Infection with the Human Immunodeficiency Virus: Clinical Manifestations and Their Relationship to Immune Deficiency

A Report from the Multicenter AIDS Cohort Study

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In 1984 a large prospective study of gay and bisexual men was begun to elucidate the natural history of the human immunodeficiency virus (HIV) infection. At two successive semiannual examinations, clinical or hematologic abnormalities were found up to 13 times more often among HIV-seropositive men (n = 1611) than HIV-seronegative men (n = 2646). More than 30% of the seropositive participants had persistent generalized lymphadenopathy, independent of T-helper lymphocyte (CD4) counts and most other signs and symptoms. Other clinical manifestations such as thrush, anemia, thrombocytopenia, neutropenia, fever, and fatigue occurred with only slightly reduced CD4 counts (400 to 700/mm^3) and appeared to increase exponentially with progressively lower counts. A simple systematically derived clinical index using these manifestations identified more than 70% of the seropositive men with significant T-helper cell depletion. This kind of clinical index may be useful for assessing groups of HIV-infected persons, especially those whose T-lymphocyte numbers and function cannot be readily measured.

VARIOUS symptoms and signs including persistent generalized lymphadenopathy have been recognized in homosexual men and others (1-15) at risk for developing the acquired immunodeficiency syndrome (AIDS). The early finding of persistent generalized lymphadenopathy in the presence of depleted T-helper lymphocytes and subsequently in connection with human immunodeficiency virus (HIV) infection has implied a strong relationship between persistent generalized lymphadenopathy and AIDS. Collectively, lymphadenopathy and the other symptoms and signs have been commonly termed *lymphadenopathy syndrome* or *AIDS-related complex* and seen repeatedly in conjunction with HIV-induced quantitative and qualitative T-cell alterations (2, 4-9, 11-14). However, despite numerous reports, the frequency of these clinical manifestations, the interrelationships between them and T-cell alterations, and their position in the natural history of HIV infection have not been definitively established. For example, not all investigators have agreed on whether or not persistent generalized lymphadenopathy is pathophysiologically linked to quantitative CD4 cell depletion (4, 5, 8-12). Similarly, although several studies have emphasized the prognostic significance of thrush (5, 6, 9, 13, 14), the connection between loss of CD4 cells and the numerous clinical manifestations of HIV-induced immunodeficiency remain uncertain.

A major purpose of the Multicenter AIDS Cohort Study (16) is to characterize the clinical and immunologic events in the course of HIV infection and the relationships among them. Homosexual and bisexual men without AIDS were enrolled in the study for semiannual evaluations beginning in April 1984. The detailed cross-sectional analyses of findings of the first two visits further define the relationship between the HIV-induced T-cell changes and the clinical findings that accompany them.

Material and Methods

STUDY POPULATION

Between April 1984 and April 1985, 4955 homosexual and bisexual men without AIDS were enrolled in the study in four metropolitan areas using various publicity and recruitment techniques. Participants agreed to semiannual follow-up. At each 6-month interval they were evaluated as reported elsewhere (16, 17) with a questionnaire covering the previous 6 months, a physical examination, and laboratory tests including T-cell phenotyping and enzyme-linked immunosorbent assay (ELISA) for HIV at each visit. Examiners were unaware of the participant's serologic status.

For these analyses participants had to have completed two successive evaluations approximately 6 months apart. Only participants unequivocally seropositive or seronegative by ELISA at both evaluations were included; men who seroconverted between the two clinic visits were excluded. Clinical features were tabulated for all members of the cohort who had interview data on symptoms, pertinent data from the physical examination, a hematologic profile, and results of T-lymphocyte phenotyping.

