Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 5404–5408, August 1987
Immunology

Nonrandom development of immunologic abnormalities after infection with human immunodeficiency virus: Implications for immunologic classification of the disease

(acquired immunodeficiency syndrome/acquired immunodeficiency syndrome-related complex/lymphadenopathy/staging)

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Communicated by Michael Heidelberger, April 22, 1987

ABSTRACT **Blood specimens from 165 intravenous drug users who were seropositive for the human immunodeficiency virus (HIV), from 158 seropositive homosexual men with lymphadenopathy, and from 77 patients with acquired immunodeficiency syndrome (AIDS) were assessed immunologically. Immunologic parameters were analyzed by the Guttman scalogram technique to determine if immunologic abnormalities occurred in a nonrandom pattern. The following four patterns emerged: (*i*) seropositivity for HIV with no immunologic abnormalities; (*ii*) seropositivity for HIV with a depressed T4/T8 cell ratio; (*iii*) seropositivity with a depressed T4/T8 cell ratio and T4-cell depletion; and (*iv*) seropositivity with a depressed T4/T8 cell ratio, T4-cell depletion, and lymphopenia. Ninety-two to 100% of subjects in each of the three groups of patients were found "to scale" because the abnormalities occurred in the cumulative, ordered fashion described. This nonrandom occurrence of abnormalities indicates an ordered progression of immunologic abnormalities in individuals infected with HIV, a finding useful in the staging of both symptomatic and asymptomatic HIV-seropositive subjects.**

Various studies have shown that different manifestations of infection with the human immunodeficiency virus (HIV, ref. 1)—formerly known as human T-cell lymphotropic virus type III (HTLV-III) and lymphadenopathy-associated virus (LAV)—are associated with quantitatively different immunologic abnormalities (2–4). In addition, several immunologic criteria have been used in the staging of HIV infection (5) and acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma (6). However, little is known about the evolution of immune dysfunctions after infection with HIV, and no consensus has developed about the particular panel of laboratory tests that would be most useful in constructing an immunologic staging system that could be used independently from, or in conjunction with, clinical staging systems.

The studies described below were designed to understand the biological and clinical relevance of the immunologic abnormalities in HIV infection and to analyze and identify the immunologic variables most useful in the classification of this disease. The data reveal a nearly invariant pattern in the occurrence of immunologic abnormalities in three groups of HIV-infected individuals and document that immunologic parameters provide a basis for staging HIV infection.

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To examine the immunologic status of individuals infected with HIV but having no or only minimal AIDS-related symptoms, a group of intravenous drug users (IVDU) from New York City was studied. The study was later extended to homosexual men and to patients with AIDS. Analysis of the data has led to the development of a proposed immunologic staging system to which 96% of the individuals studied conform.

METHODS

Subjects. *Intravenous drug users.* A group of 334 IVDU were recruited from drug detoxification and methadone-maintenance programs in New York City during 1984. At entry into the study, none of the subjects had sought or was seeking treatment for either AIDS or AIDS-related complex. They participated with informed consent and full assurances that participation or refusal to participate would not affect their status within the drug-treatment program. A questionnaire was used to gather information on frequency of drug injection, noninjected drug use, and medical history. The medical history included questions about the following symptoms that may be associated with HIV infection: lymphadenopathy lasting >4 weeks, unexplained fever for >4 weeks, unexplained weight loss of at least 10 pounds (4.5 kg), night sweats for >4 weeks, unexplained diarrhea for >1 week, and oral candidiasis diagnosed by a doctor.

Homosexual men. Immunologic data were analyzed from 40 seronegative and 158 seropositive homosexual men with lymphadenopathy, some of whom were participants in a study at the Centers for Disease Control (7). Subjects in this study were enrolled between 1981 and 1983 and were characterized by unexplained lymphadenopathy in at least two extrainguinal sites for at least 3 months. These subjects had no concurrent illness that could account for the lymphadenopathy, and none had diagnosed AIDS.

