ORIGINAL RESEARCH ARTICLE

Seroprevalence of hepatitis C, hepatitis B virus and syphilis in HIV-1 infected patients in Shandong, China

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Summary: To determine the seroprevalence of hepatitis C virus (HCV), hepatitis B virus (HBV) and syphilis in HIV-1-infected patients and related risk factors in Shandong province, China, we tested all eligible participants between 2000 and 2010 for the presence of anti-HCV antibody, hepatitis B surface antigen (HBsAg) and non-treponemal antibodies for syphilis after informed consent. Among 2087 HIV-infected patients, anti-HCV antibody was present in 41.2%, HBsAg in 12.6% and rapid plasma reagin (RPR) reactivity in 19.6%. In the multivariate logistic regression model, male gender (adjusted odds ratio [aOR] = 1.41), minority ethnicity (aOR = 1.72), syphilis infection (aOR = 1.40), former paid blood donors (aOR = 3.36), blood transfusion recipients (aOR = 2.91) and injection drug users (aOR = 1.98) were significantly associated with HCV infection. HCV infection (aOR = 1.40) and being men who have sex with men (aOR = 2.38) were significantly associated with syphilis infection. Co-infection with HCV, HBV and syphilis was observed frequently in all described subgroups of HIV infection. The results of this study suggest that it is necessary to screen for these viruses and syphilis in all Chinese HIV-infected patients.

Keywords: HIV, hepatitis C, hepatitis B, syphilis, co-infection, seroprevalence, China

INTRODUCTION

Shandong is an eastern province in China with a total population of 94 million. Since 1991 when the HIV/AIDS epidemic started in Shandong province, HIV surveillance has been conducted by reporting newly diagnosed HIV-infected individuals. By the end of 2009, a total of about 740,000 HIV-1-infected individuals were reported cumulatively in China (UNAIDS, 2010). Of these HIV-infected Chinese, those living with HIV in Shandong accounted for 0.27% (2009). Over the past 20 years, Shandong has experienced dramatic changes in the course of its HIV/AIDS epidemic, which featured several different subepidemics with sequential phases. In the first subepidemic (1991–1995), several sporadic and non-indigenous HIV-infected participants were found. In the second subepidemic (1996–2004), HIV-infected participants from former-paid blood donors (FBD) accounted for the majority of infections and individuals infected through sexual transmission began to rise. In the 1990s, many blood and plasma collection stations were found in Shandong. It is probable that the blood supply was initially contaminated by HIV-positive individuals who were injection drug users (IDUs) and failure on the part of the blood/plasma collection stations to adequately screen resulted in further HIV infection. During the third subepidemic (since 2004), sexual transmission became the primary means of HIV spread.

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Sharing the same risk factors, hepatitis C virus (HCV), hepatitis B virus (HBV) and syphilis (*Treponema pallidum* [TP]) infection are very common in HIV-infected participants.[1,2] However, results in studies of HCV co-infection have varied depending on the geographical area, type of exposure and different risk behaviour populations. In China, prevalences of HCV co-infection among HIV-infected patients ranging from 12% to 85% have been reported.[3–5] The differences in co-infection rates may result from various primary transmission routes. Previous studies have indicated that the prevalence of HCV co-infection in IDUs and FBD were significantly higher than other subgroups.[6,7]

Patients with HCV and HBV co-infection with HIV have an increased risk of progression of HCV- and HBV-related liver disease (chronic hepatitis, cirrhosis and hepatocellular carcinoma [HCC]), compared with HCV mono-infected patients.[8–11] There have been debatable reports concerning whether HCV or HBV infection changes the natural history of HIV disease.[12–15] Thus it is unclear whether the improvement of the long-term outcome of HIV-positive patients is influenced by co-infection with hepatotropic viruses. Despite transient changes in CD4 counts and viral loads, syphilis does not appear to affect HIV disease progression.[16] However, syphilis infection does increase the risk of transmission and acquisition of HIV.[17,18] To date, little is known about the prevalence of co-infections in different populations in China.[6] As a consequence, regardless of whether these microorganisms increase HIV disease progression, it is necessary to determine the prevalence of co-infections in HIV-infected participants.

