

Effect of Splenectomy on Slowing Human Immunodeficiency Virus Disease Progression

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Background: Lymphoreticular tissue is the most important site for human immunodeficiency virus (HIV) replication in HIV-infected individuals.

Objective: To compare the long-term effect of splenectomy on survival and time to development of acquired immunodeficiency syndrome in subjects who had undergone splenectomy with subjects who had not undergone splenectomy.

Design: A cohort study with a follow-up of up to 13.4 years.

Setting: Subjects were recruited from a hospital outpatient clinic population and a multicenter study of patients with hemophilia.

Participants: Forty-five HIV-infected individuals were observed prospectively for up to 13.4 years (17 had undergone splenectomy and 28 had not undergone splenectomy). Five subjects underwent splenectomy before acquiring HIV infection and 12 underwent splenectomy during the asymptomatic phase of HIV infection. The group who did not undergo splenectomy consisted of HIV-infected individuals who were asymptomatic at study enrollment.

Main Outcome Measures: A Cox proportional hazards model was used to test the effects of splenectomy on survival and time to development of acquired immunodeficiency syndrome when adjusting for potential confounders (age, initial CD4⁺ cell count, and treatment with antiretroviral drugs). Splenectomy was treated as a time-dependent covariate to account for the variation in its timing.

Results: During the average follow-up of 8.6 years, 9 (53%) of the 17 subjects who underwent splenectomy and 23 (82%) of the 28 subjects who did not undergo splenectomy died; acquired immunodeficiency syndrome developed in 6 (35%) of the subjects who underwent splenectomy and 23 (82%) of the subjects who did not undergo splenectomy. Splenectomy was associated with a significant reduction of risk of developing acquired immunodeficiency syndrome (adjusted relative risk [RR] <0.4, *P*<.05), whereas the effect on risk of mortality approached, although it did not reach, significance (adjusted RR≈0.5, *P*≈.10).

Conclusion: The absence of a spleen during the asymptomatic phase of HIV infection seems to have a beneficial effect on HIV disease progression.

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THE PATHOGENESIS of human immunodeficiency virus (HIV) infection can be divided into 3 phases: (1) primary infection, which is associated with a burst of viremia and, in a proportion of cases, with a nonspecific mononucleosis-like clinical syndrome of variable severity; (2) a period of clinical latency of variable duration (median, 10 years); and (3) a clinically active phase characterized by susceptibility to neoplasms and opportunistic infections.¹⁻⁵ Human immunodeficiency virus replicates preferentially and through all stages of infection in lymphoreticular tissues, such as the lymph nodes and the spleen.⁶⁻⁸ Recent studies addressing the kinetics of virus replication

reveal a rapid turnover rate for plasma virions (half-life ≈ 2 days) as well as for virus-producing cells and a high long-term level of virus replication in all stages of disease.^{9,10} Peripheral blood mononuclear cells likely contribute little to plasma virion levels, suggesting that lymphoreticular tissue is a major site for virus replication.⁹

Idiopathic thrombocytopenic purpura (ITP) has a prevalence of 10% to 20% among asymptomatic patients infected with HIV.^{11,12} While various treatments have

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PARTICIPANTS AND METHODS

STUDY POPULATIONS

Forty-five HIV-infected subjects were studied (17 who underwent splenectomy and 28 control subjects who did not undergo splenectomy). Fourteen subjects were recruited from the Montreal General Hospital Immune Deficiency Treatment Centre, Montreal, Quebec, patient population and 31 were recruited from a Canadian multicenter study of immune dysfunction in those with hemophilia. Enrollment into this study began in September 1982 and was based on a diagnosis of either hemophilia or Von Willebrand disease.²⁸⁻³⁰ All subjects were observed prospectively at 6-month intervals. Individuals in whom ITP was diagnosed or who had undergone splenectomy were identified on enrollment into the multicenter study or during the course of their clinical follow-up.

