

PAPERS AND SHORT REPORTS

Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort

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Abstract

The three year actuarial progression rate to the acquired immune deficiency syndrome (AIDS) in a cohort of men in San Francisco who were seropositive for the human immunodeficiency virus (HIV) was 22%. An additional 26 (19%) developed AIDS related conditions. β_2 Microglobulin concentration, packed cell volume, HIV p24 antigenaemia, and the proportion and number of T4 lymphocytes each independently predicted progression to AIDS. β_2 Microglobulin was the most powerful predictor. The 111 subjects tested who were normal by all predictors (40%) had a three year progression rate of 7%, and the 68 subjects who were abnormal by two or more predictors (24%) had a progression rate of 57%. Two thirds of all men who progressed to AIDS were in the last group. The median T4 lymphocyte count in subjects who did not progress to AIDS

fell from 626×10^6 to 327×10^6 /l. HIV p24 antigenaemia developed in 7% of the subjects per year. The proportion who were abnormal by two or more predictive variables rose to 41%. At three years an estimated two thirds of the seropositive subjects showed clinical AIDS, an AIDS related condition, or laboratory results that were highly predictive of AIDS.

It is concluded from the observed rates and the distribution of predictive variables at three years that half of the men who were seropositive for HIV will develop AIDS by six years after the start of the study, and three quarters will develop AIDS or an AIDS related condition.

Introduction

The acquired immune deficiency syndrome (AIDS) was first reported in the United States in 1981,¹ and its association with infection by the human immunodeficiency virus (HIV) was shown in 1983-4.^{2,3} But the likelihood of a person who is infected with HIV developing clinical AIDS has not been made clear. Goedert *et al* recently showed three year actuarial progression rates of 34% and 17% respectively in cohorts of homosexual men who were recruited in New York and Washington, DC,⁴ whereas Polk *et al* reported a crude 15 month progression rate of only 3.2% in the Multicenter AIDS Cohort Study.⁵ In the San Francisco City Clinic cohort of 63 men with long term infection 19 (30%) developed AIDS at a median of five years from seroconversion (N Hessol *et al*, presented at the third international conference on AIDS, Washington, DC, June 1987). One cohort of haemophiliacs shows an 18% actuarial progression rate at six years after seroconversion.⁶

We report on progression to AIDS in a cohort of homosexual men who were recruited in San Francisco.

Methods

A total of 462 homosexual men were initially chosen for a case-control study of AIDS.⁶ Group 1 comprised randomly selected neighbourhood

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control subjects, group 2 control subjects from clinics for sexually transmitted diseases, and group 3 sexual partners of patients with AIDS. Control subjects were excluded if they reported having oral candidiasis, herpes zoster, persistent lymphadenopathy, or any two of persistent unexplained fevers, night sweats, shortness of breath, or weight loss. For this study all were seen at the AIDS clinic at San Francisco General Hospital in 1983-4, median date May 1984, and then at 12 month intervals.

HIV serology was performed at the University of California, Davis, by enzyme immunoassay and confirmed by Western blot.⁷ Two subjects who were positive on Western blot for p24 antigen only were excluded. HIV p24 antigen was detected using the enzyme immunoassay of Abbott Laboratories.⁸ T lymphocyte subsets were determined by direct immuno-

fluorescence using monoclonal antibodies and flow cytometry.⁹ Serum concentrations of β_2 microglobulin were measured using the Phazazym B₂ Micro Test competitive enzyme immunoassay (Pharmacia Diagnostics, Piscataway, NJ).

Lymphadenopathy on physical examination was determined by the presence of two or more extrainguinal sites of at least 1.0 cm. An AIDS related condition (ARC) was defined as one or more of the following in a seropositive man: thrush, hairy leucoplakia, unexplained weight loss of over 4.5 kg, or fevers, night sweats, or diarrhoea persisting for more than a week. ARC2 was defined as ARC and fewer than 400 T4 lymphocytes $\times 10^6/l$. (ARC2 is similar to Walter Reed stage 5.¹⁰)

Progression to AIDS (Centers for Disease Control revised surveillance

TABLE 1—Two year actuarial progression rates to AIDS, relative hazards from the proportional hazards model, and relative hazards adjusted for number of T4 lymphocytes by selected clinical values at first follow up

