Hepatitis C Prevalence in Children With Perinatal Human Immunodeficiency Virus Infection Enrolled in a Long-term Follow-up Protocol

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Objective: To evaluate the prevalence of hepatitis C virus (HCV) infection in children with perinatal human immunodeficiency virus (HIV) infection.

Design: Cross-sectional substudy.

Setting: Multicenter study from 41 sites in the United States.

Patients: Children with perinatal HIV infection were randomly selected from a large, long-term, follow-up protocol.

Main Outcome Measure: Hepatitis C infection was defined as having positive test results on both HCV antibody and HCV RNA assays.

Results: Five hundred thirty children enrolled in the substudy; definitive HCV test results were available for 525 children. Eighty-three percent were of a minority race or ethnicity. They were equally distributed by sex, had a median age of 10.7 years, and were relatively healthy, with 75% having CD4+ lymphocyte counts greater than 500 cells/mm³. Eight of 525 children (1.5%; 95% confidence interval [CI], 0.7%-3.0%) infected with HIV were coinfected with HCV. In contrast, the rate of HCV infection in a serosurvey of more than 2700 children aged 6 to 11 years from the National Health and Nutrition Examination Survey was 0.2% (95% CI, 0.04%-0.6%). In our study, there were no differences between children coinfected with HIV and HCV and those without HCV infection in terms of demographic characteristics, CD4+ or CD8+ T-lymphocyte counts, HIV 1 RNA levels, preterm or mode of delivery, or liver disease; however, the number of children coinfected with HIV and HCV was small.

Conclusion: While HCV prevalence infection rates are low in children with perinatal HIV infection, they are 8 to 10 times higher than reported in HCV serosurveys of children in the United States.


In the United States, one third to one half of adults infected with human immunodeficiency virus (HIV) are coinfected with hepatitis C virus (HCV), primarily acquired through intravenous drug use.¹ Mother-to-child transmission of HCV is the predominant mode of HCV acquisition in children. Between 2% and 18% of women infected with HCV will transmit it to their infants.²⁻⁹ However, higher HCV vertical transmission rates of 8% to 40% are reported for women coinfected with HIV and HCV.¹⁰⁻¹⁹ Although these data suggest that the burden of HCV coinfection may be significant in children with perinatal HIV infection, there have been no large-scale studies of HCV prevalence in this population. The purpose of this study was to investigate the prevalence of HCV infection in a large cohort of children perinatally infected with HIV who participated in a long-term follow-up protocol in the United States.

Patient Population

Pediatric Late Outcomes Protocol (PACTG 219C) is a multicenter, prospective cohort study of HIV-infected and HIV-exposed but uninfected children. This protocol was designed to examine late outcomes of HIV infection and the effects of exposure to antiretroviral medications given either as prophylaxis to prevent perinatal HIV transmission or as therapy for HIV infection. In 1993, PACTG 219C opened to enrollment, and to date has enrolled more than 3000 subjects at 84 participating sites in the mainland United States and Puerto Rico. Chil-
Children infected with HIV are followed up on a regular basis to age 24 years. At each visit, a routine physical examination, neurological examination, and laboratory evaluations are performed and data on baseline and intercurrent illnesses and diagnoses are collected.

We conducted a cross-sectional prevalence survey of HCV infection in a randomly selected subset of children with perinatal HIV infection enrolled in PACTG 219C. Forty-one PACTG 219C sites agreed to participate in this substudy. Approval for the study was obtained from an institutional review board at each participating site. The study opened to accrual in July 2002 and completed patient follow-up in March 2003. Children were eligible for study enrollment if they were older than 1 year and younger than 21 years, were perinatally infected with HIV, and were actively being followed up in PACTG 219C. Anticipating a 20% ineligibility and refusal rate, the study planned to enroll approximately 600 subjects to yield 500 subjects with evaluable results. Using a probability determined by the sampling fraction (a function of the number of subjects participating in the substudy and the number of eligible children infected with HIV enrolled in PACTG 219C at these sites), 604 of the 1841 potentially eligible subjects were randomly selected for possible study participation. Written informed consent was obtained from each child's parent or guardian prior to study entry. To reduce study bias, children with known HCV infection were also eligible to enroll. Subjects agreeing to participate in the study had a single blood specimen obtained at the next PACTG 219C study visit for HCV antibody and HCV RNA assays. If a patient had discordant results on these 2 tests, a second blood sample was obtained for repeat HCV testing. All positive HCV test results were discussed in person with the child's parent or legal guardian. Supplemental data collected from PACTG 219C used for this analysis included patient demographics, CD4⁺ and CD8⁺ T-lymphocyte counts and percentages, HIV 1 (HIV-1) RNA levels, and Centers for Disease Control and Prevention (CDC) HIV disease categories. 20

