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Hepatitis B and hepatitis C seroprevalence in children receiving antiretroviral therapy for human immunodeficiency virus-1 infection in China, 2005–2009

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Abstract

Background—Coinfection of hepatitis B virus (HBV) or hepatitis C virus (HCV) may compromise pediatric antiretroviral therapy (ART) in China. In this study, we evaluated the seroprevalence of HBV and HCV in children receiving ART and associated factors.

Methods—Patients were selected from human immunodeficiency virus type 1 (HIV-1) infected children under age 16 enrolled in the China National Pediatric ART Cohort since July 2005. Medical assessments, hepatitis B surface antigen (HBsAg) and anti-HCV antibody serologies, and transaminase levels were obtained for analysis.

Results—53 of 1082 children tested were HBsAg seropositive (4.9%; 95% confidence interval [CI] 3.6%-6.2%), and 90 of 938 children tested were anti-HCV antibody-positive (9.6%; 95% CI 7.7%-11.5%). No other serologic assays were performed for HBV detection. Age was associated with HBV coinfection in univariate analysis; older children were more likely to be HBsAg positive. Multivariate analysis revealed that children infected with HIV through transfusion of contaminated blood or blood products were more likely to be anti-HCV antibody positive than those infected with HIV through other routes (adjusted odds ratio [AOR] = 6.2; 95% CI 3.3–11.7).

Conclusion—The high prevalence of HBV and HCV coinfection in HIV-infected children in China receiving ART demands routine screening for viral hepatitis coinfection, intensive prevention of childhood HBV and HCV transmission, and modification of the management of pediatric HIV infection.

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Keywords

coinfection; blood-borne transmission; mother-to-child transmission; hepatitis B and C prevalence; pediatrics HIV

Introductions

China faces an HIV epidemic of over 260,000 reported HIV cases through 2008, 3,000 of which were found in children under age 15.1, 2 Although China launched its national free antiretroviral therapy program (NFATP) in 2003 with the "Four Frees and One Care" policy, pediatric formulations did not become available until July 2005 through a donation from the Clinton Foundation HIV/AIDS Initiative.3 As antiretroviral therapy (ART) in Chinese children has shown initial success4, the challenge of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection may now be addressed in the development of new treatment policies.

HBV and HCV are commonly found in patients with HIV-1 infection due to shared routes of transmission. Children may acquire all three viruses by perinatal transmission and blood transfusion. Sexual exposure and injection drug use also are factors in older children. Worldwide, the burden of HBV and HCV infection is greatest in Asia.[5] In China, 9.8% and 3.2% of the general population are HBV and HCV carriers, respectively, with large geographic variation.[6, 7]

Maternal HIV coinfection increases the risk of perinatal HCV transmission, with perinatal HCV transmission rates of 6–23% reported for infants born to women coinfected with HCV and HIV, in contrast with 4–10% for those born to women infected with HCV alone.[8–10] More than 90% of newborns who are exposed to HBV and HIV from coinfected mothers who do not receive postexposure prophylaxis for HBV develop chronic HBV infection.[11] However, such prophylaxis does not exist for HCV.

Currently existing research on the impact of HCV infection on HIV disease progression in adults demonstrate conflicting results.[12, 13] The impact of HCV coinfection on HIV disease progression in children is also unclear. Several studies failed to observe rapid progression of HIV disease in HCV/HIV coinfected children.[10, 14] However, one study in a thalassemia major population revealed that HCV infection may be an important contributor to rapid disease progression and increase in mortality in HCV/HIV coinfected children.[15]

Children who are infected with HIV-1 in China potentially face risks of HBV and HCV coinfection morbidity but the prevalence of HBV and HCV in HIV-1 infected children is currently poorly described. This study evaluated the seroprevalences of HBV and HCV and their associated factors among HIV-infected children receiving ART in China.

Methods

The China National Pediatric ART Cohort, established in 2005, is an observational cohort covering children receiving ART in 21 provinces, 84 cities and 183 counties in China. Data collection for this cohort was approved by the institutional review board of the China CDC and written informed consent was obtained from parents/legal guardians of each child enrolled. At each visit to pediatric HIV clinics, clinical information is collected and transmitted to the national CDC for entry into the Pediatric ART Database via DataFax (Clinical DataFax Systems Inc., Hamilton, Ontario, Canada).