Patients with AIDS. A group of 77 patients were included who met the Centers for Disease Control surveillance definition of AIDS (8). Forty-two were IVDU; 35 were homosexual or bisexual men.

Controls. Data from 65 blood donors from New York City were obtained to determine normal values for peripheral

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; IVDU, intravenous drug users; β_2m, β_2-microglobulin.

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lymphocyte counts and numbers of lymphocytes, T4-positive lymphocytes (helper/inducer T cells), T8-positive lymphocytes (suppressor/cytotoxic T cells), and T4/T8 cell ratio. Data from 219 blood donors from New York City were obtained to calculate normal levels for serum β_2-microglobulin (β_2m).

Laboratory Studies. Lymphocyte enumeration and subtyping of specimens from IVDU were performed at the New York City Department of Health Laboratory with 5 ml of blood collected in EDTA-containing tubes. Lymphocyte subsets were determined with the whole blood lysis methods using fluorescein-labeled monoclonal antibodies OKT3, OKT4, OKT8 (Ortho–Mune, Raritan, NJ), and B1 (Coulter). A Coulter EPICS C flow cytometer was used. The percentage of each lymphocyte subset was based on the percentage of fluorescent-positive cells within the population of viable lymphocytes defined by gating the cytofluorographic analysis of mononuclear cells using narrow-angle and 90° light scatter. The absolute number of lymphocytes for each subset was obtained by multiplying the percentage for that subset by the number of lymphocytes per mm^3 determined by a differential leukocyte count. Lymphocyte studies and tests for HIV antibody on serum from the group of homosexual men were performed at the Centers for Disease Control as described by Fishbein *et al.* (7).

Aliquots of serum from IVDU were analyzed at the New York City Department of Health Laboratories for antibody to HIV by an ELISA (Abbott); all tests were confirmed by immunoblot (9). Immunoglobulins were quantitated at Beth Israel Medical Center with a rate nephelometer using anti-IgG, anti-IgA, and anti-IgM reagents (Beckman). Serum β_2m was measured at the New York Veterans Administration Medical Center by a microtiter ELISA developed there (10).

Establishment of Limits Between Normal and Abnormal for Each Test. To determine if the data revealed a pattern reflecting the cumulative development of immunologic abnormalities, we used variables that either decreased from the seronegative group to the seropositive group to the patients with AIDS [as do the T4/T8 cell ratio, T4-cell count, lymphocyte count, and B-cell count (see Table 1)] or increased consistently (as do IgA and β_2m). Values that increased in early infection and later decreased, e.g., T8-cell count, IgM, and IgG (3, 4, 11), were excluded from use in establishing the staging system since their nonlinearity created statistical ambiguity; thus, a T8 cell count of 600, for example, could characterize a seronegative individual or an individual with AIDS. The need for data showing unidirectional change was also imposed by the requirements of the Guttman scalogram method.

For values separating normal from abnormal, the following definitions were used: Lymphopenia was defined as $\leq$1500 lymphocytes per mm^3 of blood (12, 13); 5% of the seronegative IVDU were lymphopenic by this definition. Although no absolute standard exists as a definition for an abnormal T4/T8 cell ratio, a value of <1.0 was considered abnormal according to the generally accepted use of this parameter; whereas 21% of seronegative IVDU were abnormal by this criterion (see *Results*), the mean for this group (1.44) fell within normal limits.

No standard definition or generally accepted value exists as a lower limit of normal for T4 cells. Therefore, to define abnormality, the level of T4 cells was determined in blood specimens from seronegative IVDU, seronegative homosexual men, and blood donors. In all three groups, it was found that 5% of the individuals had T4 cell counts <513–558 cells per mm^3. Therefore, a value of <500 T4 cells per mm^3 was defined as abnormal.