	No who progressed to AIDS/total No	Two year actuarial progression rate (%)	Relative hazard	Relative hazard adjusted for No of T4 lymphocytes
Total cohort	31/219	19		
Lymphadenopathy at follow up				
Yes	17/118	20	1.0	0.8
No	14/100	19	1.0	
Lymphadenopathy for one year				
Yes	5/30	22	1.3	1.5
No	22/151	21	1.0	
Shingles				
Yes	2/8	25	1.8	2.2
No	29/210	19	1.0	
Thrush				
Yes	7/20	39	2.9*	2.0
No	24/195	17	1.0	
Hairy leucoplakia				
Yes	3/9	42	3.4*	3.9*
No	28/206	18	1.0	
Symptoms (night sweats, fever, or weight loss)				
Yes	4/4	100	21.9**	8.7**
No	27/214	18	1.0	
ARC (thrush or hairy leucoplakia or symptoms)				
Yes	10/26	44	3.9**	2.8*
No	21/192	16	1.0	
ARC2 (ARC and ≤ 400 T4 lymphocytes $\times 10^6/l$)				
Yes	8/10	88	12.2**	3.9**
No	23/209	15	1.0	

** $p < 0.01$; * $p < 0.05$.

Note: Not all tests were carried out on all subjects so totals may not add up to 219.

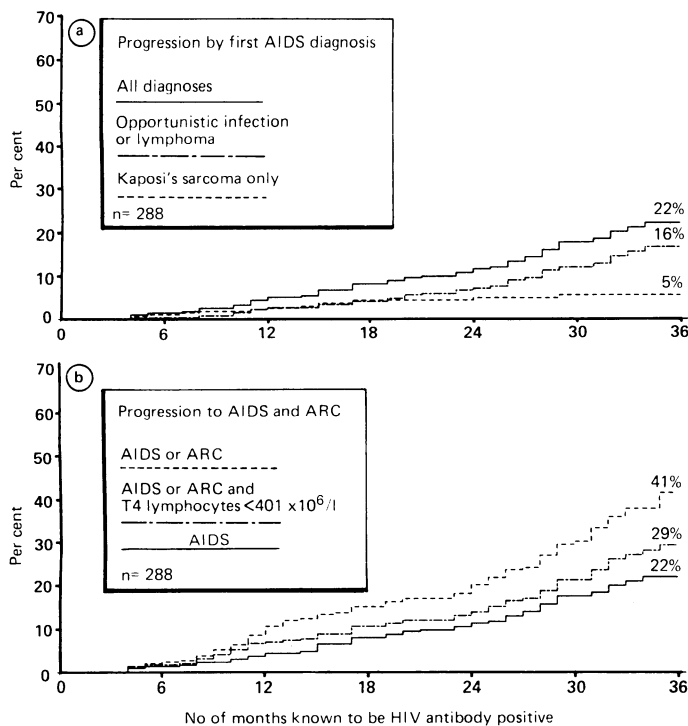


FIG 1—Progression curves to AIDS and AIDS related conditions (ARC) in 288 HIV seropositive men. (a) Progression to AIDS by first AIDS diagnosis. (b) Progression to AIDS, AIDS or ARC, and AIDS or ARC and ≤ 400 T4 lymphocytes $\times 10^6/l$.

definition, 1985¹¹) was established by diagnosis at the clinic, by a confirmed report to the Centers for Disease Control, or, for subjects who were not from California, by a death certificate or the report of a physician. At the first follow up 237 (82%) eligible subjects were examined and at the second follow up 183 (81% of those who continued in the study). The third cycle of examinations is still being carried out. A further 19 (7%) subjects have consented to continued morbidity follow up by a telephone interview with confirmation by their physician.

Subjects who did not have AIDS at a clinic visit or telephone interview were considered to be free of AIDS through June 1986. Subjects who did not progress towards developing AIDS and did not have a physical examination after June 1986 were assumed to be free of ARC if free of AIDS. This assumption underestimates ARC. One man in whom Kaposi's sarcoma was diagnosed immediately on entering the study was excluded from the current analysis.

Loss to follow up may cause bias on observed laboratory values over time; thus figures 3 and 4 show both raw and baseline adjusted medians and proportions. The baseline adjusted value in each case is the change from baseline in those seen at follow up applied to the baseline value for all subjects.

Since the follow up ranged from 19 to 44 months actuarial progression rates were calculated using the product limit method, and progression data were analysed using the proportional hazards model.¹² Both methods take the differing amounts of follow up into account.