Children under age 16 years in the cohort with existing HBV or HCV test results from cohort inception in July 2005 through August 31, 2009, when the data was locked, were included in

the analysis. Patients possessing available HBsAg results were defined as the HBV testing group and those possessing available anti-HCV antibody results were defined as the HCV testing group. Demographic characteristics, date of HIV diagnosis and ART initiation, risk factors for transmission, past medical history including blood transfusion, WHO stage at time of cohort entry, clinical assessment and laboratory tests at baseline including HBV and HCV screening serology of study subjects in the cohort were obtained from the Pediatric ART Database for analysis.

The Chinese provinces of Henan, Anhui, Shanxi, and Hubei were classified as central and all others as non-central because of the striking predominance of plasma donation in the HIV epidemics of central provinces. In central China, poor, rural farmers sold plasma to unscrupulous collectors under unsanitary conditions during the early to mid-1990s, causing large numbers of infection in what are now termed former blood donors (FPD) [16, 17].

HIV infection was determined on the basis of positive test results on at least two separate peripheral blood samples assayed with an HIV enzyme immunoassay with confirmatory Western blot for children older than 18 months. Those younger than 18 months were diagnosed by positive testing of plasma HIV-1 RNA or DNA PCR. Hepatitis B surface antigen (HBsAg) was detected using an enzyme-linked immunosorbent assay (ELISA) technique. Second or third generation ELISA techniques were used for detection of anti-HCV antibody. All laboratories were under national surveillance and quality control. Data of laboratory tests at baseline of ART were used for analysis. However, as qualified HBV and HCV serology testings were not available in some rural areas, screening of HBV and HCV was not performed among all pediatric patients.

The seroprevalence of HCV and HBV were expressed in percentages for each study group by residency in central Chinese provinces, age, sex, transmission risk factor, WHO stage at baseline and laboratory test results. Data was analyzed using Statistical Analysis System (SAS) software version 9.1.3 (SAS Institute, Cary, NC). Comparison of categorical variables was performed using either $\chi 2$ or Fisher exact tests. Continuous variables were compared using the Wilcoxon rank sum test. Stepwise maximum likelihood estimation was used to estimate coefficients of regression and their standard errors in an unconditional multivariate logistic regression model.[18] Significant level of entry (SLE) in the regression model was 0.10. The associations were presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). All hypothesis testing was two-sided with $\alpha = 0.05$.

Results

Present in the Pediatric ART database were 1672 children receiving ART from July 2005 to the end of August 2009, when data was locked for analysis. Seventy-eight patients either older than 16 or without birthday were considered incorrectly submitted and excluded. Fifteen patients were excluded because their clinical records were unsigned. Of the 1579 eligible subjects, HBsAg and anti-HCV antibody testing results were available for 1082 and 938 patients, respectively, of whom 925 children had both results. Analysis comparing those with or without HBV/HCV testing showed that those without HBV/HCV testing **were more likely to have missing data also on** other laboratory tests (e.g. CD4 testing, LFTs) ($P < 0.0001$) and lower proportion of children with WHO stage 3 or 4 at baseline than those with HBV/HCV testing ($P = 0.0012$).

Table 1 describes the demographic, HIV transmission, clinical, and lab characteristics of the study population. HBV and HCV testing groups shared similar characteristics. Both groups had a male majority (60%). Median age for both groups was 7 years (interquartile range [IQR], 4–11). Most children acquired HIV through mother-to-child transmission (81% in both

groups). The second most common route was blood-borne transmission (15%). Approximately two thirds of patients in each group were HIV WHO stage 3 or 4 at time of cohort entry. Almost two thirds of patients were from the central Chinese provinces of Henan, Anhui, Shanxi, and Hubei. Ten percent of patients showed significantly elevated (≥2 times the upper limit of normal [ULN]) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, and 30% had mildly elevated transaminase (<2×ULN) levels.

Fifty-three of 1082 children with available HbsAg results were HBsAg positive (4.9%; 95% CI: 3.6%-6.2%), and 90 of 938 children with available anti-HCV antibody results were anti-HCV antibody positive (9.6%; 95% CI: 7.7%-11.5%). Four patients (0.4%; 95% CI: 0–0.7% in the HBV testing group, 0.4%; 95% CI: 0–0.8% in HCV testing group) were both HBsAg and anti-HCV antibody positive.

