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Predictors of Clinical AIDS in Young Homosexual Men in a High-Risk Area

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One hundred and sixty-seven homosexual men in Los Angeles characterized by HIV antibody, T-cell numbers, titres to cytomegalovirus (CMV), and specific sexual practices were followed for two years for immune changes and for more than three years for development of clinical AIDS. Thirty-five per cent had antibody to HIV at baseline. The mean level of T-helper (Th) cells was significantly lower and of T-suppressor (Ts) cells significantly higher in HIV seropositives than in seronegatives. The annualized incidence of HIV seroconversion was 7%. Eight men developed AIDS, an attack rate of 14% in those with HIV antibody at baseline. A number of observations were made: (1) T-cell alterations, except a transient elevation in Ts cells, were unusual in the absence of HIV antibody; (2) a seropositive man with a T-cell alteration was significantly less likely to revert to 'within normal limits' than was a seronegative man; (3) a steady decline in the number of Th cells preceded onset of clinical AIDS; (4) the number of Ts cells remained higher in men subsequently developing AIDS than in other seropositive men; (5) clinical AIDS occurred only in men with HIV antibody whose CMV antibody levels were above the median for the group (1:1600); and (6) the attack rate for clinical AIDS was 50% in men with HIV antibody and elevated CMV who at baseline had either: (a) fewer than 325 Th cells/cc, or (b) whose Th/Ts ratio was below 0.8 (but whose levels of Th and Ts cells were within normal limits). This information should be helpful to clinicians caring for homosexual and bisexual men and for identifying suitable populations for future early intervention efforts.

The association between infection with the retrovirus, human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) has been firmly established and strongly suggests that infection with the virus is a necessary factor for disease to occur.[1–8] The characteristic low level of T-helper cells in AIDS has also been described.[9,10] We and others have shown the relationship of T-cell numbers to receptive anal-genital intercourse, receptive anal-hand intercourse (fisting), and cytomegalovirus (CMV) infection.[11–16] We suspected that T-cell levels might be predictive of risk of developing AIDS but a recent study by Weber *et al* has suggested that T-cells are not of prognostic value for AIDS.[17] The study reported in this paper suggests that T-cell levels are related to the risk of developing clinical AIDS, especially when considered in conjunction with antibody titres to cytomegalovirus.

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METHODS

The Study Cohort

The study cohort of young homosexual men was recruited from June 1982 to March 1983 through the Gay and Lesbian Association (GALA) at UCLA.

The Examination

Participants completed a self-administered questionnaire at each visit which requested demographic information, age, history of venereal diseases and other illnesses, specific sexual practices, and proportion of anonymous sexual partners. The questionnaires were reviewed for completeness and coherence by a member of the study staff and blood specimens were taken. At each revisit, an interval questionnaire was completed by the participants and additional blood samples were taken. Participants who did not come for re-examination were contacted by phone or mail to ascertain current status with respect to a diagnosis of AIDS.

Laboratory Investigation

Heparinized venous blood was collected from each participant for determination of T-cell subsets. The procedures for determination of levels of Leu-2 (Ts,T8) and Leu-3 (Th,T4) cells have been described previously.[10,11,18-21] We have used the terms 'T-helper' (Th) and 'T-suppressor' (Ts) in this report to conform with other reports and because the subpopulations distinguished by the Leu-2 and Leu-3 antigens include these functions.

In this report the T-cell distribution is divided hierarchically into four categories—T-helper deficiency (ThD), T-suppressor augmentation (TsA), 'low ratio only' (LRO), and within normal limits (WNL)—on the basis of their T-cell numbers as shown in Table 1. The level of 326 Th cells per mm^3 (ThD) represented the lower 95% limit and of 1021 Ts cells per mm^3 (TsA) the upper 95% limit of the respective distributions in a healthy reference population of 49 individuals at the time this study was initiated.[21]

Sera were tested by enzyme-linked immunosorbent assay (ELISA) for the presence of HIV antibody using procedures developed by Genetic Systems (LAV), Litton Industries (HTLV-III), and Electronucleonics (HTLV-III) (Virgo).[4] All positive tests were confirmed by repeat testing. There was disagreement between the three tests on 20 of the 382 specimens tested (5%). The results of the Genetic Systems test have been used in this paper except in instances where there was insufficient serum for that test to be performed, because the test results using the Genetic Systems were slightly more consistent for serially tested individuals, were in close agreement with the results of Western Blot test (99% in a series of 207 men), and included the highest number of men. For those 54 sera for which only the Litton and Virgo tests were performed, the results of those two tests (which in all 54 specimens were in agreement) have been used.