MATERIALS AND METHODS

Study population

Blood samples (10 mL), collected from HIV/AIDS high-risk populations, were screened at Centers for Disease Control and Prevention (CDC) in Shandong, Medical Institutions, Maternity and Child Health Care Institutions, Public Security and Judicial Institutions, Blood and Plasma Collection Stations, Entry-exit Inspection and Quarantine Institutions after ethical approval and informed consent were obtained. Screened HIV-positive samples were confirmed by Shandong CDC and sera specimens separated after centrifugation, aliquoted into 2 mL cryotubes tubes were stored at $-20^{\circ}C$ until the time for testing for the presence of anti-HCV antibody, hepatitis B surface antigen (HBsAg) and non-treponemal syphilis antibody by rapid plasma reagin (RPR) testing. Trained medical staff asked HIV-positive patients to complete a standardized questionnaire form as soon as they were confirmed HIV-positive, which was approved by the institutional review board of the Shandong CDC. The questionnaire pertained to age, gender, ethnicity, education level, marital status, high-risk behaviour and possible HIV transmission routes. Their guardians finished the questionnaires if participants were immature or had serious physical or intellectual disability. This research was approved by the ethics committee of Shandong CDC. From 2000 to 2010, 3254 individuals were confirmed HIV-1-positive by Provincial Key Laboratories of Shandong CDC. Between August and October 2010, specimens from 2087 participants included in the study were tested for the presence of anti-HCV antibody, HBsAg and RPR antibodies; 1167 participants were excluded due to insufficient serum. Individuals were defined as AIDS patients when they had AIDS-related signs or symptoms or $CD4^+$ T cells <350 cells/mm^3 by the Shandong CDC.

Laboratory methods

Serum was screened for antibodies against HIV-1 and HIV-2 enzyme-linked immunosorbent assay (ELISA) technology and HIV-1-positive participants were defined as those having a positive ELISA test result, Western blot analysis or those in whom HIV RNA was detected via polymerase chain reaction (PCR). All participants were tested for anti-HCV antibody by means of a third generation ELISA (Lizon Diagnostics, Zhuhai, China) and those who tested positive for the presence of antibody by serological testing were HCV-positive participants. HBV-positive participants were those who tested positive for markers of HBV infection (HBsAg) by means of a third generation ELISA (Lizon). RPR-positive samples (Lizon) were considered to be positive for current syphilis infection. All laboratories were under national surveillance and quality control.

Data analysis

Descriptive analyses were employed for presenting the distributions of new HIV-1-infected participants, proportions of different HIV-infected populations, and sociodemographic characteristics. The prevalence of HBV, HCV and syphilis in all instances is expressed as the number of new cases with positive test results every year divided by the total number of new cases tested every year. The χ^2 or Fisher's exact test was used for discrete variables. Multivariate logistic regression was performed to examine the risk factors of co-infection. The significance level required for inclusion was set at 0.05 and P values <0.05 were deemed significant. Multivariate logistic regression was applied for determining the risk factors of HCV, HBV and syphilis. Independent variables include age group, gender, occupation, HIV status, marital status, ethnicity and education level. In addition, two out of HCV, HBV and syphilis would be defined as risk factors when the other was selected as the dependent variable. Stepwise selection was used in the multivariate logistic regression and the entry probability for stepwise was 0.05, the removal was 0.1. Statistical analyses were performed using SPSS, version 17.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 3254 HIV-infected individuals were recruited from 2000 to 2010. Participants were excluded from this study due to insufficient serum ($n = 1167$) leaving 2087 remaining for analyses. Baseline demographic and characteristics of included and excluded individuals shown in Table 1 indicate that both groups were comparable, except that the excluded population had higher education levels.

