Persistent Parvovirus B19 Infection without the Development of Chronic Anemia in HIV-Infected and -Uninfected Children: The Women and Infants Transmission Study

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We evaluated the prevalence of persistent parvovirus B19 (B19) infection and associated anemia in human immuno deficiency virus (HIV)-infected and HIV-uninfected children. B19 persistence was defined as B19 DNA detected in specimens collected >16 weeks apart. Of 182 children, 3 HIV-infected children and two HIV-uninfected children had evidence of persistent B19 infection. Of the 5 children, none had evidence of B19-associated anemia. Our data suggest that B19 infections can persist in children without the development of symptomatic anemia.

Parvovirus B19 (B19) is a common pathogen that infects >50% of all individuals by adulthood. B19 infection is often asymptomatic, but, when symptomatic, typically causes erythema infectiosum in children or arthropathy in adults [1]. B19 infection among fetuses and among anemic or immunocompromised individuals can lead to a severe anemia caused by lytic infection of red blood cell precursors [2]. Among immunocompromised individuals, including those receiving immunosuppressive therapy, those with congenital immune deficiencies, or those infected with HIV-1 infection, B19 infection can become persistent and cause chronic reticulocytopenic anemia. The diagnosis of B19-associated chronic anemia is important, because administration of intravenous immune globulin therapy (IGIV) can effectively treat both B19 viremia and, indirectly, anemia [3].

HIV-infected adults and children, usually those with CD4+ cell counts <100 cells/µL, can develop persistent B19 infection with an associated persistent anemia, presumably because of an inadequate immune response to B19 [3–6]. No studies have investigated the frequency of persistent B19 infection among HIV-infected children and compared the frequency of identified cases of persistent infection among HIV-infected and HIV-uninfected children; however, in 1 study, persistent B19 infections were identified in 3% of congenitally immunocompromised children [7].

In the adult HIV-infected population, the reported prevalence of persistent B19 infection and associated anemia has varied, likely due to differences in patients' degree of immune suppression and receipt of antiretroviral therapy (ART). In studies of HIV-infected adults, the prevalence of persistent B19 infection ranged from ≤1% (patients without anemia) [8] to 3.3% (patients with anemia) [9].

Because B19 infection occurs most often in childhood, we investigated whether HIV-infected children were more likely to have persistent, symptomatic B19 infection, compared with HIV-exposed but HIV-uninfected children. In the present study, we evaluated plasma specimens for evidence of B19 infection among children born to HIV-infected women enrolled in the Women and Infants Transmission Study (WITS). We determined the proportion of children with evidence of any B19 infection and, among these children, the proportion with persistent B19 infection and with anemia.

Subjects, materials, and methods. WITS is a prospective cohort study of HIV-infected women and their children that began enrollment in 1989. The objectives of WITS are to describe HIV disease progression among HIV-infected women and children and to evaluate risk factors for mother-to-child transmission of HIV [10]. The Institutional Review Board at each study center approved the protocol, and written informed consent was obtained from all participants before enrollment. Clinical data and blood specimens were collected from children at regularly scheduled visits occurring at birth, at 1, 2, 4, 6, 9, 12, 18, and 24 months of age, and then every 6 months thereafter. Blood samples were collected by venipuncture at study visits and were processed within 6 h of collection. Plasma samples were stored on site at −70°C until they were transported.
to the central WITS repository, where they were stored at
−70°C.

Data regarding HIV-infected children enrolled in WITS by
June of 1998 who met the following criteria were analyzed: (1)
age ≥2 years at the time that their most recent repository spec-
imen was obtained; (2) no receipt of IGIV at the time of or
during the 6 months prior to the most recent specimen col-
lection; and (3) presence of at least 5 remaining plasma spec-
imens in the WITS repository for serial testing. These HIV-
infected children were matched to HIV-uninfected children
enrolled in WITS in a 1:1 ratio according to the following
criteria: (1) age within 2 months of the HIV-infected child; (2)
availability of a repository specimen obtained within 1 year of
the most recent specimen obtained from the HIV-infected child;
and (3) study site.

For all children in the study population, information from
the WITS computerized database was compiled according to
the following characteristics: maternal income and source, mar-
itual status, and sex; child’s birth date, race/ethnic-
ity, and education; and mean values of continuous
demographic variables, such as sex, were cross-tabulated
with dichotomous variables, such as sex, were cross-tabulated
with dichotomous variables. All analyses were performed by use
of the SAS statistical software system (version 8.01; SAS Institute). For the
comparison of HIV-infected and HIV-uninfected children, all di-
chotomous variables, such as sex, were cross-tabulated with
HIV infection status for comparison of the frequency distri-
butions and χ² P values of each variable. Continuous variables
were analyzed by use of a paired t test for comparison of dif-
fferences in mean values. For the comparison of B19 infection
risk factors, mean values of continuous demographic variables,
and the laboratory results of children with evidence of B19
infection, differences were assessed by use of the nonparametric
Wilcoxon-rank sum test and McNemar’s test for matched case-
control study comparisons.