Results

SEROPOSITIVITY AND ANTIGENAEMIA

Of 462 men in the cohort, 288 were seropositive for HIV at entry (62%), including 57 of 145 (39%) in group 1, 106 of 149 (71%) in group 2, and 125 of 168 (74%) in group 3. Of 281 men who were HIV antibody positive, 46 were antigenaemic for HIV p24 (16%), and 210 had antibody to p24 (75%). Seven subjects had both p24 antigen and antibody, and 32 had neither.

PROGRESSION TO AIDS AND ARC

Fifty of 288 seropositive subjects progressed to clinical AIDS during follow up (17%). The rate of progression increased over the period of follow up. Actuarial progression rates with 95% confidence intervals were 5% (2 to 7) at one year, 11% (8 to 15) at two years, and 22% (16 to 30) at three years (fig 1a). Fifteen men were first diagnosed with Kaposi's sarcoma only, two with lymphoma, 32 with opportunistic infection, primarily *Pneumocystis carinii* pneumonia, and one with both Kaposi's sarcoma and *P. carinii* pneumonia. The incidence of Kaposi's sarcoma decreased: seven of 14, six of 18, and one of 17 progressors were first diagnosed with Kaposi's sarcoma in three successive 12 month periods (fig 1a). (In one man it was diagnosed at 41 months.)

The actuarial progression rate to AIDS or ARC at three years was 41%. The actuarial progression rate to AIDS or ARC2 was 34% (fig 1b).

PROGRESSION TO AIDS FROM ARC

We examined progression to AIDS from ARC at the first follow up visit because most subjects were screened for AIDS related conditions at baseline. Thrush, hairy leucopenia, and systemic symptoms all predicted progression to AIDS, but shingles and lymphadenopathy (at first follow up or lasting for one year) did not (table I). Twenty six of 217 men had ARC, as defined, and 11 of 26 progressed to AIDS over the remaining two years (actuarial rate 44%). Ten men had ARC2 at first follow up and eight of 10 progressed to AIDS (actuarial rate 88%). (The 24 month actuarial rate for men with T4 lymphocytes $\leq 400 \times 10^6/l$ but without ARC was 29%.) Six men with ARC were also HIV p24 antigenaemic. Four progressed to AIDS (actuarial rate 67%).

PREDICTORS OF PROGRESSION TO AIDS

Progression to AIDS was strongly associated with the absolute number and proportion of T4 lymphocytes. Progression was also strongly associated with HIV p24 antigenaemia (table II, fig 2a, b). Presence of p24 antigen was closely comparable with $T4 \leq 400 \times 10^6/l$ as a predictive variable ($\chi^2=24.8$ and 24.7 respectively). The two predictors were largely independent, only 15 men having both $T4 \leq 400 \times 10^6/l$ and p24 antigen. p24 antigen remained a strong predictor after adjustment for T4 lymphocytes.

There was a weaker association with loss of antibody to p24 antigen (table II), which was not significant when controlled for presence of antigen (relative hazard = 1.5, $p=0.27$). Thus antigenaemia was the better predictor. Antigen quantity was not statistically associated with progression, though five of seven subjects with $p24 > 350$ mg/l progressed to AIDS.

Progression was strongly associated with the β_2 microglobulin concentration, which was a better predictor of progression than T4 lymphocytes when both were expressed as trichotomies ($\chi^2=42.2$ and 31.3 , respectively), and remained a strong predictor after adjustment for T4 lymphocytes (table II and fig 2a, c).

Progression was also associated with an increased number of suppressor/cytotoxic (T8) lymphocytes, with T4/T8 ratio, with increased IgA but not IgG or IgM, with anaemia (measured by haemoglobin, packed cell volume, or red cell count) and with erythrocyte sedimentation rate, and these associations persisted after adjustment for T4 lymphocytes (table II). There was no association with platelet count after adjustment for T4 lymphocytes, with lymphadenopathy at baseline, or with white cell count.