LABORATORY TESTING AND INFECTION STATUS DEFINITIONS

Human immunodeficiency virus infection was defined as positive test results on at least 2 separate peripheral blood samples assayed for any combination of the following: HIV culture; HIV DNA polymerase chain reaction (PCR); or plasma HIV-1 RNA greater than 10,000 copies/mL at any age; positive p24 antigen assay for children older than 1 month; or positive HIV enzyme immunoassay with confirmatory Western blot for children older than 18 months.

Hepatitis C infection status was determined using 2 assays: a third-generation HCV enzyme immunoassay (EIA) (Abbott HCV EIA 2.0; Abbott Laboratories, North Chicago, Ill) and qualitative HCV reverse-transcriptase PCR (RT-PCR) assay (Roche AMPLICOR HCV 2.0 kit; Roche Diagnostic Systems, Branchburg, NJ). Blood samples were processed within 30 hours of collection and serum for the EIA and plasma for the RT-PCR assay were stored on site at −20°C. Samples were shipped on dry ice within 1 month of collection to a single central laboratory (New Jersey Medical School, Newark) for EIA and RT-PCR testing.

A child with positive test results for both HCV EIA and HCV RT-PCR assays on the initial specimen was defined as infected with HCV. A child with negative test results for both HCV EIA and HCV RT-PCR assays was defined as uninfected with HCV. Any child who had discordant results (a positive test for 1 assay but a negative test for the other assay) on the initial specimen had a second blood specimen drawn. On the basis of the second test, a final classification of HCV status was made using the criteria detailed above. Subjects whose EIA and PCR results continued to be discordant were classified as HCV-determinate.

STATISTICAL METHODS

Statistical analysis was performed using Statistical Analysis System (SAS) software (SAS Institute, Cary, NC). To determine whether the children enrolled in the substudy differed from the PACTG 219C children who were eligible but not randomly selected for possible study participation, certain characteristics were compared, including sex, race and ethnicity, age, CD4⁺ and CD8⁺ T-lymphocyte counts and percents, HIV-1 RNA levels, and CDC HIV-disease categories. The HCV prevalence was calculated as the percentage of subjects with 2 positive test results (both EIA and RT-PCR) from 1 sample among subjects with definitive positive or negative test results. Comparisons for categorical data were performed using either χ² or Fisher exact tests and continuous variables were compared using Wilcoxon rank sum tests.

RESULTS

Of the 604 children eligible for this substudy, 530 (88% of the targeted sample) consented to study enrollment; definitive HCV results were available for 525 subjects. The 74 (12% of the targeted sample) randomly selected subjects who did not enroll were either ineligible at the time the study opened to accrual (n=17), refused to participate (n=15), could not be contacted (n=14), were not approached, or were not included for other reasons (n=28). At the time the random selection was performed (June 4, 2002), the 530 participating subjects did not differ in terms of age, sex, race or ethnicity, CD8⁺ T-lymphocyte counts and percents, HIV-1 RNA levels, or HIV CDC disease categories from the children with perinatal infection who were enrolled in PACTG 219C but were not randomly selected for possible study participation (data not shown). However, median CD4⁺ T-lymphocyte counts in the study population were significantly higher than those counts for children not selected for substudy participation (813 cells/mm³ vs 726 cells/mm³; P = .04).

Table 1 describes the baseline characteristics of the 530 children at the time of study enrollment. The median age of the children was 10.7 years (interquartile range [IQR], 7.8-13.5 years). Three quarters of the study population had CD4⁺ T-lymphocyte counts greater than 500 cells/mm³ and 42% had HIV-1 RNA levels below detection (median HIV-1 RNA was 1143 copies/mL; range, <400 to >750,000 copies/mL). More than one quarter of the children had a prior history of acquired immunodeficiency syndrome (AIDS) (CDC category C). The majority of children (68%) were receiving combination antiretroviral therapy including at least 1 protease inhibitor. One hundred thirteen children (21%) reported past receipt of blood products, with one third of these prior to 1992.