Three remaining parameters—B-cell concentration, IgA, and β_2m levels—were examined. This analysis revealed that whereas decreasing B-cell numbers correlated with disease progression (see below), the use of B cells was disadvantageous because the method of measurement used differed between the laboratories participating in the study and because a decrease in B-cell numbers was found to be associated with heavy alcohol consumption among IVDU (data not shown), a finding that would have necessitated the exclusion of a significant proportion of the IVDU. Data analysis also disclosed that use of IgA and β_2m levels was unrevealing since the vast majority of seropositive individuals were in the normal range for IgA and in the abnormally high range for β_2m, precluding their usefulness in this analysis.

Statistical Analyses. Guttman scale analysis was used to test for a cumulative unidimensional structure in the data set (14) by means of the Guttman scaling program of the SAS statistical package (Statistical Analysis System Institute, Carey, NC). Guttman scale analysis is a method for determining whether a set of variables can be ordered along a single dimension. The variables used must be dichotomous, e.g., normal or abnormal, present or absent, etc. Each dichotomous variable can be thought of as a characteristic that a subject may or may not possess. The characteristics are then ranked from the most to the least common within the subject population. The data are said "to scale" if this frequency ranking shows a cumulative order such that any subject possessing a characteristic "X" also possesses all of the characteristics that occur more frequently in the population. The scale score for an individual is then simply the number of characteristics that the individual possesses. Because no data set is likely to scale perfectly, two statistical tests—the coefficients of reproducibility and scalability—have been developed to decide if the data set is within acceptable limits for scaling. Conventional criteria for accepting the existence of a cumulative Guttman scale require a coefficient of reproducibility $\geq$0.9 and a coefficient of scalability $\geq$0.6.

The Duncan multiple range test was used to test the significance of changes in variables across multiple groups. Student's t test and χ^2 analyses were also used.

RESULTS

Studies of IVDU. Of 334 IVDU who entered into the study in 1984, 169 (51%) were seronegative for HIV. Marked differences were noted between the values for seronegative IVDU and controls (Table 1). The increase in the serum IgM level is consistent with findings for IVDU documented prior to the AIDS epidemic (16). The lymphocytosis in the seronegative IVDU studied here is also similar to that observed in IVDU prior to the AIDS epidemic (17, 18) and is primarily associated with an increase in the absolute number of T8 cells that also contributes to the significant drop in the T4/T8 cell ratio to 1.44 ($t = 6.75$; $P < 0.001$). The differences between seronegative IVDU and controls are presumably due to the effects of frequent nonsterile injections, to lifestyle differences, and/or to the effects of the injected drugs themselves.

Multiple statistically significant differences were found between the 51% of IVDU who were seronegative and the 49% who were seropositive (Table 1). These included significant differences in the T4/T8 cell ratio, T4-cell count, lymphocyte count, B-cell count, T8-cell count, and serum IgG and β_2m levels. Comparisons between seropositive IVDU and IVDU with AIDS showed a significant decrease in all variables related to lymphocyte and lymphocyte subset counts. In addition, patients with AIDS had significantly decreased levels of IgM and IgG and significantly increased levels of IgA and β_2m compared to seropositive IVDU without AIDS. These latter changes are consistent with the well-documented immunologic abnormalities that are associated with confirmed AIDS (19, 20).

Table 1. Immunologic parameters among controls, HIV seronegative and seropositive IVDU, and IVDU with AIDS

Group	T4/T8 cell ratio	Cells, no. per mm³				Immunoglobulin, mg%			β_2m, mg/liter
		T4 cells	Lymphocytes	B cells	T8 cells	IgG	IgA	IgM	
Control	2.25 (0.86)	977 (376)	1890 (620)	ND	487 (236)	639–1349	70–312	86–352	1.5 (0.5)
Seronegative	1.44 (0.69)	1150 (443)	3024 (1110)	320 (222)	932 (494)	1593 (449)	255 (113)	317 (186)	2.85 (0.74)
Seropositive	0.64 (0.40)	623 (375)	2415 (1146)	176 (142)	1123 (682)	2465 (1041)	271 (153)	369 (226)	3.76 (0.87)
AIDS patient	0.15 (0.13)	57 (63)	873 (736)	40 (64)	492 (504)	2011 (735)	479 (235)	247 (150)	6.23 (2.35)
Statistical significance	N>P>A	N>P>A	N>P>A	N>P>A	P>N>A	P>A>N	A>N,P	N,P>A	A>P>N