IgG antibody titres to cytomegalovirus (CMV) were determined at baseline only by the ELISA technique as reported by Castellano *et al* on all the men.[12,22] The IgG antibody titres to Epstein–Barr viral capsid antigens (EB-VCA) were determined by the indirect fluorescent antibody technique on the first 77 men only.[12]

TABLE 1 *Glossary—Definitions of T-cell status*

Distribution category	Number of Ts cells	Number of Th cells	Th/Ts ratio
T-helper deficiency (ThD)	—	≤326*	—
T-suppressor augmentation (TsA)	>1022	>326	—
'Low-ratio only' (LRO)	≤1022	>326	≤0.80
Within normal limits (WNL)	≤1022	>326	>0.80

* cells/ml

Identification of Clinical Cases of AIDS

Subjects developing AIDS were identified through systematic follow-up of all participants regardless of whether they agreed to be re-examined at the clinic. Men developing very low levels of T-helper cells were referred for a diagnostic workup. Cases were diagnosed by a physician and met the Centers for Disease Control criteria for AIDS, with one exception: a man who had a diagnosis of 'AIDS encephalopathy' made independently at two university medical centres in Los Angeles and New York.[23]

RESULTS

Cohort Characteristics

The mean age of the 167 men participating in the study was 27 years. The mean number of lifetime partners was 323 and of partners in the last six months, 18. The men reported an average of seven venereal disease episodes. Thirty-nine per cent of the men had T-cell alterations at baseline.

One hundred and thirty-seven men (82%) were seen at least twice; of these, 136 had determinations of HIV antibody on at least two visits. The mean duration of follow-up for the immune parameters was two years. Follow-up for clinical disease was continued through January 1986.

Prevalence of HTLV-III/LAV antibody

The prevalence of men with antibody to HIV at baseline was 35% (58/167) (Table 2), and was highest among those with either ThD (67%) or low ratio only (64%). The prevalence of T-cell alterations was higher among those with antibody to HIV than among those without antibody: 34/58 (59%) compared to 26/109 (24%) ($p < 0.001$).

Changes in T-cells

The mean number of Th cells at baseline was significantly lower ($p < 0.01$) and of Ts cells significantly higher ($p < 0.006$) in seropositive men than in seronegative men (Table 3). The number of Th cells was borderline significantly lower in subsequent cases than in seropositives ($p = 0.053$).

The rate of reversion from any T-cell alteration to WNL was almost five times more frequent among persistently seronegative men than among seropositive men (7/9 vs 5/29, $p < 0.001$). Only 1 of 63 persistently seronegative men as compared to 10 of 49 persistently seropositive men had ThD ($p < 0.001$).

The presence of antibodies to HIV at baseline was

TABLE 2 *Prevalence of men with antibody to HIV at baseline stratified by T-cell status*

T-cell status	N	HIV- positive	HIV- negative
ThD	6	4 (67%)	2 (33%)
LRO	25	16 (64%)	9 (36%)
TsA	29	14 (48%)	15 (52%)
WNL	107	24 (22%)	83 (78%)
Total	167	58 (35%)	109 (65%)

found by stepwise regression analysis to be the best predictor for both the subsequent number of Th cells (standardized regression coefficient = −0.37) and for the subsequent number of Ts cells (standardized regression coefficient = 0.38). The variables considered are listed in Appendix 1.

Levels of IgG and IgM

The mean level of IgG at their most recent visit was significantly higher ($p < 0.001$) among seropositive men, excluding cases (2122 mg/dl ± 904) than among seronegative men (1236 mg/dl ± 404). The mean levels of IgG and IgM were not significantly different among those with CMV antibody above and below the median titre of 1:1600.

Seroconversion

The attack rate for seroconversion to HIV antibody positivity was 15/109 (14%), an annualized incidence of 7%. Among the various sexual practices (Appendix 1), only receptive anal intercourse had a risk ratio for seroconversion which was greater than one (2.92), and had 95% confidence limits which did not include one (1.21 to 7.03).

