Multidisciplinary Baseline Assessment of Homosexual Men With and Without Human Immunodeficiency Virus Infection

I. Overview of Study Design

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• Although much is known about the virus believed by most experts to be the cause of the acquired immunodeficiency syndrome and about its pathogenic actions, major areas of ignorance remain. Among these are the reasons for the varying time between infection with human immunodeficiency virus and development of acquired imunodeficiency syndrome, the relationship between neurologic and medical aspects of the disease, the time course of neuropsychological findings, and the prevalence of psychiatric morbidity. We assessed 124 homosexual men who were positive for human immunodeficiency virus and 84 who were negative for the virus. In this article we describe the study design, method of recruitment, and medical and demographic characteristics of the cohort, which will be followed up for 5 years.

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The acquired immunodeficiency syndrome (AIDS) is an illness that is transmitted by "high-risk" behavior and results in widespread neuropsychiatric morbidity,[1-3] making it important to study the behavioral and nervous system aspects. Although much is now understood about the genetic structure, life cycle, and pathogenesis of the agent that causes AIDS[4-6]—human immunodeficiency virus (HIV)—our only tool in preventing infection remains promotion of behavioral change. At present, we also know little about the relationship of neuropsychiatric symptoms to medical and immunologic symptoms of HIV infection.

To address these issues, we began a 5-year follow-up study of HIV-infected subjects in March 1988. This study provides cross-sectional and longitudinal information from well-matched HIV-seropositive and HIV-seronegative homosexual men and parenteral drug users.

Data are now available from the first evaluation of the homosexual male cohort, thereby providing a cross-sectional look at the relationship between HIV infection and behavior, psychiatric morbidity, psychosexual function, and the nervous system at a relatively early stage in the disease.

Because of the multidisciplinary nature of this study, it was thought best to report the baseline data on the homosexual men in a series of related articles. This article will therefore provide information on the method of recruitment, study design, demographics, and medical status of the subjects. The accompanying articles describe psychiatric/psychosocial and neurologic/neuropsychological findings, respectively.

SUBJECTS AND METHODS

Recruitment of the homosexual male cohort was initiated in the winter of 1987 and early spring of 1988. A single announcement in each of two New York, NY, homosexual organization monthly newsletters, one paid newspaper announcement, and word of mouth drew most of the study participants.

The baseline evaluations were completed between March 1988 and

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March 1989. To be eligible for entry into the study, a subject had to meet the following inclusion criteria: (1) homosexual or bisexual man between 18 and 60 years of age, (2) previous HIV testing, including knowing the test result for at least 1 month before study entry, (3) not having self-administered parenteral drugs more than 10 times since 1981, and (4) not having any of the infections or tumors classified as meeting criteria for AIDS according to the Centers for Disease Control (CDC) National Surveillance Criteria.[7]

We made some exceptions to CDC criteria for AIDS before starting the study. Because we wished to assess nervous system abnormalities independently, we did not exclude subjects from study entry because of neuropsychological impairment even though the CDC criteria that were revised between the time our protocol was designed and the beginning of field work included dementia as sufficient to warrant a diagnosis of AIDS.[8] We also began our study before this revision of CDC criteria came to include "constitutional symptoms," such as weight loss, persistent diarrhea, night sweats, and fatigue, as AIDS diagnoses. Subjects with these symptoms were, therefore, not excluded. Finally, because the clinical distinction between oral and esophageal candidiasis is difficult to make on routine physical examination, we did not follow CDC criteria by excluding men with esophageal candidiasis as meeting the criteria for AIDS. The reason for excluding subjects who already had AIDS was to ensure that we began our study with relatively medically asymptomatic subjects.

The reason for requiring that all subjects already know their HIV status before study entry was that at the time the study began (1987) we did not wish to be in the position of appearing to encourage testing. The decision to have an HIV test is a highly individual one; knowing HIV status may help a person obtain treatment early in the course of infection but may also subject the individual to discrimination and social isolation. Since 1987, with increased ability to treat HIV infection and its consequent opportunistic infections, many authorities have recommended early HIV testing.