For the present analysis, 3 groups of subjects were selected from the populations previously described. Subjects in group 1 had their spleens removed as a result of trauma or as a treatment for thalassemia prior to becoming infected with HIV. Subjects in group 2 underwent splenectomy after infection with HIV, during the asymptomatic phase of HIV disease, as a treatment for ITP, thalassemia, or trauma. Subjects in group 3 were asymptomatic HIV-infected men with ITP who never underwent splenectomy. Idiopathic thrombocytopenic purpura was defined as platelet levels less than $130 \times 10^9/L$ on at least 2 occasions within a 12-month period. Risk categories for HIV acquisition in group 3 were hemophilia, thalassemia, and homosexual transmission. All individuals were asymptomatic for HIV disease at study enrollment.

Study enrollment (time 0) was defined as the presumed date of HIV infection. For most subjects, this date was taken as the time at which a subject's serum sample first tested positive for antibodies to HIV by the enzyme-linked immunosorbent assay and Western blotting. This date was used for all those infected through sexual transmission and for those blood product recipients who first tested positive before January 1, 1985. In 1985, the

initiation of donor screening and the availability of heat-treated coagulation factors eliminated the risk of HIV infection by blood products. Cohort studies show that most individuals who seroconverted as a result of multiple transfusions of blood products became infected with HIV prior to January 1, 1985. Pre-1985 serum samples were available for all but 14 blood product recipients. For these 14 subjects, 2 different strategies were used to assign a default infection date. The first, more conservative, strategy assigned all 14 subjects the date of January 1, 1985, as the presumed date of HIV infection. The second strategy used the presumed median time of infection of October 1982 as the common date for these 14 subjects. This later date is based on published reports indicating that most subjects with hemophilia treated with factor VIII concentrates were infected from 1981 to 1983³¹⁻³⁵ and on HIV screening results of frozen stored samples obtained from members of the Montreal hemophilic population in 1982 indicating that 50% of this population was infected by October 1982.³⁶

Subjects were observed until death of AIDS-related or AIDS-unrelated causes or until March 1996. The date of the AIDS diagnosis was based on the development of any AIDS-defining condition other than ITP, according to the 1987 Centers for Disease Control and Prevention, Atlanta, Ga, criteria.³⁷

The data for all individuals receiving antiretroviral drugs are documented in a registry; these individuals receive their medication from a single pharmacy and duplicate prescription forms are kept in the subjects' medical records. Use, and timing of use, of antiretroviral drugs within each subject's follow-up period was cataloged by a retrospective review of the subject's clinic medical record.

DIAGNOSIS OF INFECTION WITH HIV-1

Serum samples were tested for antibodies to HIV-1 and screened in duplicate (Dupont Biotechnology Systems, Markham, Ontario). The seropositivity of serum samples testing positive by enzyme-linked immunosorbent assay was confirmed by Western blotting. Whole viral lysates were the antigen source in immunoblotting experiments (Organ Technika, Scarborough, Ontario).

been used to increase platelet levels in patients with ITP,¹¹⁻¹⁷ several reports have suggested that splenectomy is a safe, effective procedure for the treatment of ITP in HIV-infected individuals.¹⁸⁻²⁶ Results from several studies indicate that splenectomy produces long-lasting increases in platelet levels in more than 80% of the patients.^{12,27}

If the spleen is an important reservoir for HIV and an important site for virus replication during the asymptomatic phase of disease, its removal may have an effect on the course of infection. To verify this hypothesis, we studied the effect of splenectomy, prospectively, on time to development of acquired immunodeficiency syndrome (AIDS) and survival time following HIV infection.

RESULTS

BASELINE RISK FACTOR DISTRIBUTION

Subjects in group 1 (n=5) had their spleens removed as a result of trauma (n=3) or as a treatment for thalassemia (n=2)

prior to becoming infected with HIV. Risk categories for HIV infection were hemophilia (n=2), thalassemia (n=2), or homosexual transmission (n=1). Subjects in group 2 (n=12) underwent splenectomy after infection with HIV, during the asymptomatic phase of HIV disease, as a treatment for ITP (n=10), thalassemia (n=1), or trauma (n=1). Seven were infected through blood or blood products (6 had hemophilia and 1 had thalassemia) and 5 through sexual transmission. Subjects in group 3 (n=28) were asymptomatic HIV-infected men with ITP who never underwent splenectomy. The risk categories for HIV acquisition in group 3 were hemophilia (n=20) and homosexual transmission (n=8).

