

## STUDIES IN SUBJECTS WITH LONG-TERM NONPROGRESSIVE HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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**Abstract Background.** In a small percentage of persons infected with human immunodeficiency virus type 1 (HIV-1), there is no progression of disease and CD4+ T-cell counts remain stable for many years. Studies of the histopathological, virologic, and immunologic characteristics of these persons may provide insight into the pathogenic mechanisms that lead to HIV disease and the protective mechanisms that prevent progression to overt disease.

**Methods and Results.** We studied 15 subjects with long-term nonprogressive HIV infection and 18 subjects with progressive HIV disease. Nonprogressive infection was defined as seven or more years of documented HIV infection, with more than 600 CD4+ T cells per cubic millimeter, no antiretroviral therapy, and no HIV-related disease. Lymph nodes from the subjects with nonprogressive infection had significantly fewer of the hyperplastic features, and none of the involuted features, characteristic of nodes from subjects with progressive disease. Plasma levels of HIV-1 RNA and the viral bur-

den in peripheral-blood mononuclear cells were both significantly lower in the subjects with nonprogressive infection than in those with progressive disease ( $P=0.003$  and  $P=0.015$ , respectively). HIV could not be isolated from the plasma of the former, who also had significantly higher titers of neutralizing antibodies than the latter. There was viral replication, however, in the subjects with nonprogressive infection, and virus was consistently cultured from mononuclear cells from the lymph nodes. In the lymph nodes virus "trapping" varied with the degree of formation of germinal centers, and few cells expressing virus were found by *in situ* hybridization. HIV-specific cytotoxic activity was detected in all seven subjects with nonprogressive infection who were tested.

**Conclusions.** In persons who remain free of disease for many years despite HIV infection the viral load is low, but viral replication persists. Lymph-node architecture and immune function appear to remain intact. (*N Engl J Med* 1995;332:209-16.)

THE typical course of human immunodeficiency virus (HIV) infection includes an acute clinical syndrome of variable severity, a prolonged period of clinical latency, and then a stage of clinically apparent disease characterized by increased susceptibility to opportunistic infections and certain neoplasms.<sup>1</sup> The acute phase of infection progresses to the latent phase in the vast majority of HIV-infected people even though vigorous HIV-specific cell-mediated and humoral immune responses are generally present early in primary infection.<sup>1-7</sup> These early responses almost invariably curtail replication of the virus, resulting in a marked decrease in plasma viremia, but they usually fail to eliminate HIV from the body.<sup>2,3,8</sup> The duration of clinical latency varies widely, and the progression to the acquired immunodeficiency syndrome (AIDS) occurs over a median period of 8 to 10 years.<sup>9-11</sup> More than a decade into the AIDS epidemic, it has become clear

that there is a group of infected persons whose HIV disease does not progress over an extended time.<sup>11-15</sup>

Even during the period of clinically latent HIV infection, there is active viral replication and histologic changes in lymphoid tissue.<sup>1,16,17</sup> Therefore, we compared the histopathological features of the lymph nodes and virologic characteristics of subjects with long-term nonprogressive infection with those of subjects with progressive disease. In addition, we analyzed both humoral and cellular immune responses to HIV in subjects with long-term nonprogressive infection.

### METHODS

#### Study Subjects

Fifteen subjects with long-term nonprogressive HIV infection were studied (Table 1). The criteria used to define nonprogression included documented HIV infection for more than seven years, stable CD4+ T-cell counts greater than 600 per cubic millimeter, the absence of symptoms, and no antiretroviral therapy. Seven subjects with long-term nonprogressive infection were from the Multicenter AIDS Cohort Study, four were from the San Francisco City Clinic Cohort Study, and four were from the lymph-node study of the National Institute of Allergy and Infectious Diseases. Thirteen of the 15 subjects had been infected with HIV for at least 10 years (Table 1). For Patient 11 the date of seroconversion was determined retrospectively from a serum sample collected in 1980 during a trial of hepatitis B virus vaccine. Analysis of serial CD4+ T-cell counts in six subjects with long-term nonprogressive infection from the Multicenter AIDS Cohort Study showed no decrease (a slope of 0 or above) (Fig. 1). All subjects with long-term nonprogressive HIV infection had high CD8+ T-cell counts (ranging from 527 to 2483 per cubic millimeter). No particular patterns of HLA haplotypes were observed. HIV was transmitted through homosexual contact in all these subjects except Subject 7, in whom it was transmitted heterosexually.