Table 2 describes patient characteristics by HBV and HCV serostatus. In the HBV testing group, sex distribution was similar for HBsAg postive and negative patients. However, the proportion of children older than 11 years old in the HBsAg positive sub-group was significantly larger than that in the HBsAg negative sub-group ($P = 0.007$). There was no significant difference between HBV/HIV coinfected and HIV monoinfected sub-groups with regard to residence in a central Chinese province, HIV transmission route, WHO stage at baseline, and transaminase levels. In the HCV testing group, sex distribution was similar for HCV positive and negative patients. Anti-HCV antibody positive patients were older than negative patients, with median age 11 years (IQR 7–12) compared to 7 years (IQR 4–10) ($P < 0.0001$). A higher proportion of HCV coinfected children were infected with HIV through contaminated blood or blood products than HIV monoinfected children (53.3% vs. 10.7%, $P < 0.0001$), and less children acquired HIV vertically in the HCV coinfected sub-group than in the monoinfected sub-group (37.8% vs. 85.1%, $P < 0.0001$). The HCV coinfected sub-group contained a higher proportion of patients from central Chinese provinces compared to the monoinfected sub-group (81.1% vs. 55.5%, $P < 0.0001$). No significant differences were found in WHO stage at baseline and transaminase levels between anti-HCV antibody positive and negative sub-groups. Figure 1 and Figure 2 describe the HBV and HCV seropositivity rate by demographic and HIV characteristics respectively.

As only age was associated with HBV serology status in previous univariate analysis, multivariate logistic regression was only applied for the HCV group including analysis of age group, HIV transmission route, and residence in a central Chinese province. Multivariate analysis revealed that children who were infected with HIV through contaminated blood or blood product transfusion were more likely to be anti-HCV antibody positive (adjusted OR=6.2, 95% CI: 3.3–11.7) Age group and residency in central China failed to show association with HCV serostatus (see Table 3).

Discussion

Very few studies worldwide have reported the prevalence of HBV and HCV coinfection in HIV infected children. A multicenter cross-sectional study in the United States reported that 8 of 525 children (1.5%) with perinatally acquired HIV infection were coinfected with HCV, higher than the 0.2% rate of HCV monoinfection in American children.19 A hospital-based study of 228 children found chronic HCV infection in 3.1% and chronic HBV infection in 2.6% of patients tested.20 A similar study conducted in Tanzania reported HBV and HCV seroprevalence in HIV-infected children of 1.2% and 13.8%, respectively.21 This study, using baseline laboratory data from the China National Pediatric Antiretroviral Treatment Cohort, found HBsAg and anti-HCV antibody seropositivity rates of 4.9% and 9.6% respectively for Chinese HIV pediatric patients. With data from one quarter of all Chinese pediatric HIV

patients (over 3000)1 included for analysis, this study's findings reflect the condition of a large proportion of Chinese patients.

Since the implementation of the Hepatitis B immunization program in 1992, HBV vaccination coverage has widely increased in China22, greatly lowering the prevalence of HBV in children.[23] This vaccination campaign may explain why HBV seroprevalence in HIV-infected children was comparable with that of HIV uninfected children and lower than that of general population (9.8%). It also explains why older children were more likely to be infected with HBV as they were less likely to have been vaccinated after birth. However, maternal HBV status and history of HBV vaccination after birth were not obtained in this study. Besides, it is noted that the prevalence of HBV infection can increase with age due to greater cumulative opportunities for exposure.[11]

False-negative anti-HCV immunoassay results may occur among HIV-infected persons with advanced immunosuppression, but this is uncommon with the most sensitive immunoassays (third-generation assays).[24, 25] False-positive anti-HCV antibody serology results may also occur especially in young infants born to HCV-infected women. In a large cohort of HCV-exposed but uninfected children, anti-HCV antibodies were present in 15% of children at 12 months, 5% at 15 months, and 2% at 18 months.26 Positive results of anti-HCV antibody in 3 children aged ≤18 months in our study are therefore indeterminate. However, we included these three patients in the analysis. Also, a proportion of children spontaneously clear HCV infection.[27–29] Therefore, these results may reflect overestimated prevalence of HCV coinfection rate and could not distinguish those with active or resolved hepatitis C infection. More specific assays to confirm HCV infection such as HCV RNA PCR is consequently necessary to avoid the reporting of false-positive results. Furthermore, as comorbidity and mortality due to chronic active hepatitis infection may compromise the benefit of ART, providing pediatric patients with HCV RNA testings could eventually identify active disease patients who may need intervention in the future.