The baseline characteristics of the study subjects are compared in **Table 1**. All but one of the study subjects were men. Although baseline differences between subjects who underwent splenectomy and those who did not undergo splenectomy are not statistically significant, subjects who underwent splenectomy had, on average, lower initial CD4⁺ cell counts and were younger (Table 1). These differences were taken into account in our multivariate analyses. On the

LYMPHOCYTE IMMUNOPHENOTYPING

T-lymphocyte phenotyping was determined on Ficoll-Hypaque gradient-separated lymphocytes. Gradient-purified lymphocytes are free of the cell debris often encountered in samples obtained from subjects who have undergone splenectomy. Commercially available fluorochrome-conjugated monoclonal-specific reagents were used to stain CD3⁺, CD4⁺, and CD8⁺ cells (Becton Dickinson, San Jose, Calif). Fluorometric analysis was performed on a fluorescence-activated cell sorter (B-D FACS, Becton Dickinson) or a fluorescence-activated cell scanner (B-D FACScan, Becton Dickinson).

STATISTICAL ANALYSES

Independent group *t* tests and χ^2 tests were used to compare distributions of continuous and categorical risk factors in subjects who underwent splenectomy and in those who did not undergo splenectomy, respectively. Survival analytic methods were employed to assess the effect of splenectomy on survival and on the progression to AIDS in 2 separate analyses. The first analysis focused on the risks of mortality from any cause; subjects who were alive at the end of the study were censored at that time. The second analysis compared the length of the asymptomatic phase of the HIV infection, equivalent to the time elapsed between time 0 (presumed date of HIV infection) and the date when the criteria for AIDS were met. In this analysis, subjects who were alive at the end of the study and those who died of causes unrelated to AIDS were censored at the respective date only if they remained asymptomatic until that date. The Kaplan-Meier product limit method was used to estimate the unadjusted probability of survival or remaining free of AIDS in the different study groups. In all descriptive and univariate survival analysis, the median date of October 1982 was used as a default presumed date of infection for the 14 blood product recipients referred to previously.

To reduce the risk of confounding bias, our main analyses relied on the multivariate Cox proportional hazards model,³⁸ using computer software (S plus, Statistical

Sciences Inc, Seattle, Wash).³⁹ Accordingly, relative risks (RRs) were measured by hazard ratio. To account for the timing of splenectomy, we represented it by a time-dependent binary covariate that takes the value 0 over the interval preceding the spleen removal and the value 1 thereafter. This approach ensures that, for subjects who underwent splenectomy after HIV infection (group 2), the protective effect of undergoing splenectomy is assessed based only on the subjects' survival experience after the surgery. If splenectomy were treated as a fixed-in-time covariate, corresponding to a simple grouping of subjects as either undergoing splenectomy at some point in time or never undergoing splenectomy, the length of time the subject was alive before splenectomy would be incorrectly attributed to the effect of the surgery.

In the Cox proportional hazards model, we adjust the effect of splenectomy for the following risk factors, selected a priori and kept in the model regardless of their statistical significance: initial CD4⁺ cell count, age, and treatment with antiretroviral therapy (ART). Because of substantial variation among subjects receiving these drugs, in the total duration or the timing of the treatment or both, ART was also represented as a time-dependent binary covariate. Thus, when estimating RRs at any given time, we take into account whether a subject received ART at that specific time rather than whether the subject was treated at any time (in the past or future).

Finally, in the post hoc analyses we have introduced an additional variable indicating what method was used to estimate the presumed time of HIV infection for a given subject. The motivation was to verify whether there was any systematic difference between estimated length of survival in subjects for whom the date of the first seropositive test result was used as time 0 and those recipients of blood products for whom time 0 was a default date. A significant ($P < .05$) difference between these 2 subsets of subjects would indicate a possibility of a differential bias between the 2 methods, which would have to be controlled for in the analysis. Multivariate analyses were repeated twice using either October 15, 1982, or January 1, 1985, as the default date. Likelihood ratio tests with $\alpha = .05$ were used to assess significance in all survival analyses.

other hand, the mean time elapsed between the presumed date of HIV infection and the first available CD4⁺ cell count in subjects who underwent splenectomy and in subjects who did not undergo splenectomy is almost the same. Thus, the variation in the individual's timing of the first available CD4⁺ cell count does not bias the subsequent comparisons of these 2 groups. Moreover, the time elapsed between the presumed date of infection and the first CD4⁺ cell measurement did not correlate with the CD4⁺ cell count ($P > .50$). The results in Table 1 also show a considerable variation in the timing of splenectomy vis-à-vis the presumed date of HIV infection. This variation was taken into account by representing splenectomy as a time-dependent covariate in our multivariate analyses.

