Predicting AIDS Onset for Individual Patients

Today’s physician may be confronted with a modern dilemma—the need to apply accumulating research information regarding markers predictive of acquired immunodeficiency syndrome (AIDS) to an individual patient who is infected with human immunodeficiency virus (HIV). Every physician would like to have precise estimates of risk to guide the choice of therapy and to allow him or her to concentrate on the treatment of the patient and on the psychosocial complications of HIV infection.

Many studies have shown that AIDS risk is inversely related to CD4+ lymphocyte count (1–8). This fact partly justifies current recommendations to use prophylaxis with aerosolized pentamidine for Pneumocystis carinii pneumonia (9) in persons with CD4+ counts <200 cells/μL and to begin treatment with zidovudine (AZT) to reduce AIDS incidence in persons with counts <500 cells/μL (10–13). Following up early interest in serological markers (14–16), recent work has shown that AIDS risk for many (5, 6, 17–20) but not all (8) cohorts can be predicted more precisely by measuring not only CD4+ lymphocyte count but also the concentration of β2-microglobulin, neopterin, or interferon in serum. Improved risk models not only are helpful for managing individual patients, but also can be used to form homogeneous strata to increase the power of clinical trials. The work of Reibnegger et al. (21), reported in the March issue of Clinical Chemistry, not only showed that neopterin adds useful prognostic information to CD4+ counts but also presented a model that predicts absolute risk.

Reibnegger et al. (21) reported the development of a statistical model for predicting individualized probabilities of developing AIDS over a 4.5-year follow-up period, based on initial CD4+ lymphocyte counts and neopterin concentrations in a cohort of 68 HIV-infected homosexual men. Their statistical model implies that the probability of disease in time interval t (t = 1, 2, . . . , 9, corresponding to successive half-year intervals), conditional on being at risk at the beginning of interval t, is

\[
P(t) = \frac{\exp(\mu + at + \beta_1 \times CD4 + \beta_2 \times Neopt)}{1 + \exp(\mu + at + \beta_1 \times CD4 + \beta_2 \times Neopt)}
\]  

(1)

where (from model 5, their Table 2) \( \mu = -4.5459 \), \( \alpha = 0.29596 \), \( \beta_1 = -0.00354 \), and \( \beta_2 = 0.00325 \). The quantity \( P(t) \) is a hazard for this discrete probability model. The hazard \( P(t) \) in model 1 (above) increases almost exponentially in \( t \), because the denominator is near unity for small \( P(t) \). For example, for an individual with an initial CD4+ lymphocyte count of 480 cells/μL and a neopterin concentration of 307 μmol/mol creatinine (the population median values), the semi-annual hazard \( P(t) \) is 0.013 at year 1 (\( t = 3 \), 0.023 at year 2 (\( t = 5 \), 0.040 at year 3, 0.070 at year 4, 0.120 at year 5, and 0.198 at year 6. Note that the hazard in each semester increases very rapidly, and that \( t \) represents the time since the patient was first examined rather than the time from HIV infection.

An important feature of model 1 is that the hazard \( P(t) \) has the same dependence on CD4+ lymphocyte count and neopterin concentration for all times \( t \). This assumption was tested by adding interaction terms to the model. For small values of \( P(t) \), model 1 essentially reduces to the proportional hazards model of Cox (22), and similar estimates of \( \beta_1 \) and \( \beta_2 \) would probably be obtained by using the Cox model with hazard proportional to \( \exp(\beta_1 \times CD4 + \beta_2 \times Neopt) \).

It is of interest to compare model 1 with other studies of the effects of markers and of the incubation distribution. Studies of cohorts of persons with hemophilia and homosexual men, whose dates of seroconversion can be estimated from stored sera, indicate that the hazard of AIDS increases as a power of the time, \( w \), since seroconversion. Brookmeyer and Goedert (23) estimated the hazard function for hemophilic subjects, measured in years from seroconversion, as 0.0053 \( w^{5.16} \) (corresponding to a Weibull incubation distribution), and Hessol et al. (24) and Bacchetti and Moss (25) found a similar rate of increase for the hazard function. Some studies (25, 26) suggest the hazard rate may increase less rapidly after eight years after HIV seroconversion. Thus, although model 1 may provide an adequate description of risk for three or four years, it may seriously overestimate risk in the longer term. In the previous example, the semi-annual hazard for a typical cohort member at year 5 (0.120 by model 1) exceeds observed semi-annual hazard rates considerably. The Weibull model of Brookmeyer and Goedert would predict half-year chances of AIDS of 0.032 at year 5, 0.042 at year 6, 0.052 at year 7, and 0.063 at year 8. Thus, even if one supposed that the population studied by Reibnegger et al. (21) had been infected two years before entry into the study, the nearly exponential increase in hazard implied by model 1 would seem to be too fast. It might be interesting to see whether model 1 would be in better accord with the literature on the incubation distribution if, instead of \( t \), \( \log(t + 4) \) were the independent variable. This would imply that the hazard increased approximately as a power of \( t + 4 \), where the number 4 represents an average of two years (four semesters) from seroconversion to entry in the cohort.

Reibnegger et al. (21) suggest that their model can be modified for application to an individual from some other cohort, simply by using information on the prior odds of disease. This amounts to adjusting the intercept term in model 1 and might be applicable, for example, to young hemophilic patients with HIV infection, who
have a lower hazard than older patients (2, 4). Although such an adjustment may work well for cohorts for whom the distributions of previous times since seroconversion are similar to the distribution in the cohort studied by Reibnegger et al. (21), it is an inherent difficulty of modeling cohorts of individuals with unknown dates of seroconversion ("prevalent cohorts") that the results may not be generalizable to cohorts with different distributions of times from seroconversion. Thus, it will be necessary to validate the concept that simple adjustment of the intercept allows model 1 to be applied reliably in other populations.

Although risk models of the natural history of AIDS are useful for epidemiologic investigations, for designing clinical trials, and for deciding when to begin antiviral or prophylactic therapy, effective treatments have reduced the probability of developing AIDS and may even have improved AIDS incidence trends in the United States (27). Thus, models of the "natural history" do not apply once a patient has been started on therapy with a drug such as zidovudine. Models for estimating AIDS risk in treated patients need to be developed. Meanwhile, the work of Reibnegger et al. contributes to the development of risk models for patient management and for use in clinical trials.

References

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