Our study found an HCV seropositivity rate in HIV-infected children of 9.6%, higher than the rate of 3.2% found in previous studies of the general population.[6] We found a strong association between HCV seropositivity and history of transfusion of HIV contaminated blood or blood products. Children who acquired HIV through contaminated blood or blood products were significantly more likely to be anti-HCV seropositive than those who acquired HIV through other transmission routes. The screening of blood for HCV antibody prior to transfusion was not developed until the mid-1990s in China likely explaining higher rates of HCV seropositivity in older children. However, HBV coinfection status was not associated with HIV blood-borne transmission likely because blood was routinely screened for HBsAg upon donation.

It is noteworthy that we found no association between elevation of transaminase levels and either HBV or HCV serology status. Although one prior study suggested that elevated ALT was associated with hepatitis viral coinfection[21], few other studies exist in the literature to describe liver function in viral hepatitis/HIV coinfected children.

Potential selection bias may have affected the findings in this study. Children enrolled in this study were all receiving ART. Therefore, enrolled subjects likely were older, had more severe HIV disease, and were more adherent compared to HIV patients not enrolled. Disease progression in children who acquire HIV through mother-to-child transmission is generally rapid; without treatment, half of such children have been shown in an African study to die by two years of age.[30] Hence, fewer infants survived before the implementation of NFATP in 2003 and were thus not present for inclusion in this study. Also, children co-infected with HBV/HCV may have experienced rapid HIV disease progression and thus may not have survived to be included in the study sample. Additionally, baseline HBV/HCV serology testing

was not performed in all pediatric patients. Comparison between patients with or without HBV/HCV testing suggested that HBV/HCV testing was more likely to be performed in those with severe disease and in some situations lack of resources might be an obstacle for routine HBV/HCV screening.

Limitations in laboratory capacity may also have affected the results. As we did not perform HCV RNA testing, active HCV infection was not ascertained. Laboratory tests such as liver function tests were not obtained from some of the children. Finally, although most children likely acquired HBV and HCV via mother-to-child transmission, maternal hepatitis infection status and information on HBV vaccination after birth were not obtained.

Currently, HIV infected children can access free antiviral therapy through the NFATP. Screening, prevention, and treatment of HBV and HCV co-morbidities were not included in the ART program. The high prevalence of HCV and HBV in children with HIV revealed in our study raises several public policy concerns. In our study, viral hepatitis testing was only performed among two-thirds of eligible patients; the relatively low screening rate in this vulnerable population calls for routine screening in HIV-infected children and more intensive and specific care and treatment guidelines need to be developed for those found to be positive. HIV infected women of childbearing age should be monitored for HBV and HCV infection so that timely prevention of mother-to-child transmission of both HIV and hepatitis viruses can be provided. Recently, a randomized, double-blind, placebo-controlled trial suggested that lamivudine reduced HBV transmission from highly viraemic mothers to their infants.[31] As lamivudine is already available as part of the national ART program, it may easily be integrated into future efforts to prevent vertical transmission of HBV in HIV infected mothers. HBV vaccination right after birth, as available through the national Hepatitis B immunization program, significantly reduces the risk of chronic HBV infection, and would thus benefit HIV infected children. We also found that contaminated blood or blood products contributed greatly to HIV/HCV coinfection. However, with eradication of illegal blood collection and stricter regulations for blood donation and screening starting in 1996[32], the risk of either HIV or HCV infection through blood transfusion has been significantly reduced. Although HBV and HCV coinfection complicate the pediatric HIV epidemic in China, improved screening for hepatitis will allow for better understanding and management of these comorbidities.