Of 2087 individuals, 62.8% (1311/2087) were men and 37.2% (776/2087) were women. The mean age of the sample was

Table 1 **Characteristics of study participants**

Characteristics	Included subjects	Excluded subjects	*P* value
Gender			
Women	776 (37.2)	420 (36.0)	0.519*
Men	1311 (62.8)	747 (64.0)	
Total	2087 (100)	1167 (100)	
Age, mean (SD)	31.4 (10.5)	31.2 (10.8)	0.706†
HIV status			
HIV-infected (non-AIDS)	785 (67.3)	1444 (69.2)	0.271*
AIDS	382 (32.7)	643 (30.8)	
Total	2087 (100)	1167 (100)	
Ethnicity			
Han	1291 (64.4)	693 (61.2)	0.083*
Minority	715 (35.6)	439 (38.8)	
Total	2006 (100)	1132 (100)	
Marital status			
Unmarried	571 (29.4)	323 (29.0)	0.949*
Divorced or widowed	243 (12.5)	137 (12.3)	
Married	1131 (58.1)	655 (58.7)	
Total	1945 (100)	1115 (100)	
Education			
College or university	142 (7.1)	112 (9.9)	<0.001*
Senior high school	217 (10.8)	174 (15.5)	
Junior high school	556 (27.8)	335 (29.8)	
Primary school	591 (29.5)	275 (24.4)	
Illiteracy	496 (24.8)	230 (20.4)	
Total	2002 (100)	1126 (100)	
Exposure group			
FBD	152 (8.6)	82 (7.8)	0.113*
IDUs	405 (23.0)	206 (19.5)	
Blood transfusion recipients	103 (5.8)	55 (5.2)	
Heterosexual	873 (49.5)	569 (53.8)	
MSM	230 (13.0)	146 (13.8)	
Total	1763 (100)	1058 (100)	
Total	2087 (100)	1167 (100)	

FBD = former-paid blood donor; IDUs = injection drug user; MSM = men who have sex with men; SD = standard deviation
*Fisher's exact test
†*t*-test

Table 2 **The annual prevalence rates of HIV-1-infected subjects co-infected with HCV, HBV or syphilis, *n* (%)**

	2000–2003	2004	2005	2006	2007	2008	2009	2010	*P* value
Anti-HCV positive	62 (70.5)	45 (46.5)	117 (40.9)	123 (42)	111 (38.3)	147 (42.1)	146 (41.8)	108 (32.4)	<0.05
HBsAg positive	7 (8.0)	13 (13.1)	38 (13.3)	32 (10.9)	40 (13.8)	59 (16.9)	38 (10.9)	35 (10.5)	0.132
RPR positive	17 (19.3)	14 (14.1)	58 (20.3)	56 (19.1)	40 (13.8)	67 (19.2)	68 (19.5)	89 (26.7)	<0.05
Total	88	99	286	293	290	349	349	333	

Note: numbers are new cases with positive test results and the (% prevalence)

31.4 years old (range, 1–84 years). The majority of participants (74.8%) of HIV infection occurred in the age group 21–40 years old. About 69.2% (1444/2087) cases were HIV-infected and 30.8% (643/2087) were classified as AIDS patients. The education level was relatively low in this studied population: 82.1% (1643/2002) of participants had junior high school education or less. Sexual contact (SC) transmission was the major mode of HIV transmission, accounting for 62.6% (1103/1763), followed by blood–blood transmission for 37.4% (659/1763). Han ethnicity accounted for 64.4% (1291/2006) and farmers accounted for 57.5% (1200/2087). The prevalence of HCV co-infection based on anti-HCV detection was 41.2% (860/2087). HCV, HBV or syphilis co-infected with HIV was highest in the 21–30 years age group (44.9%, 41.6% and 44.7%, respectively) followed by the age group 31–40 years old (30.9%, 29.8% and 30.5%, respectively). Co-infection with HIV and HBV was present in 12.6% overall (262/2087) while the prevalence of syphilis co-infection was 19.6% overall (409/2087).