Data are means with standard deviations in parentheses. For controls, specimens from 65 blood donors were used to determine the mean T4/T8 cell ratio, and 46 specimens were used for the mean T4- and T8-cell counts. Data for normal immunoglobulin ranges are cited from ref. 15, and β_2m values were obtained from the sera of 219 blood donors. ND, not done. For computation of data for HIV-seronegative and HIV-seropositive subjects, n = 169 and 165, respectively, for cellular values; n = 146 and 159, respectively, for immunoglobulin quantitation; n = 42 and 72, respectively, for β_2m levels. For computation of data for AIDS cases, n = 42 for cellular values, n = 37 for immunoglobulin quantitation, and n = 12 for β_2m levels. The Duncan multiple range test was used to test for significant differences between seronegative subjects (N), seropositive subjects (P), and AIDS patients (A), with significance defined as $P < 0.05$. Control mean values for lymphocytes, lymphocyte subsets (except B cells), and for β_2m were compared by Student's t test to values from all other groups. All comparisons were statistically significant ($P < 0.05$) except for the difference in the mean number of T8 cells between controls and AIDS patients.

Evidence for the Ordered Progression of Immunologic Abnormalities Among Seropositive IVDU. The T4/T8 cell ratio, T4 cell count, and lymphocyte count for each of the 165 seropositive IVDU were categorized as normal or abnormal. The data were then analyzed by Guttman scale analysis, and an ordered pattern of immunologic abnormalities emerged (Table 2). Thus, 162 of 165 (98%) seropositive IVDU could be stratified into one of the following four immunologic categories: (*i*) a category in which seropositive individuals had normal values for each of the three immunologic parameters; (*ii*) a category in which seropositive individuals had abnormally low T4/T8 cell ratios (<1.0) but normal numbers of T4 cells (≥500 cells per mm³) and lymphocytes (>1500 cells per mm³); (*iii*) a category in which seropositive individuals had abnormally low T4/T8 cell ratios and abnormally low numbers of T4 cells (<500 cells per mm³) but normal numbers of lymphocytes; and (*iv*) a category in which seropositive individuals had abnormally low T4/T8 cell ratios, abnormally low numbers of T4 cells, and abnormally low numbers of lymphocytes (≤1500 cells per mm³). The data set exceeds conventional criteria for accepting the existence of a cumulative Guttman scale in that the coefficients of reproducibility and scalability are 0.99 and 0.96, respectively. By these criteria, the data were said to scale, indicating that the immunologic abnormalities occur in an ordered fashion. This scale is shown graphically by the triangular pattern of pluses in Table 2. Other combinations of immunologic abnormalities, e.g., a normal T4/T8 cell ratio with a normal T4 count and an abnormally low lymphocyte count, did not occur or were extremely rare (see below).

Table 2. Pattern of lymphocyte abnormalities among 162 seropositive IVDU

Abnormality present*			Distribution of scale scores		
T4/T8 cell ratio	T4 cells	Total lymphocytes	Scale score†	Individuals, no.	%
−	−	−	0	26	16
+	−	−	1	62	38
+	+	−	2	45	28
+	+	+	3	29	18
84%‡	46%‡	18%‡			

+, Abnormality present; −, abnormality absent.
*Abnormal values were defined as a T4/T8 cell ratio <1.0; a T4-cell count <500 cells per mm³, and a lymphocyte count ≤1500 cells per mm³.
†Scale score is defined by the number and pattern of abnormalities among these three immunologic tests.
‡% of individuals with the abnormality.