LABORATORY METHODS

Serum taken from each participant at entry and at each follow-up visit was tested for antibody to HIV by ELISA (DuPont, Wilmington, Delaware) (18). On repeated testing by ELISA, specimens with a ratio of 0.5 or greater for the test serum to the positive control serum were considered seropositive for HIV; those with a ratio less than 0.5 were considered seronegative. Standard techniques were used for leukocyte, differential, and platelet counts. The percentage and number of lymphocytes of different phenotypes were determined using monoclonal antibodies (Becton/Dickinson, Mountainview, California) with standard methods (19). Fifty microliters of whole blood in preservative-free heparin was mixed with 10 µL of anti-Leu 2a FITC and anti-Leu 3a phycoerythrin. Alternatively, Ficoll-Hypaque separated lymphocytes were stained with these reagents. An EPICS-C flow cytometer (Coulter, Inc., Miami, Florida)

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Table 1. Frequency of Symptoms and Signs in Seronegative and Seropositive Men and in Seropositive Men With and Without Lymphadenopathy

	Seronegative with Manifestations		Seropositive with Manifestations				
	One Visit* (2571-2644)‡	Both Visits† (2571-2644)‡	One Visit* (1562-1603)‡	Both Visits† (1562-1603)‡	No Adenopathy* (130-463)‡	Localized Adenopathy* (130-463)‡	Persistent Generalized Lymphadenopathy* (492)‡
	%						
Symptoms							
Fever	0.6	0.2	1.6	0.2	1.5	1.1	1.8
Diarrhea	3.0	1.2	3.7	1.1	2.3	4.1	3.7
Fatigue	6.7	2.6	7.6	2.9	10.0	7.1	8.1
Night sweats	1.6	0.5	3.1	0.9	0.8	3.2	4.1
Weight loss ≥ 4.5 kg	1.9	0.3	2.6	0.4	1.5	1.5	3.3
Thrush or white patches in mouth	1.0	0.4	3.9	0.9	1.5	3.7	5.3
Enlarged nodes	4.2	1.6	17.7	9.8	6.2	17.5	29.9
Herpes zoster	0.5	0.04	2.0	0.3	1.5	2.0	2.7
Herpes simplex virus disease worse in last 6 months	2.3	0.6	5.3	2.0	7.0	4.6	6.8
One or more symptoms at either visit	30.6		51		37.7	48.6	65.5
Physical findings							
Persistent generalized lymphadenopathy	3.3		30.8		...	...	...
Localized adenopathy	18.5		28.9		...	...	...
Weight loss ≥ 4.5 kg	5.5		4.3		6.9	3.1	4.7
Spleen palpable	0.3	0	1.3	0.5	0.8	0.9	2.9
Thrush§	1.4	0.04	5.9	0.6	1.5	7.6	6.3
Fungus-like skin lesions	9.6	3.4	13.1	5.9	12.3	13.8	11.0
Herpes lesions							
Anal or genital	0.9	0.08	2.4	0.4	0.8	4.1	2.0
Oral	0.6	0	1.1	0	0	1.5	1.8
One sign or more at either visit	42.7		73.6		31.5‖	39.2‖	41.0‖
Hematologic findings							
Hematocrit ≤ 40%	2.8	0.6	7.6	3.2	5.4	7.2	10.1
Platelet count < 150 000/mm^3	1.5	0.6	6.7	2.6	7.8	5.9	7.8
Neutrophil count < 1800/mm^3	1.8	0.4	6.4	1.5	7.8	5.0	7.8
Lymphocyte count < 1000/mm^3	1.5	0.08	5.2	1.0	6.2	2.0	7.6
CD4 count < 400/mm^3	1.9	0.1	24.7	15.0	23.4	21.4	27.5
CD8 count > 1200/mm^3	4.4	1.5	16.8	6.7	11.3	16.0	17.0
CD4/CD8 ratio < 0.9	6.2	3.0	64.1	52.8	52.4	65.6	64.7
More than one laboratory abnormality at either visit	32.9		84.4		79.0	84.3	84.6
More than one abnormality at either visit	76.0		96.7		87.3	94.0	96.1

* Symptom or sign present at a single observation (second visit).
† Symptom or sign present at each of two 6-month observations (both visits).
‡ Range of numbers of participants with requisite data available.
§ Confirmed microscopically at one visit: seronegative men, 1.0%; seropositive men, 4.2%.
‖ Refers to signs other than lymphadenopathy.

was used at each center to determine the percentage of T-cell subsets: total (CD3, Leu4), T-helper (CD4, Leu3a), or T suppressor/cytotoxic (CD8, Leu2) lymphocytes.

