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## Relation between humoral responses to HIV gag and env proteins at seroconversion and clinical outcome of HIV infection

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### Abstract

**Objective**—To study the contribution of the humoral response to HIV-I at seroconversion to disease outcome after 84 months.

**Design**—A retrospective longitudinal study.

**Setting**—Two haemophilia centres in the United Kingdom.

**Patients**—88 Haemophiliac patients infected with HIV-I for whom sera were available from before seroconversion and in whom clinical follow up data were available.

**Results**—Kaplan-Meier survival analysis showed a significant difference between a high titre (>1600) p24 antibody response at seroconversion and prolonged time before the development of HIV related disease ( $p=0.0008$ ). In contrast, higher titres of antibody to gp120 at seroconversion (>25 600) correlated with more rapid clinical deterioration ( $p=0.025$ ).

**Conclusions**—The first humoral response to HIV proteins at seroconversion is associated with clinical outcome; patients with an initial low titre antibody response to the gagp24 protein have a significantly faster rate of progression to CDC stage IV disease. Patients with a high titre p24 antibody response progress to AIDS more slowly, and these data provide an explanation why p24 antigenaemia is not universally detected in patients with AIDS. It is unclear whether the association between a strong initial p24 antibody response and slower progression of HIV disease is causal and if so whether it is due to viral or host factors.

### Introduction

After infection with HIV-I there is a vigorous humoral response to structural and regulatory viral antigens.<sup>1-8</sup> Antibodies to the env gene products

gp160/gp120 and gp41 are produced early followed shortly by antibodies to the gag gene product p24.<sup>9-10</sup> By studying sequential serum samples from infected patients we and other investigators have found that there is an apparent lowering of titre of p24 (gag) antibodies in patients with more rapid progression to HIV related disease (AIDS related complex and AIDS)<sup>11-17</sup> whereas no such change is seen with gp41 (env) antibodies.

Subsequently, it has been repeatedly shown that 50-70% of patients with AIDS have detectable titres of serum p24 antigen whereas only rarely is p24 antigen detectable in asymptomatic patients<sup>18-21</sup>; detection of p24 antigen before symptomatic disease correlated significantly with prognosis over 27 months.<sup>19</sup> The loss of antibody precedes p24 antigenaemia by 12-18 months,<sup>22</sup> and this has been interpreted as being due to the formation of immune complexes of p24 antibodies with rising concentrations of p24 antigen.<sup>23-24</sup> We have recently shown, however, that undetectable titres of p24 antibodies in antigenaemic patients do not rise after the reduction of p24 antigen titre with zidovudine treatment<sup>25</sup>; this suggests that the mechanism for the decline in titre of p24 antibody is unlikely to be the simple formation of immune complexes. Cohort data have shown that over time increasing numbers of patients with preserved high titres of p24 antibody and without detectable titres of p24 antigen develop AIDS, and the association of loss of p24 antibodies with prognosis becomes less significant (unpublished data).<sup>25</sup> No explanation has yet been offered for these findings or for the failure to detect viral antigens in 30-50% of patients with AIDS, even when plasma viraemia can be readily detected.<sup>26-27</sup> As the presence of p24 antigen has been used as a surrogate marker of virus replication these data require elucidation.

We thus studied the role of the first humoral response to HIV gag, env proteins at seroconversion

in relation to disease outcome and to provide an explanation for the pattern of p24 (gag) antibody and antigen over time.

## Methods

**Patients**—Two cohorts of haemophilic patients from Hammersmith Hospital (n=19) and the Treloar Haemophilia Centre at the Lord Mayor Treloar College (n=69) were studied. All haemophilic patients attending the centres who had been infected with HIV-I between 1979 and 1985 were included if serial serum samples were available through seroconversion and clinical follow up data were available. Thus 35 patients were excluded because they joined the centres after seroconversion to HIV-I and 17 were lost to follow up. Serial serum samples from eligible patients had been stored at  $-20^{\circ}\text{C}$  since venesection. Patients were categorised by the Centers for Disease Control (CDC) clinical classification system<sup>28</sup> into those who remained asymptomatic (stage II) or with persistent generalised lymphadenopathy alone (stage III) and all those who had progressed to symptomatic disease, AIDS related complex (stages IVa, IVc2, and IVe), and AIDS (stages IVb, IVc1, and IVd). At the time of analysis (October 1989) 22 patients had progressed to stage IV disease, and the remaining 66 had remained in stage II or III.

