Use of CD4 lymphocyte count to predict long term survival free of AIDS after HIV infection

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Abstract

***Objective*—To estimate the probability of remaining free of AIDS for up to 25 years after infection with HIV by extrapolation of changes in CD4 lymphocyte count.**

***Design*—Cohort study of subjects followed from time of HIV seroconversion until 1 January 1993. Creation of model by using extrapolated linear regression slopes of CD4 count to predict development of AIDS after 1993.**

***Setting*—Regional haemophilia centre in teaching hospital.**

***Subjects*—111 men with haemophilia infected with HIV during 1979-85. Median length of follow up 10·1 years, median number of CD4 counts 17. The model was not fitted for three men because only one CD4 measurement was available.**

***Main outcome measures*—Development of AIDS.**

***Interventions*—From 1989 prophylaxis against candida and *Pneumocystis carinii* pneumonia and antiretroviral drugs when CD4 count fell below 200×10^6/l.**

***Results*—44 men developed AIDS up to 1 January 1993. When AIDS was defined as a CD4 count of 50×10^6/l the model predicted that 25% (95% confidence interval 16% to 34%) would survive for 20 years after seroconversion and 18% (11% to 25%) for 25 years. Changing the CD4 count at which AIDS was assumed to occur did not alter the results. Younger patients had a higher chance of 20 year survival than older patients (32% (12% to 52%) for those aged <15, 26% (14% to 38%) for those aged 15-29, and 15% (0% to 31%) for those aged ≥30).**

***Conclusions*—These results suggest that even with currently available treatment up to a quarter of patients with HIV infection will survive for 20 years after seroconversion without developing AIDS.**

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Introduction

Current knowledge of the natural course of infection with the HIV type 1 is limited by the length of follow up studies. The longest running studies have followed infected subjects for a maximum of around 14 years since seroconversion, although few studies have followed many patients beyond 10 years.[1-11] Depending on the age of the groups studied current estimates suggest that between 25% and 60% of people do not develop AIDS over this period.[1-11] Since AIDS tends to develop only after patients' CD4 lymphocyte counts have reached low levels[12-19] useful projections can now be made of its long term course. These provide a background against which to make decisions concerning early intervention with antiretroviral drugs. In this paper, we update analyses done four years ago[20] and use serial CD4 lymphocyte counts measured in a cohort of 111 haemophilic men followed for up to 13 years from seroconversion to estimate the probability of not developing AIDS for up to 25 years after seroconversion.

Patients and methods

The cohort which has been described,[7 15 20] consisted of 111 haemophilic men infected with HIV who were under the care of our haemophilia centre and haemostasis unit. All except two patients had received unheated factor VIII concentrates; one had been treated with unheated factor IX concentrate and the other with cryoprecipitate.

The dates of the last negative and first positive HIV antibody test results were available for 63 patients. The date of HIV seroconversion was estimated as the midpoint between these two dates (median difference between the dates 11 months; 10th centile 41 days, 90th centile 21·5 months; range 15 days-24 months). The earliest seroconversion was estimated as October 1979 (difference between dates of last negative and first positive result=seven days) and the latest July 1985 (difference between dates of last negative and first positive result=10·1 months). These dates roughly agree with data from other sources on the period in which contaminated blood products were infused.[6] Patients' estimated dates of seroconversion showed a roughly uniform distribution.[21] For 36 of the 48 patients in whom no negative HIV test result was available, the date of seroconversion was estimated as the midpoint between October 1979 (the presumed first possible date of infection) and the date of the first HIV test (median difference 44 months; 10th centile 5·5 months, 90th centile 64·3 months; range 1·5-67 months). This approach minimises the maximum error in seroconversion date. For the remaining 12 patients the first positive HIV test result was after the presumed last possible date of infection (July 1985), and the date of seroconversion was estimated as the midpoint between October 1979 and July 1985—that is, September 1982 (difference 68 months).