CLINICAL MANIFESTATIONS

We tabulated the following symptoms lasting 2 weeks or more during the 6 months before each visit: temperature greater

Table 2. Frequency of Abnormalities of Lymph Node Groups in Men with Persistent Generalized Lymphadenopathy by Human Immunodeficiency Virus Antibody Status

	Percent with Enlarged Node	
	Seronegative Men ($n=88$)	Seropositive Men ($n=493$)
Node group		
Occipital	3.4	14.4*
Posterior auricular	1.1	7.3†
Preauricular	2.3	3.5
Submental	31.8	27.6
Anterior cervical	38.6	39.8
Posterior cervical	28.4	51.9‡
Supraclavicular	2.3	13.0*
Axillary	96.6	96.8
Epitrochlear	3.4	5.1
Inguinal	36.4	45.6
Femoral	19.3	28.2
Mean number of abnormal node groups	4.5 ± 0.21	5.7 ± 0.15*

* $p < 0.005$ comparison of seronegative men with seropositive men with persistent generalized lymphadenopathy.
† $p < 0.05$ comparison of seronegative men with seropositive men with persistent generalized lymphadenopathy.
‡ $p < 0.0005$ comparison of seronegative men with seropositive men with persistent generalized lymphadenopathy.

than 37.8 °C, diarrhea, night sweats, persistent fatigue, enlarged nodes or "glands," and thrush or white patches in mouth; and these other symptoms: unintentional weight loss of more than 4.5 kg, and new or worse anal, genital, or oral herpes simplex, or zoster in the previous 6 months. The following findings were noted at physical examination: enlarged lymph nodes; palpable spleen; skin, hair, and nail lesions suggestive of fungus infection in any area outside the genital area; coating of the mucosal surface of oropharynx consistent with yeast infection (with and without microscopic confirmation); documented weight loss between first and second visits of greater than 4.5 kg; and anal and genital lesions suggesting herpes simplex infection. The following clinical laboratory test results were recorded: hematocrit, 40% or less; neutrophil count, less than 1800/mm^3; platelet count, less than 150 000/mm^3; and total lymphocyte count, less than 1000/mm^3.

Generalized lymphadenopathy was defined as the finding on physical examination of lymph nodes 1 cm or greater in diameter in two or more noncontiguous extrainguinal sites, with any number and site of cervical nodes counted only once. Persistent generalized lymphadenopathy was generalized lymphadenopathy present at two successive semiannual examinations. Localized lymphadenopathy was extrainguinal adenopathy persistent at both examinations but not sufficiently generalized to meet the preceding criteria.

Symptoms, signs, and laboratory abnormalities were initially tabulated for a single visit; we used data from the second visit so that reports of symptoms and lymphadenopathy would both refer to the 6-month interval after entry. Measured weight loss was based on the difference in weight between the two examinations. Manifestations noted at both evaluations were also tabulated.

In subsequent analyses we used the best estimate of the proportion of men with a manifestation present during the first half-year interval (that is, period prevalence). For symptoms during the 6 months, we took those reported at the second visit. For the physical signs prevalent during the interval, we took features present at either the first or the second examination. However, objective weight loss was based on the difference in weights between the first two examinations; and for persistent generalized lymphadenopathy the tabulation was based on the presence of abnormalities at both visits. A hematologic abnormality was prevalent during the 6-month interval if its mean value for the two visits fell below the chosen lower limit.

CLINICAL-IMMUNOLOGIC CORRELATIONS

To analyze the relationship between CD4 counts and clinical features (symptoms, signs, and hematologic abnormalities) present during the 6-month interval under study, we used the mean of the CD4 counts at the two visits $[(CD4_1 + CD4_2)/2]$ for each man and the manifestations prevalent in that interval as described earlier. Through analyses similar to those done for CD4 counts, we searched for any relationships between clinical findings and CD8 counts.

We further attempted to determine how strongly and independently each clinical feature was associated with significant CD4 depletion, as defined by a mean CD4 count less than 250/mm^3. All symptoms and signs related to low CD4 count (except the total lymphocyte count) were entered into a multiple logistic regression model. The model yielded a regression coefficient for the relationship of each clinical feature ($p < 0.1$) to mean CD4 count. Based on these coefficients, from 0 to 2 points were assigned to each symptom or sign that entered into the model. The sum of those points constituted the participant's clinical score for the 6-month study period.