Definitive testing for positive or negative HCV infection status, based on the EIA and PCR results, was determined for 525 (99%) of the 530 enrolled subjects. There was excellent concordance between EIA and RNA testing for HCV. Five hundred fourteen children tested negative on both HCV assays on the first sample, and were determined to be definitively uninfected with HCV. Eight chil-
Children tested positive on both HCV assays on the first sample, and were determined to be definitively infected with HCV. Five (1%) children had discordant results on the first sample. On the second sample, 3 of these 5 children tested negative on both assays and were therefore definitively uninfected with HCV. One child had discordant results on both the first and second sample (testing positive using EIA, and testing negative using RT-PCR on both occasions) and was therefore HCV indeterminate. Another child had discordant results on the first sample (testing positive using EIA and testing negative using RT-PCR) and did not return for follow-up testing, and therefore could not be classified. No HCV data were available for 3 subjects; 1 had no sample drawn, 1 withdrew consent, and 1 sample was lost. The prevalence of HCV infection was 8 children of 525, or 1.5% (95% CI, 0.7%-3.0%). Five (63%) of these 8 children infected with HCV had been identified as being infected with HCV at study entry. Two additional patients reported to be infected with HCV at study entry tested negative for HCV on both EIA and RT-PCR assays. One of these children had had a previously positive test result for HCV EIA at 5 years old without a confirmatory HCV RNA assay. The other child tested positive for HCV EIA at 6 months old, which may have represented a maternally derived antibody. Alternatively, spontaneous clearance of HCV viremia with subsequent loss of anti-HCV antibody may have occurred in these children.

Selected demographic and HIV-related disease characteristics of the 8 children coinfected with HIV and HCV are depicted in Table 2. Three of the coinfected children were boys and 5 were girls; 6 children were from a minority race or ethnicity. The median age of the children infected with HCV had been identified as being infected with HIV at study entry. Two additional patients reported to be infected with HCV at study entry tested negative for HCV on both EIA and RT-PCR assays. One of these children had had a previously positive test result for HCV EIA at 5 years old without a confirmatory HCV RNA assay. The other child tested positive for HCV EIA at 6 months old, which may have represented a maternally derived antibody. Alternatively, spontaneous clearance of HCV viremia with subsequent loss of anti-HCV antibody may have occurred in these children.

Although subjects’ mothers and siblings did not undergo HCV testing during the course of the study, historical information on HCV status was available for 260 (50%) of the 525 mothers and for 233 (63%) of the 370 subjects with siblings. Eleven (4%) of the 260 mothers were reported to have tested positive for HCV while pregnant. All 11 women had children who were not infected with HCV. Of the 8 children coinfected with HIV and HCV, data on maternal serostatus were available for only 1 child’s mother who reportedly tested seronegative for HCV during pregnancy. None of the mothers or children infected with HCV had received specific anti-HCV viral therapy. None of the subjects infected with HCV had any known siblings known to be infected with HCV, but sibling information was available for only 3 of these subjects. No information was collected on breastfeeding practices in PACTG 219C; hence, this information was not available for children coinfected with HIV and HCV. Three of the children infected with HCV had received a blood product, intravenous gamma globulin (IVIG), prior to study enrollment. One child received a single IVIG infusion in 2002; 1 had 2 IVIG infusions between December 1997 and January 1998; and 1 child received periodic IVIG infusions, presumably for prophylaxis of serious bacterial infections, between 1991 and 1998.

Comparisons of birth events and liver diseases between children infected with HCV and those uninfected are shown in Table 3. There were no significant differences between children infected with HCV and uninfected children in the rate of preterm delivery or mode of delivery. Hepatomegaly was reported in a high percentage of both children infected with HCV (63%) and children who were uninfected (53%) (P = .73). None of the children coinfected with HIV and HCV had jaundice, serum alanine aminotransferase abnormalities, or other viral infections of the liver, including hepatitis A or B.
Our results demonstrate that children with perinatal HIV infection are much less likely than adults infected with HIV to be coinfected with HCV. Differences in the routes of HCV exposure between the 2 populations most likely account for this difference. Intravenous drug use predominates as a shared route of transmission for both HCV and HIV infection in adults, but not in children, most of whom acquire HCV infection through mother-to-child transmission.21