Eighteen HIV-infected subjects who were enrolled in a lymph-node study and who had progression of disease in varying degrees

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Table 1. Clinical Characteristics of 15 Subjects with Long-Term Nonprogressive HIV Infection.\*

SUBJECT NO.	AGE (YR)/SEX	YEAR OF SEROCONVERSION	LYMPH-NODE BIOPSY	CD4+ CELLS		CD8+ CELLS		HLA HAPLOTYPE	
				no./mm <sup>3</sup>	percent	no./mm <sup>3</sup>	percent	CLASS I	CLASS II
1	46/M	1983	Inguinal	685	32	1178	55	A31,3; B8; C7; B6	DQ2; DR3; DR52
2	34/M	1984	Inguinal	817	38	1010	47	A11; B35,53; C4; B4,6	DQ1,3; DR15,4; DR53
3	41/M	1985	Axillary	1238	32	2090	54	A29,30; B44,14; C4; B4,6	DQ2,3; DR7,11; DR52,53
4	36/M	1985	Axillary	637	27	1274	54	A3,24; B27,63; C2; B4	DQ1,3; DR6,4; DR52,53
5	32/M	1984	Cervical	1287	44	1141	39	A2,25; B51,18; Cx; B4,6	DQ3; DR4,11; DR52,53
6	42/M	1984	Axillary	720	20	2483	69	A24,33; B60,63; C3,x; B4,6	DQ1,3; DR15,11; DR52
7	34/F	1985	Cervical	714	38	742	40	A2,3; B27,70; C2,7; B4,6	DQ1; DR15,6; DR52
8	45/M	1987	Inguinal	1038	37	1291	46	A2; B52,44; C5; B4	DQ1,3; DR15,11; DR52
9	40/M	1985	Inguinal	1053	27	2379	61	A2,3; B44,14; C5; B4,6	DQ1,3; DR15,6; DR52,53
10	36/M	1984	Inguinal	702	38	979	53	A1,24; B57,18; C5,6; B4,6	DQ2,3; DR3,7; DR52,53
11	41/M	1980	Inguinal	773	38	855	42	A2,28; B7,13; C6,7; B4,6	DQ21,2; DR15,7; DR53
12	39/M	1984	Axillary	810	40	878	43	A2,25; B27,18; C2; B4,6	DQ1,3; DR1,4; DR53
13	41/M	1984	ND	1142	44	961	37	A2,3; B44,61; C2,5; B4,6	DQ1,3; DR6,11; DR52
14	33/M	1986	Inguinal	674	41	527	32	A25,32; B44,18; C5; B4,6	DQ1,3; DR15,11; DR52
15	40/M	1983	Inguinal	690	41	858	51	A2,24; B63,50; C3,7; B4,6	DQ1,3; DR4,6; DR52,53

\*CD4+ and CD8+ cell counts shown were determined by cytofluorometry at the time of the lymph-node biopsy. Percentages shown are percentages of the total number of lymphocytes. ND denotes not done, and x haplotype of undetermined specificity.

were studied similarly, as controls. These control subjects with progressive HIV disease were randomly selected from among patients for whom clinical specimens (i.e., plasma and mononuclear cells from peripheral blood and lymph nodes) were available. Lymph-node biopsies were performed in control subjects with palpable nodes. In

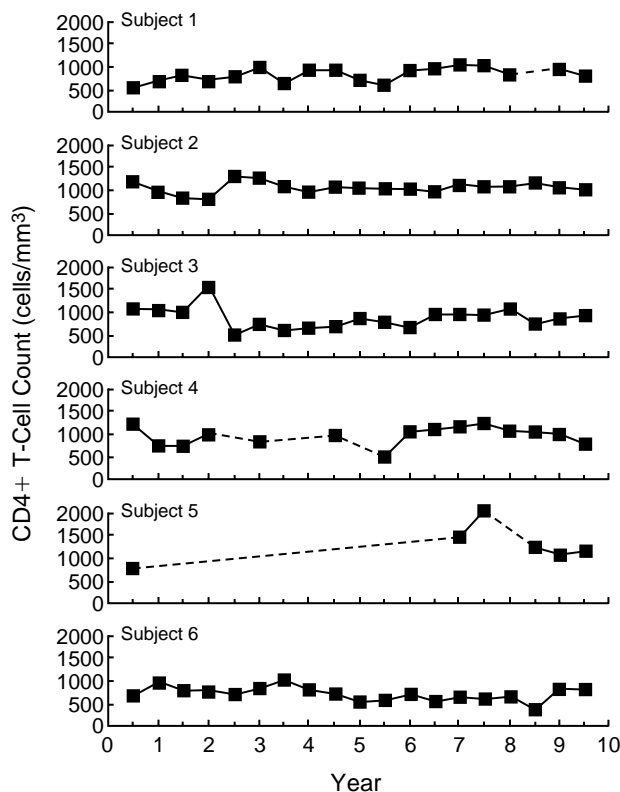


Figure 1. Serial CD4+ T-Cell Counts over a 10-Year Period in Six Subjects from the Multicenter AIDS Cohort Study Who Had Long-Term Nonprogressive HIV Infection.

The points represent the CD4+ T-cell counts obtained at six-month intervals. The broken lines indicate clinic visits that were missed.