Subjects arrived at the clinic at the New York State Psychiatric Institute, New York, at 8:30 AM for the assessment day. They first met with the project director for explanation of the procedures and to give informed consent. Next, the subject met with one of the project research nurses, who offered pre-HIV test counseling and obtained the following information: a complete medical history with the use of a semistructured interview, devised by our group, that focuses on HIV-related medical symptoms; a demographic questionnaire, also devised by our group, that assesses socioeconomic status, living arrangements, and religious affliations; vital signs; and blood for the following tests: complete blood cell count, platelet count, T-cell subset enumeration, p24 antigen level, and acid-labile interferon-α titer. We also obtained blood for confirmatory HIV testing, which was done by enzyme-linked immunosorbent assay and Western blot by the New York City Health Department.

After seeing the nurse, subjects underwent five separate assessments as follows: (1) a physical examination conducted by a physician, focusing on HIV-related signs; (2) a neurologic examination, conducted by a neurologist; (3) a neuropsychological test battery; (4) structured and semistructured psychiatric and psychosocial interview conducted by trained interviewers; and (5) structured and semistructured psychosexual interview.

Further details about the psychiatric/psychosocial and neurologic/neuropsychological assessments are found in the accompanying articles. The physical examination, neurologic examination, and neuropsychological tests were all performed without knowledge of the subject's HIV status. The issues surrounding blindedness in conducting psychiatric interviews are more complex and are discussed in one of the accompanying articles.

We devised two systems for staging HIV infection. The first is a four-tier system. On the basis of the medical history and physical examination alone, HIV-seropositive subjects were assigned a number from 0 to 39. A score of 0 to 9 represents a seropositive but physically asymptomatic subject (ie, with no physical symptoms assumed to be related to HIV infection that in themselves are severe enough to warrant clinical attention). A score of 10 to 19 represents a seropositive subject with mild medical symptoms (history or evidence of generalized lymphadenopathy or any clinically significant physical symptoms not meeting criteria for stage III, eg, diarrhea for 2 weeks, fever for 2 weeks, or fatigue every other day for 1 month). A score of 20 to 29 represents a seropositive subject with serious symptoms, including a history or evidence of any of the following: oral or esophageal thrush, night sweats for more than 30 days, fever for more than 30 days, loss of more than 10% of body weight, diarrhea for more than 30 days, fatigue for more than 30 days, oral hairy leukoplakia, pulmonary tuberculosis, *Salmonella* septicemia, pneumococcal bacteremia, herpes zoster, *Haemophilus influenzae* bacteremia, and idiopathic thrombocytopenic purpura. A score of 30 to 39 represents a subject with AIDS, ie, seropositive with opportunistic infections or secondary cancer. By definition, no subject with a score of 30 or above was entered in the study. Within each scoring decade, the examining physican was free to assign a score using subjective judgment of severity of medical signs and symptoms. The three examining physicians (R.K., J.D., and J.M.G.) later reviewed all of the medical histories, examinations, and medical stage scores in a conference.

Table 1.—Demographic Characteristics*

	Positive HIV (N=124)	Negative HIV (N=84)	t	P
Age, y	38.4±8.2	37.7±8.9	0.55	NS
Socioeconomic status (Hollingshead)	49.2±12.4	53.1±9.3	2.61	.01
Education, y	15.9±2.5	16.5±2.1	1.83	.07
Race, %				
White	85	86	...	...
Hispanic	7	7	...	...
Black	3	4	...	...
Black/Hispanic	1	0	...	...
Asian/Pacific island	2	2	...	...
Unknown	2	1	...	...

*HIV indicates human immunodeficiency virus; NS, not significant.

The second system involves a 20-item symptom checklist. These 20 items represent common signs and symptoms of HIV infection (but not AIDS) found on physical examination and/or by medical history. The time frame for the presence of symptoms identified by history was usually the 3-month period before the baseline assessment. The score on the checklist is simply the number of items recorded for the subject at baseline assessment.

Blood samples were always drawn in the morning. They were then immediately transported to the laboratory for HIV test (by enzyme-linked immunosorbent assay with Western blot confirmation), T-cell subset enumeration (by fluorescent cell sorter [EPIC-C, Coulter Electronics, Hialeah, Fla]), p24 antigen assay (by standard kit [Dupont, Wilmington, Del]), and acid-labile interferon-α titer (methods available on request).

At the conclusion of the day, subjects again met with the research nurse and project director for debriefing. At this time subjects were also given counseling about risk reduction, and a decision was made whether the subject needed referral for medical or psychiatric care. Subjects were then paid $10 per hour for their time and given an appointment to return in 6 months.

