 1.

**Myth:** *HIV cannot be the cause of AIDS because the body develops a vigorous antibody response to the virus.*

**Fact:** This reasoning ignores numerous examples of viruses other than HIV that can be pathogenic after evidence of immunity appears. Measles virus may persist for years in brain cells, eventually causing a chronic neurologic disease despite the presence of antibodies. Viruses such as cytomegalovirus, herpes simplex and varicella zoster may be activated after years of latency even in the presence of abundant antibodies. In animals, viral relatives of HIV with long and variable latency periods, such as visna virus in sheep, cause central nervous system damage even after the production of antibodies.

Also, HIV is well recognized as being able to mutate to avoid the ongoing immune response of the host.

**Myth:** *Only a small number of CD4+ T cells are infected by HIV, not enough to damage the immune system.*

**Fact:** New techniques such as the polymerase chain reaction have enabled scientists to demonstrate that a much larger proportion of CD4+ T cells are infected than previously realized, particularly in lymphoid tissues. Macrophages and other cell types are also infected with HIV and serve as reservoirs for the virus.

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; other data suggest that HIV infection is sustained by a dynamic process involving continuous rounds of new viral infection and rapid turnover of an estimated 2 billion CD4+ T cells daily.

**Myth:** *HIV is not the cause of AIDS because many individuals with HIV have not developed AIDS.*

**Fact:** HIV disease has a prolonged and variable course. The median period of time between infection with HIV and the onset of clinically apparent disease is approximately 10 years, according to prospective studies of homosexual men in which dates of seroconversion are known. Similar estimates of asymptomatic periods have been made for HIV-infected blood-transfusion recipients, injection drug users and adult hemophiliacs.

As with many diseases, a number of factors can influence the course of HIV disease. Factors such as age or genetic differences between individuals, the level of virulence of the individual strain of virus, as well as exogenous influences such as co-infection with other microbes may determine the rate and severity of HIV disease expression. Similarly, some 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. Co-factors probably also determine why some smokers develop lung cancer, while others do not.

**Myth:** *Some people have many symptoms associated with AIDS but do not have HIV infection.*

**Fact:** Most AIDS symptoms result from the development of opportunistic infections and cancers associated with severe immunosuppression secondary to HIV.

However, immunosuppression has many other potential causes. Individuals who take glucocorticoids and/or immunosuppressive drugs

to prevent transplant rejection or for autoimmune diseases can have increased susceptibility to unusual infections, as do individuals with certain genetic conditions, severe malnutrition and certain kinds of cancers. There is no evidence suggesting that the numbers of such cases have risen, while abundant epidemiologic evidence shows a staggering rise in cases of immunosuppression among individuals who share one characteristic: HIV infection.

**Myth:** *HIV does not fulfill Koch's postulates as the cause of AIDS.*

**Fact:** Koch's postulates, formulated before the discovery of viruses, stipulate that an infectious agent must be found in all cases of the disease, the agent must be isolated from the host's body, the agent must cause disease when injected into healthy hosts, and the same agent must once again be isolated from the newly diseased host.

Koch's postulates have been fulfilled with laboratory workers and health care workers accidentally exposed to HIV, and in cases of AIDS developing after HIV seroconversion in blood transfusion cases. The postulates have also been fulfilled in baboons inoculated with HIV-2 and in macaques exposed to SIV.

**Myth:** *AIDS is not exploding into the population as one would expect if caused by HIV, a new virus.*

**Fact:** HIV is spread by certain types of risk behavior and not by casual contact and is therefore not epidemic in the same way as influenza or the common cold. The more relevant issue is whether the spread of HIV and the appearance of AIDS correlate, and they do.

**Myth:** *The spectrum of AIDS-related infections seen in different populations proves that AIDS is actually many diseases not caused by HIV.*

**Fact:** The diseases associated with AIDS, such as PCP and *Mycobacterium avium* complex (MAC) are not caused by HIV but rather result from the immunosuppression caused by HIV disease. As the immune system of an HIV-infected individual weakens, he or she becomes susceptible to the particular viral, fungal and bacterial infections common in the community. For example, HIV-infected people in certain midwestern and mid-Atlantic regions are much more likely than people in New York City to develop histoplasmosis, which is caused by a fungus. A person in Africa is exposed to different pathogens than is an individual in an American city. Children may be exposed to different infectious agents than adults.

**Myth:** *There is no AIDS in Africa. AIDS is nothing more than a new name for old diseases.*

**Fact:** The diseases that have come to be associated with AIDS in Africa

-- such as wasting syndrome, 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.

In a recent study in rural Uganda, adolescents and young adults testing positive for HIV antibodies were 60 times more likely to die during the subsequent two-year observation period than otherwise similar persons who tested negative. In a study in Zaire, infants with HIV infection had an 11-fold increased risk of death from diarrhea compared with uninfected children. Elsewhere in Africa findings are similar.

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NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies and immunology.

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