While the rate of HCV infection in the children infected with HIV in our study is low (1.5%; 95% CI, 0.7%-3.0%), it is much higher than that reported in several recent serosurveys that evaluated the prevalence of HCV infection in American children. In a cross-sectional serosurvey of 1034 children without HIV infection from inner-city Baltimore, only 1 child (0.1%; 95% CI, 0.002%-0.05%) had antibodies to HCV;22 Jonas et al23 also found a low seroprevalence (0.1%) of HCV in 869 adolescents attending an urban adolescent medicine clinic or a school-based clinic in Boston. Similarly, in a serosurvey using stored serum specimens from participants in the Third National Health and Nutrition Examination Survey, only 0.2% (95% CI, 0.04%-0.6%) of more than 2700 children ages 6 to 11 years in the sample tested positive for HCV antibodies (rates were similar in children regardless of race or ethnicity); this increased to 0.4% (95% CI, 0.2%-0.9%) among more than 2900 children ages 12 to 19 years and was highest (3.9%) among adults 30 to 39 years old.24 Thus, the HCV infection rate in our study of children with perinatal HIV infection is 8 to 10 times higher than previously reported for children of similar age and race or ethnicity in the United States.
This study was not designed to determine the route of HCV transmission for coinfected children. However, the most likely routes of HCV transmission for the 8 children infected with HCV identified by our study include vertical transmission or receipt of blood products. Other potential sources of HCV infection include accidental needlestick injury, household contact, injection drug use, tattooing, body piercing, and sexual exposure.5,25,30

The pathophysiology and timing of perinatal HCV transmission is not well understood, but it is known that perinatal transmission of HCV occurs less efficiently than perinatal transmission of HIV or hepatitis B virus.27 Evidence supports both intrauterine and intrapartum transmission of HCV. It has been detected in amniotic fluid, and several studies have shown a substantial proportion of children infected with HCV test positive for HCV-RNA on the first day of life, supporting in utero transmission of HCV.7,28-32 The primary risk factor for mother-to-child HCV transmission is the level of maternal HCV viremia.5,6,9,11,14,30,31,33 However, this type of transmission has been reported in asymptomatic women with normal transaminase levels and undetectable HCV viral loads.5,31 As noted previously, data on maternal HCV infection in PACTG 219C are limited. Maternal intravenous drug use, duration of HCV infection, mode of HCV acquisition, and status of liver disease have also been reported to influence HCV vertical transmission.5,14,27,31 Obstetric factors such as mode of delivery, premature rupture of membranes, and exposure to maternal blood (eg, presence of a perineal or vaginal laceration) may also influence vertical passage of HCV to the neonate, supporting intrapartum transmission of HCV.6,17,21 In our study, prematurity and mode of delivery did not correlate with the risk of HCV infection, although the number of infants infected with HCV was small, limiting the power of the study to detect other than very large differences. Transmission of HCV through breast milk appears to be rare.4,9,13,20,31,34,35 It is unlikely that any infants in our study were breastfed, as the CDC has recommended since 1985 that women infected with HIV not breastfeed.36

Maternal coinfection with HIV and HCV has been associated with higher risk of mother-to-child HCV transmission in most studies.2,11,13,15,16,33 It has been found, in at least 1 study, that maternal HCV infection increased the risk of perinatal HIV infection, and women who transmitted HIV appeared to have higher levels of HCV viremia.37 Thus, maternal HIV and HCV coinfection may increase the risk of both HIV and HCV transmission to the infant. In our study, the few women with known HCV infection during pregnancy did not transmit HCV to their infants. However, our study lacked information on maternal HCV status for more than half of the women, and data on maternal serostatus were available for only 1 of the 8 infants coinfected with HIV and HCV.

