Published in final edited form as:
AIDS. 2006 June 26; 20(10): 1429–1435. doi:10.1097/01.aids.0000233577.33973.fa.

Co-infection with HIV and hepatitis C virus in former plasma/blood donors: challenge for patient care in rural China

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Abstract

Background—Illegal commercial plasma donation in the late 1980s and early 1990s caused blood-borne infections in China.

Objectives—To estimate the prevalence of HIV and hepatitis C virus (HCV) infections and to identify associated risk factors in central China with a history of illegal plasma collection activities.

Design and methods—A cross-sectional study was carried out in 2004, in which all adult residents in four villages in rural Shanxi Province were invited for a questionnaire interview and testing of HIV and HCV antibodies.

Results—Of 3062 participating villagers, 29.5% reported a history of selling whole blood or plasma. HIV seropositivity was confirmed in 1.3% of subjects and 12.7% were HCV positive. Their co-infection rates were 1.1% among all study subjects, 85% among HIV-positive subjects, and 8.7% among HCV-positive subjects. Selling plasma [odds ratio (OR), 22.5; 95% confidence interval (CI), 16.1–31.7; $P < 0.001$] or blood (OR, 3.1; 95% CI, 2.3–4.2; $P < 0.001$) were independently associated with HIV and/or HCV infections. Although a spouse's history of selling plasma/blood was not associated with either infection, the HIV or HCV seropositivity of a spouse was significantly associated with HIV and/or HCV infections (both OR, 3.2; 95% CI, 2.0–5.2 in men, 2.0–4.9 in women; $P < 0.001$). For men, residence in the village with a prior illegal plasma collection center (OR, 2.5; 95% CI, 1.7–3.7; $P < 0.001$) and for women, older age (OR, 3.4; 95% CI, 1.2–14.0; $P = 0.04$) were associated with HIV and/or HCV infections.

Conclusions—HIV and HCV infections are now prevalent in these Chinese communities. HIV projects should consider screening and care for HCV co-infection.

Keywords

HIV; hepatitis C virus; cross-sectional study; plasma donors; rural health; China

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Introduction

During the late 1980s and early 1990s, illegal commercial plasma and blood collection activities were common in selected rural areas of central China. The practice of pooling blood and re-infusing red blood cells into donors of the same blood types caused a rapid spread of several blood-borne diseases, including hepatitis C virus (HCV) and HIV infections [1–3]. The first recognized outbreak of HCV infection among plasma donors occurred in the late 1980s [1]. Since then, cross-sectional studies have investigated HCV infection among former plasma or blood donors, in whom prevalence rates have varied from 9.6 to 72.8% [2,4–7]. The spread of HIV among donors was first reported around 1995 [8]. In subsequent epidemiologic studies, HIV prevalence ranged from 0.2 to 56.1% among donors in village surveys from areas in Henan, Anhui, Hubei, Shanxi and Shangdong provinces with known illegal plasma donation practices [2–4,9]. Two previous studies found that HIV-infected blood or plasma donors were frequently co-infected with HCV (68 and 87%, respectively) [4,10].

Due to shared risk factors for transmission, co-infection with HIV and HCV is common, especially among injection drug users (IDUs) and recipients of contaminated blood or products [11–13]. Epidemiological and treatment issues for HIV and HCV co-infection in China are addressed only rarely. HIV co-infection may accelerate the natural course of chronic hepatitis C infection, increase the risks for liver cirrhosis, hepatocellular carcinoma, and/or liver failure, and lead to failure of hepatitis C therapy [14–16]. Some but not all studies have shown an increased risk of progression to acquired immunodeficiency syndrome (AIDS) and AIDS-related death among HIV and HCV co-infected persons, suggesting that HCV co-infection may accelerate the course of HIV disease [17,18]. In addition, hepatitis C infection may inhibit the successful management of HIV infection by increasing the incidence of liver toxicity associated with certain antiretroviral regimens [19,20]. We undertook the current study among rural Chinese communities with former plasma/blood donors and HIV/AIDS cases to estimate the prevalence of and characterize risk factors for HIV and/or HCV infections.