While the three variables found to be most useful in generating the scale are intercorrelated, it was found that no single variable could, by itself, account for the scale. For example, although the T4 count correlated best with the scale scores ($r = -0.76$), the T4 count was not as critical as the T8 count in determining the T4/T8 cell ratio for individuals with scale scores 0 and 1. Thus the scale of cumulative immunologic abnormalities is significantly related to its various components but is not determined by any single component.

Table 3 presents the mean values for various immunologic parameters as a function of the scale scores for the 162 seropositive IVDU conforming to the Guttman scale. Inspection indicates that an increase in the T8-cell count and a decrease in the T4-cell count contribute to the drop in the T4/T8 cell ratio associated with a scale score of 1. An increase in serum β_2m is also associated with this change. The drop in T4 cells, which defines scale score 2, is accompanied by an increase in IgG levels. Progressive decreases in the absolute B-cell count begins with seroconversion.

Determining the relationship of scale score to the existence of AIDS-related symptoms was complicated by the facts that (*i*) selection criteria had already eliminated those with symptoms sufficiently severe to seek treatment for them, (*ii*) 55% of seronegative IVDU reported one or more AIDS-related symptoms, and (*iii*) self-reported weight loss, a common characteristic of IVDU, was the most frequently reported symptom, regardless of serologic status. Consequently, no significant correlation was found between scale scores and the presence of AIDS-related symptoms ($r = 0.154$, $n = 132$, $P = 0.08$). However, when the percentage of individuals with symptoms who had scale scores of 0 or 1 was compared to the percentage of symptomatic individuals who had scale scores of 2 or 3, the difference was significant ($\chi^2 = 4.87$, $n = 132$, $P = 0.03$).

Application to Male Homosexuals. To determine whether the scale generated with immunologic data from seropositive IVDU was useful in the study of other groups at risk for HIV infection, we applied the scaling procedure to a group of 158 HIV-seropositive male homosexual patients with lymphadenopathy. The identical pattern of cumulative lymphocyte abnormalities was found, and the data set met the criteria for acceptance as a Guttman scale (coefficients of reproducibility and scalability = 0.95 and 0.83, respectively). One hundred forty-five of the 158 subjects (92%) conformed to the scale (Fig. 1).

Application to Patients with AIDS. We applied the scaling technique to 42 IVDU with AIDS. One of these drug users

Table 3. Immunologic parameters and frequency of AIDS-related symptoms among 162 seropositive IVDU

Scale score	T4/T8 cell ratio	Cells, no. per mm³				Immunoglobulin, mg%			β_2m, mg/liter	% with AIDS-related symptom(s)
		T4 cells	Lymphocytes	B cells	T8 cells	IgG	IgA	IgM		
0	1.34	1040	2602	249	805	1900	216	391	2.79	71
1	0.58	819	3207	212	1562	2197	263	393	3.68	60
2	0.40	367	2081	149	1087	2931	283	338	4.27	78
3	0.43	239	1187	78	598	2847	318	350	3.78	86
Statistical significance	0>1>2,3	0>1>2>3	1>0>2>3	0,1>2>3	1>2>0,3	2,3>0,1	3>0	NS	0<1,2,3	(0+1)<(2+3)

Data are the mean. Except for β_2m and % with AIDS-related symptoms, n = 24–26 for scale score 0, 61–62 for scale score 1, 43–45 for scale score 2, and 27–29 for scale score 3. For β_2m and % with AIDS-related symptoms, n = 9 and 24, respectively, for scale score 0; n = 21 and 50, respectively, for scale score 1; n = 20 and 37, respectively, for scale score 2; n = 21 and 21, respectively, for scale score 3. Duncan multiple range test used except for comparison of frequency of subjects with symptoms where χ^2 analysis was performed. Significant differences shown where $P < 0.05$.

had Kaposi sarcoma as the initial AIDS diagnosis; the rest had opportunistic infections. The same pattern of cumulative immunologic abnormalities was found, and all 42 patients conformed to the scale: 36 of the IVDU with AIDS had all three lymphocyte abnormalities (scale score 3); 6 had two abnormalities (scale score 2); none of the IVDU with AIDS fell into scale scores 0 or 1 (Fig. 1).