We analysed information on patients up to 1 January 1993. The median length of follow up from seroconversion to this date was 10·1 years. A series of CD4 lymphocyte counts was recorded for each patient.[15] The median number of counts was 17 (range 1 to 50). Five or more counts were available for 90% of patients. The median age at seroconversion was 24 years (range 2 to 77). AIDS was defined according to the 1987 Centers for Disease Control definition.[22]

Zidovudine has been used to treat AIDS and people with Centers for Disease Control group IV disease since August 1987. The current protocol for treating asymptomatic patients is to start antiretroviral therapy with zidovudine and primary prophylaxis with pentamidine or co-trimoxazole and fluconazole at a CD4 lymphocyte count of 200×10^6/l. Treatment of asymptomatic patients began in November 1988, when 25 patients were recruited into the Medical Research Council and Agence Nationale de Recherches sur le SIDA Concorde trial of early versus deferred zidovudine.[23] Thirteen of these patients are now known to have been treated with zidovudine in the trial. Forty four patients have been openly treated with zidovudine (some of whom were formerly in the Concorde trial), 40 with prophylaxis against *Pneumocystis carinii* pneumonia, and 36 with prophylactic fluconazole. Since 1989 patients have also been given monoclonal high purity factor VIII concentrate instead of intermediate purity product when the CD4 count fell below 200×10^6/l. After 1991 all patients were switched to this product, which may slow the fall in CD4 count in HIV infected men with haemophilia.[24 25]

STATISTICAL METHODS

We fitted linear regression slopes through CD4 lymphocyte counts on time for each patient using least squares. We also used square root and square transformations for the CD4 count. The square root transformation is consistent with the rate of CD4 cell loss decreasing with time, while the square transformation is consistent with a more rapid loss with time. Since the average CD4 count at the development of AIDS has been found to be close to 50×10^6/l, the "modelled" date to develop AIDS was the time at which the negatively sloped linear regression line crossed 50×10^6/l (square root of 50 and square of 50 when using these transformations) on the y axis (see fig 1). When the slope was positive it was assumed the patient would not develop AIDS within 25 years from seroconversion. This was also assumed for patients in whom the slope of the linear regression line was zero (that is, a horizontal line) unless their CD4 count was less than 50×10^6/l, in which case the modelled date of AIDS was the date of the first CD4 count. For four patients only one CD4 count had been measured. These patients were excluded unless the count was below 50×10^6/l (one patient), in which case the date of this count was the modelled date of AIDS. We also did analyses using 30×10^6/l and 80×10^6/l as the count at which AIDS occurs and another in which the count for AIDS was taken as 80×10^6/l before routine prophylaxis and antiviral therapy was started (November 1988) and 50×10^6/l thereafter. This last analysis was also done with counts of 50×10^6/l and 30×10^6/l instead of 80×10^6/l and 50×10^6/l. This analysis was done because AIDS may occur at lower CD4 counts in those given prophylaxis and antiviral therapies. We also allowed patients' CD4 count at the time AIDS developed to be determined by sampling from the following probability distribution: 100×10^6/l=5%, 75×10^6/l=25%, 50×10^6/l=30%, 25×10^6/l=25%, 0×10^6/l=15%.

Kaplan-Meier estimates of the probability of remaining free of AIDS up to 25 years after seroconversion were made as follows. For those in whom AIDS had developed by 1 January 1993 the survival time free of AIDS was taken as the observed time to AIDS. For those who did not have AIDS on 1 January 1993 (median of 20 CD4 counts per subject over a median of nine years) the time to AIDS was taken as the time to the modelled date of AIDS. Follow up was censored in seven who died before AIDS was diagnosed. Weibull and Gamma distributions[26] were fitted to the observed survival times free of AIDS (by using the program PROC LIFEREG in SAS) to compare the projected survival rates with those obtained by our CD4 count modelling.

Results

Figure 1 gives the CD4 lymphocyte counts for one patient together with the linear regression slope to show how the modelled date of AIDS was obtained. When this was done for all patients, regardless of whether they actually have developed AIDS, the timing of the modelled dates of AIDS corresponded well with the actual dates (table I). Forty one of the 108 patients included in the modelling had developed AIDS by 1 January 1993. The modelled date was before the actual date of development for 36 (sensitivity 88% (36/41)). The modelled date of AIDS was after 1 January 1993 for 57 of the 67 patients who had not developed AIDS by this date (specificity 85%). Of the 36 patients who developed AIDS before 1 January 1993 as the model had predicted, 33 had a modelled date of AIDS within three years of the actual date and 29 had a modelled date within two years of the actual date.