6 of the 18 controls, biopsies of inguinal lymph nodes were performed, because lymph nodes in other sites were not palpable. Biopsies of axillary lymph nodes were performed in the 12 remaining controls. Seropositivity was documented in 5 of the 18 controls between 1989 and 1991 and in the remaining 13 between 1984 and 1987. This group of HIV-infected persons with progressive disease included 3 with CD4+ T-cell counts above 500 cells per cubic millimeter, 11 with counts from 200 to 500 per cubic millimeter, and 4 with counts below 200 per cubic millimeter. In the three control subjects with CD4+ T-cell counts above 500 cells per cubic millimeter, the status of disease progression was determined on the basis of declining CD4+ T-cell counts over time. In one subject the count was 670 cells per cubic millimeter at the time of the lymph-node biopsy (April 1993), but at the time of seroconversion (1986) it was 1100 cells per cubic millimeter. In the second control subject, the count was 550 cells per cubic millimeter at the time of the lymph-node biopsy (April 1993), but it had been 1920 in 1988, and it dropped to 351 in 1994. In the third subject the CD4+ T-cell count was 600 cells per cubic millimeter at the time of the biopsy (September 1993), but since the time of seroconversion (1986) this subject has had progressive constitutional symptoms during the development of which his CD4+ T-cell count ranged from 200 to 500 cells per cubic millimeter.

### Clinical Specimens

All excisional lymph-node biopsies were performed at the National Institutes of Health Clinical Center under an approved protocol. The tissue specimens were processed immediately after their removal.<sup>16</sup> Two small tissue specimens obtained from each lymph node were fixed in formaldehyde and glutaraldehyde for routine histologic analysis, in situ hybridization, and electron microscopy. The remaining specimens were minced with a scalpel, and cells were teased out. A small aliquot was fixed in glutaraldehyde for electron microscopy, and cell pellets were immediately prepared for study by the polymerase chain reaction (PCR) and stored at  $-80^{\circ}\text{C}$ .

### Quantitation of Proviral HIV-1 DNA

Proviral HIV type 1 (HIV-1) DNA was quantitated by a semiquantitative PCR assay with a primer pair specific for the *gag* (SK145/101) gene segment.<sup>16,17</sup> The results were expressed as the number of copies of DNA per million cells.

### Quantitation of HIV-1 Genomic RNA

Whole blood was centrifuged at  $200\times g$  for 10 minutes. The plasma fraction was then centrifuged twice at  $1000\times g$  for 10 minutes to en-

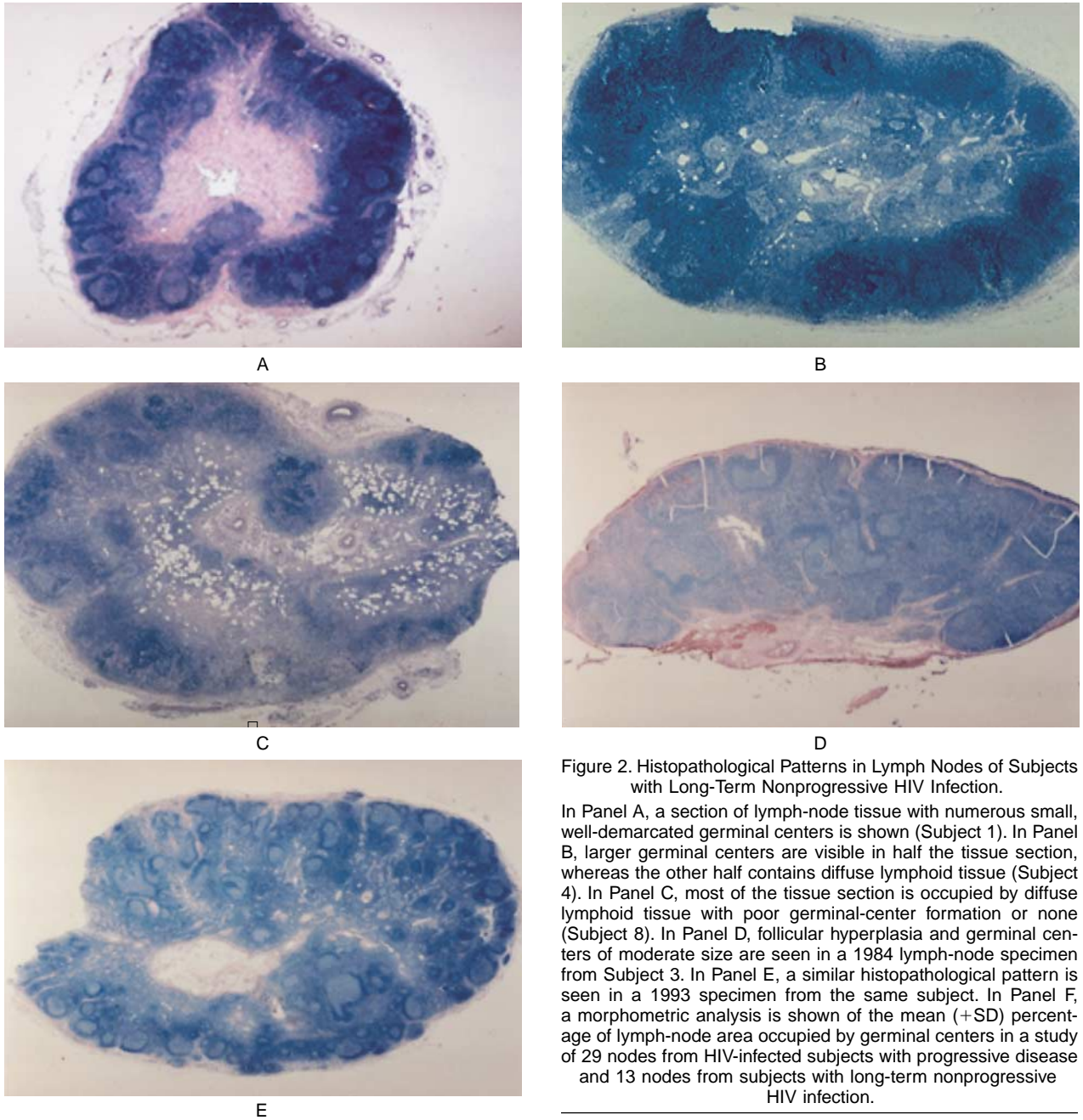
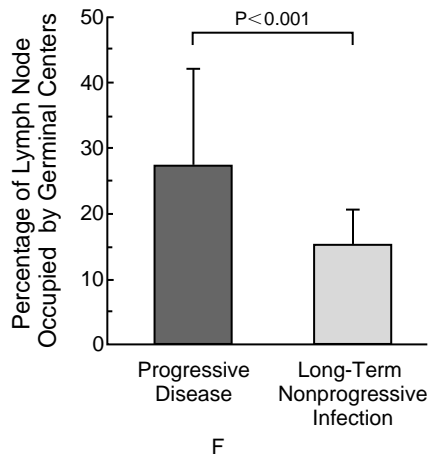