Finally, we applied the scaling technique to data from 35 male homosexuals with AIDS. Seventeen of these patients were diagnosed with Kaposi sarcoma and 18 with opportunistic infections. All 35 subjects conformed to the scale. The distribution of scale scores for male homosexuals with Kaposi sarcoma was intermediate between the distributions seen for the homosexual men with lymphadenopathy and those with opportunistic infections (Fig. 1). This is consistent with the findings suggesting that Kaposi sarcoma may develop in homosexual men with a lesser degree of immunosuppression than that found in patients with opportunistic infections (3).

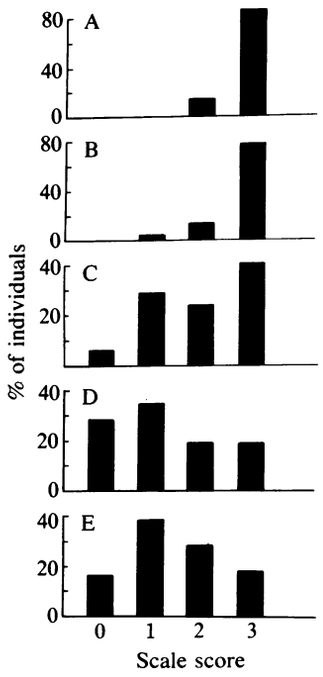

FIG. 1. Distribution of scale scores for seropositive IVDU, seropositive homosexual men with lymphadenopathy, and AIDS patients. Scale scores in these subjects are defined by the number and pattern of abnormalities among three immunologic tests (T4/T8 cell ratio, number of T4 cells, and number of lymphocytes) as defined in the text and in Table 2. (*A*) IVDU with AIDS. (*B*) Homosexual men with AIDS-related opportunistic infection. (*C*) Homosexual men with AIDS-related Kaposi sarcoma. (*D*) Seropositive homosexual men with lymphadenopathy. (*E*) Seropositive IVDU.

DISCUSSION

Ninety-six percent (384/400) of HIV-seropositive subjects could be stratified into the following four categories on the basis of their immune characteristics: (*i*) a category, designated by a scale score of 0, in which subjects were HIV-seropositive but had normal values for the T4/T8 cell ratio, for the absolute number of circulating T4 cells, and for total lymphocytes; (*ii*) a category, designated as scale score 1, in which seropositive subjects had a depressed T4/T8 cell ratio but had normal values for the absolute number of circulating T4 cells and for total lymphocytes; (*iii*) a category, scale score 2, in which seropositive subjects had a decreased T4/T8 cell ratio and abnormally low numbers of circulating T4 cells but had a normal number of total lymphocytes; and (*iv*) a category, scale score 3, in which seropositive subjects had a decreased T4/T8 cell ratio and abnormally low numbers of circulating T4 cells and total lymphocytes.

The occurrence of these discrete patterns indicates that each immunologic abnormality reflects a further step in the evolution of immunologic destruction caused by HIV. Thus, the conformation of these data to a Guttman scale (as denoted by the triangular pattern of pluses in Table 2) demonstrates that there is an ordered progression in the development of immunologic abnormalities occurring in HIV infection. This method of analysis permits the values of several variables, for a given individual, to be combined into a composite measurement, the scale score, and places the individual at a particular point in the continuum of HIV-associated immune dysfunction. The scale score describes the immunologic status of the individuals at one point in time but, on the basis of present information, cannot be used to predict whether the individual will ultimately remain stationary or will move in one direction or the other along the continuum.