Incident AIDS cases

Eight men among those with HIV antibody at baseline developed clinical AIDS over the three years of follow-up, an attack rate of 14%. The age at onset ranged from 25 years to 41 years (mean = 32 years). The T-cell status, the HIV antibody status, and the CMV antibody titre at baseline are shown in Table 4 for these men. The interval between the first visit and the diagnosis of clinical AIDS ranged from 9.5 months to 39 months. Five of the men initially had Kaposi's sarcoma (KS) without opportunistic infection (OI), two had opportunistic infection, and one had 'AIDS encephalopathy'. At their first visit, four had LRO, two had ThD, one had TsA, and one had T-cells within normal limits, although his ratio was borderline (0.84). The titres to EBV at baseline among the three cases tested fell both above and below the median EBV titre for the group but the CMV antibody titres for all eight were above the median for the group (1:1600). All had antibody to HIV at baseline. At diagnosis all seven of the men with known T-cell status had ThD. The mean interval between the baseline and diagnosis was 16 months for the two men with ThD at baseline, 18 months for the four men with 'low ratio only', 35 months for the man with TsA, and 39 months for the man with WNL.

Changes in levels of Th and Ts cells between visits one, two and three were compared between the five cases and 33 men who completed the first three visits. The levels of Th cells in both groups declined but was significantly lower in subsequent cases than in persisting seropositives by the third visit ($p < 0.02$). No significant differences between cases and seropositives were observed in levels of Ts cells over time.

Markers of Risk for AIDS-KS

The attack rate for clinical AIDS by factors present at baseline is given in Table 5. Clinical AIDS did not occur among men who had CMV titres at or below the median for the whole group (1:1600), nor among men without HIV antibody. All eight cases occurred among those with a combination of HIV antibody and an elevated CMV antibody titre.

A significant linear trend ($p < 0.007$) in per cent subsequently developing clinical AIDS was observed for the various T-cell alterations. The highest attack rates were observed for those with HIV antibody, an elevated CMV titre, and either ThD or LRO. As noted above, the interval between visit one and diagnosis was also half as long for men in these categories as for men with TsA or WNL at their first visit.

DISCUSSION

A specific pattern of changes in T-cell distribution is suggested by our findings. We and others have found a low level of Th cells to be apparently specific to infection with HIV.[24-26] In this study, only 1 of 63 (2%) persistently seronegative men, compared to 10 of 49

TABLE 3 *Comparison of baseline T-cell levels among HIV seronegatives, HIV seropositives, and cases*

	No. Th cells	p	No. Ts cells	p
Seronegatives* (N = 79)	839±321	<0.01	676±281	<0.006
Seropositives** (N = 42)	679±293	<0.053	877±454	NS
Cases (N = 8)	465±187		920±233	

* Does not include men who subsequently seroconverted

** Does not include men who developed AIDS

TABLE 4 *T-cell, HIV antibody and CMV antibody status at baseline and at visit nearest to time of diagnosis for AIDS cases*

Case No.	Baseline visit: HIV antibody	Baseline visit: CMV titre	Baseline visit: T-cell status	Diagnostic visit: Diagnosis/ interval from baseline	Diagnostic visit: T-cell status
1	+	1:8192	ThD	KS/9.5 mos	ThD
2	+	1:3200	LRO	KS/11 mos	ThD
3	+	1:4096	LRO	KS/12 mos	—*
4	+	1:3200	LRO	KS/21 mos	ThD
5	+	1:3200	ThD	OI/23 mos	ThD
6	+	1:8192	LRO	KS/28 mos	ThD
7	+	1:4096	TsA	Encephalopathy/ 35 mos	ThD
8	+	1:4096	WNL	OI/39 mos	ThD

* Absolute T-cell count not determined at diagnostic visit

(20%) persistently seropositive men, had fewer than 325 Th cells.

Of potentially greater significance was the observation on follow-up that a continuing decline in Th cells was present in all eight men who subsequently developed clinical AIDS, including those manifesting Kaposi's sarcoma, opportunistic infection, and AIDS encephalopathy. These negative slopes cannot be discerned by single tests. Thus, serial testing of Th (T4, CD4) cell levels may be important in discerning the critical effect of HIV infection, ie progressive deterioration of Th cells, leading to clinical disease.

Another observed pattern was a sharp increase in the level of Ts cells associated with initial infection with HIV, which has also been reported by Schwartz and Cooper.[25,26] Although the levels of Ts cells fluctuated, they remained generally elevated compared to levels in seronegatives. Ts cells may be responding to subsequent immunological stimuli occurring after HIV infection.

