Does drug use cause AIDS?

M. S. Ascher, H. W. Sheppard, W. Winkelstein Jr & E. Vittinghoff

A hypothesis identifying substance abuse as a main cause of AIDS has naturally excited much publicity. But such claims have no basis in fact.

SINCE 1987, Peter H. Duesberg, a professor of molecular biology at the University of California, Berkeley, has maintained that the human immunodeficiency virus (HIV) is not the infectious aetiological agent for AIDS (acquired immune deficiency syndrome)[1]. Responses to Duesberg have presented a strong case that HIV has a central role in AIDS pathogenesis[2,3]. Duesberg did not at first present a clear alternative hypothesis, but recently, based on an ecological analysis of drug use in the United States, he has proposed that "either drug consumption (frequently associated with malnutrition) by recently established behavioral groups or conventional clinical deficiencies and their treatments are necessary and sufficient to cause indicator diseases of AIDS"[4,5]. Because of the wide publicity attracted by this assertion, we decided to assess this hypothesis.

In the first case reports of AIDS in the United States, recreational drug use was considered as an aetiological factor[6]. Subsequently, an association between drug use, acquisition of HIV and development of AIDS has been extensively documented among those sharing needles for injecting drugs[7]. But the first major case-control study of AIDS in homosexual men showed no association between drug use and the development of AIDS[8]. Later, Kaslow and colleagues analysed data from more than 4,500 homosexual/bisexual men in the Multicenter AIDS Cohort Study (MACS) and found no association between the use of alcohol or other psychoactive drugs and HIV seroconversion or progression of HIV infection to AIDS[9]. Because amyl nitrite inhalants were thought to be aetiologically related to Kaposi's sarcoma[10], Lifson and colleagues compared the use of 10 psychoactive drugs in 72 incident cases of Kaposi's sarcoma with 109 incident AIDS cases without Kaposi's sarcoma from the well-characterized San Francisco City Clinic Cohort, and found no differences[11]. The most commonly used drugs were marijuana, nitrite inhalants, cocaine and amphetamines.

Direct test

To test Duesberg's drug-use hypothesis directly, we analysed data from a unique population-based cohort study, the San Francisco Men's Health Study (SFMHS)[12]. This study is based on a cohort of 1,034 single men 25–54 years of age at the time of recruitment (June–December 1984), selected by stratified, random, household sampling from neighbourhoods of San Francisco where the AIDS epidemic had been most intense before 1984. Participants were recruited without regard to sexual preference, lifestyle or HIV serostatus (not known at the time), and thus constitute a representative cross-section of men in this community. We believe that this sampling method is critical in the assessment of drug-use data, which can be strongly affected by recruitment bias.

Duesberg has stated[5] that there are no controlled studies of drug use and AIDS, and that previous studies "failed to match the HIV-free control group with the HIV positives for the extent and duration of drug consumption". We performed our study in part to respond to this criticism. We examined the cohort at 6-monthly intervals for 96 months, and obtained drug-use data and determined HIV serostatus at each examination. Data for the variables we considered were available from 1,027 study subjects.

We compared heavy drug use (weekly or more frequent use of the four recreational drugs mentioned above) for the 24-month period before entry into the study among 215 heterosexual and 812 homosexual/bisexual cohort members. Except for amyl nitrite, with 18% heavy use in homosexuals versus no heavy use among heterosexuals, the percentage of subjects reporting heavy use of each drug was similar in both sexual preference groups: 36 versus 39% for marijuana; 7 versus 4% for cocaine; and 1 versus 5% for amphetamines, respectively. During 96 months of follow-up, 215 cases of AIDS occurred among the homosexual/bisexual men (cumulative incidence, 26%) compared with none among the heterosexuals. If heavy use of marijuana, cocaine or amphetamines is casually associated with AIDS, a cumulative incidence of 56 (0.26×215) cases among the heterosexual subjects would be expected.

Survey results

Table 1 summarizes the cumulative incidence of AIDS and total mortality according to sexual preference and HIV serostatus on entry into the SFMHS. Of the 215 heterosexual men, none was HIV seropositive on entry and one seroconverted during the follow-up period. Among these men, no cases of AIDS and one death (0.5%) were recorded. Among the 812 homosexual/bisexual study subjects, 367 were HIV seronegative on entry and have remained so for 96 months. No cases of AIDS and seven deaths (2%) have been recorded among these men. Forty-five men seroconverted during the 96-month follow-up period. Among the seroconverters, eleven cases of AIDS (24%) and five deaths (11%) have been recorded. Among the 400 study subjects who were HIV seropositive on entry and throughout the follow-up period, 204 (51%) have developed AIDS and 169 (42%) have died.

