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Progression to AIDS

M. Smith *et al.* (1) suggest that failure to observe an association between the chemokine receptor mutation CCR2-64I and delayed progression to AIDS or death in seroprevalent [HIV-1 (human immunodeficiency virus-1) seropositive at enrollment] cohorts (2) could be the result of imprecision in estimating the date of seroconversion, resulting in a masking

of the protective effects of the genotype. We present evidence that biased exclusion of more rapid progressors to disease among seroprevalent cohorts would contribute to limited discrimination for such cohorts.

The Hemophilia Growth and Development Study (HGDS) has contributed data for studies of CCR2 conducted by the Laboratory of Genomic Diversity at the National Cancer Institute (NCI). The HGDS is a "seroprevalent" cohort, with most HIV+ participants ($n = 207$) exposed during a narrow window between 1982 and 1983. Participants were enrolled in the study in 1989 and 1990, a mean of 6.7 years after infection. In June 1992, centers began shipping fresh whole blood to NCI for the development of lymphoblastoid B-cell lines, the source of the DNA used to classify genotype. Cryopreserved cells were used to prepare cell lines for participants who had died or had dropped out of the study before June 1992. Cell lines were successfully developed for 90% of the cohort.

The characteristics of participants missing from an analysis are at least as important as those who are included (3). Missing a cell line occurred more frequently in the HIV+ than in the HIV- cohort (15% versus 2%), and missing a cell line was associated with increased severity of HIV disease. The median

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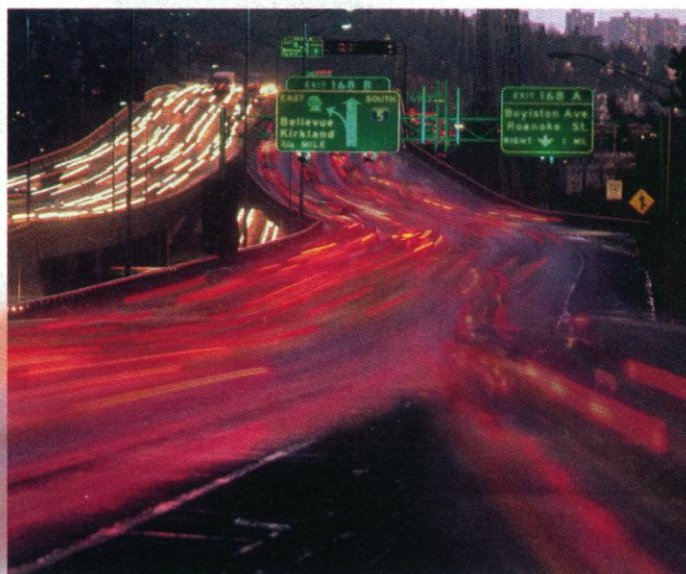


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baseline CD4+ count for those with cell lines was 458 per cubic millimeter compared with 27 per cubic millimeter for those without; the median HIV RNA was 2935 copies per milliliter compared with 8896 copies per milliliter in the same respective groups. Seventy-five percent of participants with no cell lines were diagnosed with AIDS by their 6-year follow-up, and mortality in those without cell lines was 2.7 times higher than in those with cell lines. Absence of a cell line precluded genotyping and inclusion in analyses. To explore the effect missing data might have on results presented in table 1 of the paper by Smith *et al.*, we performed regression imputation (4) to predict missing genotypes for HGDS study participants. Before imputation, there was no association between the genotype for CCR2 and disease progression. After imputation, there was a significant association between the genotype for CCR2 and progression to AIDS-1987 (relative hazard, 3.2, $P = 0.05$) and death (relative hazard 2.9, $P = 0.04$).

We conclude that incomplete genotyping, biased to exclude rapid progressors to AIDS, may have reduced the statistical power contributed from a seroprevalent cohort for Smith *et al.*'s investigation. These findings are likely to apply to other seroprevalent cohorts (1, 2). We believe that by offering a

plausible explanation for why the associations were not seen in a seroprevalent cohort, we strengthen the conclusions reported by Smith *et al.* (1) in their investigation of the association between the genotype for CCR2 and HIV disease progression among participants who were under study at the time of seroconversion and whose dates of HIV-1 infection were more precisely known.

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Response: Donfield, Lynn, and Hilgartner make and provide data to support an excellent point: that seroprevalent AIDS cohorts, particularly those with a delay between likely infection and enrollment dates (such as hemophiliac AIDS studies begun in the late

1980s, several years after HIV screening of blood supplies was introduced) will be depleted of rapid progressors to AIDS. This aspect, as well as uncertainty in the date of seroconversion (M. W. Smith *et al.*, Reports, 15 Aug., p. 959) (1), likely would account for a lack of detection of gene variants that influence AIDS pathogenesis in seroprevalent cohorts (1, 2), even if these effects are seen in seroincident (seroconverter) cohorts. The affirmation of the CCR2-64I protection against rapid progression to AIDS in several seroconverter cohorts (1), but not in seroprevalent cohorts (2, 3), is consistent with this point.

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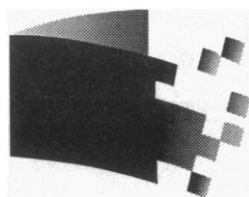
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