In a stepwise multivariate analysis of progression we found independent predictive effects associated with (i) β_2 microglobulin concentration at entry (>5.0 and >3.0 mg/l); (ii) packed cell volume <40 ; (iii) p24 antigenaemia;

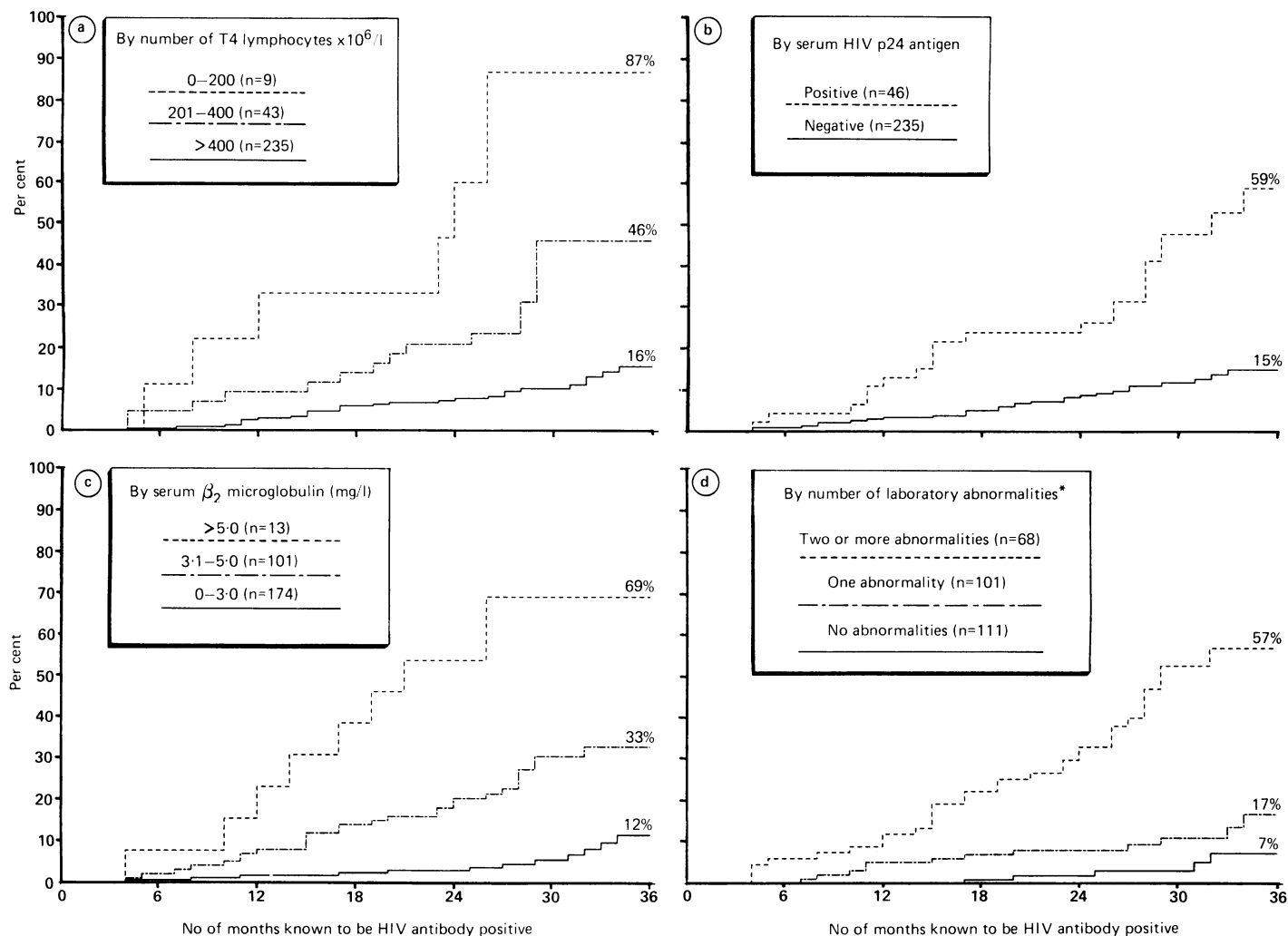


FIG 2—Progression curves to AIDS by laboratory results at baseline examination. (a) By number of T4 lymphocytes $\times 10^6/l$. (b) By presence or absence of HIV p24 antigen. (c) By serum β_2 microglobulin concentration. (d) By number of laboratory abnormalities. * (β_2 Microglobulin >3 mg/l; packed cell volume <40 ; HIV p24 antigen present; T4 lymphocytes $<25\%$ of all lymphocytes; T4 lymphocytes $\leq 200 \times 10^6/l$).

(iv) proportion of T4 lymphocytes <25%; and (v) absolute number of T4 lymphocytes $\leq 200 \times 10^6/l$ (table III).