Results were similar when the square root of the CD4 count was assumed to fall linearly over time

TABLE I—*Comparison of observed and modelled date of development of AIDS*

Modelled date of AIDS	AIDS by 1 January 1993		
	Yes	No	Total
Before 1993	36	10	46
1993 Onwards	5	57	62
Total	41	67	108

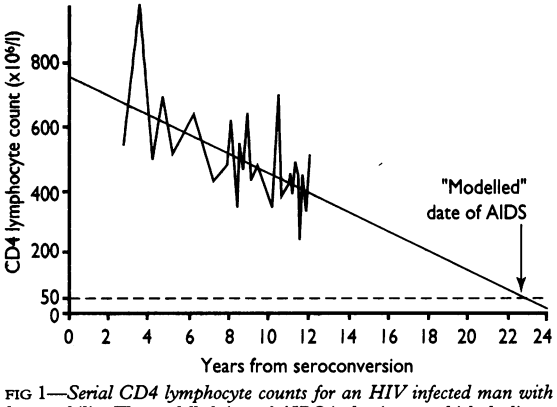

FIG 1—*Serial CD4 lymphocyte counts for an HIV infected man with haemophilia. The modelled time of AIDS is the time at which the linear regression slope reaches a CD4 lymphocyte count of 50×10^6/l*

(sensitivity 83%, specificity 88%). The model that used the square of the CD4 count, however, did not provide such good agreement (sensitivity 88%, specificity 63%). The results were not greatly affected by changing the CD4 count of AIDS from 50×10^6/l to 30×10^6/l (sensitivity 83%, specificity 88%) or 80×10^6/l (sensitivity 90%, specificity 81%). The results were also unaffected by using the CD4 count at AIDS sampled from the probability distribution rather than a fixed value for all subjects. The models in which a higher CD4 count was used to define AIDS before November 1988 (when prophylaxis was started) also did not greatly improve fit (sensitivity 90%, specificity 76% for model with 80×10^6/l and 50×10^6/l; sensitivity 90%, specificity 84% for model 50×10^6/l and 30×10^6/l). The results were essentially the same when patients with fewer than five CD4 counts were excluded (sensitivity 88%, specificity 87%) or when those aged below 15 at seroconversion were excluded (sensitivity 91%, specificity 84%).

Figure 2 shows the observed probability of surviving free of AIDS up to 13 years from seroconversion, This is based on the development of AIDS not on predicted

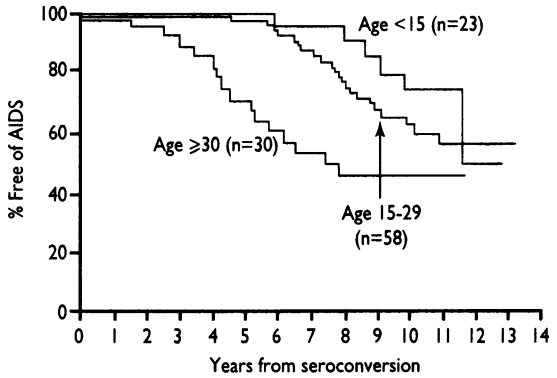

FIG 2—*Kaplan-Meier estimates of the percentage of patients surviving free of AIDS by years from seroconversion according to age at seroconversion. Estimates are based on actual times of occurrence of AIDS*

development from the CD4 count model. Eleven year AIDS free survival rates were 74% (95% confidence interval 55% to 93%) for patients aged <15, 57% (43% to 71%) for those aged 15-29, and 46% (27% to 65%) for those aged ≥30 (P=0·002, log rank test). Figure 3 shows the Kaplan-Meier curves based on the modelled date of AIDS in those free of AIDS on 1 January 1993. The probability of remaining free of AIDS 20 years after seroconversion was 32% (12% to 52%) in those aged <15 at seroconversion, 26% (14% to 38%) in those aged 15-29, and 15% (0% to 31%) in those aged >30 (table II). Over all age groups together the predicted percentage remaining free of AIDS for 20 years was 25% (16% to 34%). In all three age groups

TABLE II—*Percentage likelihood of survival free of AIDS for 20 years after seroconversion for different prediction models*

Age group (years)	AIDS defined as CD4 count 50×10⁶/l: No transformation of CD4 count	Square root transformation of CD4 count	Square transformation of CD4 count	Patients with <5 CD4 counts excluded	Patients with <10 CD4 counts excluded	Patients with <1 CD4 count/year excluded	AIDS defined as 30×10⁶/l	AIDS defined as 80×10⁶/l
<15	32	45	9	32	26	29	32	27
15-29	26	39	16	25	27	27	26	25
≥30	15	26	12	7	8	7	15	16