Results. Of 171 HIV-infected children enrolled in WITS
as of June 1998, 91 met the inclusion criteria for this analysis
and were matched with 91 HIV-uninfected children who were
also enrolled in WITS. Study children were 2.0–7.6 years of age
(mean age, 4.5 years), and 48.3% were female. Forty-five per-
cent were black, 31% were Hispanic (black or white), 17% were
white, 4% were American Indian/Alaskan Native or Asian, and
3% had no ethnic or racial background listed. Seventy-three
percent of the children’s mothers earned <$10,000/year, 41.7% received welfare or public assistance, and 51.1% had less than
a high school education. HIV-infected and HIV-uninfected
children were similar in terms of maternal income, income
source, and education; age, sex, and race/ethnicity; and mean
WBC count and CD8+ cell count. As expected, mean hemog-
lphin levels, platelet counts, and CD4+ cell counts were all
significantly lower in the HIV-infected children (P ≤ .003). Of
the HIV-infected children, 84.4% were receiving at least 1 anti-
retroviral medication. Thirty-three (36.3%) were not immu-

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848 • JID 2004:189 (1 March) •
nocompromised (Centers for Disease Control and Prevention [CDC] immunologic category 1), 37 (40.7%) were moderately immunocompromised (category 2), 17 (18.7%) were severely immunocompromised (category 3), and 4 (4.3%) were missing CD4+ cell count data.

B19 infection was detected serologically in 24 (13%) of 182 children (table 1). Of these 24 children, 19 (79.7%) had a previous or recent infection, and 5 had a persistent infection. Of the 5 children with persistent B19 infections, 3 were among HIV-infected children and 2 among HIV-uninfected children. The duration of B19 persistence among these 3 HIV-infected children was estimated at a minimum of 51, 83, and 86 weeks, compared with 22 and 50 weeks among the 2 HIV-uninfected children. At the time of the first positive specimen for B19 infection, the mean hemoglobin concentration was 10.6 g/dL for the HIV-infected children, compared with 12.1 g/dL for the HIV-uninfected children (P = 1.0). Over time, 2 of 3 persistently B19-infected HIV-infected children experienced a mild-to-moderate decrease in hemoglobin concentration (hemoglobin concentration range during B19 infection, 9.5–13.2 g/dL), and the third child had a 27% decrease in hemoglobin concentration (13.2 to 9.7 g/dL; figure 1).

Among the HIV-infected children, persistently B19-infected children had a mean CD4+ cell count of 944 cells/µL (range, 624–1280 cells/µL), compared with 853 cells/µL (range, 52–1234 cells/µL) among children with recent or previous B19 infection. One of the 3 HIV-infected children with persistent B19 infections was classified as severely immunocompromised (category 3) at the time that B19 infection was first detected, but, within 6 months, the CD4+ cell count normalized (1280 cells/µL).

Discussion. Although the majority of reported cases of persistent B19-associated anemia have occurred among HIV-infected individuals with CD4+ cell counts <50 cells/µL [3–5], symptomatic, persistent B19 infections can occasionally occur in patients with less severe or no immunosuppression. Persistence infection with and without anemia in apparently immunocompetent healthy persons also has been reported but is unusual. Kerr et al. [15] found B19 DNA positivity for ≥26 months in 7 (13.2%) of 53 immunocompetent healthy adults after recent B19 infection, with 1 possible B19-associated anemia. Consistent with this report, the present study identified 24 (13.2%) children with evidence of B19 infection, of whom 5 (20.8%) developed persistent infections. Three of these children were HIV infected, and 2 were HIV uninfected (12.5% and 8.3%, respectively). None of these children developed severe, chronic anemia, with a hemoglobin level <9.5 g/dL persisting for >16 weeks. Two of the 3 HIV-infected children with persistent B19 infections had a decrease in hemoglobin, which was possibly associated with the B19 infection. In the 2 HIV-infected children, the decrease in hemoglobin level did not require treatment, and the hemoglobin level subsequently increased without specific therapy. Although one of the HIV-infected children with persistent B19 infection was categorized as severely immunosuppressed at the time of initial B19 infection, her hemoglobin level never decreased <10.9 g/dL. It is possible that some children with severe immune suppression may have lacked the ability to produce detectable antibody to B19, and only children with detectable antibody were further tested by use of PCR.

The minimum known duration of persistent infection appeared to be longer for HIV-infected than for HIV-uninfected children. However, the interval between the collection of specimens was ≥6 months, thus precluding precise estimates. On the basis of observations of the hemoglobin levels and duration of infection for the 5 children with persistent B19 infection, there were differences according to HIV infection status, albeit not statistically significant; 1 of the HIV-infected children with persistent B19 infection had a recurrence of IgM antibody (figure 1), which has been described elsewhere [16]. This result suggests reinfection, but could not be verified, because the IgM antibody was detected in the last available specimen for this patient.

**Table 1.** Hematologic parameters of HIV-infected (n = 91) and HIV-uninfected (n = 91) children with recent, previous, or persistent parvovirus B19 infection (B19) enrolled in the Women and Infants Transmission Study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV infected</th>
<th>HIV uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recent or previous B19</td>
<td>Persistent B19</td>
</tr>
<tr>
<td>Children, no. (%)</td>
<td>9 (10)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Mean hematologic parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.5</td>
<td>10.9</td>
</tr>
<tr>
<td>CD4+ cell count, cells/µL</td>
<td>853</td>
<td>944</td>
</tr>
<tr>
<td>WBC count, ×10⁹ cells/mm³</td>
<td>6.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Platelet count, ×10⁹ cells/mm³</td>
<td>276</td>
<td>284</td>
</tr>
</tbody>
</table>

**NOTE.** Children with recent and previous B19 infections are grouped together for comparison with children with persistent B19 infection. WBC, white blood cell.
Our data suggest that persistent, symptomatic B19 infection associated with severe chronic anemia is an uncommon problem in HIV-infected children who survive to age 2 years and are not severely immunocompromised. However, because persistent B19 infection is a treatable cause of anemia (i.e., through the administration of IGIV), B19 infection should continue to be considered in the differential diagnosis of anemia in HIV-infected children.
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**References**