The annual prevalence of HIV-1 infected participants co-infected with HCV, HBV or syphilis was analysed from 2000 to 2010. As shown in Table 2, the prevalence rates of HCV-HIV-1 co-infected participants were significant different between years ($P < 0.001$) and declined slightly over time. Similarly, syphilis prevalence rates of HIV-1 infected participants were also significantly different ($P = 0.008$) between years; however, after several years of declining, the prevalence rates of syphilis have increased in recent years. For HBV–HIV-1 co-infected participants, there was no statistical difference ($P = 0.132$) observed in this study over time.

HCV prevalence did vary significantly between Han and minority ethnicities (37.1% vs. 49.7%, $P < 0.001$). Further analysis by characteristics showed that ethnic minorities were more likely to be IDUs (53.3%) than Han (5.8%). Heterosexual individuals accounted for 52.7% in Han while it accounted for 44.1% in minority. FBD, blood transfusion recipients and men who have sex with men (MSM) accounted for 0.3%, 1.3% and 1.0%, respectively, in ethnic minorities versus 13.3%, 8.2% and 20.1% in Han (analysis not shown). There were 1763 of 2087 (84.5%) HIV-positive participants with definite transmission routes (FBD, IDUs, blood transfusion recipients, heterosexual and MSM, not including vertical transmission to children). Of these five subgroups, the prevalence rates of HIV–HCV and HIV–syphilis co-infections were significantly different ($P < 0.001$; Table 3).

Multivariate analysis revealed that men were more likely to be HIV–HCV co-infected (adjusted odds ratio [aOR] = 1.42, 95% confidence interval [CI]: 1.07, 1.80) than women. Ethnic minority participants had more HCV infection (aOR = 1.72, 95% CI: 1.30, 2.26; Table 4). MSM and heterosexuals who were HIV-positive were more likely to be RPR-positive than other subgroups (aORs = 2.38, 1.43, respectively; Table 5). Risk factors in this study failed to show an association with HBV status (data not shown).

DISCUSSION

In this study 41.2% HIV-infected patents tested anti-HCV-positive, which was a little higher than reported in Western countries (10–30%),[19] but much higher than in Slovenia (10.7%), which was the country with the lowest prevalence of HCV infection among HIV-infected individuals.[20] The prevalence of HIV–HCV co-infection was 59.9% in FBD, 55.1% in IDUs and 58.3% in blood transfusion recipients, which was lower than previously documented. Remarkably, we also detected high rates of HCV infection (36.3% in heterosexuals and 24.3% in MSM) among people who acquired HIV-1 infection through sexual contact. Although the prevalence of HIV–HCV co-infection among HIV-1-positive SC participants was lower than that in FBD, IDUs and blood transfusion recipients, it was still significantly higher than the HCV prevalence reported for the general population (0.55%).[21]

The current study also found that men were more likely to be co-infected with HCV than women. This trend may be explained on the basis of higher rate of IDU and other exposure risks in men but the specific reason for the differences in gender is unclear. Another study done by Jobarteh *et al.*[22] observed a striking gender difference between the two HIV groups, registering a female-to-male ratio of over 2.5. Since this was a clinic-based study, in the absence of incidence data, it is unclear whether the gender distribution of HIV–HCV co-infection reflects the general population. In this study, minority ethnic groups were more affected (49.7%) than Han (37.1%), which was concordant with a meta-analysis.[23] It indicated that ethnicity was a potential reason for differences in standard of living, habits and customs. Besides, medical resources, sanitation and access to therapy vary and these factors should be considered. This study indicated that higher exposure to IDU in ethnic minority and sexual contact in Han may contribute to higher HIV–HCV co-infection prevalence in minority than Han.