Because Duesberg has specifically implicated amyl nitrite in the aetiology of Kaposi's sarcoma, we performed additional analyses to assess this relationship. As can be seen in Table 2, among the 144 homosexual/bisexual men who reported heavy use of amyl nitrite inhalants during the 24 months before study entry, 54 developed AIDS during the ensuing 96 months (cumulative incidence, 37.5%). Among the 668 homosexual/bisexual men reporting none or less than weekly use of amyl nitrite inhalants during the same time period, 161 developed AIDS in 96 months (cumulative incidence, 24%) for a relative risk of 1.56. This crude association is apparently the basis for Duesberg's hypothesis. Further analysis of the data reveals a similar association between

TABLE 1 Incidence of AIDS and death according to sexual preference and HIV serostatus

Sexual preference	Serostatus		AIDS cases		Deaths	
		n	*n*	%	*n*	%
Homo/bisexual	Negative	367	0	0.0	7	1.9
	Converted	45	11	24.4	5	11.1
	Positive	400	204	51.0	169	42.3
Heterosexual	Negative	214	0	0.0	1	0.5
	Converted	1	0	0.0	0	0.0
	Positive	0	0	0.0	0	0.0

TABLE 2 Effect of nitrite use on incidence of HIV, AIDS and Kaposi's sarcoma in homosexual/bisexual men

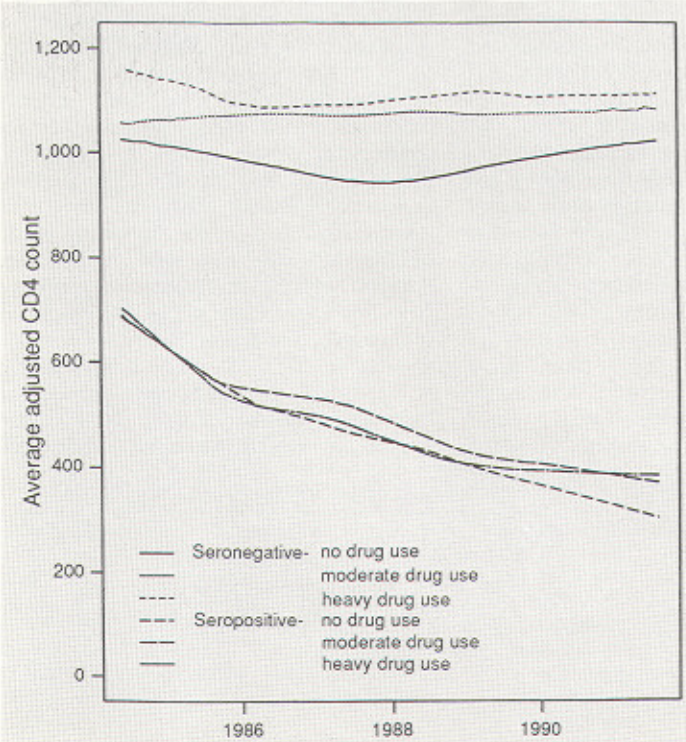
		AIDS cases		HIV positives		AIDS in HIV+		AIDS in HIV−		KS cases		KS in HIV+		KS in HIV−	
Nitrite Use	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Heavy	144	54	37.5	105	72.9	54	51.4	0	0.0	26	18.1	26	24.8	0	0.0
Light	668	161	24.1	340	50.9	161	47.4	0	0.0	66	9.9	66	19.4	0	0.0
Relative risk (conf. interval)		1.56 (1.21–2.01)		1.43 (1.26–1.63)		1.09 (0.87–1.36)		NA		1.83 (1.19–2.80)		1.28 (0.85–1.91)		NA	

drug use and HIV positivity, and when controlled for HIV serostatus, there is no overall effect of drug use on AIDS. A similar effect, a marginal association that drops after controlling for HIV serostatus, is seen in cases which end in Kaposi's sarcoma. Thus, when proper methods are used to assess the role of confounding variables, there is no evidence of a drug effect. In addition, we have performed a logistic analysis of the longitudinal drug-use data which shows no positive association between long-term or continued drug use and the development of AIDS.

