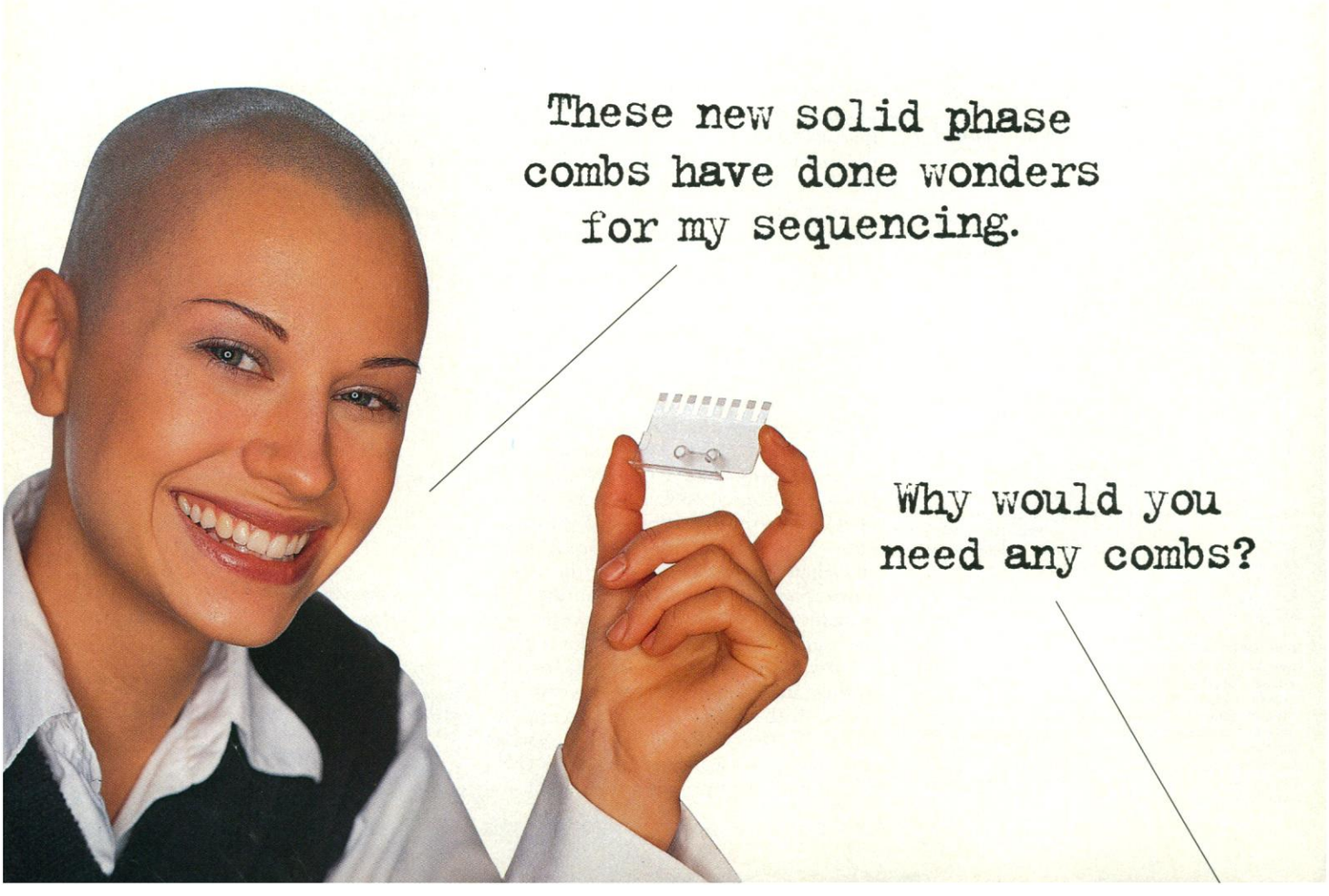
AIDS-Associated Kaposi's Sarcoma

We read with interest the report "Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma" by Y. Chang *et al.* (16 Dec., p. 1865), which presents evidence for a new human herpesvirus in Kaposi's sarcoma (KS) lesions. We hypothesized that if KS is caused by a herpesvirus, antiviral agents with activity against herpesviruses might also decrease the incidence of KS. To test this hypothesis, we examined data collected in the Adult/Adolescent Spectrum of Disease (ASD) project (*1*), a follow-up study of the medical records of persons 13 years old or older with human immunodeficiency virus (HIV) infection or with AIDS carried out in more than 100 medical facilities in 10 metropolitan areas in the United States. Since January 1990, medical records have been examined for HIV-related illnesses, medications, laboratory tests, and mortality at 6-month intervals. We analyzed ASD data from the first recorded $CD4^+$ T-lymphocyte count through the last date of follow-up or the date of diagnosis of KS using Cox proportional hazards regression (*2*) with time-dependent covariates. Patients with KS at the time the study was begun were excluded. Medications were recorded if they were prescribed at any time during a semester.