CLINICAL OUTCOMES: DESCRIPTIVE STATISTICS

Five subjects who underwent splenectomy before HIV infection were observed for a period ranging from 8.2 to

13.4 years (mean [\pm SD], 11.14 \pm 2.3 years) from the date of presumed HIV infection. (All results reported in this section are based on the median infection date of October 15, 1982, for the 14 blood product recipients for whom data on seropositivity were not available prior to 1985.) One individual died of AIDS-related causes and a second of AIDS-unrelated causes. Twelve individuals who underwent splenectomy after infection were observed for a period ranging from 3.8 to 13.4 years (mean [\pm SD], 8.8 \pm 2.9 years). Seven members of this group have died, 2 of causes unrelated to AIDS and 5 of AIDS-related causes. The 28 subjects in the unsplenectomized control group of HIV-infected patients with ITP were observed for a period ranging from 0.9 to 13.4 years (mean [\pm SD], 7.2 \pm 3.9 years) from the presumed date of HIV infection. Three subjects in this group died of AIDS-unrelated causes, 20 died of AIDS-related disease, 3 are alive and have AIDS, and 2 are in the asymptomatic phase of HIV disease, yet have CD4⁺ cell counts of less than $0.10 \times 10^9/L$. Eleven (64.7%) of the subjects who underwent splenectomy re-

Table 1. Baseline Risk Factor Distributions

Risk Factors	Subjects Who Underwent Splenectomy (n=17)	Subjects Who Did Not Undergo Splenectomy (n=28)
Absolute CD4 ⁺ T-lymphocyte count, ×10 ⁹ /L*	0.63 (0.27)	0.94 (0.70)
Time to first CD4 ⁺ T-lymphocyte count, y*	1.9 (1.8)	2.0 (1.5)
Age, y*	27.6 (11.2)	32.2 (12.4)
Antiretroviral therapy†	64.7	64.3
Time to splenectomy, y*	1.4 (2.7)	NA‡

*Data are given as the mean (SD).

†Data are given as the percentage of subjects.

‡NA indicates data not applicable.

ceived ART, while 18 (64.3%) of the subjects who did not undergo splenectomy received ART for a portion of the follow-up period.

Figure 1 compares unadjusted Kaplan-Meier survival curves for different groups of subjects, using death by any cause as an end point, whereas **Figure 2** focuses on the duration of the asymptomatic phase of the HIV infection. Subjects who have undergone splenectomy seem to have a longer overall survival and a lower rate of progression to full-blown clinically defined AIDS. However, some caution is necessary when interpreting the results for subjects who underwent splenectomy after HIV infection (group 2), as the Kaplan-Meier method is not able to account for the variation in the timing of splenectomy. Accordingly, the initial portions of the corresponding survival curves for group 2 partly reflect the experience of subjects who did not yet undergo splenectomy. For this reason, in Figures 1 and 2 the subjects in group 2 have been separated from the subjects in group 1 for whom the previously described concern does not apply as they had their spleens removed before the HIV infection.

CLINICAL OUTCOMES: MULTIVARIATE ANALYSES

To adjust for imbalances in risk factors and to avoid the previously described difficulty in interpreting the results for group 2, our main analyses are based on the multivariate Cox proportional hazards model. Splenectomy is represented by a time-dependent covariate that takes into account the exact timing of spleen removal rather than by a grouping factor so that there is no need to separate subjects who underwent splenectomy prior to (group 1) or after (group 2) HIV infection. **Table 2** provides information on the estimated effects of undergoing splenectomy on the risks of survival and developing AIDS corresponding to various modeling strategies. The upper half of Table 2 provides the results obtained when the median date of HIV infection of October 15, 1982, was used as the presumed default date for 14 blood product recipients who did not have their serum samples stored prior to 1985, while the lower part of Table 2 corresponds to a more conservative default date (January 1, 1985). In all analyses, the effect of splenectomy is ad-