RESULTS

A total of 215 men underwent the baseline assessment. Seven of these were dropped from data analysis for the following reasons: four subjects were found to have a history of serious neurologic disorder preceding the beginning of the HIV epidemic and therefore unrelated to HIV infection (one of the four had a seizure disorder and the other three had Tourette's syndrome; the interpretation of neurologic and neuropsychological data for these patients was believed to be too confounded by the preexisting illness), one subject was blind and therefore unable to complete the neuropsychological tests, one patient was found to have an opportunistic infection characteristic of AIDS at the time of the baseline assessment, and one subject had a history of recent parenteral drug abuse that was not ascertained until the psychiatric interview was conducted.

The remaining 208 subjects are the subject of these reports. One hundred twenty-four were HIV positive and 84 were HIV seronegative. Table 1 shows the age, ethnicity, and Hollingshead socioeconom-

Table 2.—Number of Subjects Positive for Individual SCS-20 Items*

Symptom	HIV Positive (N=124)	HIV Negative (N=84)	χ^2†	P
Herpes (oral/genital) (ever)	67	36	2.50	NS
Oral candidiasis (ever)	38	6	15.20	.001
Lymphadenopathy (by examination presently)	34	7	10.35	.002
Nonallergic body rash (Hx)	28	9	4.04	.05
Shingles (ever)	28	4	10.88	.001
Sinusitis (Hx)	18	10	0.11	NS
Leukoplakia or thrush (by examination presently)	17	0	10.78	.001
Fever (Hx)	9	0	4.74	.05
Night sweats (Hx)	8	1	2.20	NS
Rash or scaling around eyes (Hx)	7	1	1.62	NS
Diarrhea (Hx)	6	1	1.08	NS
Psoriasis (Hx)	5	2	0.06	NS
Shortness of breath (Hx)	4	5	0.36	NS
Easy bruising (Hx)	4	1	0.23	NS
Sore throat (Hx)	4	0	1.32	NS
Persistent cough (Hx)	2	1	0	NS
Meningitis (Hx)	1	2	0.12	NS
Hair loss (Hx)	1	0	0	NS
Pneumonia (Hx)	0	0	...	...
Weight loss (>10%) (Hx)	0	0	...	...

*SCS-20 indicates 20-item symptom checklist; HIV, human immunodeficiency virus; NS, not significant; and Hx, history during the last 3 months.
†With Yates' correction.

Table 3.—Immunologic Measures*

	HIV Positive, Mean ± SD (N)	HIV Negative, Mean ± SD (N)	t	P
CD4, $\times 10^9$/L	0.405 ± .0223 (123)	0.833 ± 0.267 (84)	12.50	.000
CD8, $\times 10^9$/L	0.838 ± 0.448 (123)	0.539 ± 0.203 (84)	6.49	.000†
CD4/CD8 ratio	0.56 ± 0.35 (123)	1.67 ± 0.60 (84)	15.17	.000†
Total Lymphocytes, $\times 10^9$/L	1.815 ± 0.676 (123)	2.019 ± 0.052 (84)	2.43	.016†
Platelets, $\times 10^9$/L	202 ± 52 (119)	254 ± 61 (82)	6.39	.000

*HIV indicates human immunodeficiency virus.
†Separate variance estimate.

Table 4.—Immunologic Measures Indicating Advanced Infection*

	No. (%)			
	HIV Positive	NIV Negative	χ^2	P
p24 Antigen (>30 pg/mL)	14/124 (11)	0/84 (0)	10.05	.002
Interferon = α (>1:32)	4/124 (3)	0/84 (0)	1.32	NS
CD4 (<0.2 × 10^9/L)	19/123 (15)	1/84 (1)	10.05	.002

*HIV indicates human immunodeficiency virus; NS, not significant.

ic status[9] by serologic status for these subjects. The HIV-positive and HIV-negative subjects were obviously well matched for all of these variables. Although socioeconomic status was significantly higher for the HIV-negative subjects (53.2) than for the HIV-positive subjects (49.1), the difference is clearly very small.

Forty-nine of the 124 seropositive men had medical stage scores between 0 and 9 (asymptomatic); 29 had scores from 10 to 19 (mild symptoms); and 46 had scores from 20 to 29 (moderate symptoms, AIDS-related complex). The mean stage score was 12.5 ± 9.0, corresponding to a group with only mild medical symptoms.