AIDS definition

The clinical case definition for AIDS has been criticized as having subjective features and low specificity. We have attempted to circumvent this problem by assessing the effects of drug use on a more objective and, indeed, the primary pathognomonic feature of AIDS, $CD4^+$ T-lymphocyte depletion. The relationship between HIV serostatus, drug use during the 24 months before entry into the study, and CD4 cell levels is shown in the figure. A consistent loss of $CD4^+$ T lymphocytes is limited to HIV-seropositive subjects, among whom there is no discernible difference between the counts according to composite drug-use scores. The apparent flattening of the trajectories over time is due to the death of rapidly progressing HIV-seropositive subjects. Among HIV seronegatives, the $CD4^+$ T-lymphocyte count trajectories are essentially flat with slight but consistent differences between the drug-use groups. By contrast with Duesberg's hypothesis, moderate or heavy drug users have consistently higher counts than non-users, for unknown reasons. Taken together, these data do not support Duesberg's hypothesis that drug use causes AIDS.

Duesberg has argued repeatedly that studies of the associations of HIV infection, drug use and AIDS have been "uncontrolled". However, the population-based SFMHS provides a rigorously controlled epidemiological model for the evaluation of aetiological hypotheses. Duesberg has also argued that the case definition of AIDS is "circular" and that HIV-seronegative AIDS cases are exluded by definition. In the SFMHS, AIDS cases were diagnosed by the clinical criteria defined by the Centers for Disease Control (CDC), which are irrespective of HIV infection status. Incidentally, the CDC's criteria for defining AIDS do not require HIV positivity, provided that the CD4 count is less than 400 and the clinically defining conditions are not explainable by established aetiologies[13]. Furthermore, in the data presented here, mortality as well as AIDS incidence support the HIV aetiological hypothesis.



$CD4^+$ T-lymphocyte counts according to HIV serostatus and use of selected recreational drugs (see text) during 8 years' observation of the SFMHS. The drug use for each individual was scored as follows: no use, 0; less than monthly, 1; monthly, 2; weekly, 3; daily, 4. The composite score for each person is the sum of the scores for the four drugs (minimum score, 0; maximum score, 16). Three groups were defined with composite scores of 0 (no drugs use); 1–6 (moderate drug use); and ≥7 (heavy drug use).

Conclusions

The main purpose of the cohort studies conducted in San Francisco and elsewhere has been to look for associations of environmental or behavioural factors with the development of AIDS. Had any factor other than HIV infection been found, it would have been reported immediately. The fact that not every failure to find such associations has been reported does not undermine the well-established causal relationship between HIV and AIDS, particularly as it relates to prevention strategies.

The energies of Duesberg and his followers could better be applied to unravelling the enigmatic mechanism of the HIV pathogenesis of AIDS. To this end, we have proposed an alternative model[14,15] based on HIV signalling at CD4 cells. This model and others are now being evaluated, and we cordially invite Duesberg to participate in this endeavour. □

Michael S. Ascher and Haynes W. Sheppard are in the Viral and Rickettsial Disease Laboratory, California Department of Health Services, 2151 Berkeley Way, Berkeley, California 94704, USA. Warren Winkelstein Jr and Eric Vittinghoff are in the Department of Biomedical and Environmental Health Sciences, School of Public Health, University of California, Berkeley, California 94720, USA.*

*Author for correspondence.

1. Duesberg, P. H. *Cancer Res.* **47**, 1199–1220 (1987).
2. Weiss, R. & Jaffe, H. *Nature* **345**, 659–660 (1990).
3. Pinching, A. J. *et al. Nature* **347**, 328 (1990).
4. Duesberg, P. H. *Proc. natn. Acad. Sci. U.S.A.* **88**, 1575–1579 (1991).
5. Duesberg, P. H. *Pharmac. Theor.* **55**, 201–277 (1992).
6. Centres for Disease Control *Morbid. Mortal. Wkly Rpt* **30**, 250–252 (1981).
7. Friedland, G. in *The Epidemiology of AIDS* (eds Kaslow, R. A. & Francis, D. P.) 153–178 (Oxford University Press, 1989).
8. Jaffe, H. W. *et al. Ann. Intern. Med.* **99**, 145 (1983).
9. Kaslow, R. A. *et al. J. Am. med. Ass.* **261**, 3424 (1989).
10. Haverkos, H. W. in *Health Hazards of Nitrite Inhalants* (eds Haverkos, H. W. & Dougherty, J. A.) 96–105 (US Dept Health and Human Welfare Services, Washington, DC, 1988).
11. Lifson, A. R. *et al. Am. J. Epidemiol.* **131**, 221–231 (1990).
12. Winkelstein, W. Jr *et al. J. Am. med. Ass.* **257**, 321–325 (1987).
13. Centres for Disease Control *Morbid. Mortal. Wkly Rpt* **36**, 3S–15S (1987).
14. Ascher, M. S. & Sheppard, H. W. *J. AIDS* **3**, 177–191 (1990).
15. Sheppard, H. W. & Ascher, M. S. *J. AIDS* **5**, 143–147 (1992).