Of 20,228 persons meeting the study criteria, 1033 (5%) were diagnosed with KS, and 7717 (38%) were prescribed acyclovir, 1475 (7%) ganciclovir, and 320 (2%) foscarnet. The median follow-up time was 14 months (25th percentile, 6 months; 75th percentile, 26 months). In a model controlling for CD4 count, age, race, sex, exposure mode, other AIDS opportunistic illnesses, and antiretroviral treatment, the risk for KS was slightly increased with acyclovir [odds ratio (OR), 1.4; 95% confidence interval (CI), 1.2–1.5; $P < 0.001$)], minimally affected with ganciclovir (OR, 1.0; 95% CI, 0.8–1.3; $P = 0.8$), and decreased with foscarnet (OR, 0.3; 95% CI, 0.1–0.6; $P = 0.001$) (*3*). Results were similar when the analysis was restricted to men who have sex with men or when herpes simplex virus type 2 was included in the model. Interactions between the drugs and between the drugs and other covariates were not significant. However, because 91% of KS occurred among men who have sex with men, the power to detect the effect of antivirals in other subgroups was limited.

Of the three antiviral medications evaluated, only foscarnet was associated with a significant reduction in the risk for KS. Foscarnet works by interacting with the pyrophosphate binding sites on DNA polymerase; in contrast, acyclovir and ganciclovir work by competitively inhibiting the incorporation of deoxyguanosine triphosphate into DNA after phosphorylation (*4*). Therefore, foscarnet may have a greater effect because it works by a mechanism different from that of acyclovir or ganciclovir. It is also possible that a newly discovered herpesvirus might have a low sensitivity to acyclovir or be resistant to acyclovir because acyclovir is used frequently, and resistance to it is common among herpesviruses (*5*).

Our study was limited in that we only have information on the semesters in which medications were prescribed, not the actual dates, and we were unable to assess compliance in taking medications. We also did not evaluate how the use of antiviral agents such as foscarnet might affect the course of KS. However, a recent report indicated that KS improved in three of five patients with the use of foscarnet (*6*). While it is known that foscarnet has some antiviral activity against HIV (*7*), it is doubtful that the activity against HIV alone could account for the reduced risk of KS, as other antiretroviral medications (AZT or DDI or DDC, or any combination of these drugs) were



included as one covariate in our analysis and did not decrease the risk for KS.

Nevertheless, these data from a large population of persons with HIV infection and AIDS suggest a reduced risk of KS associated with foscarnet use. The association of a decreased risk of KS with the use of an antiviral medication active against herpesviruses lends support to the laboratory findings of Chang *et al.* Although it is premature to suggest that foscarnet be used to reduce the risk of KS in HIV-infected persons, we hope others will evaluate the relation between antiviral medications and KS while scientific inquiry into the proposed new herpesvirus proceeds.

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References and Notes

1. K. M. Farizo *et al.*, *J. Am. Med. Assoc.* **267**, 1798 (1992).
2. D. R. Cox, *Analysis of Survival Data* (Chapman and Hall, London, 1984). Each of the antiherpesviral drugs was included as a separate variable so that the independent risk for KS could be obtained for each drug. The amount of time on each drug was also included in the calculation (time-dependent covariates).
3. The odds ratios estimate the risk for KS among persons prescribed the medication (acyclovir, ganciclovir, or foscarnet) compared to the risk for KS among those persons not prescribed the medication.
4. R. G. Douglas Jr., in *The Pharmacological Basis of Therapeutics*, A. G. Gilman, T. W. Rall, A. S. Nies, P. Taylor, Eds. (Pergamon, New York, ed. 8, 1990), pp. 1182–1201.
5. H. H. Balfour *et al.*, *J. Acquired Immune Defic. Syndr.* **7**, 254 (1994); S. Safrin, T. Elbeik, J. Mills, *J. Infect. Dis.* **169**, 879 (1994).
6. L. Morefeldt and J. Torsander, *Scand. J. Infect. Dis.* **26**, 749 (1994).
7. E. G. Sandstrom, J. C. Kaplan, R. E. Byington, H. S. Hirsch, *Lancet* **i**, 1480 (1985).