Figure 2. Histopathological Patterns in Lymph Nodes of Subjects with Long-Term Nonprogressive HIV Infection.

In Panel A, a section of lymph-node tissue with numerous small, well-demarcated germinal centers is shown (Subject 1). In Panel B, larger germinal centers are visible in half the tissue section, whereas the other half contains diffuse lymphoid tissue (Subject 4). In Panel C, most of the tissue section is occupied by diffuse lymphoid tissue with poor germinal-center formation or none (Subject 8). In Panel D, follicular hyperplasia and germinal centers of moderate size are seen in a 1984 lymph-node specimen from Subject 3. In Panel E, a similar histopathological pattern is seen in a 1993 specimen from the same subject. In Panel F, a morphometric analysis is shown of the mean (+SD) percentage of lymph-node area occupied by germinal centers in a study of 29 nodes from HIV-infected subjects with progressive disease and 13 nodes from subjects with long-term nonprogressive HIV infection.



sure the removal of residual cellular or platelet debris. RNA was extracted from both plasma and mononuclear cells by the guanidium thiocyanate method. In the case of plasma, RNA was extracted either from the plasma virion pellet after ultracentrifugation (at 30,000 rpm) of 1 ml of plasma diluted in 9 ml of RPMI-1640 or from 20  $\mu$ l of undiluted plasma. In the case of mononuclear cells, RNA was extracted from a sample containing 1 million cells. Reverse transcription, amplification, and quantitation of HIV-1 genomic RNA were performed as described elsewhere.<sup>18,19</sup>

**In Situ Hybridization and Immunohistochemical Analysis**

In situ hybridization was performed with a mixture of RNA probes synthesized by five DNA templates that represent 90 percent of the HIV-1 genome.<sup>20</sup> In experiments using double-labeling (immunohistochemical analysis plus in situ hybridization), slides were first stained with anti-CD21 antibody (Dako, Carpinteria, Calif.), which

stains follicular dendritic cells in formaldehyde-fixed, paraffin-embedded tissues.

### Morphometric Analysis of Lymph Nodes

For the morphometric analysis of lymph nodes (Molecular Histology Laboratories, Gaithersburg, Md.), a video-planimetry computer program based on National Institutes of Health (NIH) image 1.48 was developed and was run on a Macintosh IIfx, and a videoscope camera (International CCD 200E, Reston, Va.) was used to capture the image. To determine the area of the germinal center, sequential central sections of the lymph-node specimens were stained with Giemsa and imaged, and the mean of the three measurements was calculated.

### Statistical Analysis

Statistical analyses of all virologic and morphometric measures in the two study groups were performed with the Wilcoxon rank-sum test.

## RESULTS

### Lymph-Node Architecture

Lymph-node biopsies were performed in 14 of the 15 subjects with long-term nonprogressive HIV infection who had palpable nodes. Three general histopathological patterns were observed (Fig. 2). The first, seen in four lymph nodes, was characterized by many small, well-demarcated, round-to-oval cortical germinal centers with intact mantle zones and no evidence of follicle lysis (Fig. 2A). The second pattern, seen in five lymph nodes, involved germinal centers that were mostly regular and of medium size but were occasionally large and irregular with evidence of follicle lysis, together with diffuse, nonorganized lymphoid tissue (Fig. 2B). The third pattern, seen in the remaining five nodes, was characterized by nonorganized lymphoid tissue with features of either of the other two patterns (Fig. 2C). In contrast, lymph nodes from the 18 control subjects with progressive HIV disease had histologic features typically observed in HIV-associated lymphadenopathy, such as large, irregular, fusing germinal centers; follicle lysis; loss of mantle zones; hypervascularity; plasma-cell hyperplasia; focal fibrosis; and lymphocyte depletion.