STATISTICAL TECHNIQUES

The chi-square test for association or Fisher exact test was applied to comparisons of proportions. Means and standard errors were computed in the usual manner. The methods described by Armitage (20) were used to calculate values of chi square for a linear trend. Logistic regression analysis was done with the Walker-Duncan technique (21).

Results

Table 1 shows the number and proportions of seropositive and seronegative men with selected clinical features recorded at a single evaluation and at both evaluations. Half of the seropositive and nearly one third of the seronegative men reported one symptom at that evaluation. More than 70% of seropositive and more than 40% of seronegative men had one of the physical signs. Almost 85% of seropositive compared with 33% of seronegative men had a hematologic abnormality. Almost all (97%) of the seropositive and about three quarters of seronegative men had at least one finding at one visit. In the 6-month period between the first and second visits, persistent generalized lymphadenopathy was about nine times more frequent in the seropositive than the seronegative participants. Other physical signs and symptoms were as high as 4 to 5 times more frequent in the seropositive than the seronegative men. A low CD4 count was 13 times commoner, and other hematologic abnormalities were 3 to 10 times more common in seropositive men. Symptoms and signs often occurred during only one of the two 6-month intervals, and some were actually less commonly described at the second visit than at the first. Some symptoms and signs were commoner in the group of men who had localized or persistent generalized lymphadenopathy than in the group without lymphadenopathy, but abnormal total lymphocyte and CD4 counts and abnormal CD4/CD8 ratios were almost equally frequent in the three groups.

Men with persistent generalized lymphadenopathy were categorized by serologic status and by each of the 11 node sites examined (Table 2). About 31% (493 of 1601) of the seropositive and 3.5% (88 of 2639) of the seronegative men had persistent generalized lymphadeno-

Table 3. Proportion of Men with Clinical Manifestations Present During the 6 Months Between First and Second Visits, by Mean CD4 Counts for Two Visits

Clinical Feature	Seronegative with Mean CD4 Count of	Seropositive with Mean CD4 Count of				Regression Coefficient	Clinical Score*
	700+ (1947-2008)†	700+ (304-313)†	400-699 (642-655)†	250-399 (216-223)†	0-249 (65-67)†		
	%						
Fever	0.5	0.9	1.2	0.9	9.0‡	1.40	2
Diarrhea	3.4	3.2	3.7	5.4	6.0	...	...
Fatigue	6.9	6.9	6.7	8.5	19.4§	0.83	1
Night sweats	1.4	3.0	3.5	3.1	6.0	...	...
Herpes zoster	0.4	1.6	1.7	2.7	7.5§	...	...
Herpes simplex new or worse in last 6 months	4.7	6.3	10.6	10.8	12.1§	...	...
Weight loss	7.3	5.6	5.7	8.1	16.4§	...	...
Oral thrush or white patches	3.7	5.8	10.4	13.0	31.3‖	1.35	2
Persistent generalized lymphadenopathy	3.7	30.4	32.0	27.4	32.8	...	...
Palpable spleen	0.8	1.4	2.5	2.7	4.5	...	...
Fungal skin infection	19.8	17.6	28.1	32.1	37.3‖	...	...
Low hematocrit	1.2	3.2	3.4	9.1	20.9‖	1.38	2
Low platelet count	0.7	2.8	3.4	10.2	10.8‖	0.85	1
Low neutrophil count	0.8	3.5	3.2	6.4	13.4‡	1.11	2

* Clinical score points based on logistic regression coefficient.
† Range of numbers of participants with requisite data available.
‡ $p < 0.005$, chi square for linear trend over CD4 categories.
§ $p < 0.05$, chi square for linear trends over CD4 categories.
‖ $p < 0.0005$, chi square for linear trend over CD4 categories.

pathy. Although seropositive men had a significantly higher mean number of involved node groups than the seronegative men (5.7 compared with 4.5 nodes, $p < 0.005$), the numerical difference in the means is not striking. Axillary nodes were nearly universal in both seronegative and seropositive men with persistent generalized lymphadenopathy. In contrast, posterior cervical, posterior auricular, occipital, and supraclavicular node groups showed abnormalities significantly more often in seropositive than seronegative men with persistent generalized lymphadenopathy ($p < 0.05$). Besides persistent generalized lymphadenopathy, considerable proportions of both seropositive and seronegative men had localized lymphadenopathy (29% and 18%, respectively).