The mean number of symptoms on the 20-item symptom checklist was 2.1 ± 1.6. As indicated in Table 2, the most common symptoms were a history of oral/genital herpes, a history of oral candidiasis, enlarged lymph nodes, nonpsoriatic rash, history of herpes zoster (shingles) infection, sinusitis, oral leukoplakia or thrush by examination, persistent fever, night sweats, rash around the eyes, and diarrhea. It should be noted that by χ^2 statistic, five of these—diarrhea, history of oral/genital herpes, night sweats, rash around the eyes, and sinusitis—were not statistically more common in HIV-positive than HIV-negative subjects (Table 2). This medical symptom pattern indicates that the HIV-positive subjects represented a range of medical severity but overall were a relatively mildly symptomatic group.

Table 3 shows comparisons of baseline immunologic data between HIV-positive and HIV-negative subjects. As expected, the HIV-positive subjects had significantly fewer total lymphocytes, fewer platelets, fewer $CD4^+$ lymphocytes, lower CD4/CD8 ratio, and more $CD8^+$ lymphocytes than did HIV-negative subjects. The mean CD4 number for the HIV-positive group was $0.405 \pm 0.223 \times 10^9$/L, and the mean CD4/CD8 ratio was 0.56 ± 0.35.

Immunologic signs of advanced HIV illness include CD4 count less than 0.2×10^9/L, presence of p24 antigen in serum in an amount greater than or equal to 30 pg/mL,[10] and acid-labile interferon-α titer greater than or equal to 1:32.[11] Table 4 shows the number of subjects in our cohort who had these findings at baseline. Again, the relatively few subjects who had these signs indicates that this group of patients in general was relatively early in disease progression. It is interesting to note that one of our HIV-negative subjects had a low CD4 count. This subject was HIV negative by enzyme-linked immunosorbent assay and Western blot, and therefore we considered him HIV negative in all data analyses. It is possible that he was indeed a carrier of HIV who will be so identified when the polymerase chain reaction test is performed.[12] On the other hand, low CD4 counts can occur transiently because of other infections.[13]

A few of our HIV-positive subjects were taking, at baseline, a variety of prescribed and nonprescribed drugs specifically aimed at treating HIV infection. These included zidovudine (formerly azidothymidine or AZT), AL721, pentamidine, acyclovir, and diethyldithiocarbamate. Only seven of the 124 seropositive subjects were taking zidovudine.

COMMENT

Several points can be made about the cohort of homosexual men under study in the follow-up project. Recruitment was easy. A few advertisements and several talks to community groups were all that was needed to fill the cohort quickly. This indicates that our cohort is probably composed of relatively well-connected homosexual and bisexual men.

We recognize that our sample may not represent the broad populations that are affected by HIV, or even the homosexual community as a whole. The study also suffers from the usual bias of volunteerism. Given these limitations on generalizability, we believe this cohort provides useful information because it is composed of well-matched HIV-positive and HIV-negative men and therefore gives a picture of the impact of HIV infection at an early stage of illness. Furthermore, by

studying a relatively small but homogeneous group, we were able to obtain a great deal of in-depth information from an 8-hour assessment that would be impossible to gather if a larger sample were involved. Studies of HIV-infected homosexual and bisexual men of lower socioeconomic status and minority groups are clearly lacking, and we hope to address this in future work.

The accompanying articles have two main purposes. First, within each domain, they evaluate the prevalence of pathologic findings in HIV-positive subjects compared with HIV-negative subjects. Included in this goal is the examination of whether psychiatric or neuropsychological symptoms are more prevalent among HIV-infected subjects and therefore may be the result of central nervous system infection by HIV.

Second, the articles examine several hypotheses concerning the relationships between psychiatric/psychosocial pathologic findings and neurologic/neuro-psychological impairment on the one hand and medical and immunologic complications of HIV infection on the other. It is possible that some of the factors we assess are actually "cofactors" that influence disease progression. The literature suggests that stress and psychiatric illness can lead to impaired immunologic function and lower resistance to infection.[14] This literature, reviewed extensively elsewhere,[15] also documents the mounting evidence of direct communication and reciprocal influence between the central nervous system and the immune system. There is absolutely no proof at present, however, that any psychological factor influences the course of HIV infection. Our study is designed at baseline and through the 5 years of follow-up to evaluate this possibility.

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