For Subject 3 with nonprogressive HIV infection, lymph nodes were available from both 1984 and 1993; they were essentially identical, showing the second pattern (follicular hyperplasia with mostly small but in rare cases large germinal centers) (Fig. 2D and 2E). Morphometric analysis of the germinal centers of lymph nodes from the subjects with long-term nonprogressive infection showed that the mean ( $\pm$ SD) area they occupied was significantly less than that occupied by such centers in lymph nodes of the controls with progressive HIV disease ( $15.2\pm 6.2$  percent vs.  $27.4\pm 14.3$  percent) ( $P<0.001$ ) (Fig. 2F).

### Viral Burden and Replication

The viral burden in mononuclear cells (the number of cells containing HIV-1 provirus DNA) was determined by semiquantitative PCR. The viral burden in the subjects with long-term nonprogressive HIV infection was significantly (at least five times) less than that in the controls in both peripheral blood and lymph nodes (Fig. 3A). The mean number of HIV-1 DNA

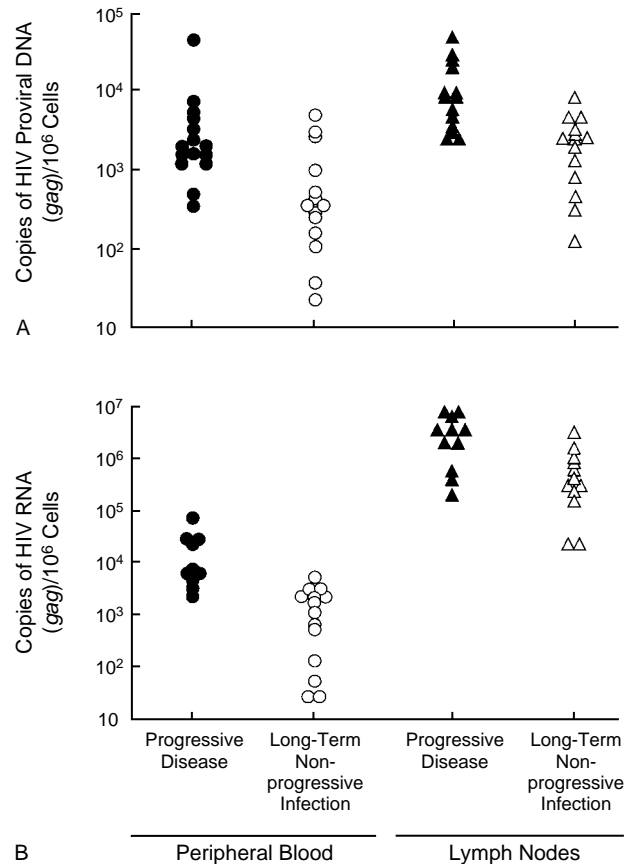


Figure 3. Viral Burden and Viral Replication in Mononuclear Cells from Peripheral Blood and Lymph Nodes of Subjects with Long-Term Nonprogressive HIV Infection and Those with Progressive HIV Disease.

In the upper panel, viral burden in 14 subjects with long-term nonprogressive infection is compared with that in 15 controls with progressive disease. In the lower panel, viral replication in 14 subjects with long-term nonprogressive infection is compared with that in 10 controls with progressive disease.

copies per million cells was  $638\pm 876$  in the peripheral-blood mononuclear cells of the subjects with long-term nonprogressive infection, as compared with  $4937\pm 10,412$  in the controls ( $P=0.015$ ), and it was  $2194\pm 1795$  in the lymph-node mononuclear cells of the former as compared with  $11,394\pm 11,791$  in those of the latter ( $P=0.004$ ).

Similarly, levels of viral replication in the subjects with long-term nonprogressive HIV infection were 4 to 10 times lower than in the controls (Fig. 3B). The mean number of HIV-1 RNA copies per million cells was  $1072\pm 1009$  in peripheral-blood mononuclear cells of the subjects with long-term nonprogressive infection, as compared with  $10,450\pm 8890$  in the controls ( $P=0.003$ ), and it was  $743,270\pm 857,967$  in lymph-node mononuclear cells of the former as compared with  $2,590,080\pm 2,093,850$  in the latter ( $P=0.016$ ).

### Plasma Viremia

Plasma levels of HIV-1 RNA in the subjects with long-term nonprogressive HIV infection were substantially (up to 20 times) lower than those in the controls with progressive HIV disease (Fig. 4). The mean

number of copies of HIV-1 RNA per milliliter of plasma was  $70,818 \pm 67,931$  in the subjects with long-term nonprogressive infection, as compared with  $1,586,967 \pm 2,200,198$  in the controls ( $P = 0.003$ ). A retrospective analysis of five subjects with nonprogressive infection from the Multicenter AIDS Cohort Study, involving specimens collected over a period of five years (from 1988 to 1993), demonstrated that plasma viremia and CD4+ T-cell counts remained relatively stable (Fig. 4). Only in Subject 2 did plasma viremia increase greatly (10-fold between 1988 and 1993) (Fig. 4); the subject's CD4+ T-cell count dropped slightly, to 817 cells per cubic millimeter, but remained essentially unchanged after one year (798 cells per cubic millimeter in 1994).