List of abbreviations

HIV	human immunodeficiency virus
ART	antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
OR	odds ratio
CI	confidence interval
NFATP	national free antiretroviral therapy program
FPD	former blood donor
HBsAg	hepatitis B surface antigen
ELISA	enzyme-linked immnunosorbent assay
SAS	Statistical Analysis System
SLE	significant level of entry
IQR	interquartile range

ULN	upper limit of normal
ALT	alanine aminotransferase
AST	aspartate aminotransferase

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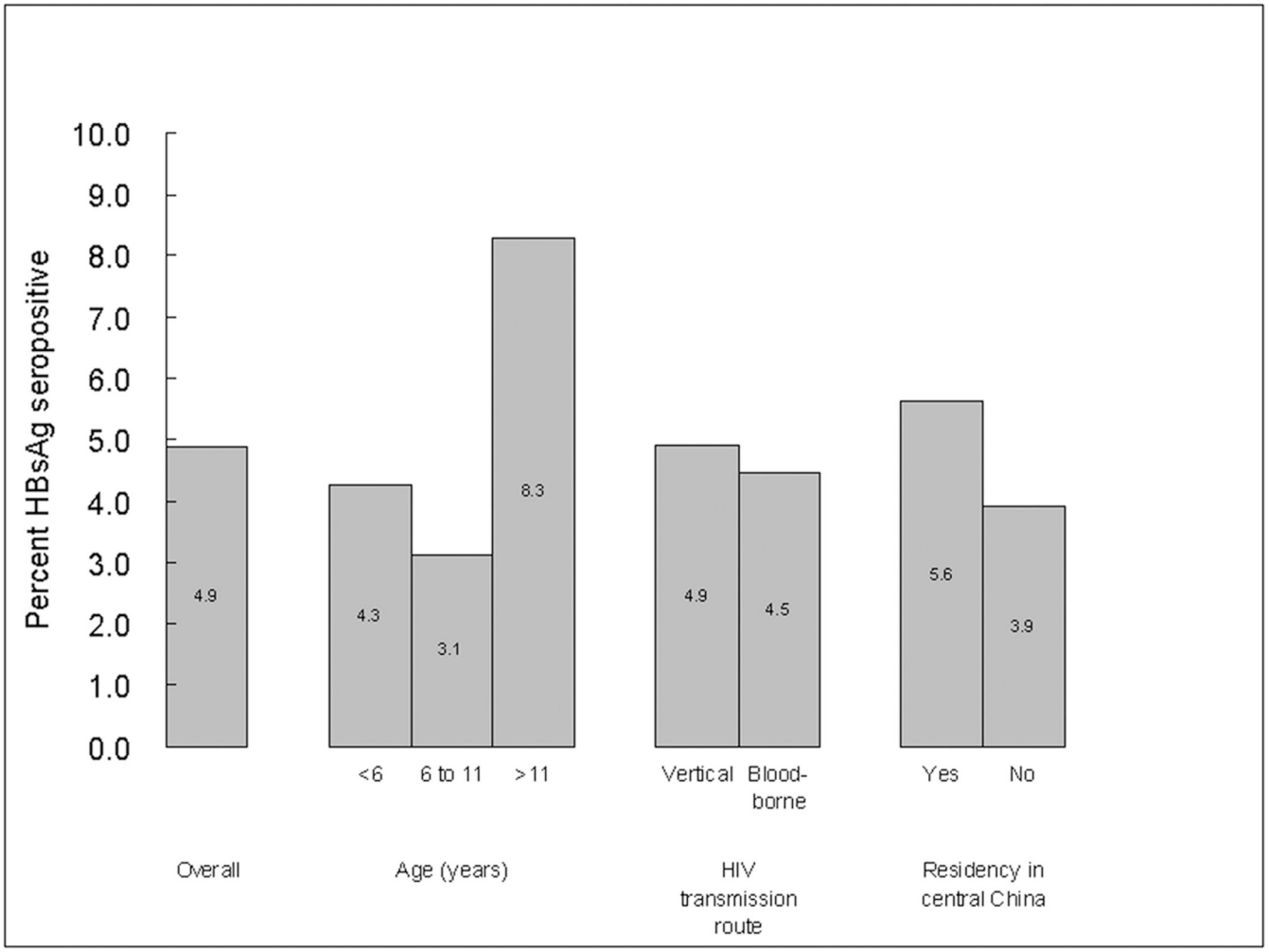

Figure 1.
describes HBsAg seropositivity rate (%) overall and divided by age group, HIV transmission route and residency in central Chinese provinces.