**Serology**—Longitudinal serum samples from each patient were initially screened with a direct enzyme linked immunosorbent assay (ELISA) (DuPont); this uses the direct coating of the env9 recombinant envelope protein on the solid phase with antihuman IgG conjugated with alkaline phosphatase as the

detector. Seroconversion was defined as the first positive serum sample in the assay performed according to the manufacturer's instructions. The samples had been taken at roughly three monthly intervals, and so the date of seroconversion could be ascertained to within 12 weeks in all cases.

**Antigens used in quantitative serology on recombinant HIV antigens**—Recombinant env(gp120) was a fully glycosylated CD4 binding protein made in Chinese hamster ovary cells (Celltech) and made available through the AIDS directed programme. The p24 protein was a  $\beta$ -galactosidase fusion protein expressed in *Escherichia coli* and derived from the HIV-I(CBL-1) isolate. The recombinant nef(p27) was expressed in *E. coli* and based on the HIV-I(BRU) sequence. The specific direct ELISA immunoassays using these recombinant antigens have been described in detail previously.<sup>29</sup> The specificity of these assays was first assessed using a panel of 300 HIV negative sera; eight HIV negative control sera were included on each enzyme immunoassay plate and the cut off calculated as the mean optical density at 492 nm of the negative sera plus three standard deviations. Sera were considered positive if the test optical density was higher than the relative threshold value for that plate.

**p24 antigen assay**—The commercial p24 antigen assay (DuPont) was used throughout the study according to the manufacturer's instructions.

**Statistical analysis**—The effect of titre of env(gp120), gag(p24), and nef(p27) antibodies at the first sero-positive serum after infection with HIV on the time to progression of members of the cohort to AIDS and AIDS related diseases (stage IV) was assessed by Kaplan-Meier survival analysis. The significance of difference in time to progression from asymptomatic to stage IV disease was tested by the log rank test with  $\chi^2$  approximation. The significance of differences in titres of the first antibody responses was assessed by the Mann-Whitney U test.

## Results

The pattern of the antibody response to the gag, env, and nef proteins for the whole cohort over the follow up period is shown in figures 1a-c. Patients who progressed to stage IV disease over this period differed from those who remained asymptomatic in the pattern of p24(gag) antibody titres (fig 1a) from the first measurement and subsequently but not in p27(nef) antibody titres (fig 1c); the gp120(env) antibody titres discriminated only at the first measurement (fig 1b). The first positive sera at seroconversion were therefore analysed in greater detail. Figure 2 shows the median and range of the titres of p24(gag), gp120(env), and p27(nef) antibodies for the first positive serum sample after seroconversion from each of the 88 patients in the cohort; values are shown for the 66 patients maintaining stage II or III disease compared with the 22 progressing to stage IV disease. Those maintaining stage II or III disease had a median p24 antibody titre of 1600 and those progressing to stage IV disease had a median of 200 ( $p=0.0008$ ). Higher titres of gp120 antibody at seroconversion were associated with progression to stage IV disease (median=51 200) compared with maintaining stage II or III disease (median=12 800,  $p=0.01$ ). In contrast, there was no discrimination in terms of disease outcome in the p27 assays ( $p=0.13$ ). The median values of the antibody titrations were calculated for the sera of the two cohorts together and used as the cut off for the comparison of patients with high and low titre responses in the survival analysis; there was no difference in the time between the last negative and first positive sera in the two groups.