**In Situ Hybridization and Electron Microscopy**

Variable levels of virus "trapping" were observed in the follicular-dendritic-cell networks of the germinal centers by in situ hybridization. Virus was detected in 9 of 14 lymph nodes, and its presence was strictly dependent on the presence of germinal centers. In fact,

virtually no virus was detected in the five lymph nodes in which few germinal centers, or none, had formed (Subjects 8, 9, 11, 14, and 15). Typical examples of the patterns of virus trapping in the lymph nodes are shown in Figures 5A and 5B. The absence of trapped virus did not result from the lack of follicular dendritic cells, since such cells were still detected in lymph nodes that had poor or nonexistent formation of germinal centers, as indicated by immunohistochemical analysis (Fig. 5C). Electron-microscopical analysis showed that follicular dendritic cells in the lymph nodes of subjects with long-term nonprogressive HIV infection were generally healthy. In addition, virus particles were rarely detected (in only 3 of 12 cases) by electron microscopy in either tissue or cell suspensions, and cells expressing virus were rarely observed (Fig. 5D) by in situ hybridization.

**Isolation of Virus**

HIV could not be isolated from the plasma of subjects with long-term nonprogressive HIV infection, but it could be isolated from lymph-node mononuclear cells

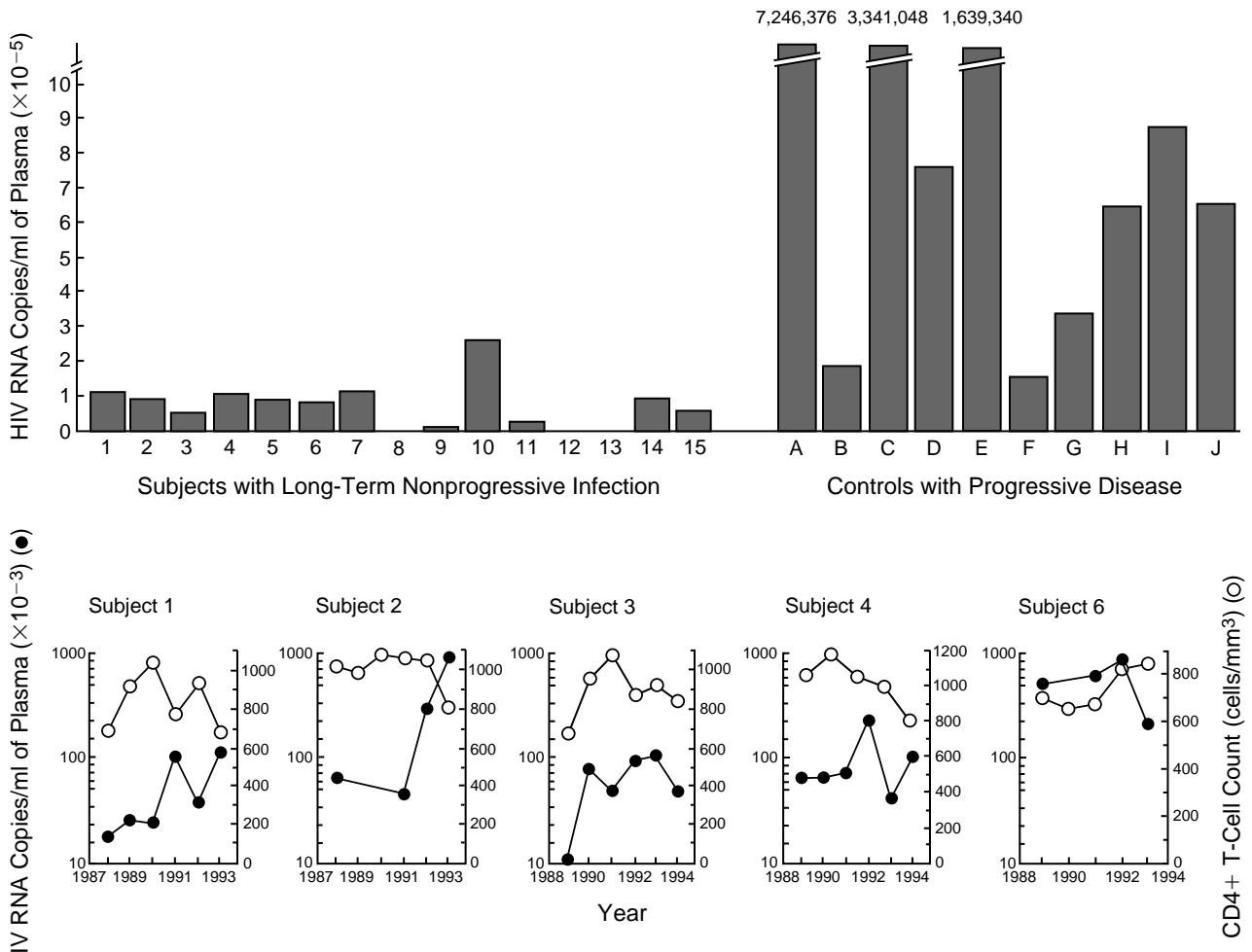


Figure 4. Plasma Viremia in the Study Subjects.