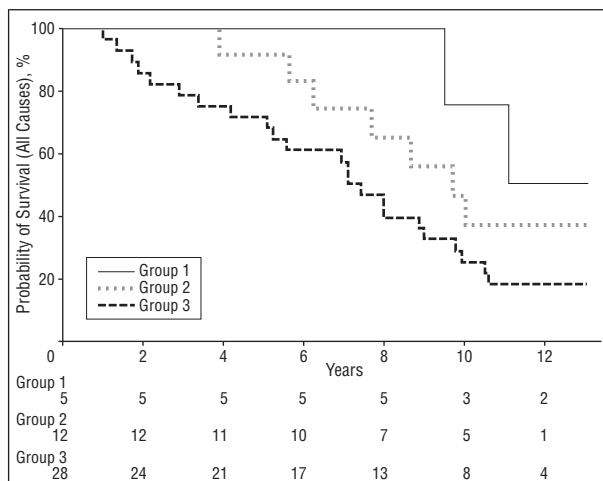


Figure 1. Effect of splenectomy on overall survival. Kaplan-Meier curves are given for the groups of subjects: group 1 (n=5) subjects underwent splenectomy prior to human immunodeficiency virus (HIV) infection, group 2 (n=12) subjects underwent splenectomy during the asymptomatic phase of HIV infection, and group 3 (n=28) subjects did not undergo splenectomy. The numbers below the graphs indicate the number of subjects at risk in the respective groups.

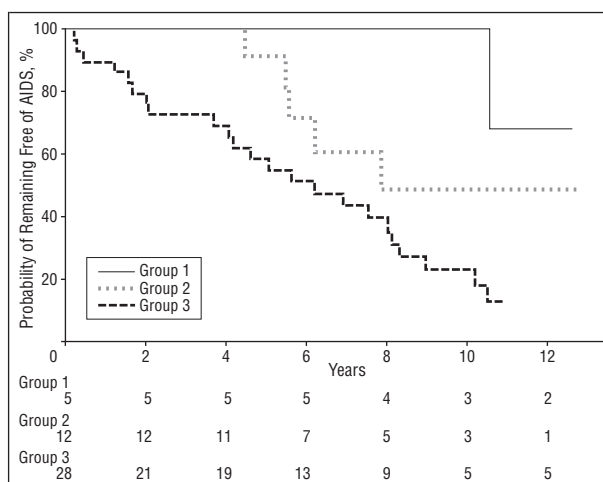


Figure 2. Effect of splenectomy on the duration of the asymptomatic phase of human immunodeficiency virus (HIV) infection. Kaplan-Meier curves are given for the groups of subjects: group 1 (n=5) subjects underwent splenectomy prior to HIV infection, group 2 (n=12) subjects underwent splenectomy during the asymptomatic phase of HIV infection, and group 3 (n=28) subjects did not undergo splenectomy. Numbers below the graphs indicate the number of subjects at risk in the respective groups; AIDS, acquired immunodeficiency syndrome.

justed for the age at the time of presumed infection and first available CD4⁺ cell count. In most analyses, older age was associated with a significantly higher risk. In all analyses, a higher CD4⁺ cell count was associated with lower risk, but these effects did not reach statistical significance. When logarithmic and square root transformations of the original CD4⁺ cell count were employed, to account for the considerable positive skewness of its distribution, the results did not change substantially (data not shown). In addition, we decided a priori to take into account information on treatment with ARTs. Use of ART was systematically associated with higher (occasionally significant) risk. A post hoc explanation of this finding is that ART might be prescribed more often for subjects

Table 2. The Results of Cox Proportional Hazards Analyses for Subjects Who Underwent Splenectomy Compared With Subjects Who Did Not Undergo Splenectomy*