The prevalence of p24 antigenaemia at any time after

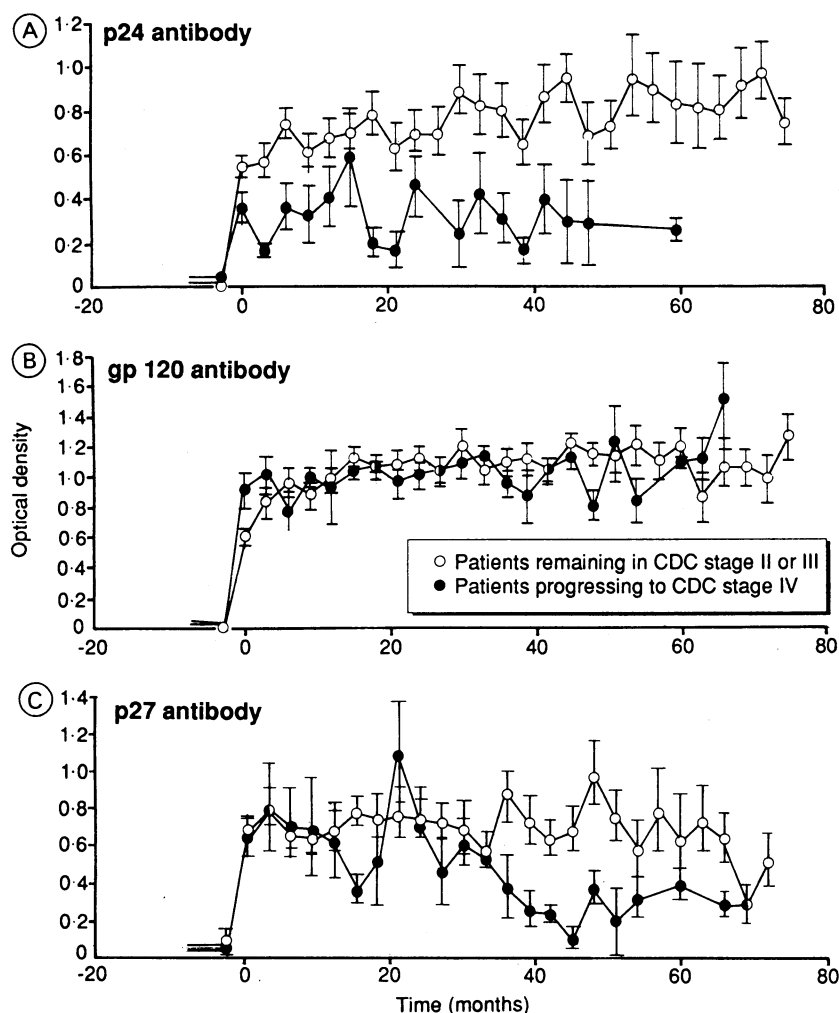


FIG 1—Mean of titres to p24(gag), gp120(env), and p27(nef) antibodies in 88 patients by clinical outcome over the study period. Number of observations: time 0 n=88; time 30 n=48; time 60 n=43. Bars are SD

infection was compared with the titre of first antibody response to p24 after infection with HIV. Whereas 6 out of 27 (22%) of the patients with an initial low titre response to p24 had developed p24 antigenaemia only 1 out of 24 (4%) of those with a high titre p24 antibody response developed detectable titres of p24 antigen within 84 months. Antigenaemia developed mainly in patients with an initial low titre antibody response to p24 after HIV infection (Fisher's exact test;  $p=0.10$ ).