Response: The interventional data of Jones and his co-workers is important and adds significantly to a growing body of evidence suggesting that KS is caused by a newly discovered human herpesvirus. We encourage other scientists to review existing data sets to confirm the ASD data on foscarnet, which may allow rational design of future clinical trials for currently licensed drugs. As Jones and his co-authors suggest, our data and the data from the ASD project should be cautiously interpreted by physicians and patients. Not only are additional studies needed to establish the cause of KS, but some antiherpesviral drugs have significant side effects. These retrospective studies were not designed to specifically evaluate foscarnet or other antiherpesviral drugs in preventing or treating KS. Clinical trials will be needed to optimize new therapies for KS and minimize coincident toxicities regardless of the cause of KS. Foscarnet has wide antiviral activity, but we agree with Jones *et al.* that it is unlikely that their findings result from its antiretroviral activity.

The convoluted logic of Duesberg (Letters, 20 Jan., p. 313) suggesting that our findings (Y. Chang *et al.*, Reports, 16 Dec., p. 1865) support his hypothesis that HIV is not the cause of AIDS escapes us. There are no data which in any way support an alternative contention that this herpesvirus may be a cause of AIDS. We appreciate the thought, but will leave the discovery of the cause of AIDS to others. If one assumes that KS is caused by a herpesvirus that may be transmitted both sexually and nonsexually, continued safe sex practices by both HIV-positive and -negative individuals may limit the spread of this agent as well as that of HIV.

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In his rebuttal of 20 January to Jon Cohen's articles about the "Duesberg phenomenon" (Special News Report, 9 Dec., p. 1642), Duesberg misrepresents data from the San Francisco Men's Health Study (SFMHS) cited by us. Duesberg asserts that all of the AIDS cases occurring in the reported 96-month follow-up of the SFMHS cohort "had used poppers in addition to other recreational drugs. . . ," implying a causal role for the drug. In fact, we reported that of these 215 patients (not 213 as stated by Duesberg), 54 had a history of "heavy" popper use, weekly or more often, during the 2 years before they entered the study, and 161 had a history of "light" use, defined as no use or less than weekly. There were 27 nonusers of poppers among the 161. With respect to other recreational drugs, 36% of homosexual men in the cohort reported heavy use, as defined above, of marijuana, 7% reported heavy use of cocaine, and 1% reported heavy use of amphetamines.

Duesberg also says that our commentary included data that can be interpreted as supportive of a causal role for AZT use in AIDS. Although we made no mention of AZT (*1*), relevant data from the SFMHS are available. Among 233 AIDS patients, 169 (73%) had been treated with AZT at one time or another. However, 90 (53% of the 169) had received their AIDS diagnosis before beginning AZT treatment, and another 51 (30% of the 169) had $CD4^+$ lymphocyte counts of less than 300 cells per microliter before initiation of AZT treatment. These data are not consistent with the hypothesis of a causal role for AZT in AIDS.

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Fungicide Regulation and Food Safety

I take exception to Philip H. Abelson's editorial (25 Nov., p. 1303) about the Environmental Protection Agency's (EPA's) proposed settlement of a lawsuit with Natural Resources Defense Council, the State of California, and others over the EPA's implementation of the anticancer Delaney clause. Abelson cites the settlement as an immediate cause for concern that could lead to the "banning of fungicides" and eventually to "food scarcities." It will not.

While the settlement commits EPA to decide about the applicability of the Delaney clause, as the law requires, it does not require that we ban any pesticides. It addresses only the use of certain carcinogenic pesticides—those that are applied directly to processed food or that appear to concentrate when raw food is processed.

Abelson says that distribution of the widely used fungicide captan "is slated eventually to cease." In fact, of its more than 50 uses, only three—application to grapes, tomatoes, and plums—would be covered by the settlement; and EPA may conclude that the Delaney clause does not affect them. Similarly, his forecast of drastic cuts in production of fruits and vegetables