Covariates in the Model According to the Presumed Date of HIV Infection for 14 Blood Product Recipients†	Outcome‡	
	Death by Any Cause	AIDS
October 15, 1982 (median infection date)		
Age and CD4 ⁺ cell count	0.51 (0.22-1.16)[.11]	0.39 (0.15-0.99)[.05]
Age, CD4 ⁺ cell count, and ART	0.49 (0.21-1.13)[.10]	0.36 (0.13-0.95)[.04]
Age, CD4 ⁺ cell count, ART, and "date"§	0.49 (0.21-1.14)[.10]	0.40 (0.15-1.07)[.07]
January 1, 1985		
Age and CD4 ⁺ cell count	0.50 (0.22-1.12)[.09]	0.37 (0.14-0.90)[.04]
Age, CD4 ⁺ cell count, and ART	0.51 (0.22-1.17)[.11]	0.37 (0.14-0.91)[.04]
Age, CD4 ⁺ cell count, ART, and "date"§	0.51 (0.22-1.18)[.17]	0.39 (0.15-1.04)[.06]

*HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; and ART, antiretroviral therapy.

†For all other subjects, the presumed date of HIV infection was defined as the date of the first HIV-positive test result.

‡Data are given as the adjusted relative risk, which is expressed as a hazards ratio. The hazards ratio range is given in parentheses. P values are given in brackets.

§"Date" is a binary covariate indicating 14 subjects for whom the default date was used (either October 15, 1982, or January 1, 1985).

||The risk reduction due to splenectomy was significant at $\alpha=.05$ (2 tailed).

exhibiting clinical progression or rapid loss of CD4⁺ cells. Therefore, the estimated effect of ART may partly be due to the phenomenon of "confounding by indication," common in nonrandomized studies of drug effects. Given this difficulty in interpreting the effect of ART, we have also reported the results of the models in which information on ART was ignored.

The 2 last columns of Table 2 indicate that the estimated effect of splenectomy is quite robust for the choice of the "default" date, the decision whether to adjust for ART or not, or both. The results suggest that splenectomy may be associated with a 50% reduction of the risk of death by any cause but that this risk reduction is marginally nonsignificant ($P \approx .10$ for all), possibly reflecting low power due to the relatively small sample size. The beneficial effect of splenectomy on the risk of developing AIDS is even stronger, with more than 60% RR reduction, and is statistically significant at $\alpha=.05$ (1-tailed tests). Wide confidence intervals reflect a small sample size.

In additional analyses reported in Table 2, we included in the multivariate Cox proportional hazards models a binary variable "date" to assess whether the use of an arbitrary default date for a subset of subjects might have biased the results. The inclusion of this variable had a minor effect on the estimated hazards ratios (Table 2). However, the P value for the effect of splenectomy on the risk of developing AIDS increased from less than .05 to a marginally nonsignificant value of less than .07. This change in P values may be partly explained by a loss of an additional degree of freedom (with date included in the model, the ratio of observed outcomes to the number of variables in the model falls below the recommended value of at least 10) and partly by a slightly nonproportional distribution of subjects who underwent splenectomy and subjects who did not undergo splenectomy among the 14 subjects for whom the default date was used. More importantly, we did not find evidence of a differential bias induced by using this method of establishing the date of infection (P values between .17 and .57 in all analyses).

To investigate further the robustness of our results, we repeated the multivariate analysis in a subset

of 31 subjects infected by blood products. The estimated effects of splenectomy were similar to those obtained for the entire sample. In particular, splenectomy was associated with a 35% to 45% reduction of risk of death by any cause and a 65% to 79% RR reduction of AIDS. However, a smaller sample size affected the precision and the power of these additional analyses.

COMMENT

This article examines the effect of splenectomy on survival and the length of the asymptomatic phase in a group of HIV-infected patients. Individuals who underwent splenectomy prior to HIV infection or during the asymptomatic phase of HIV were found to have a significantly reduced risk of developing AIDS (adjusted RR < 0.4, $P < .05$) and had a marginally nonsignificantly reduced risk of mortality (adjusted RR ≈ 0.5 ; $P \approx .10$).

