

AIDS #175

SHORT REPORTS

HIV-1 and the aetiology of AIDS

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The belief that HIV-1 infection causes AIDS has been questioned, and the suggestion made that to know the correct cause of AIDS the incidence of disease in patients with and without risk behaviours and with and without antibody to HIV-1 must be known. We describe findings in such a cohort. In 715 homosexual men followed for a median of 8.6 years, all 136 AIDS cases occurred in the 365 individuals with pre-existing HIV-1 antibody. Most men negative for HIV-1 antibody reported risk behaviours but none developed any AIDS illnesses. CD4 counts fell in anti-HIV-1-positive men but remained stable in antibody-negative men, whether or not risk behaviours were present. The hypothesis that AIDS in homosexual men is caused not by HIV-1 infection but by drugs and sexual activity is rejected by these data. HIV-1 has an integral role in the pathogenesis of AIDS.

Lancet 1993; 341: 658-59.

Controversy continues to surround the question of whether human immunodeficiency virus 1 (HIV-1) infection causes the acquired immunodeficiency syndrome (AIDS).¹ The conventional hypothesis proposes that HIV-1 infection leads to depletion of CD4 cells and hence to progressive immune deficiency.² Some investigators have questioned this conventional "virus-AIDS" theory,³ proposing instead a "risk-AIDS" hypothesis. The latter hypothesis asserts that it is not HIV-1 infection per se but rather the risk behaviours associated with HIV-1 infection that cause disease.^{4,5} Duesberg has cited specifically chronic promiscuous male homosexual activity⁶ and the use of drugs—including nitrite inhalants^{7,8}—as exposure risks responsible for the epidemic of AIDS in homosexual men. He has stated that to identify the correct cause of AIDS the incidence of AIDS in controlled cohorts of risk-takers and non-risk-takers, with and without antibody to HIV-1, must be known, but that no such data are available.⁹ We present the results of just such a controlled study.

We have followed 715 homosexual men recruited from six general practices in central Vancouver.⁶ During recruitment from November, 1982, to February, 1984, any homosexual patient already enrolled in the practice who attended for any reason was asked by his doctor to participate in the study. The refusal rate was 5%. Follow-up visits occurred about once every six months until September, 1986, after which time subjects attended annually. During each visit, subjects completed a self-administered questionnaire concerning lifestyle and illness, underwent a complete physical examination, and had blood samples drawn for

weakness: drug use ever/never

immunologic and HIV-1 antibody testing.² Median duration of follow-up for all subjects was 8.6 years. As well as clinical follow-up, the British Columbia provincial and Canadian national AIDS registries were searched regularly from 1988 to identify any additional cases of AIDS in the entire cohort. Seroprevalent men (n = 237, 33%) were defined as those who were HIV-1-antibody positive when they entered the study, seroincident men (n = 128, 18%) as those who seroconverted while under study, and seronegative men (n = 350, 49%) as those who remained HIV-1-antibody negative at the most recent follow-up visit. The seroprevalent and seroincident groups combined are referred to as the seropositive group. All reported p values are two-sided.

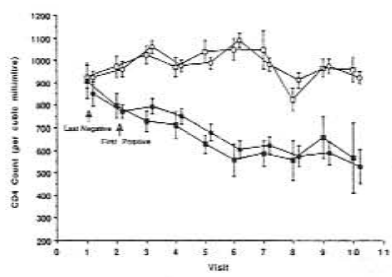
By April, 1992, 136 cases of AIDS-related illnesses had been diagnosed in our cohort. These illnesses included *Pneumocystis carinii* pneumonia (54), Kaposi's sarcoma (34), lymphoma (11), oesophageal candidiasis (8), *Mycobacterium avium-intracellulare* infection (7), cytomegalovirus infection (4), wasting syndrome (4), and other illnesses (14). Every case of AIDS-associated illness occurred in individuals with pre-existing HIV-1 antibody, and no AIDS illnesses occurred in men who remained persistently negative for HIV-1 antibody.* There were 101 AIDS-related deaths in the seropositive men. Excluding AIDS-related mortality, there were 6 deaths in the seropositive men: 2 cases of hepatitis, 1 lung cancer, 1 homicide, 1 suicide, and 1 drug overdose. In the seronegative group, there were only 2 deaths—1 myocardial infarction and 1 suicide—and no deaths due to any AIDS-related conditions.