Seronegative men with persistent generalized lymphadenopathy closely resembled seronegative men without lymphadenopathy in their frequencies of past sexual activities and sexually transmitted infections, and in their laboratory test results for exposure to hepatitis B and cytomegalovirus (data not shown). The mean $\pm$ SE CD4 counts in the seronegative men with (1048 ± 42) and without (1034 ± 8) persistent generalized lymphadenopathy also were quite similar. In contrast, seronegative men with persistent generalized lymphadenopathy differed from seropositive men with this condition in many of the preceding characteristics, with the seronegative men reporting significantly less sexual activity than the seropositive.

The proportions of individual clinical findings in seropositives during the first 6 months of folow-up are shown in Table 3; the data are stratified according to the mean CD4 count for the two visits. The relationship of persistent generalized lymphadenopathy to mean CD4 count is especially noteworthy: its overall prevalence was not significantly greater among men with the lowest CD4 counts (32.8%) than among those with higher counts (27% to 32%; $p = 0.9$). In the absence of symptoms, seropositive men with persistent generalized, localized, or no lymphadenopathy had nearly identical but abnormally low mean CD4 counts (651 ± 16, 658 ± 15, and 685 ± 31, respectively).

For each other individual clinical manifestation (Table 3), the proportions of affected men rose to varying extent with progressively lower CD4 counts; the strongest upward trends were seen for thrush, low hematocrit, low platelet count, fever, low neutrophil count, and superficial fungal infection ($p < 0.005$). We also determined that there were equally strong quantitative relationships between the occurrence of these clinical characteristics and each of the three common indices of T-cell derangement: CD4 counts, CD4 percents, and CD4/CD8 ratios (data now shown).

None of the findings had obvious alternative explanations. In particular, few of the men with these abnormalities had recently taken any kind of drug, and exclusion from analysis of men with evidence of recent hepatitis B or syphilis or men who used parenteral drugs did not alter the findings.

Taken individually, a number of symptoms and signs were related to CD4 counts. Using multiple logistic regression techniques to examine the interrelationships, thrush, low hematocrit, fever, and low neutrophil count were strongly and independently correlated with a mean CD4 count less than 250; fatigue and low platelets were

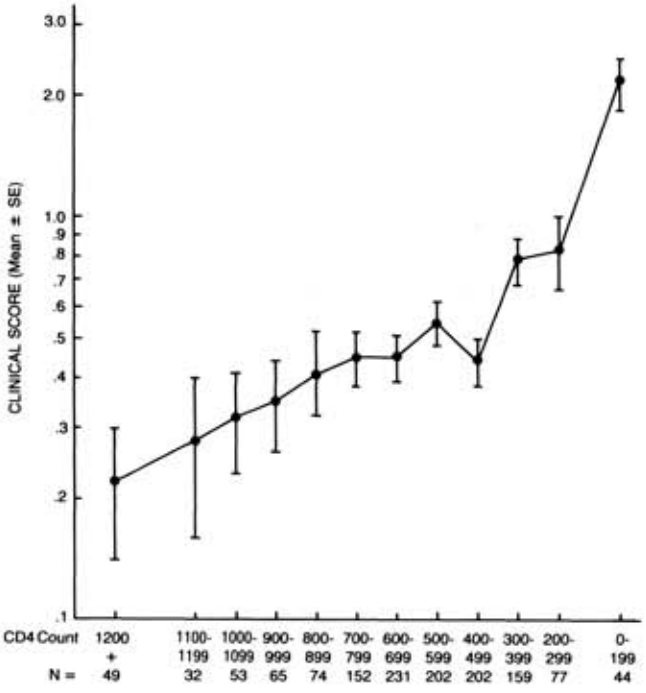

Figure 1. Mean clinical score for 6-month interval in seropositive men, by mean CD4 count.

weaker correlates; and the other symptoms and signs showed little independent correlation with a mean CD4 count less than 250. Point values approximately proportional to the regression coefficients were assigned to the symptoms and signs (Table 3). Using these point values, we computed a clinical score reflecting the relative contribution of the six manifestations strongly and independently associated with loss of T-helper lymphocytes. For example, from Table 3, a man with only fever and low platelets would be given a score of 3, whereas one with only oral thrush and a low hematocrit would be given a score of 4.