Previous reports have shown that splenectomy does not increase the risk of developing AIDS.^{12,23,25-27,40-44} Oksenhendler et al²⁷ also treated splenectomy as a time-dependent variable and adjusted for baseline CD4⁺ cell count. They reported no difference in AIDS progression rate, survival, and AIDS-free survival between 68 patients with ITP who underwent splenectomy and 117 patients with ITP who did not undergo splenectomy during a median follow-up of 5.2 years (range, 0.5-10.5 years). In a separate study during a 1.8-year follow-up of 45 patients, 17 of whom had undergone splenectomy, Sanderson et al⁴⁵ found no increased risk of disease progression. Morlat et al⁴⁶ compared 28 subjects who had undergone splenectomy and who were observed for a median of 51 months with 389 individuals observed for a median of 29 months and matched with the subjects who had undergone splenectomy for year of diagnosis for HIV infection, interval between diagnosis and enrollment into the study, and absence of AIDS and CD4⁺ cell counts at enrollment. They reported significant differences in favor of the subjects who had undergone splenectomy for survival, development of AIDS, and CD4⁺ T-lymphocyte decline below $0.20 \times 10^9/L$.⁴⁶

The cohort studied for this article provides new perspectives on the effect of splenectomy in the progress of HIV disease. First, the individuals in this study were observed prospectively and for a longer period than those in any of the previous studies (mean [\pm SD] follow-up, 8.6 \pm 3.7 years; range, 0.9-13.4 years from the date of presumed HIV infection). Second, sensitivity analyses were performed to assess the robustness of the adjusted effect of splenectomy. In particular, we have adjusted for age, a significant risk factor in our analyses.

Similar to results reported by others,¹¹⁻¹⁷ in 9 of the 11 subjects for whom presplenectomy test results were available, a rapid, adequate, and sustained increase in platelet levels was noted in response to surgery. None of these subjects required further treatment for ITP. Splenectomy in this group of subjects was an effective treatment for HIV-associated ITP. In these subjects, an increase in lymphocytes and usually in absolute CD4⁺ and CD8⁺ T-lymphocyte subset levels was found following splenectomy (data not shown). Splenectomy is accompanied by an increased risk of bacterial sepsis,^{47,48} an outcome preventable by an antipneumococcal vaccine prior to splenectomy and by the administration of prophylactic doses of antibiotics.

The spleen is regarded as an important organ for the maintenance of immune competence. Concerns relating to its removal in those with acquired immune dysfunction have been based on the possibility that such individuals would be more prone to the development of sepsis or opportunistic infections. In this article, splenectomy not only has been shown to be safe and beneficial in the long-term treatment of our patients with HIV-associated ITP but also relatively safe in asymptomatic HIV-infected individuals without ITP. An important new finding of this study is the association of a longer asymptomatic clinical course with splenectomy.

There are 2 possible explanations for the observation that HIV-infected patients lacking a spleen seem to exhibit slower HIV disease progress than those with a spleen. The spleen makes up approximately 50% of lymphoreticular tissue. Lymphoreticular tissue seems to be a major site for HIV sequestration and replication.⁶⁻⁸ If the spleen or lymph node microenvironment is ideally suited to efficient viral replication, removal of a large proportion of an individual's lymphoreticular tissue through splenectomy may reduce the size of the reservoir available for maintenance of the HIV replicative cycle. Splenectomy is also usually associated with a relative leukocytosis and lymphocytosis, indicative of a reduced clearance or a reactive increase in the production of these cells. Increases in lymphocyte numbers, as well as possible changes in cytokine environment, following splenectomy may play a role in modifying the course of HIV infection. These immunomodulatory changes may or may not be related to the simple removal of a reservoir for HIV and HIV replication.

The correlation between the absence of a spleen and resistance to pathogenic microorganisms is not without precedent. Splenectomy of strain A mice renders animals normally susceptible to the facultative intracellular bacterial parasite *Listeria monocytogenes* extremely resistant to infection with this pathogen.⁴⁹ In a study of splenectomized and control nonsplenectomized rhesus *Macaca* monkeys that were inoculated with the patho-

genic simian immunodeficiency virus (SIV) isolate SIV-mac239, the splenectomized animals had a lower simian burden and longer survival than the nonsplenectomized controls.⁵⁰ These findings are consistent with the concept we propose, that splenectomy confers a clinical benefit in HIV disease.

Our results need to be replicated in an independent study. The strongest evidence of the benefit of splenectomy would be provided by a randomized, controlled, clinical trial. Such a study would entail an intervention in the early asymptomatic phase of HIV disease and require many years to complete. An alternative approach would be to perform a meta-analysis of all available cohorts that had undergone splenectomy.

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