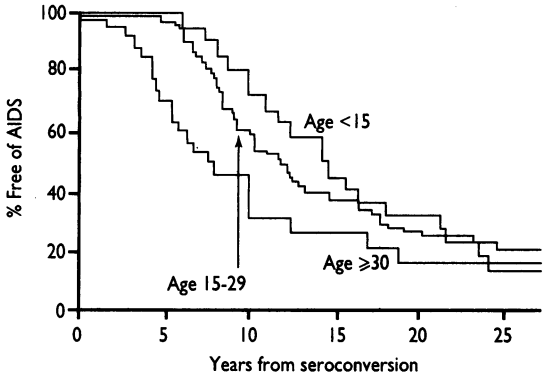

FIG 3—*Kaplan-Meier estimates of the percentage of patients surviving free of AIDS by years from seroconversion according to age at seroconversion. For those patients alive and free of AIDS on 1 January 1993, the modelled date of AIDS was used*

there was a 15-20% probability of remaining free of AIDS 25 years after seroconversion (over all age groups 18%; 11% to 25%), although the projections are less certain than for 20 years. Table II shows the effects of varying the model for estimating survival.

To give further detail on the 25 patients whom the model suggests will remain free of AIDS 20 years after seroconversion figure 4 shows the geometric mean CD4 lymphocyte count by years from seroconversion. Two of these men received zidovudine openly and a further three received zidovudine as part of the Concorde trial. The slow average rate of loss of CD4 lymphocytes is clearly seen. Twenty year survival free of AIDS seems highly plausible for these men.

Although clinical AIDS is unlikely to develop at 200×10⁶/l we also used this value in our model as this is the new definition of the Centers for Disease Control AIDS surveillance.[27] The resulting estimates of 20 and 25 year survival free of AIDS over all age groups were 18% and 15%, respectively.

Table III compares estimates of survival free of AIDS obtained by our methods with those obtained from fitting Weibull and Gamma distributions through the observed survival times for all subjects aged 15 and over at seroconversion. The Gamma distribution seems to give results much closer to ours than the Weibull distribution.

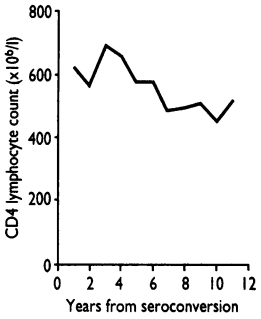

FIG 4—*Geometric mean CD4 lymphocyte count by years from seroconversion in 25 patients for whom the modelled time of AIDS is more than 20 years after seroconversion*

TABLE III—*Estimated percentages surviving free of AIDS by years from seroconversion obtained by assuming that the times from seroconversion to AIDS fit Weibull and Gamma distributions and by CD4 count model. All subjects aged 15 or over at seroconversion*

	Years from seroconversion: 5	10	15	20	25
Weibull (median 11·5, index 2·0)	88	60	30	11	3
Gamma (median 11·8, index 1·3)	88	60	38	25	17
CD4 count model	90	51	33	23	19

Discussion

We have used the well recognised ability of the CD4 lymphocyte count to predict the development of AIDS to assess the long term prospects for survival free of AIDS in patients with HIV infection. The projections suggest that there is roughly a 25% chance of remaining free of AIDS 20 years after infection with HIV. Although the projections up to 25 years from seroconversion are more speculative, they suggest that 15-20% of infected people will not develop AIDS by this time.

These estimates for long term survival free of AIDS are based on a cohort of men most of whom attend regularly for care and since 1989 have been offered prophylaxis against *P carinii* pneumonia and candida and antiviral drugs, particularly zidovudine, when their CD4 lymphocyte count reaches 200×10⁶/l. It seems reasonable to assume that those patients in whom AIDS developed before 1989 (that is, at most within 10 years of seroconversion) would have developed AIDS within 20 years after seroconversion even if they had received these therapies. The long term survival estimates given in this paper therefore apply to people receiving treatment when the CD4 count falls below 200×10⁶/l. Further advances in treatment may increase the proportion surviving free of AIDS for at least 20 years. Our estimates suggest that use of antiretroviral drugs as soon as HIV infection is diagnosed may in some patients entail over 20 years of therapy with drugs of uncertain long term risk to benefit ratios.[23 28 29]