On the basis of their clinical scores for the 6-month interval, 28% of the seropositive men (419 of 1523) had one of these manifestations, and 2% (36 of 1523) had substantial HIV-related clinical involvement (score, 4 or greater). Substantial involvement was seen in about 7% (20 of 280) of all seropositive men with CD4 counts less than 400. Counts less than 400 were found in 20 of 28 men with scores of 4 or greater. Thus, the clinical abnormalities were considerably better at reflecting concurrent CD4 lymphocyte depression than the low CD4 lymphocyte counts were at determining clinical involvement. Figure 1 shows that clinical expression began with the mildest depressions of T-helper cell count and that mean clinical scores increased further in groups of men with successively lower CD4 counts.

When data on persistent generalized lymphadenopathy were stratified by mean CD8 count in a manner similar to that described for CD4, that clinical feature occurred no more often in seropositive men with higher CD8 counts than in those with lower ones, regardless of the CD4 counts. Among asymptomatic men, the mean CD8 counts for those with persistent generalized lymphadenopathy (832 ± 19), those with localized lymphadenopathy (873 ± 24), and those without any lymph node abnormality (774 ± 36) were not significantly different from each other, although CD8 counts for those with localized node enlargement did show a trend toward higher means ($0.05 < p < 0.1$). We could discern no systematic variation in any other clinical findings across the categories of CD8 counts.

Discussion

This cross-sectional analysis of one of the largest cohorts of homosexual men currently under observation extends earlier knowledge about clinical manifestations of HIV-induced immunodeficiency. Three quarters of the 2646 seronegative men and all but 3% of the 1620 seropositive men had some symptom or sign on at least one of two clinic visits 6 months apart. Clinical findings, particularly symptoms, were often present at one visit and absent at the other. Many of these findings were obviously nonspecific for HIV infection. It is also important to stress that, beginning in 1984, the open recruitment for any gay man without AIDS undoubtedly attracted some men because they had lymphadenopathy or other symptoms. Selection of ill participants might have produced unrepresentatively high prevalence figures in both seropositive and seronegative men but should have had minimal effects on the interrelationships we have observed.

Previous analyses have tended to aggregate the symptoms and signs into "lymphadenopathy syndrome" or "AIDS-related complex" (5), in various combinations. Because there were no standard definitions for these syndromes, we approached the analysis empirically. Symptoms and signs were examined separately first and then systematically combined on the basis of their relationship to CD4 count as the indicator of HIV-induced immunodeficiency.

Because the large numbers of cases of persistent generalized lymphadenopathy were drawn from entire cohorts of seropositive and seronegative men, we were able to study lymphadenopathy in greater detail than others have reported (5, 22). Although the distribution of abnormal nodes in seropositive men with persistent generalized lymphadenopathy resembled that noted by others, several findings suggest that our study participants were being seen earlier in their infection than subjects of other studies. Fewer men with persistent generalized lymphadenopathy in the current study (32%) than in others (4, 8) reported awareness of lymph node enlargement before entry; even among our volunteers who did recognize it, the duration was relatively briefer (median, 10 months) (8). Compared to men in other studies, our cohort members with persistent generalized lymphadenopathy also had a lower mean number of involved node groups (5), fewer accompanying symptoms (2, 4, 5, 8), and less T-lymphocyte derangement (4, 8, 9, 14, 23). It is also possible that some men with more serious immunodepletion at enrollment may have already had loss of lymph node tissue as reported elsewhere (24).

The proportion of seronegative men with persistent generalized lymphadenopathy was similar to that found

elsewhere (10, 22). Seronegative men with persistent generalized lymphadenopathy resembled seronegative men without lymphadenopathy more than seropositive men with lymphadenopathy in sexual exposure and lymphocyte counts. In general this lymphadenopathy probably does not represent infection with HIV in the absence of antibody production, but further study is clearly needed to rule out an atypical response to HIV and to identify alternative causes.