Figure 3a-c shows the relation between time to progression to stage IV disease and high or low titres of the antibody response at seroconversion analysed by Kaplan-Meier survival analysis. Figure 3a shows a significant relation between an initial p24 antibody response and time to progression to stage IV disease; patients with initial titres less than 1600 had significantly shorter times to stage IV disease than those with titres greater than 1600 ( $p=0.0008$ ). Figure 3c (p27 antibody) shows a similar pattern to p24 but is less pronounced and is not significant ( $p=0.128$ ). In figure 3b patients with titres of gp120 antibody greater than 25 600 showed a significantly shorter time to progression to stage IV disease than those with initial titres of gp120 antibodies of less than 25 600 ( $p=0.025$ ). Analysis of the p24 and gp120 antibody titres for the first seropositive serum by regression

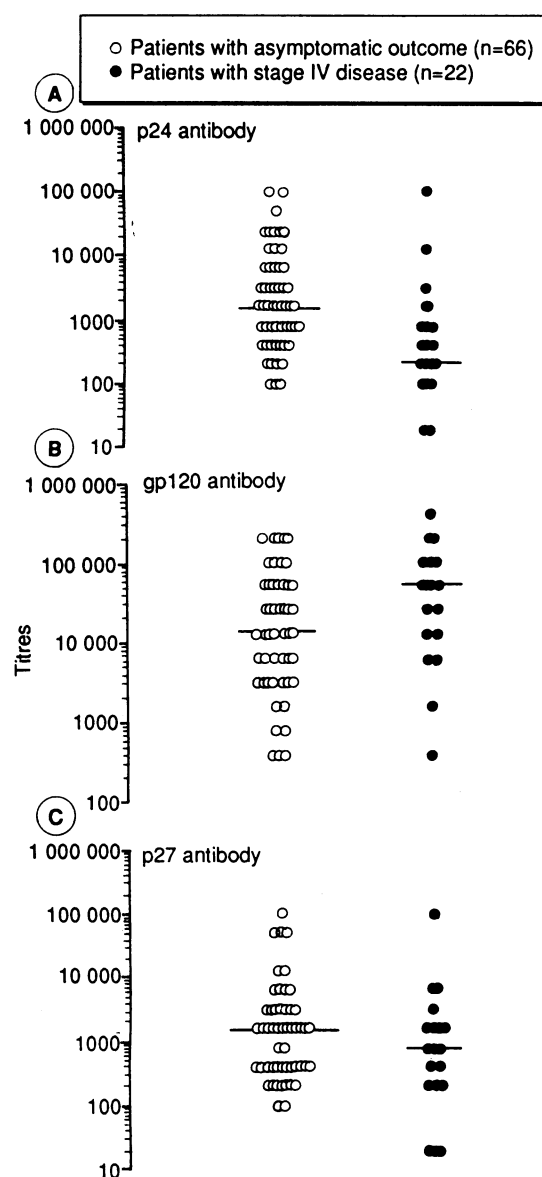


FIG 2—Range of antibody responses to p24(gag), gp120(env), and p27(nef) at the first seropositive sample by clinical outcome over the study period. Bars are median

