To the Editor:

In the November 15 issue of this journal, Gibbons et al reported that the rate of human immunodeficiency virus (HIV) infection among high-risk antibody-negative individuals with hemophilia is very low to absent, in the range of 0% to 2%. However, we have recently experienced a patient with hemophilia B who became seropositive for HIV-1 more than 3 years after switching to heat-treated prothrombin complex concentrates (PCCs).

This is a 17-year-old boy with severe hemophilia B. At 1 year of age, he was diagnosed to have congenital factor IX deficiency, and treatment with PCCs was started. In 1979, at the age of 6, he developed antibody to factor IX. However, to induce immunologic tolerance and/or to use its “inhibitor bypassing activity,” we have
Table 1. Changes of Serum Antibodies, Antigen, and Sequences of HIV-1

<table>
<thead>
<tr>
<th>Year/Month</th>
<th>'80/7</th>
<th>'83/10</th>
<th>'85/8</th>
<th>'86/3</th>
<th>'86/7</th>
<th>'87/3</th>
<th>'87/7</th>
<th>'88/1</th>
<th>'89/3</th>
<th>'89/9</th>
<th>'90/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 antibodies</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NT</td>
<td>+</td>
</tr>
<tr>
<td>HIV-1 antigen</td>
<td>NT</td>
<td>NT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HIV-1 sequences†</td>
<td>NT</td>
<td>NT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*NT, not tested.
†Detected by RNA-PCR and liquid hybridization.

continued to treat him with PCCs, imported mainly from the United States.

As shown in Table 1, his anti-HIV-1 antibodies had been negative by particle agglutination, enzyme-linked immunosorbent assay, indirect immunofluorescence, and Western blotting methods until September 1989. However, in July 1990 we found that his anti-HIV-1 antibody was positive. All of the samples listed in the table were retested carefully, and the results were confirmed. He denies any other risk factors except for PCCs, and it is supported by the fact that about 90% of HIV carriers registered in Japan are hemophilia patients.

Because of this delayed development of antibodies to HIV-1 in the hemophilia B patient, we studied on his frozen serum samples that were stored separately. As shown in Table 1, HIV-1 RNA sequences have been detected by RNA-PCR (polymerase chain reaction in combination with reverse transcription) from his serum samples. His serum samples were handled very carefully to avoid even the slightest chance of contamination because PCR methods are very sensitive. At the same time, serum samples of other hemophilia patients collected during the past 3 years were also tested anonymously and at random fashion. As a result of this study of controls, 38 of 39 serum samples of 16 seropositive hemophilia patients were positive through the RNA-PCR method. However, none of the 43 serum samples of 29 seronegative hemophilia patients were positive.

The detection of HIV-1 RNA is not a direct evidence for the existence of infectious HIV-1. However, it strongly suggests that the HIV-1 infection has occurred before August 1985. It was in January 1986 when all of the nonheated PCCs were switched to heat-treated PCCs in Japan. HIV-1 antigen, ie, p24 antigen, was not detected in the patient's serum samples studied, as shown in Table 1. His CD4 lymphocyte count has always been between 600 and 700/µL since July 1986. However, CD4/CD8 ratio has sharply decreased from 1.08 (March 1989) to 0.38 (September 1989), and has remained at the same level thereafter. His other immunologic findings have been within the normal limits thus far.

Yamada3 has also reported that none were positive for HIV through DNA-PCR among 53 high-risk antibody-negative individuals with hemophilia in Japan. Although the rate must be very low, so-called "silent infection with HIV" does exist among hemophilia patients, too.

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REFERENCES
Delayed human immunodeficiency virus-1 seroconversion in a hemophilia B patient in Japan [letter; comment]

T Nagao, K Honda, N Yoshihara and K Nakanaga