Our data confirm the growing suspicion (12, 25) that the occurrence of persistent generalized lymphadenopathy is independent of quantitative T-helper cell deficiency. The proportion of all seropositive men who had persistent generalized lymphadenopathy varied little with CD4 count (Table 3); in the absence of symptoms, men with and without persistent generalized lymphadenopathy had similarly abnormal mean CD4 counts. Also, many of the clinical signs and symptoms occurred more independently of lymphadenopathy than earlier reports have indicated (2, 4, 5, 8, 26) (Table 1).

Previous studies have not made direct comparisons (seropositive men with and without lymphadenopathy or lymphadenopathy with and without symptoms) among large enough groups to establish these relationships firmly. If the lymphadenopathy is caused by HIV, it is most likely a frequent early expression of HIV infection that develops with seroconversion (27, 28) and persists until later stages. The CD4 counts were probably equally depressed in our asymptomatic seropositive men with or without persistent generalized lymphadenopathy simply because infection in both groups, although recent, was sufficiently established to permit comparable amounts of T-helper cell destruction by the retrovirus. A more remote possibility is that persistent generalized lymphadenopathy influences the clinical outcome of the infection but does so independently of CD4 count; however, reports from other studies (29) and data from our own (30, 31) have not shown any association between presence of persistent generalized lymphadenopathy and development of AIDS in 1 to 3 years. Finally, persistent generalized lymphadenopathy alone was not significantly associated with any appreciable increase in the mean number of T-suppressor and cytotoxic cells, although the data indicated a trend toward higher mean CD8 counts, and some (25, 32, 33) but not others (12, 23) have suggested such an association.

Our analyses have also clarified certain relationships between T-helper cell deficiency and clinical features other than persistent generalized lymphadenopathy. Stronger, independent relationships were found with thrush, anemia, fever, and neutropenia. Fatigue and thrombocytopenia were more weakly correlated after accounting for the first four symptoms. However, symptoms like diarrhea and night sweats showed little independent correlation. Thrush, which has repeatedly been found to denote advancing immunodeficiency (5, 6, 9, 13, 14, 22), was a strong correlate of CD4 depletion in our study participants. Serious thrombocytopenia in homosexual men has been characterized as an autoimmune phenomenon possibly linked to HIV infection (7, 34, 35); more recently, a number of reports (36-38) have noted pronounced platelet deficiency with HIV infection at unspecified stages. Neutropenia has been mentioned but not emphasized as much (4, 34, 36). Anemia has also received relatively minor attention (5, 10, 24, 39) in connection with CD4 depletion, although it was a strong correlate in our cohort.

It has been suggested that the syndrome of "wasting" (fever, diarrhea, or weight loss alone or in combination) is a common manifestation of severe immune depletion in some groups with HIV infection (4, 5, 15, 22). In fact, although about 20% of the participants who had very low CD4 counts (less than 250) did have one or more of those features, all but one of those men also had at least one of the other more strongly associated manifestations described earlier. It may be that, at least in homosexual men, the wasting syndrome seldom occurs until other features (such as thrush or hematologic abnormalities) have already developed. In a similar vein, recent zoster was clearly associated with CD4 cell depletion, but its relationship in our data was not so strong after accounting for the other manifestations.

For clinical and epidemiologic reasons it is important to characterize the interrelationships between HIV-induced T-lymphocyte depletion and other AIDS-related manifestations. Because individual clinical features varied considerably in their association with CD4 depletion, we used a logistic regression analysis to identify those features most strongly and directly associated and then assessed each seropositive participant according to a clinical index based on those features. We found that persistent generalized lymphadenopathy was common but unrelated to immunodeficiency; a significant proportion (28%) of all seropositive men had one or more of the features most specifically indicative of immune depletion; clinical involvement became evident with only slight depressions of the CD4 counts and occurred at exponentially higher frequency with much lower counts; and higher clinical scores accurately reflected the presence of low CD4 counts in seropositive men. This kind of clinical index, reflecting a continuum of T-helper cell loss, could be particularly useful for evaluating infected persons in settings where surface phenotyping and other T-cell indices are not so readily measured. We have begun to examine how rapidly the clinical and immunologic abnormalities are accumulating in the cohort, how much prognostic value these clinical manifestations themselves have for development of AIDS, and whether they improve upon the capability of a low CD4 count to predict poor outcome.

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