As with a national study,[24] we also observed a steady, significant decrease in the serial prevalence of co-infection with HIV and HCV during an 11-year period, which was driven by a change in HIV transmission patterns. However, this trend would be largely attributed to reduction of FBD than reduction of IDUs. In this study, apart from 2000 to 2003 (4.9%), the rate of IDUs was relatively steady (20.4–27.4%); in contrast, the rate of FBD decreased from 51.2% in 2000–2003 to 1.3% in 2010. Therefore, the observed decreasing trend in co-infection with HIV and HCV by year of entry in this study was led by changes in HIV transmission patterns, which were different from Western countries like Spain.

It is important to note that a significant association was observed between HCV infection and syphilis infection. Although the association between HCV status and syphilis is still controversial,[25–27] a majority of studies suggest that HCV is not associated with syphilis in general, but with genital ulcers, inherent in syphilitic infection. As previously shown,[28]

Table 3 **The prevalence of hepatitis C virus (HCV), hepatitis B virus (HBV) and syphilis in HIV-1-infected subjects in different groups, *n* (%)**

	Anti-HCV-positive	*P* value	HBsAg positive	*P* value	RPR positive	*P* value
Gender						
Men	559 (42.6)*	0.046	171 (13.0)	0.412	253 (19.3)	0.690
Women	301 (38.8)		91 (11.7)		156 (20.1)	
Total	860 (41.2)		262 (12.6)		409 (19.6)	
Age (years)						
≤20	65 (35.5)	0.427	28 (15.3)	0.541	38 (20.8)	0.668
21–30	386 (42.1)		109 (11.9)		183 (20.0)	
31–40	266 (41.3)		78 (12.1)		129 (20.0)	
>40	143 (41.7)		47 (13.7)		59 (17.2)	
Total	860 (41.2)		262 (12.6)		409 (19.6)	
HIV status						
HIV infected	589 (40.8)	0.564	180 (12.5)	0.886	295 (20.4)	0.169
AIDS	271 (42.1)		82 (12.8)		114 (17.7)	
Total	860 (41.2)		262 (12.6)		409 (19.6)	
Ethnicity †						
Han	479 (37.1)**	<0.001	163 (12.6)	0.980	264 (20.4)	0.177
Minority	355 (49.7)		90 (12.6)		128 (17.9)	
Total	834 (41.6)		253 (12.6)		392 (19.5)	
Marital status ‡						
Unmarried	242 (42.4)	0.357	72 (12.6)	0.405	119 (20.8)	0.531
Divorced or widowed	90 (37.0)		25 (10.3)		45 (18.5)	
Married	467 (41.3)		152 (13.4)		211 (18.7)	
Total	799 (41.1)		249 (12.8)		375 (19.3)	
Exposure group §						
FBD	91 (59.9) **	<0.001	18 (11.8)	0.672	23 (15.1) **	<0.001
IDUs	223 (55.1)		59 (14.6)		65 (16.0)	
Blood transfusion recipients	60 (58.3)		13 (12.6)		11 (10.7)	
Heterosexual	317 (36.3)		104 (11.9)		179 (20.5)	
MSM	56 (24.3)		33 (14.3)		69 (30.0)	
Total	747 (42.4)		227 (12.9)		347 (19.7)	

RPR = rapid plasma reagin; FBD = former-paid blood donor; IDU = injection drug user; MSM = men who have sex with men
†2006 HIV subjects could be classified into a correct category
‡1945 subjects
§1763 subjects
*$P < 0.05$
**$P < 0.001$

blood containing HCV would penetrate more effectively through injured genital skin. In addition, HIV-positive patients were found to be more likely to have serological evidence of syphilis and ocular syphilis.[29] Syphilis was also shown to affect HIV parameters by increasing HIV viral loads and decreasing CD4 cell counts.[30] This may in part explain the finding that HCV was associated with syphilis infection.