To account for risk behaviours in our subjects, we undertook analyses involving use of nitrite inhalants (ever versus never) and illicit drugs (ever used cocaine, heroin, amphetamines, lysergic acid diethyl amide, or methylenedioxymethamphetamine), and increased frequency of receptive anal intercourse ($\geq 25\%$ of sexual encounters; this cut-off was chosen a priori to achieve an approximately equal division). Lifetime prevalences of these behaviours were similar in the 136 seropositive men who developed AIDS and in the 229 seropositive men who did not develop AIDS: use of nitrite inhalants, 88% in both groups; use of illicit drugs, 75% and 80%, respectively; and increased frequency of receptive anal intercourse, 78% and 82%, respectively. Since these risk behaviours are known to correlate to HIV-1 infection, it is not surprising that lifetime prevalences in the 350 seronegative men were lower than in the seropositive group—ie, 56%, 74%, and 58% for nitrite inhalants, illicit drugs, and increased frequency of receptive anal intercourse, respectively. However, risk behaviours were present at appreciable levels in the seronegative group without development of a single case of AIDS.

To corroborate absence of AIDS and associated effects in the seronegative group, we studied CD4 count as a measure of immune impairment. The seronegative group was compared with the seroincident group to allow observation of the entire natural history of HIV-1 infection

*A table showing AIDS-related illnesses in the three patients groups, a figure showing changes in CD4 count over ten follow-up visits in seroincident and seronegative patients, and figures showing changes in CD4 counts in seroincident and seronegative patients stratified by use of illicit drugs and the frequency of receptive anal intercourse are available on request from The Lancet.

88% sero pos/used nitrites vs. 56% neg. admitted



CD4 counts for seronegative and seroincident groups stratified by use of nitrite inhalants.

For the seronegative group, all visits are used, whereas for the seroincident group visits begin with the last anti-HIV-1-negative and first anti-HIV-1-positive results (arrows). Seronegative men who ever used (○) and never used (□) nitrite inhalants; seroincident men who ever used (●) and never used (■) nitrite inhalants. Points are mean (SE).

with control for the duration of infection. For the seroincident group, baseline was the time of the last seronegative test result and the final CD4 count was obtained from the ninth visit after seroconversion. The seroincident and seronegative groups were similar at baseline. The average rate of CD4 decline in the seroincident group, based on linear regression, was about 50 cells/μL per year (95% CI 39-61 cells/μL per year; p = 0.0001 for difference from zero), and the final mean CD4 count in the seroincident group was 547 cells/μL (n = 25; 414-680). By contrast, the average rate of CD4 decline in the seronegative group was not significantly different from zero (p = 0.73), with mean baseline and final CD4 counts of 921 (868-974) cells/μL and 937 (886-988) cells/μL, respectively.*

Stability of CD4 counts in anti-HIV-1-negative men and decline in counts in seroincident men were apparent whether or not nitrite inhalants were used (figure). A multiple regression model was fitted to explain final CD4 count in terms of the baseline CD4 count, serological group (seronegative or seroincident), and the use of nitrite inhalants. Baseline CD4 count and serological group were highly significant in explaining final CD4 count (p < 0.0001 in each case), but inhalant use was not significant (p = 0.21). Similar analyses of CD4 counts were done after stratification for use of illicit drugs and for frequency of receptive anal intercourse. In both cases, stable counts were found in the seronegative group and declining counts in the seroincident group, regardless of the presence or absence of the HIV-1 risk behaviour,* and multiple regression models showed both baseline CD4 count and the serological group to be highly significant in explaining the final CD4 count, but that risk behaviour was not significant.

The risk-AIDS hypothesis^{3,4} that AIDS in homosexual men is caused not by HIV-1 infection but by other exposures, such as drug use and male homosexual activity, is clearly rejected by our data. The evidence supports the hypothesis that HIV-1 has an integral role in the CD4 depletion and progressive immune dysfunction that characterise AIDS. A central role for HIV-1 in the pathogenesis of AIDS does not rule out a role for cofactors that might help to determine the clinical course in different

hosts. Whether these cofactors involve other microorganisms, genetic susceptibility, autoimmune processes, or other phenomena is currently the subject of debate and investigation. However, it is a disservice to the many people infected with HIV-1 and a hindrance to public health initiatives for scientists to claim that HIV-1 is harmless and not aetiologically related to AIDS.

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Magnetic resonance neurography

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Radiological methods exist for generating tissue-specific images of bone, vessels, lymphatics, abdominal viscera, and the central nervous system, but there has been no reliable means to generate a clinical image of a nerve. We present the first "image neurogram" and report a method for producing such images by use of commercial magnetic resonance imaging systems. The image depicts a human nerve in situ in relation with a nerve graft, wherein the nerve is rendered in isolation much like a vessel appears in isolation in a subtraction angiogram.

Lancet 1993; 341: 659-61.

Pain and loss of function due to neuropathy, nerve compression, and traumatic nerve injury prompt many millions of diagnostic tests every year. However, the surgical treatment of suspected nerve compression is often hindered, and is sometimes precluded, because the site of compression cannot be accurately localised. The cranial, peripheral, and autonomic nerves have remained the preserve of physical and electrical diagnosis because no imaging technique has so far proved adequate. Useful cross-sectional images of nerves cannot be made by computerised tomographic scanning.

How is AIDS defined in seronegative people?