MARKERS OF RISK IN HIV-1

To the Editor: Fahey et al. (Jan. 18 issue)[1] evaluated the usefulness of several serologic and cellular measures of immunity in predicting the onset of the acquired immunodeficiency syndrome (AIDS), using data on homosexual men infected with the human immunodeficiency virus (HIV) in the Multicenter AIDS Cohort Study (MACS). Because studies of prevalently positive subjects are potentially biased,[2] we report complementary data from a cohort with incident (i.e., dated) HIV infections followed annually for eight years.

Of 131 HIV-1–seropositive homosexual men evaluated approximately annually since 1982,[3] 48 had AIDS by the end of 1988. The dates of seroconversion (the midpoint between the last negative and first positive samples) were available for 47 of the 131 men. For the 84 men already infected at the outset of the study, the seroconversion dates were estimated by the method of back-calculation to regional norms, according to which the men in New York were found on average to have seroconverted in June 1980, and those in Washington in June 1981.[4] To check the reliability of this approach, we examined the annual and cumulative rates of AIDS incidence, using these derived seroconversion dates, and found them virtually identical to those with midpoint seroconversion dates.[5]

We evaluated the risk of AIDS on the basis of the proportion of CD4+ lymphocytes as determined by flow cytometry with OKT4 reagent (Ortho Diagnostics, Raritan, N.J.) and the serum levels of neopterin (Neopterin RIAcid, Henning-Berlin, Federal Republic of Germany) and β_2-microglobulin (Beta-2-micro, RIA, Pharmacia, Uppsala, Sweden). The levels of β_2-microglobulin and neopterin were more highly correlated (Spearman $r = 0.74$) than in the MACS results. When the test results in the first year after seroconversion were used, the incidence of AIDS at five years was strongly predicted by the proportion of CD4+ lymphocytes alone ($P = 0.001$): 15 of 29 men (52 percent) with a proportion of CD4+ lymphocytes below 25 percent had AIDS, as compared with 10 of 39 men (26 percent) who had a proportion of CD4+ lymphocytes from 25 to 35 percent and none of 12 men in whom this proportion was above 35 percent. The five-year rates of AIDS were also increased for those with high levels of β_2-microglobulin (>3 mg per liter; $P = 0.01$) or neopterin (>15 nmol per liter; $P = 0.02$) in the first year after seroconversion. When a time-dependent covariate analysis[5,6] was conducted, with the measurements grouped by terciles, the most predictive markers 2 to 12 months before the onset of AIDS were the combination of the proportion of CD4+ lymphocytes and the level of β_2-microglobulin (relative hazard of AIDS, 8.0) or the level of β_2-microglobulin alone (relative hazard, 5.0). AIDS was predicted two to three years before diagnosis by combined testing for the proportion of CD4+ lymphocytes plus either the β_2-microglobulin or the neopterin level (relative hazard, 3.2 for each combination).

We conclude that serum levels of β_2-microglobulin and neopterin may contribute to a more reliable prediction of AIDS risk than the proportion of CD4+ lymphocytes alone. Such information can help guide the frequency of immunologic monitoring and direct effective forms of therapy such as zidovudine to those at highest risk. Moreover, the highest AIDS rates were in subjects who had seroconversions associated with marked declines in the proportion of CD4+ lymphocytes and marked elevations in the β_2-microglobulin and neopterin levels. Understanding the pathogenesis of immunologically severe HIV seroconversions may provide therapeutic opportunities to reduce the risk of AIDS further.

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