The use of surrogate markers in the antiretroviral treatment of HIV-1 infection

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CHAPTER 5

Prediction of progression to AIDS with serum HIV-1 RNA and CD4 count.
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SIR-Rates of HIV-1 disease progression vary widely between individuals who are positive for HIV-1 antibody. CD4 count is currently the principal marker used to assess risk of progression to AIDS. Most patients presenting with AIDS-defining conditions have CD4 counts under 200/μL. However, a subset of patients with low CD4 counts remains free of clinical symptoms and signs of AIDS over long periods. We have developed a PCR-based method for the quantification of serum HIV-1 RNA load (qRNA)\(^1\). The assay measures the number of virions with RNA within intact HIV-1 envelope and the measures of viral load obtained from this assay have a direct numerical relation with results from plasma virus culture.\(^2\) Because of its specific nature the assay gives values 100 to 1000 times lower than more recently developed commercial assays. We have used this technology to evaluate the predictive value of qRNA for HIV-1 disease progression relative to that of CD4 count and other indirect virological markers.

Commencing in 1992, qRNA, CD4 counts, and other indirect virological markers were evaluated at baseline for 104 patients who had been recruited for a dose-ranging study of lamivudine.\(^3\) Final analysis was carried out on 85 of 104 patients with complete data for CD4 counts, qRNA, and clinical follow-up. These patients had a mean baseline CD4 count of 236/μL (range 10-495) and a mean baseline qRNA of 890 RNA copies/mL (range 10-128000). The mean follow-up time after the baseline visit was 713 days (range 17-1031). During this time 16 of 85 patients progressed to AIDS. Analysis with Cox proportional hazard rates modelling showed that low CD4 counts and high levels of qRNA were strongly associated with progression to AIDS (chi-square 17.6, \(p=0.0018\); and 21.6, \(p=0.001\)). By contrast, p24 antigen, immune complex dissociated p24 antigen, and beta-2-microglobulin were not predictive of progression in this cohort study (chi-square <2.0 for each marker). The combination of CD4 count and qRNA provided the most powerful prediction of progression to AIDS (chi-square 29.9, \(p<0.0001\)) and this could not be improved by incorporation of the other markers.
Figure: Comparison of individual serum qRNA and CD4 values in 85 patients.

Patients who progressed to AIDS (**) a mean of 713 days from baseline are clustered in or near quadrant defined by CD4 counts <200/µL and serum qRNA >500 HIV-1 RNA copies/mL (latter value represents lower limit defined by our assay for 92 patients with AIDS-unpublished data)
0=non-progressors. Serum HIV-1 RNA load expressed as log_{10} copies/mL such that 1=10 copies/mL, 2=100 copies/mL, 3=1000 copies/mL, &c.

Comparison of individual patients at baseline (figure) showed that those progressing to AIDS during a mean follow-up of about 2 years were already clustered in a quadrant defined by CD4 counts under 200/µL and serum qRNA over 500 copies/mL. 14 of 16 patients (87.5%) who progressed to AIDS had baseline values for CD4 and qRNA in this quadrant, and of the 29 patients in this quadrant 14 progressed (48%).

These data suggest that the combination of serum qRNA and CD4 counts may be used to distinguish the majority of patients at high risk of progression to AIDS within 2 years, and these patients could be targeted for early antiretroviral therapy and prophylaxis against opportunistic infections. These findings need to be confirmed in other cohort studies; this cohort will be followed further to determine from which quadrant the future progressions will be derived.

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