The upper panel shows levels of plasma viremia in 15 subjects with long-term nonprogressive HIV infection and 10 controls with progressive disease. There were 270 copies of HIV RNA per milliliter of plasma in Subject 8, fewer than 500 copies in Subject 12, and 2380 copies in Subject 13. The lower panels show a retrospective analysis of plasma viremia and CD4+ T-cell counts in five subjects with long-term nonprogressive infection.

(in seven patients) after coculture with phytohemagglutinin-activated mononuclear cells from an HIV-negative donor (data not shown). In contrast, in the control subjects with progressive disease, HIV could be cultured readily, either from plasma or directly from phytohemagglutinin-stimulated lymph-node mononuclear cells. Levels of viral replication were higher after coculture with phytohemagglutinin-activated mononuclear cells from an HIV-negative donor (data not shown).

#### Neutralizing Antibodies

Neutralizing antibodies were detected<sup>21</sup> with two genetically diverse strains of HIV-1 (HIV-1<sub>III<sub>B</sub></sub> and HIV-1<sub>MN</sub>). Titers of neutralizing antibodies were significantly higher against both HIV-1<sub>III<sub>B</sub></sub> ( $552 \pm 324$  in the subjects with long-term nonprogressive infection vs.  $345 \pm 297$  in the controls with progressive disease;  $P=0.037$ ) and HIV-1<sub>MN</sub> ( $1458 \pm 925$  vs.  $680 \pm 408$ , respectively;  $P=0.02$ ).

#### HIV-Specific Cytotoxicity

HIV-specific cytotoxic activity was assayed in 7 of 15 subjects with long-term nonprogressive HIV infection

with freshly isolated or anti-CD3-stimulated unfractionated peripheral-blood mononuclear cells and sorted CD8+ T lymphocytes used as effector cells.<sup>22</sup> HIV-specific cytotoxicity against HIV *env* was consistently detected in all seven subjects, whereas HIV-specific cytotoxicity against *gag* was detected in three of six subjects studied (data not shown).

#### DISCUSSION

We studied histopathological, virologic, and immunologic measures in 15 HIV-infected subjects in whom there has been no clinical or immunologic progression of HIV disease. The study was designed to examine the lymph nodes of these subjects, since our previous studies<sup>1,17</sup> of subjects with progressive disease had demonstrated active viral replication in lymphoid tissue and histopathological abnormalities even during the clinically latent stage of HIV disease. Although the histopathological analysis was generally limited to a single lymph node, recent studies have demonstrated good concordance of the histopathological findings in lymph nodes from multiple sites in the same HIV-infected person.<sup>23</sup> The histopathological patterns in the subjects