PREDICTIVE VALUE OF CD4 COUNT

The use of the CD4 lymphocyte count to predict the progression to AIDS has a firm statistical basis. Many studies have shown the predictive value of the CD4 count in different risk groups and different settings.[12-19] Indeed, the Centers for Disease Control AIDS surveillance definition now classes people with a CD4 count below 200×10⁶/l as having AIDS, even if they have no symptoms.[27] Since we wanted to predict the development of clinical AIDS, however, we chose a CD4 count of 50×10⁶/l as the modelled date of AIDS. That AIDS occurs on average at about this CD4 count is well established from analyses of several thousand AIDS cases.[30-33]

The assumption of a linear fall in CD4 lymphocyte count was more consistent with our data than the various alternatives we fitted. The suggestion that the count falls increasingly rapidly over time[4] was not supported by our results. This model (linear in the square of CD4 count) greatly overestimated the number of AIDS cases developing before 1 January 1993 (61 compared with 41 actually developing in the 108 patients included). Other investigators who have modelled the fall in CD4 count in HIV infection have found that a linear fall in the untransformed, square root, or logarithmic scales provide the best fit.[34-36] When we used either of the last two models our projections of long term survival free of AIDS were more favourable (data for logarithmic model not shown).

CD4 lymphocyte counts tend to fall naturally from birth in uninfected children before stabilising at about age 13.[37] This phenomenon could result in underestimation of the length of time before AIDS develops in our linear model and hence underestimation of the proportion of children surviving free of AIDS for 20-25 years. Nevertheless, the agreement between actual and modelled date of AIDS was still close even in these young patients (data not shown).

Clinical implications

- The time of development of AIDS after HIV infection varies widely and few data exist on long term prognosis
- Older people tend to develop AIDS more rapidly after HIV infection than younger people
- Predictions from this study suggest that one quarter of people infected with HIV may remain free of AIDS for 20 years or more
- Patients given antiretroviral drugs as soon as they become infected with HIV may therefore require treatment for at least 20 years

WIDER APPLICATION

The extent to which these estimates will apply to non-haemophilic patients is uncertain. After differences in age are accounted for, no evidence exists of greatly different rates of progression to AIDS among people in different HIV exposure categories (J von Overbeck *et al*, IX international conference on AIDS, Berlin, 1993).[2 8 10] The higher risk of Kaposi's sarcoma in homosexual and bisexual men compared with other exposure groups seems to result in a somewhat poorer survival free of AIDS in this group.[10] Nevertheless, the incidence of Kaposi's sarcoma seems to be falling,[38] and so differences in AIDS rates between homosexual men and those in other transmission categories may become smaller.

There is increasing evidence that haemophilic patients who are coinfected with HIV and hepatitis C virus are at greater risk of liver failure than those infected with hepatitis C virus only (M E Eyster *et al*, IX international conference on AIDS, Berlin, 1993). Furthermore, the development of liver disease may be related to the degree of immunosuppression. In our cohort four patients without AIDS have died of liver disease. Thus liver disease may become important in the long term prognosis of patients infected with HIV and hepatitis C virus, and survival rates could be lower in coinfected patients.

VALIDITY OF MODEL

Predicting disease is always uncertain, and the modelled date of AIDS for an individual patient can differ substantially from the actual date of AIDS. Our model is therefore probably not clinically useful for predicting individual patients' prognosis. We believe, however, that our model is sufficiently accurate to provide useful estimates of the average experience of a whole group. Although we have given confidence intervals for our 20 and 25 year projected AIDS-free survival rates, these do not reflect all sources of uncertainty in the estimates. In particular, they do not reflect the uncertainty concerning the validity of the specified model. This uncertainty can be evaluated partly by studying the results obtained with alternative models. The results we obtained for long term survival free of AIDS were little affected by plausible changes in the formulation of the model. Further uncertainty concerns the accuracy of seroconversion dates. In almost all subjects, however, the maximum error in this date was less than two years, and thus, at worst, our estimates for 20 year survival free of AIDS would relate instead to 18 year survival.

Methods for projections of future numbers of AIDS cases in a country or community rely heavily on knowledge of the distribution of survival times free of AIDS, commonly termed the "incubation period."[39 40] Since data are available for at most only 13-14 years from seroconversion, predictions of the shape of the remainder of the cumulative distribution curve are usually made by fitting either a Weibull or Gamma distribution.[39 40] Table III shows that if our projections are correct the Weibull distribution underestimates the proportion surviving without AIDS for 15 years after seroconversion whereas the Gamma distribution gives a much better fit.