Scale scores of 0 and 1 were most common among seropositive individuals without AIDS; 54% of seropositive IVDU and 63% of seropositive homosexuals with lymphadenopathy had scale scores of 0 or 1. Since this is a common occurrence after viral infection (21–23) and since 21% of seronegative IVDU also had an inverted ratio, it is clear that this particular immunologic parameter must be viewed as highly nonspecific, i.e., a laboratory abnormality that may or may not be related to HIV infection and that is not, by itself, indicative of immunologic dysfunction. The remaining 46% of seropositive IVDU exhibited multiple immunologic abnormalities consistent with the pathogenic effects of HIV including the characteristic decline in the number of circulating T4 cells (which defines scale score 2) and the observed

decrease in total lymphocytes to abnormal levels (scale score 3). The latter underscores the effects of the virus on the various classes and subsets of lymphocytes since this reduction consists of losses sustained among the T8 and B cells as well as the T4 cells.

The data reveal several aspects about the evolution of HIV infection and about the immune response to it. Since the first immunologic abnormality to follow seroconversion is an inversion of the T4/T8 cell ratio (due primarily to increases in the concentration of T8 cells) and an increase in serum β_2m levels, it appears that the immune system can respond to this virus as it does to many other viruses. However, as the effects of the infection become more marked, significant immunologic destruction occurs. Whereas studies (5, 24, 25) have stressed the drop in the absolute number of T4 cells as the hallmark of immunologic destruction, the data presented in our study place the decrease in T4-cell count in a continuum of immunologic abnormalities induced by HIV infection.

A small proportion, 4% (16 subjects), of seropositive individuals, did not conform to the scale. Half of these individuals did not conform because of the rigidity of the definitions of abnormality. The values that prevented them from conforming were within 5% of the cut-offs from normal and thus within the limits of measurement error. The other half (eight subjects) did not conform due to abnormally low numbers of T4 cells and/or lymphocytes in individuals with T4/T8 cell ratios >1.0.

The fact that 55% of seronegative IVDU reported one or more AIDS-related symptoms (usually weight loss), compared to 71% of seropositive IVDU, makes the interpretation of the observed symptoms in seropositive IVDU problematic. Weight loss may be related to extensive drug use or to the poor nutrition associated with intensive drug injection (17); however, the increased frequency of individuals with symptoms among those who had scale scores 2 or 3 compared to those with scores 0 or 1 suggests that HIV infection also contributes to the appearance of weight loss and other HIV-related symptoms.

On the other hand, the use of immunologic parameters to classify seropositive asymptomatic individuals may prove to be one of the most useful aspects of the scale scores described here. Indeed 38 of the 165 seropositive IVDU studies were asymptomatic and had scale scores that ranged from 0 to 3 (data not shown). Since the majority of HIV-infected individuals outside of the IVDU risk group are asymptomatic (26), expanding symptom-based classification systems (27, 28) to allow the subdivision of asymptomatic individuals may prove to be particularly valuable. The Walter Reed Staging Classification (5) already combines clinical symptoms with quantitation of T4 cells and delayed hypersensitivity; however, it is a complex classification system, it is difficult for patients to understand, and it fails to subdivide the vast majority of HIV-infected individuals who are asymptomatic and have only subtle signs of immunologic alterations.

Finally, the immune classification system described here may be useful as an independent measure of the severity of HIV disease. For example, in the course of clinical trials for antiviral drugs and immune modulators, multiple tests need to be performed to quantitate the effects of the drugs on the immune system. Determination of the immunologic variables, shown here to be associated with the progression of HIV infection, and use of the scale scores as a composite measurement of immune status, could provide a valuable tool in measuring improvement or deterioration of immune status in the course of therapeutic intervention or progressive disease.

We acknowledge D. Sencer, S. Beatrice, R. Enlow, and N. Scheidt of the New York City Department of Health for the lymphocyte subset determinations and HIV antibody typing of specimens from IVDU; A. Trzeszkowski and K. Robertson for programming assistance; and D. Shonekin for handling of blood specimens. This work was supported in part by Public Health Service Grants DA 03574, AI 62542, and ES 00260, Grants C000621 and C00214 from the New York State AIDS Institute, Special Center Grant 0009 from the American Cancer Society, by the Rita and Stanley Kaplan Cancer Center, and by research funds from the Veterans Administration.

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