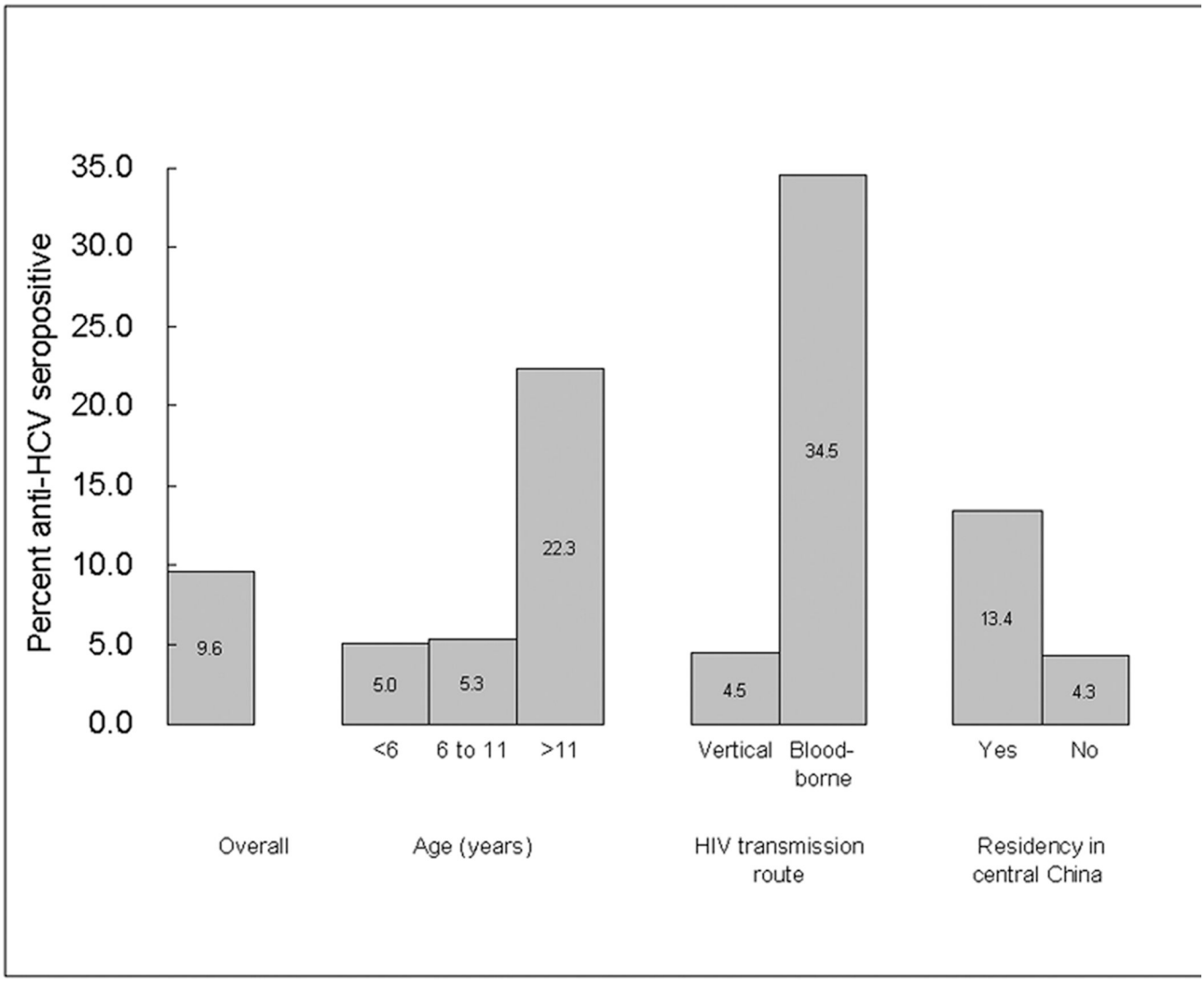

Figure 2.
describes anti-HCV seropositivity rate (%) overall and divided by age group, HIV transmission route and residency in central Chinese provinces.

Table 1

Basic characteristics of study population, China National Pediatric Antiretroviral Therapy Cohort, 2005–2009