We previously used a similar approach to project the probability of remaining free of AIDS up to 15 years from seroconversion.[20] That analysis gave an estimate of 27% for the whole patient group compared with 36% in this analysis. The first estimate was based on experience before antiretroviral therapy or prophylaxis against *P carinii* pneumonia was given to patients with a CD4 count below 200×10^6/l (November 1988) and before the introduction of high purity factor VIII concentrate. This probably largely accounts for the difference and also gives some indication of the effect of such treatment policies on survival free of AIDS.

In conclusion, we have used 11 years of CD4 lymphocyte count experience in 111 haemophilic men to forecast the probability of survival free of AIDS up to 25 years after infection with HIV. The results suggest that such prolonged survival is likely in about a quarter of patients.

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C4B*Q0 allotype as risk factor for myocardial infarction

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The prevalence of the deficient, silent allotype of the C4B gene (C4B*Q0) is lower in elderly than in young healthy people, particularly in men.[1] This may reflect increased mortality from some disease in middle aged carriers of the C4B*Q0 gene. We determined the presence of the gene in patients with acute myocardial infarction because myocardial infarction is the leading cause of death among middle aged Hungarians.

Patients, methods, and results

We studied 181 consecutive patients with confirmed Q wave myocardial infarction admitted to four hospital departments between June 1992 and January 1993 (125 men, 56 women, aged 42-78), 93 consecutive patients with symptoms of angina pectoris (65 men, 28 women; aged 43-62) who were examined by coronary angiography (coronarography), and 737 previously tested healthy controls (252 young people aged 22-45 and 485 elderly people aged 60-99).[1] Myocardial infarction was diagnosed as typical chest pain lasting at least one hour, an ST segment elevation of at least 1 mm in an electrocardiogram, and typical cardiac enzyme values. We diagnosed inferior and anterior wall infarction in 103 and 70 patients, respectively; in eight patients the localisation of the infarct was uncertain.

We took blood samples from the patients with myocardial infarction within 24 hours of admission and sent them immediately to the laboratory in tubes containing EDTA. Plasma samples were stored at −70°C until tested. C4 allotyping was performed with high voltage electrophoresis, followed by immunofixation with human C4 antibody (Atlantic Antibodies).[2,3] We determined aspartate aminotransferase and alanine aminotransferase values serially with commercially available kits (Boehringer Mannheim, Germany). In order to exclude patients with enzyme elevations unrelated to myocardial infarction, we evaluated peak aspartate aminotransferase values only in patients whose alanine aminotransferase values had not increased concomitantly. Patients with raised aspartate aminotransferase values at the first determination were also excluded from the further evaluation.

The prevalence of C4 allotypes was significantly higher in patients with myocardial infarction than in the healthy elderly controls (27·6% *v* 10·7%; $P<0·0001$)—the only significant difference between the patients and the controls. After age matching, which was possible only in those aged 60-79, 38% (24/63) of male patients and 8% (10/133) of healthy men carried the C4B*Q0 allotype ($P<0·0001$). The odds ratio of a 60-79 year old man with acute myocardial infarction being a C4B*Q0 carrier compared with his healthy counterpart was 7·57 (95% confidence interval 3·31 to 17·2); in women this odds ratio was 0·84 (0·33 to 2·16).

The C4B*Q0 carrier state influenced the outcome of myocardial infarction (table). The odds ratio of dying was significantly higher for men who carried the gene compared with those who did not (18·0 (2·1 to 153) in homozygous men and 5·53 (1·21 to 25·4) in heterozygous men). Data on women were insufficient to calculate odds ratios.

Average peak aspartate aminotransferase values were significantly higher in patients who carried the C4B*Q0 gene than in those who did not (218 U/ml (median 195 U/ml, range 20-635 U/ml) *v* 145 U/ml (median 120 U/ml, range 12-506 U/ml; $P=0·040$ by Mann-Whitney U test). Similarly, the proportion of patients with a peak aspartate aminotransferase value greater than 200 U/ml was significantly higher in

*Outcome of Q wave myocardial infarction in patients with or without C4B*Q0 allotype*

Group	No (%) who died	No (%) who survived
Carrier of C4B*Q0 gene:		
Homozygous (n=6)	3 (50)	3 (50)
Heterozygous (n=38)	8 (21)	30 (79)
Non-carrier (n=137)	17 (12)	120 (88)
Total	28 (15)	153 (85)

$P<0·05$ for difference between patients with and without C4B*Q0 by χ^2 test.