Although blood banks currently screen donor blood for HCV, recipients of blood or clotting-factor concentrates prior to 1992 are at increased risk for HCV acquisition.30 Up to 90% of hemophiliacs are now infected with HCV; 60% to 90% of hemophiliacs are coinfected with HIV and HCV.30 However, children with hemophilia and other nonperinatal modes of HIV infection acquisition were excluded from this study. A 1993 to 1994 outbreak of hepatitis C was linked to contaminated lots of IVIG from a single manufacturer (Gammagard and Polygamm; both manufactured by Baxter Healthcare Corporation, Deerfield, Ill); these products were removed from the market in 1994. Since that time, the manufacturing process has added a solvent/detergent method designed to inactivate HCV.40 Intravenous gamma globulin has been used to prevent serious bacterial infections in children infected with HIV.41 Three of the children coinfected with HIV and HCV had received IVIG, but no information is available regarding the manufacturer or product lot number to determine whether they received potentially contaminated product; however, only 1 of the children received IVIG during 1993 to 1994.

This study has several limitations. It was conducted as a substudy of the larger nationwide observational protocol PACTG 219C. We attempted to minimize selection bias by randomly selecting subjects for substudy participation, a technique not previously used by the PACTG. It is possible that the sites participating in PACTG 219C were not representative of all sites seeing children infected with HIV. However, sites participating in PACTG 219C encompass most of the sites that see large numbers of children infected with HIV in the United States. It is also possible that the sites participating in the substudy were not representative of the PACTG 219C sites, as they were self-selected, and that HCV prevalence could vary geographically or by the type of setting (urban, suburban, or rural). Children randomly selected to enroll in the substudy had higher CD4+ T-lymphocyte counts at the time of enrollment than the children not randomly selected for study participation and this may have resulted in a biased estimate of the true HCV prevalence; however, CD4+ T-lymphocyte count was not associated with HCV infection in the substudy. Importantly, since only a small number of children infected with HCV was identified by this study, the power of the statistical tests to detect anything other than very large differences was limited.

The use of both serology and RNA detection for HCV diagnosis ensured adequate screening of our study cohort for active HCV infection. Enzyme immunoassays are most widely used for HCV screening but may fail to detect early HCV infection or test falsely negative in immunosuppressed individuals.42 Sensitivity of the third-generation EIA exceeds 99%.43 However, antibody tests cannot differentiate between acute or chronic HCV infection or maternally transferred antibody. For this reason, study subjects younger than 1 year old were excluded. Detection of HCV RNA by RT-PCR is the most sensitive test currently available for HCV diagnosis with a lower limit of viral detection at approximately 50 copies/mL.44 As noted previously, some of the children enrolled in this study had prior positive EIA test results that were not confirmed by RT-PCR. This may represent false-positive EIA test results, resolved HCV infection, or HCV RNA levels below the lower limit of detection. Recent data indicate that up to 50% of individuals infected with HCV may clear HCV viremia without seroconversion, while others may show no evidence of biochemi-
Hepatitis C virus infection is common in adults infected with HIV. There have been no large-scale studies of HCV prevalence in children perinatally infected with HIV. This study reports a low prevalence (1.5%) of HCV infection in a large cohort of children perinatally infected with HIV. These results contrast with the much lower HCV prevalence rates (0.2%) reported in the Third National Health and Nutrition Examination Survey for children not infected with HIV of similar age and race and ethnicity in the United States. Routine HCV testing of children perinatally infected with HIV is not warranted unless there are serum alanine aminotransferase abnormalities, maternal HCV infection, or other risk factors for HCV infection.

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What This Study Adds

Hepatitis C virus infection is common in adults infected with HIV. There have been no large-scale studies of HCV prevalence in children perinatally infected with HIV. This study reports a low prevalence (1.5%) of HCV infection in a large cohort of children perinatally infected with HIV. These results contrast with the much lower HCV prevalence rates (0.2%) reported in the Third National Health and Nutrition Examination Survey for children not infected with HIV of similar age and race and ethnicity in the United States. Routine HCV testing of children perinatally infected with HIV is not warranted unless there are serum alanine aminotransferase abnormalities, maternal HCV infection, or other risk factors for HCV infection. Thus, actual HCV prevalence rates may be higher than those reported in this study.

In summary, HCV coinfection occurs infrequently in children with perinatal HIV infection compared to adults infected with HIV, although it occurs at higher rates than in the general pediatric population. Although US Public Health Service guidelines currently recommend routine HCV testing of all adults with HIV, our study suggests that HCV screening is not warranted for all children with perinatal HIV infection. However, HCV testing of children with perinatal HIV infection should be considered in the case of serum alanine aminotransferase abnormalities or if there is known maternal HCV infection or other HCV risk factors.