Characteristics	HBV testing group (N=1082) Patient No. (%)	HCV testing group (N=938) Patient No. (%)
Sex		
Male	646 (59.7)	561 (59.8)
Female	436 (40.3)	377 (40.2)
Age, y/o		
<6	422 (39.0)	359 (38.3)
6 to 11	383 (35.4)	337 (35.9)
>11	277 (25.6)	242 (25.8)
Median (IQR)	7 (4-11)	7 (4-11)
HIV transmission route		
Vertical transmission	875 (80.9)	756 (80.6)
Bloodborne	157 (14.5)	139 (14.8)
Others	14 (1.3)	14 (1.5)
Unknown	36 (3.3)	29 (3.1)
WHO stage at baseline		
Stage 3 or 4	702 (64.9)	612 (65.2)
Stage 1 or 2	380 (35.1)	326 (34.8)
Residency in central Chinese provinces		
Yes	621 (57.4)	544 (58.0)
No	461 (42.6)	394 (42.0)
Transaminase level		
Normal	594 (54.9)	509 (52.3)
Mildly elevated	318 (29.4)	282 (30.1)
Elevated	118 (10.9)	109 (11.6)
Missing	52 (4.8)	38 (4.1)
CD4 count, cells/mm^3		
≤200	512 (47.3)	441 (47.0)
201 to 500	316 (29.2)	281 (30.0)
>501	176 (16.3)	153 (16.3)
Missing	78 (7.2)	63 (6.7)
Median (IQR)	196 (75-314)	199 (76-311)
CD4 percentage, %		
<15	687 (63.5)	597 (63.7)
15 to 25	149 (13.8)	137 (14.6)
>25	83 (7.7)	71 (7.6)
Missing	163 (15.1)	154 (16.5)

Table 2

Demographic, HIV transmission, clinical and laboratory characteristics by hepatitis B and C virus serostatus among children from the China National Pediatric Antiretroviral Cohort with available results, 2005–2009*.

	HBV testing group (n=1082)		HCV testing group (n=938)	
	HBsAg negative (n=1029) No. (%)	HBsAg positive (n=53) No. (%)	Anti-HCV antibody negative (n=848) No. (%)	Anti-HCV antibody positive (n=90) No. (%)
Sex				
Male	618 (60.1)	28 (52.8)	500 (59.0)	61 (67.8)
Female	411 (39.9)	25 (47.2)	348 (41.0)	29 (32.2)
		P = 0.30		*P* = 0.10
Age, y/o				
<6	404 (39.3)	18 (34.0)	341 (40.2)	18 (20.0)
6 to 11	371 (36.1)	12 (22.6)	319 (37.6)	18 (20.0)
>11	254 (24.7)	23 (43.4)	188 (22.2)	54 (60.0)
Median (IQR)	7 (4-10)	10 (4-12)	7 (4-10)	11 (7-12)
		P = 0.007		*P* < 0.0001
HIV vertical transmission				
Yes	832 (80.9)	43 (81.1)	722 (85.1)	34 (37.8)
No	197 (19.1)	10 (18.9)	126 (14.9)	56 (62.2)
		P = 0.96		*P* < 0.0001
HIV bloodborne transmission				
Yes	150 (14.6)	7 (13.2)	91 (10.7)	48 (53.3)
No	879 (85.4)	46 (86.8)	757 (89.3)	42 (46.7)
		P = 0.78		*P* < 0.0001
WHO stage at baseline				
Stage 3 or 4	669 (65.0)	33 (62.3)	548 (64.6)	64 (71.1)
Stage 1 or 2	360 (35.0)	20 (37.7)	300 (35.4)	26 (28.9)
		P = 0.68		*P* = 0.22
Residency in Central Chinese provinces				
Yes	586 (56.9)	35 (66.0)	471 (55.5)	73 (81.1)
No	443 (43.1)	18 (34.0)	377 (44.6)	17 (18.9)
		P = 0.19		*P* < 0.0001
Transaminase level				
Normal	567 (57.9)	27 (54.0)	465 (56.9)	44 (53.0)
Mildly elevated	298 (30.4)	20 (40.0)	254 (31.1)	28 (33.7)
Elevated	115 (11.7)	3 (6.0)	98 (12.0)	11 (13.3)
		P = 0.23		*P* = 0.79
Missing	49	3	31	7

* *P* value estimated using chi-square test.

Table 3

Association between demographic characteristics, HIV transmission route, WHO stage at baseline and HCV serology status using multivariate logistic regression, China National Pediatric HIV Cohort, 2005–2009*

		P	OR (95% CI)
Age, y/o	<6		1
	6 to 11	0.78	0.9 (0.5–1.8)
	>11	0.13	1.8 (0.8–3.7)
HIV bloodborne transmission	No		1
	Yes	<0.0001	6.2 (3.3 – 11.7)

* The logistic regression model includes age groups, HIV transmission route, and residency in central Chinese provinces.