Of 280 subjects who were seropositive, 111 (40%) were normal on all five predictive variables at baseline, 101 (36%) were abnormal on one variable, 39 (14%) on two, 20 (7%) on three, and nine (3%) on four. Among 170 seronegative men, 149 (88%) had no abnormalities, 20 (12%) had one abnormality, and one (1%) was abnormal on two variables. Crude progression rates for seropositive subjects in the five categories were 5%, 12%,

with T4 lymphocytes $\leq 400 \times 10^6/l$ rose from 18% to 49%, and the proportion with T4 lymphocytes $\leq 200 \times 10^6/l$ from 3% to 18% (fig 4a). The proportion with detectable p24 antigen rose from 16% to 20% (fig 4b), and men became antigenaemic at 5%, 7%, and 9% per year in the three years respectively (7% a year overall). The proportion with β_2 microglobulin > 5.0 mg/l rose from 5% to 9% (fig 4c), the proportion with less than 25% T4 lymphocytes rose 29% to 42% (fig 4d), and the proportion with a packed cell volume of < 40 rose from 9% to 15% (data not shown). The proportion in the abnormal

TABLE II—Three year actuarial progression rates to AIDS, relative hazards from the proportional hazards model, and relative hazards adjusted for number of T4 lymphocytes by laboratory values at baseline

Variable	No who progressed to AIDS/total No	Three year actuarial progression rate (%)	Relative hazard	Relative hazard adjusted for No of T4 lymphocytes
Total cohort	50/288	22		
T4 lymphocytes ($\times 10^6/l$)				
≤ 200	7/9	87	13.4**	
201-400	15/43	46	3.6**	
> 400	28/235	16	1.0	
Proportion of T4 lymphocytes (%)				
< 25	31/83	48	5.1**	3.5**
≥ 25	19/204	12	1.0	
T8 lymphocytes ($\times 10^6/l$)				
≥ 1000	21/89	27	1.7	2.0*
< 1000	29/198	20	1.0	
T4/T8 ratio				
< 0.4	12/19	80	11.9**	5.7**
$0.4-0.6$	23/82	33	3.7**	3.2**
> 0.6	15/186	11	1.0	
T lymphocytes ($\times 10^6/l$)				
< 600	8/16	54	4.4**	0.9
≥ 600	42/271	20	1.0	
Total lymphocytes ($\times 10^6/l$)				
≤ 900	6/9	70	6.4**	1.1
> 900	44/279	20	1.0	
HIV p24 antigen				
Yes	22/46	59	4.6**	3.9**
No	28/235	15	1.0	
Anti-HIV p24				
No	25/70	43	3.2**	3.1**
Yes	25/210	16	1.0	
β_2 Microglobulin (mg/l)				
> 5.0	10/13	69	16.9**	11.5**
$3.1-5.0$	28/101	33	4.5**	3.7**
≤ 3.0	12/174	12	1.0	
Haemoglobin (g/dl)				
< 13.5	7/15	50	4.5**	3.4**
≥ 13.5	43/273	21	1.0	
Packed cell volume				
< 40	12/25	54	4.3**	3.7**
≥ 40	38/263	19	1.0	
White blood cells ($\times 10^9/l$)				
< 5.0	26/110	34	2.0*	1.2
≥ 5.0	24/178	16	1.0	
Red blood cells ($\times 10^{12}/l$)				
< 4.50	15/41	50	3.0**	2.5**
≥ 4.50	35/247	18	1.0	
Erythrocyte sedimentation rate (mm in 1st hour)				
≥ 15	20/56	43	3.0**	2.3**
< 15	30/232	17	1.0	
IgA (mg/dl)				
> 370	18/54	38	3.1**	3.0**
≤ 370	20/162	15	1.0	
Platelets ($\times 10^9/l$)				
< 150	12/40	37	2.5**	1.6
≥ 150	38/248	20	1.0	
Lymphadenopathy (> 2 nodes > 1.0 cm)				
Yes	14/85	26	1.0	1.0
No	21/123	21	1.0	

** $p < 0.01$; * $p < 0.05$.

Note: Not all tests were carried out on all subjects so totals may not add up to 288.

26%, 70%, and 100%, respectively. A trichotomy of zero or one or two or more abnormalities was an effective discriminator of the probability of progressing to AIDS. Among the 111 men with no abnormalities none progressed to AIDS in the first 17 months of follow up, and overall five did (fig 2d). Two thirds of all men who progressed to AIDS either at 24 months or at 36 months were among the 68 with two or more abnormalities at baseline (fig 2d).