The prevalence of HBV–HIV co-infection was 12.6% which was higher than the prevalence (9.9%) in the general population in China and 5–7% in low endemicity areas but in agreement with 10–20% in high HBV endemicity countries.[31] In this study, we found that the prevalence of HBV–HIV co-infection was the highest in MSM (14.3%) and lowest in heterosexuals (11.9%), apart from FBD (11.8%), as discussed previously. However, there was no significant difference found among exposure groups. Unlike some other studies,[32,33] the current study found no gender difference in HIV infection and gender did not show an association with HCV infection in a multivariate logistic regression model, although there were more male than female HBV infections in HIV-infected patients.

Table 4 **Multivariate logistic regression of risk factors associated with positive HCV serostatus (*n* = 1372)**

Risk factors	aOR (95% CI)	*P* value
Gender (female as the reference category)	1.42 (1.07–1.80)	0.034
Ethnicity (Han as the reference category)	1.72 (1.30–2.26)	<0.001
Syphilis status (negative as the reference category)	1.40 (1.05–1.87)	0.023
Exposure group (heterosexual as the reference category)		
FBD	3.36 (2.30–4.93)	<0.001
Blood transfusion recipients	2.91 (1.83–4.62)	<0.001
MSM	0.71 (0.48–1.06)	0.093
IDUs	1.98 (1.42–2.77)	<0.001

aOR = adjusted odds ratio; CI = confidence interval; HCV = hepatitis C virus; FBD = former-paid blood donor; MSM = men who have sex with men; IDU = injection drug user

Table 5 **Multivariate logistic regression of risk factors associated with positive syphilis serostatus (*n* = 1372)**

Risk factors	aOR (95% CI)	*P* value
Hepatitis status (anti-HCV negative as the reference category)	1.40 (1.05–1.86)	0.024*
Exposure group (IDUs as the reference category)		
FBD	1.14 (0.64–2.05)	0.651
Blood transfusion recipients	0.60 (0.27–1.37)	0.225
MSM	2.38 (1.43–3.95)	0.001**
Heterosexual	1.43 (0.94–2.18)	0.095

aOR = adjusted odds ratio; HCV = hepatitis C virus; FBD = former-paid blood donor; MSM = men who have sex with men
*$P < 0.05$
**$P < 0.01$

No risk factors associated with HBV infection were found in this study. Therefore, to our knowledge, prevalence of HBV co-infection and the prevalence of HBV serological markers mainly depend on the prevalence of HBV infection in the general population before important potential risk factors develop, at least in China.

In this study, we observed a higher prevalence (19.6%) of HIV-syphilis co-infection in HIV-infected individuals than in the general population, especially in MSM rising up to 30%. As described previously, the annual prevalence of HIV-syphilis co-infection has been increasing in recent years. During the same period, the percentage of HIV-infected patients who engaged in MSM sex increased from 0.4% in 2000–2003 to 31.7% in 2010. Consequently, the increase in the proportion of MSM could explain the steady increase in other categories.

The current study had some limitations. First, it was a retrospective study that may be unable to adequately establish a causal relationship between the time of exposure and subsequent infection. Second, plasma HCV-RNA was not quantified in patients who were anti-HCV-positive, making it difficult to distinguish active HCV infection from spontaneously cleared infection. Diagnosis of HBV infection was based on HBsAg serology that is also less indicative of active disease than HBV-DNA. However, those statuses were commonly determined in large observational studies. FTA-Abs was not performed for RPR-positive individuals in this study because of limited funds, which might be likely to overestimate the prevalence of syphilis in HIV-infected individuals due to false-positive RPRs. Third, some unidentified confounders may not have been completely excluded and some potential risk factors may not be identified, which may result in incorrect conclusions. Finally, selection bias is still possible even though participants were selected from provincial CDC that nearly covers all the areas in Shandong.

In summary, there was a high prevalence of hepatitis B, C and syphilis infections among HIV-infected individuals in Shandong province of China. Serological assessment of co-infection in such patients should be improved. In addition, focus is needed on the prevention and therapy of MSM with or without HIV infection. Furthermore, vaccination against HBV should not only be promoted among HIV-infected people with negative biological markers for hepatitis B but also in the general population, in an attempt to decrease the prevalence in the general population.

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