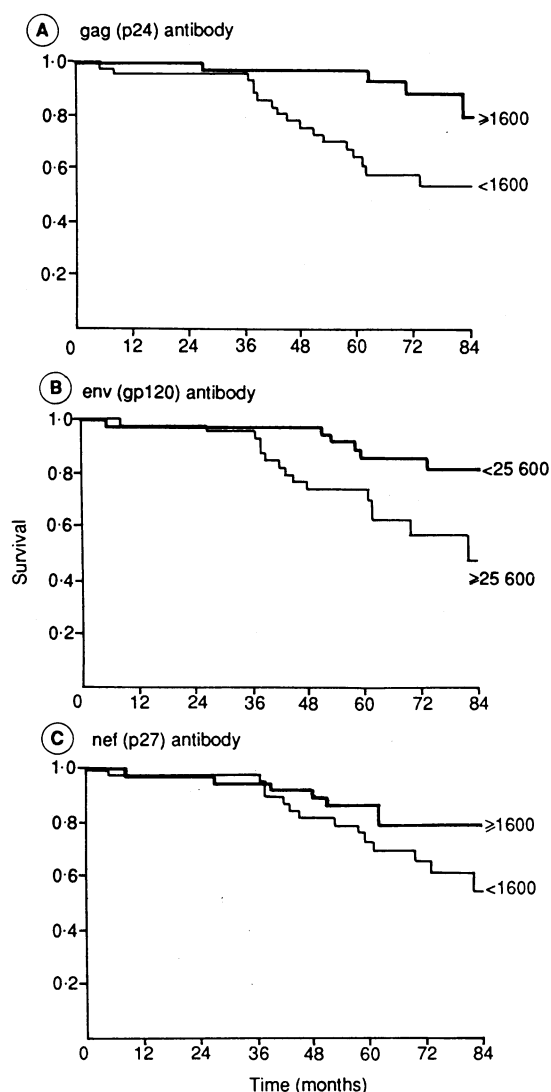


FIG 3—Kaplan-Meier survival analysis by time to progression to stage IV disease in relation to titre of antibody to HIV gag, env, and nef proteins at seroconversion

coefficient showed that these were independent variables (data not shown).

## Discussion

We have shown highly significant associations between p24 and gp120 antibody titres at seroconversion and the time to development of HIV related disease after infection through the parenteral route. Patients with low p24 and high gp120 antibody titres develop HIV related disease more rapidly than do those with high p24 and low gp120 antibody titres and are more likely to develop p24 antigenaemia; we have also shown that the antibodies to p24 and gp120 are independent variables.

As p24 antigen became detectable in this cohort mainly in the patients with low initial p24 antibody titres it is possible to see how cross sectional studies of HIV infected cohorts have shown conflicting data on the importance of p24 antibody and p24 antigen and why p24 antigenaemia is not universally present in patients with AIDS. Early in the natural history of any cohort low or negative titres of p24 antibodies correlate strongly with the rapid progression of disease.<sup>13-15</sup> These patients may become antigenaemic early because the low antibody titre enables antigen detection.<sup>30</sup> After the death of these patients, however, a higher proportion of the remaining cohort members have persisting high p24 antibody titres, are consequently not detectably antigenaemic, and may develop

AIDS later without ever becoming antigenaemic.

The observation that higher titres of p24 antibodies are associated with partial protection from disease progression is compatible with previous studies; these have studied longitudinal cohorts, generally where the date of seroconversion is not known. The difference in p24 antibody response from the time of seroconversion suggests that this phenomenon might have biological importance as well as being statistically significant. The association with protection is incomplete, however, as even the patients with a high p24 antibody titre eventually develop stage IV disease (fig 3a). The protection is indirect as there is no evidence that monoclonal p24 antibodies can neutralise HIV in vitro,<sup>29</sup> although there are reports of possible neutralising antibodies.<sup>31 32</sup> It is impossible to conclude from these data whether the different response to p24 is due to host or viral factors. Possibly, higher quantities of infecting virus might lead to more rapid progression of disease and suppress p24 antibody production. There are several reports of free gp120 binding CD4 receptors and interfering with T helper cell function and so a high level of circulating virus at seroconversion might depress the cooperation of T helper cells with B cells to produce antibody.<sup>33-35</sup> In addition, the HLA haplotypes of this population were not determined, and there might be an HLA association with p24 antibody response, such as the HLA-A1, B8, DR3 association with HIV outcome already found.<sup>36 37</sup>

The association of gp120 antibody with outcome was significant but probably of less biological importance as it was shown at one time point only; after the seroconversion sample gp120 antibody failed to predict outcome. Gp120 antibodies, however, might be capable of enhancing HIV infection by Fc receptor binding mediated by antibody.<sup>38 39</sup>

The mechanism underlying the association of the p24 antibody response with outcome of HIV infection can be answered with confidence only in an animal lentivirus model, such as simian immunodeficiency virus infection in the macaque, where viral and host variables can be controlled. If the association between p24 antibody response at seroconversion and time to disease can be confirmed in macaques then it would be possible to study the value of post exposure immunotherapy with a p24 construct with the aim of delaying the onset of disease by boosting the p24 antibody response.

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