CHANGE IN LABORATORY VALUES IN NON-PROGRESSORS

The observed median number of T4 cells in men who did not progress to AIDS fell from $626 \times 10^6/l$ at baseline to $428 \times 10^6/l$ (baseline adjusted estimate $376 \times 10^6/l$) at the third follow up (fig 3). The proportion of men examined

range on two or more predictive variables rose from 24% at baseline to 27%, 33%, and 41% at successive follow ups.

The overall proportion of men who remained free of AIDS and ARC and in the normal range on four or more predictors was 76% at baseline and 65%, 50%, and 35% at successive follow ups. Thus two thirds of the cohort had progressed to AIDS or ARC or to laboratory results that were highly predictive of AIDS or ARC at three years of follow up.

PROJECTED SIX YEAR PROGRESSION RATE

Projected progression rates at six years were calculated (i) by applying the observed three year actuarial progression rates by number of laboratory abnormalities (fig 2d) to the distribution of laboratory values at the third

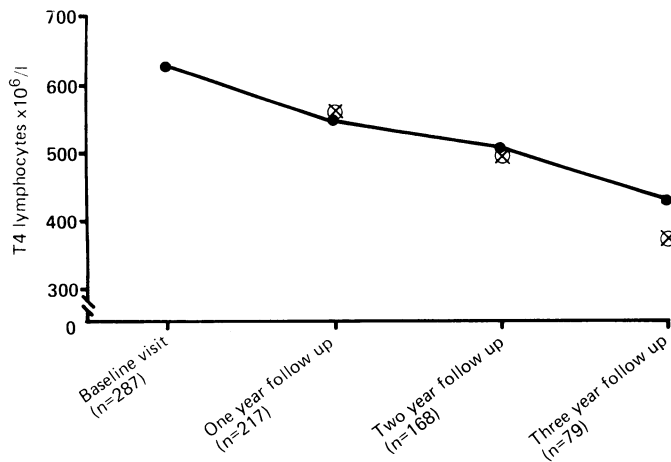


FIG 3—Median T4 lymphocytes $\times 10^6/l$ at successive follow up examinations in subjects who were not progressing to AIDS. ●=raw medians (observed values); ⊗=median changes from baseline.

TABLE III—Baseline laboratory values predictive of AIDS, relative hazards, and 95% confidence intervals, stepwise Cox proportional hazards model ($n=280$)

Variable	Relative hazard	95% Confidence intervals
β_2 Microglobulin (mg/l)		
>5.0	7.4**	2.8 to 19.4
3.0-5.0	2.6*	1.2 to 5.6
<3.0	1.0	
Packed cell volume		
<40	3.0**	1.5 to 6.1
≥ 40	1.0	
HIV p24 antigen		
Yes	2.5**	1.3 to 4.9
No	1.0	
Proportion of lymphocytes that were T4 cells (%)		
<25	2.5**	1.3 to 4.8
≥ 25	1.0	
T4 lymphocyte count $\times 10^6/l$		
≤ 200	2.9*	1.1 to 7.4
>200	1.0	

** $p < 0.01$; * $p < 0.05$.

Note: One or more values are missing for eight subjects.

follow up and (ii) by extrapolating the one year progression rate in the most recent year of follow up for three more years. The two methods predict 49% and 52% progression rates to AIDS respectively at six years of study and 75% and 79% to AIDS or ARC. These estimates are conservative because ARC is underestimated by the follow up assumption (see Methods), and AIDS is underestimated by late reporting and because subjects with symptoms were excluded at baseline. The apparent acceleration in progression rate, rate of antigen development, and proportion moving to abnormal T4 lymphocyte counts also suggest that the projections are conservative. Men who did not return for laboratory follow up after baseline examination were slightly more likely to progress than those who were seen for follow up but the difference was not significant (RH=1.4, $p=0.45$). Thus projections based on those seen at follow up are more likely to underestimate than overestimate progression.

COFACTORS FOR PROGRESSION

Of the variables we studied, only the age of the subject was a significant cofactor for progression. Men who were 35 or over had a relative hazard of 2.1 ($p=0.015$) when compared with men under 35. Prior exposure to venereal disease, sexual activity, and having had sex with a person with AIDS were not associated with progression. The crude progression rates in groups 1, 2, and 3 were 16%, 16%, and 19% respectively ($p=0.46$), thus group did not appear to be a cofactor. Median T4 lymphocyte counts in the three groups at baseline were 675, 626, and 619 respectively, suggesting similar median dates of infection.