The ratio of Th/Ts cells is still being used by some investigators as an indicator of AIDS risk. The decline in the ratio among the eight cases, however, was not as consistent as the decrease in number of Th cells because numbers of Ts cells fluctuated among individuals developing clinical AIDS even close to the time of diagnosis. Thus, we reassert that the number of Th cells is a more significant indicator of immune changes leading to clinical AIDS than is the Th/Ts cell ratio.[11]

We identified a subgroup of men whose Th/Ts ratio was low although their absolute levels of Th and Ts cells were within normal limits. This admittedly arbitrary classification, in conjunction with very high levels of antibody to CMV and antibody to HIV, does apparently identify a group of homosexual men at very high risk of developing clinical AIDS even at a stage when their Th cells are close to normal: two of the four cases developing clinical AIDS in this 'low ratio only' group had levels of Th cells at baseline that were well within normal limits (757 cells per cc, 680 cells per cc), although their ratios were less than 0.8. Thus, although the ratio of Th/Ts may not have significance for predicting AIDS, the designation of 'low ratio only' may be significant. These observations will need to be further evaluated in a larger cohort study.

We considered several explanations for the finding of 'no prognostic value' for Th and Ts cell counts observed by Weber *et al.*[17] They observed only four cases during follow-up of their 33 seropositive men. Unfortunately, they have not indicated how many of the four cases had opportunistic infection and how many had Kaposi's sarcoma. Five of our eight cases had Kaposi's sarcoma. Further, they have combined AIDS-Related Syndrome (ARC), Progressive Generalized Lymphadenopathy (PGL) and AIDS as a single end-point. Since not all individuals with ARC or PGL progress to AIDS, some dilution may have occurred and in fact T4 levels may distinguish between men with ARC and PGL who progress to AIDS.

CMV has been suggested as an aetiological factor in AIDS by a number of investigators, but its role is very difficult to establish.[19,28,29] The prevalence of CMV antibody among homosexual men is over 90% and the titre in homosexual men is higher than that observed in heterosexual populations.[19,29,30] In this study we found clinical AIDS to occur only among those individuals who had antibody titres even greater than the median in this group of homosexually active men. A similar

TABLE 5 *Attack rate for AIDS by HIV, CMV, and T-cell status*

*HIV antibody status**			
Negative	0%	(0/109)	$p < 0.001$
Positive	14%	(8/58)	
*CMV antibody status** (HIV antibody positives)*			
≤1:1600	0%	(0/12)	$p < 0.09$†
>1:1600	19%	(8/38)	
T-cell status			
HIV antibody positive			
WNL	4%	(1/24)	$p < 0.007$‡
TsA	7%	(1/14)	
LRO	25%	(4/16)	
ThD	50%	(2/4)	
HIV antibody positive, CMV antibody >1:1600			
WNL	6%	(1/16)	$p < 0.007$†
TsA	10%	(1/10)	
LRO	50%	(4/8)	
ThD	50%	(2/4)	

* Genetic Systems ELISA test
** ELISA test—IgG
† CMV antibody status missing for eight men
‡ χ^2 test for linear trend

relationship was not observed with antibody to EBV in this study. This elevated titre may be the result of repeated infection by different strains of CMV, reactivation of latent CMV, or an unusual immune response to the virus analogous to that observed with antibody titres to measles among children with subacute sclerosing panencephalitis.[31-33] Although this study may be interpreted as increasing the suspicion that CMV is a co-determinant of clinical AIDS, we cannot rule out the possibility that it is only acting as a marker for some other unknown factor or may reflect nonspecific B cell activation in men in the early stages of AIDS.[34]

This study suggests that HIV seropositive men who do not have markedly elevated antibody titres to CMV are at low risk of developing clinical AIDS, especially if they display no alterations in their levels of Th cells. On the other hand, the results indicate that men having HIV antibody together with high levels of CMV antibodies and either (1) low levels of Th cells, *or* (2) low Th/Ts ratio with Ts and Th cells within normal limits, are at high risk of developing AIDS and, therefore, should be followed for clinical signs of AIDS and should be advised to avoid exposures to infectious diseases. Further, they should be advised to see a physician at the first sign of infection and should be aggressively treated for all infections. These men may be a suitable population to consider for early intervention efforts.

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APPENDIX 1

INDEPENDENT VARIABLES CONSIDERED FOR STEPWISE REGRESSION

—Sexual practices: 1: never; 2: several/sometimes; 3: usually, always
- Anal intercourse, insertive
- Anal intercourse, receptive
- Oral intercourse, insertive
- Oral intercourse, receptive
- Anilingus, insertive
- Anilingus, receptive
- Fisting, insertive
- Fisting, receptive
- Penile adornments

—Total number of STDs in last six months
—Total number of male partners in last six months
—Per cent anonymous partners in last six months
—Duration (number of years): Fisting, insertive
" " " " Fisting, receptive
" " " " Anal, insertive
" " " " Anal, receptive
—HTLV status