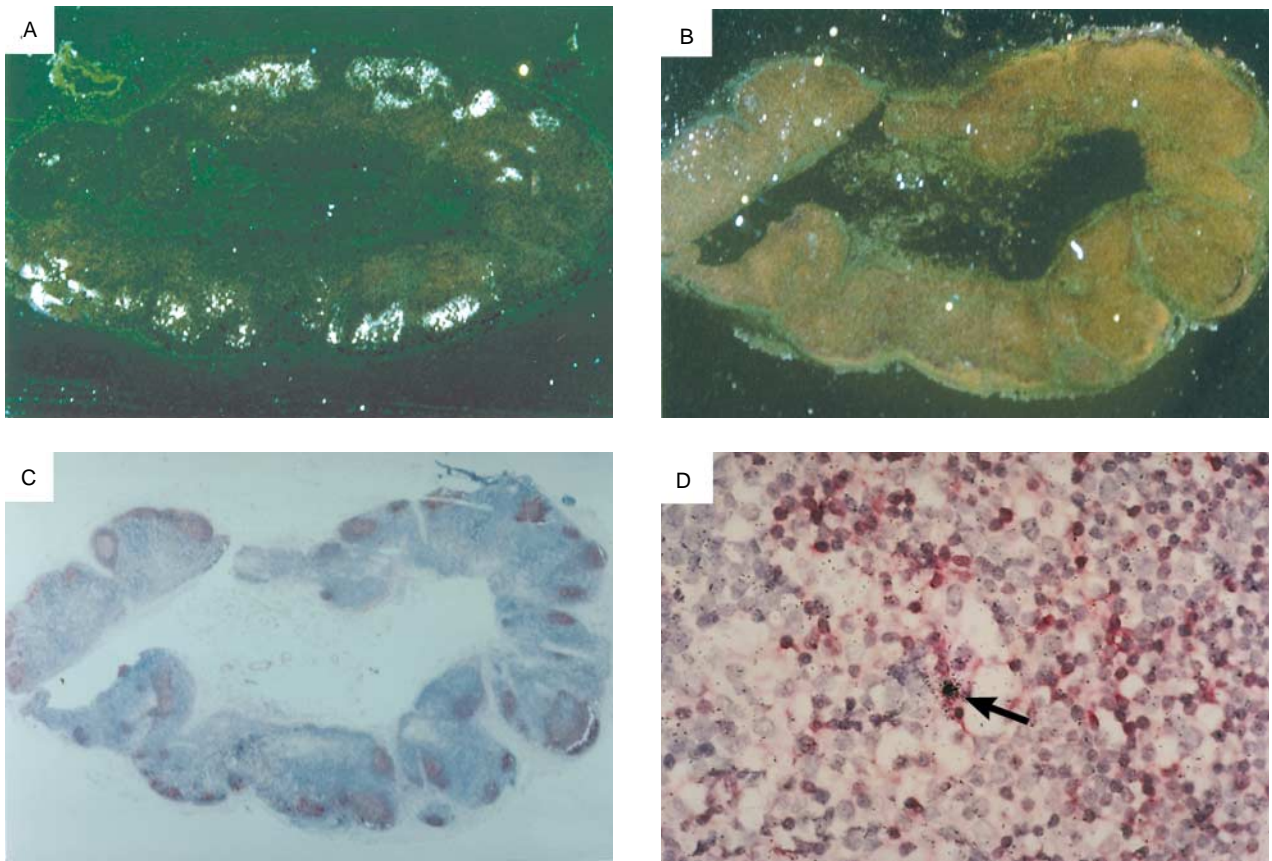


Figure 5. Distribution of Virus in Lymph Nodes of Subjects with Long-Term Nonprogressive Infection.

Panel A shows a dark-field image of in situ hybridization of a lymph-node section from Subject 5 after protease digestion. The location of HIV RNA is indicated by the silver grains, which appear as white dots. There is an intense, granular, diffuse signal, restricted predominantly to the area of the germinal centers. Panel B shows a dark-field image of a lymph-node section from Subject 11 after protease digestion. No diffuse hybridization signal is detected. Panel C shows immunohistochemical staining (new fuchsin red) of the network of follicular dendritic cells from Subject 11 after staining with anti-CD21 antibody. Panel D shows a bright-field image of a lymph-node section from Subject 11 after protease digestion and subsequent immunohistochemical analysis (with OPD-4 antibody, which stains a subgroup of CD45RO+ lymphocytes) plus in situ hybridization. The location of HIV RNA is indicated by the silver grains, which appear as black dots. An isolated cell expresses HIV RNA (arrow).

with long-term nonprogressive HIV infection were heterogeneous, and the degree of lymph-node activation (germinal-center formation) was significantly less than in control subjects with progressive disease. One cannot exclude the possibility that some degree of germinal-center activation occurred early in the course of infection and that because of a lower viral load the lymphoid tissue returned to a nonreactive state. However, the critical difference between the lymph nodes of subjects with nonprogressive infection and those of subjects with progressive disease is that the lymph nodes of the former do not show involution and lymphocyte depletion, typical features of lymph nodes in the latter after HIV infection has lasted 8 to 10 years.<sup>24</sup>

Viral replication persisted in subjects with long-term nonprogressive HIV infection, but plasma viremia, as well as viral burden and viral replication in mononuclear cells in peripheral blood and lymph nodes, was significantly (4 to 20 times) lower than in control subjects with progressive disease.

The degree of virus trapping in the follicular-dendritic-cell network in the lymph nodes of subjects with long-term nonprogressive HIV infection paralleled the extent of germinal-center formation.<sup>17,20,24-31</sup> Apparently, this was not the result of lymph-node involution and concomitant loss of the ability to trap virus, which is characteristic of the lymph nodes of persons with progressive disease<sup>17</sup>; rather, it is more likely to reflect the relatively nonreactive state of the lymphoid tissue. This lower degree of virus trapping may contribute both to the lower viral load and to the lower rate of tissue activation observed in subjects with long-term nonprogressive infection.

Virus was cultured consistently from the lymph-node mononuclear cells of these subjects, indicating that HIV is infectious and competent to replicate in such persons. The lower efficiency with which virus was isolated from the subjects with long-term nonprogressive HIV infection as compared with the controls with progressive disease may be consistent with the lower viral load in the former. However, one cannot exclude the possibility that genetic defects in the virus in the subjects with long-term nonprogressive HIV infection may account for the low efficiency of virus isolation. In this regard, the V3 region of particle-associated RNA amplified from plasma was directly sequenced in four such subjects. We found no peculiar patterns or major rearrangements with respect to known V3 sequences; the sequences studied had macrophage-tropic genotypes<sup>32-34</sup> such as are generally observed in HIV-infected persons during the clinically latent period of infection.<sup>34,35</sup> The presence of high titers of neutralizing antibodies, together with the consistent detection of HIV-specific cytotoxicity, indicates that both humoral and cell-mediated immune responses are preserved in subjects with long-term nonprogressive infection and strongly suggests that these persons are constantly exposed to HIV antigens.

In conclusion, subjects with long-term nonprogressive HIV infection have preserved lymphoid tissue with reduced formation of germinal centers and reduced HIV trapping, despite a low but persistent level of viral

replication. This finding suggests that persistent, low-level viral replication is not necessarily associated with the progression of disease if it is efficiently controlled over time. It remains unclear what are the relative contributions of host factors, such as the immune system, and virologic factors, such as a defective virus, in determining the lack of progression of HIV disease in these subjects. Understanding the importance of these factors may prove to be critical to the development and testing of vaccines and therapeutic strategies.

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