Discussion

The actuarial progression rates at three years in the San Francisco

General Hospital study were 22% to AIDS and an additional 19% to ARC.

From the dates given on stored sera the median date of infection in the widely reported San Francisco City Clinic cohort was determined as mid-1981 (N Hessel *et al.*).¹³ That cohort, recruited in the San Francisco clinic for sexually transmitted diseases, corresponds closely to group 2 in our study. Progression rates and baseline median T4 lymphocyte counts suggest that the seropositive subjects in groups 1, 2, and 3 in our study have similar median dates of infection. Thus it is likely that the median date of infection for the original cohort as a whole was about mid-1981, or three years before the median date of entry to the study. The current progression rate to AIDS of 22% may thus approximate the actuarial rate at about six years after infection. This result is consistent with those of Goedert *et al.* and Eyster *et al.*⁶ and with the San Francisco City Clinic cohort (N Hessel *et al.*).¹³ These studies are consistent with the Multicenter AIDS Cohort Study if that cohort was infected some one to two years later than the two San Francisco cohorts.⁵

In a multivariate analysis of progression to AIDS we found independent predictive effects associated with (i) β_2 microglobulin concentration, (ii) packed cell volume, (iii) HIV p24 antigenaemia, (iv) proportion of T4 lymphocytes, and (v) absolute number of T4 lymphocytes. This set of variables was both a good discriminator between seropositive and seronegative men—99% of the latter being normal on four or more variables—and a very good predictor of progression to AIDS. Of seropositive men who were normal on all five variables, none progressed before 17 months. On the other hand, two thirds of all men in whom AIDS was diagnosed either at two years or at three years were in the relatively small group who were abnormal on two or more variables at baseline.

β_2 Microglobulin concentration was the best single predictor of progression. This is a low molecular weight protein that is present on the surface of all nucleated cells as the constant subunit of the class I histocompatibility antigens.¹⁴ It is produced at a relatively constant rate in healthy subjects and is released into body fluids as a result of cell turnover. The production and turnover rate are increased in both cytomegalovirus infection and HIV infection.^{15,16} The high concentration of β_2 microglobulin observed in men who are progressing rapidly to AIDS may be a direct measure of activation in target cell populations of HIV infection (T4 lymphocytes, macrophages), or it may reflect reactivated cytomegalovirus infection, which is common in pre-AIDS patients. Serum β_2 microglobulin may be a better predictor of progression than the T4 lymphocyte count because it reflects macrophage activation as well as lymphocyte activation or perhaps because it reflects target cell activation in all tissues and not in the peripheral circulation alone. The presence of p24 antigen was also a good indicator of progression, comparable with T4 dichotomised at $400 \times 10^6/l$ as a single predictor. Since both β_2 microglobulin and p24 assays are available in EIA kits, our study suggests that good prognostic information can be obtained without counting lymphocyte subsets. In clinical trials of HIV infected people with no symptoms the combination of β_2 microglobulin and p24 levels with T4 lymphocyte counts will identify much larger groups at high risk than lymphocyte counts alone.

The most striking feature of our study was the change in the seropositive subjects who had not yet progressed to AIDS. There was a progressive loss of the T4 lymphocyte subpopulation, the baseline adjusted median T4 lymphocyte count falling about 85 cells $\times 10^6/l$ per year. There were increases in the proportions that were abnormal on all predictive variables. Clearly, the subjects who have progressed to AIDS do not represent a simple selecting out of a subgroup at risk, leaving the rest of the cohort unaffected. On the contrary, the prognosis for the rest of the cohort is worsening over time, two thirds showing AIDS or ARC or laboratory results that are highly predictive of AIDS at the third year of the study. From the declining values in the laboratory results and under conservative assumptions the course of the study can be predicted for the next three years. Half of the seropositive subjects are predicted to progress to AIDS by six years of follow up, or probably nine years from infection, and three quarters are predicted to progress to AIDS or ARC. Furthermore, since ARC as defined here is highly

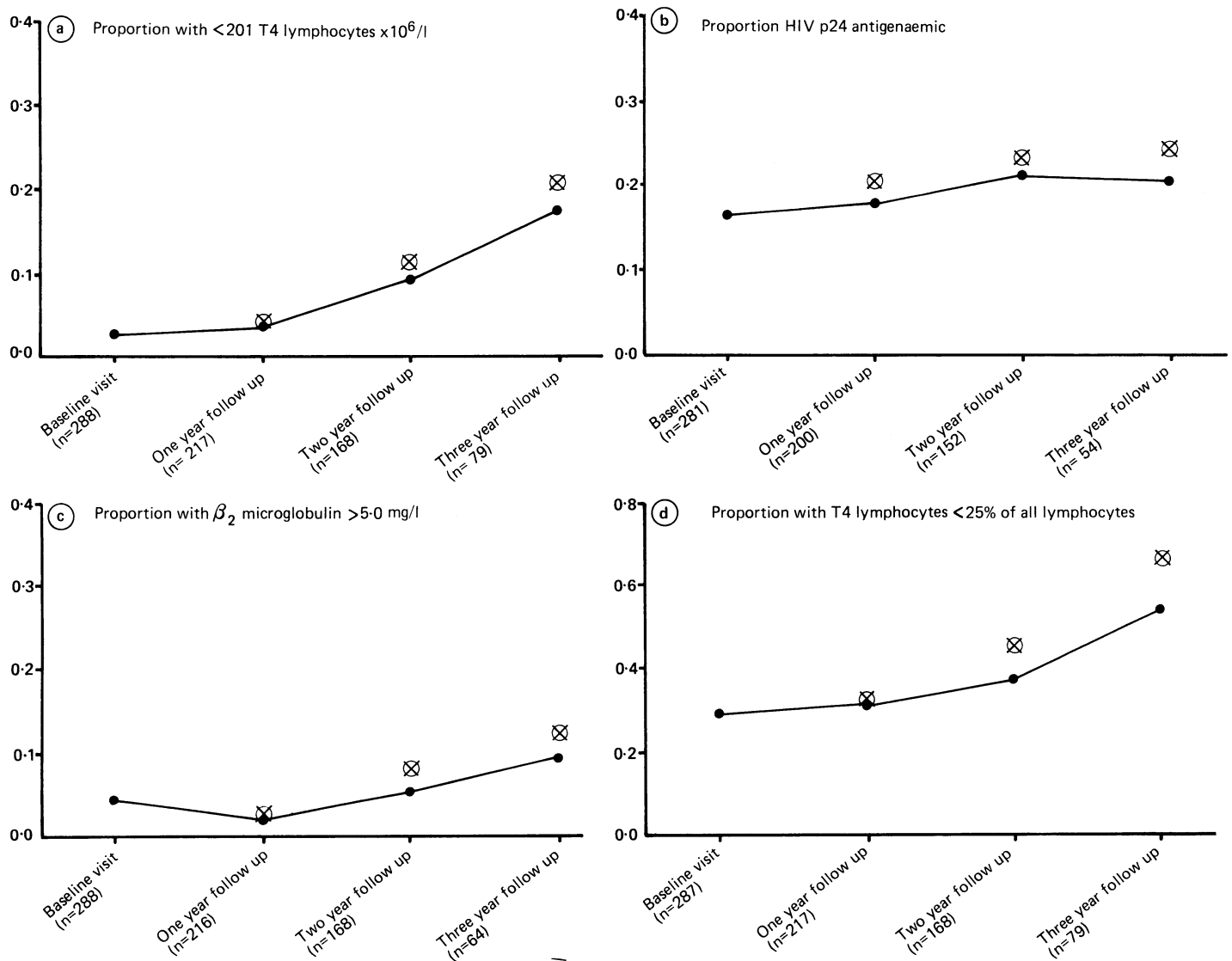


FIG 4—Abnormal laboratory results at successive follow up examinations in subjects who did not progress to AIDS. (a) Proportion with T4 lymphocytes $\leq 200 \times 10^6/l$. (b) Proportion with HIV p24 antigen. (c) Proportion with β_2 microglobulin >5.0 mg/l. (d) Proportion with T4 lymphocytes $<25\%$ of all lymphocytes. ●=raw proportions (observed values); ⊗=baseline adjusted proportions.

predictive of AIDS and as additional subjects will have progressed to abnormal laboratory results without ARC by six years our results suggest that at least three quarters of the seropositive people in the cohort will eventually develop AIDS. These results and recent successes with treatment with azidothymidine strongly support extending clinical trials to include seropositive subjects without symptoms. And the results suggest that in considering the importance of AIDS prevention we should regard progression to clinical AIDS after infection with HIV as the norm rather than the exception.

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