Methods

Study context

As a part of a large ongoing project China Integrated Programs for Research on AIDS, this cross-sectional study was conducted in southern Shanxi Province, near Henan Province, the epicenter of HIV/AIDS acquired through unsanitary plasma collection in China. Building on the results of a preparatory study [21], four villages were selected on the basis of their high estimated frequency of previous plasma or blood donation and the willingness of village leaders to collaborate. An illegal commercial plasma-collection center had operated in one of the villages in 1995 (our best estimate). The study protocol was approved by the Division of AIDS Prevention Science Review Committee of National Institute of Allergy and Infectious Diseases and the institutional review boards of the Chinese National Center for AIDS/STD Prevention and Control and the University of Alabama at Birmingham.

Study participants and data collection

A roster of all residents of the study villages was obtained from local authorities during the preparatory study [21]. Prior to study enrollment, health education campaigns (‘Village Health Camps’) were conducted in each village. The objectives of the Village Health Camps included mobilizing the community leaders to become involved in and support the epidemiological survey, introducing HIV and HCV tests and their value, reducing fear, ignorance and stigma surrounding HIV, and informing villagers about the benefits and risk of study participation and confidentiality of study results. When the study began, village physicians or leaders reminded villagers to come for the study. All villagers aged 18 to 64 years were invited to

participate during May and August 2004. The field study was conducted in the village clinic or village committee office of each village.

Standardized questionnaire-based interviews administered by same-sex, trained interviewers sought demographic, medical, and behavioral data, including plasma/blood donation history. Venous blood was collected for testing of HIV and HCV antibodies. Each blood sample was screened by enzyme-linked immunosorbent assay (ELISA; GBI Biotech Co., Ltd., Beijing, China) for HIV antibody, and positive tests were confirmed by HIV-1/2 western blot immune assay (HIV Blot 2.2 WB; Genelabs Diagnostics, Singapore). HCV antibody was tested using enzyme immuno-absorbent assay (EIA, GBI Biotech Co.). Individual pre- and post-test counseling was provided to all participants. Before any study data were solicited, written informed consent was obtained from each participant. Protocol compliance, questionnaire completion and laboratory testing were monitored with internal and external quality controls.

Data analysis

Statistical analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, North Carolina, USA). Point prevalence rates of HIV and HCV seropositivity were calculated and compared between plasma/blood donors and non-donors. Regression analyses were undertaken to compare factors associated with HIV–HCV co-infection versus HCV mono-infection and factors associated with HCV mono-infection versus absence of infection among all subjects and among male and female subgroups. The sociodemographic and risk factors significantly associated with infection status in univariate models ($P \leq 0.05$) were included in multivariate logistic regression models for all study subjects and, then, for male and female subgroups, separately. Those variables not significant in the multivariable models were eliminated in a stage-wise manner, identifying variables that were independently associated with HCV and/or HIV seropositivity.

Results

Participation rate and sociodemographics of participants

Of the 3718 villagers, 3062 (82.4%) participated in the interviews, contributed blood samples for HIV and HCV testing, and were thereby included in the analysis. Non-participants were younger (36.7% less than 30 years old; 241/656) than participants (17.8%; 550/3062), and more likely to have never been married (11.6% single; 76/654) than participants (3.8%; 116/3062), but were similar in sex distribution and educational level. Nearly half (49.1%) of these 656 non-participants were < 35 years old. The reasons for non-participation included out-migration of the villagers for a temporary job (33%), no time (15%), refusal for unknown reasons (38%), illness (4%), death (1%), and other (including being ineligible or unwilling to provide informed consent, 9%).

The mean age of the 3062 participants was 41.3 years (25–75% interquartile range, 32.7–50.7); 49.9% were male; 70.7% had attended middle school or above (> 6 years of schooling); and 96.2% were married. All participants were of Han majority ethnicity; 53.9% had other incomes in addition to farming at the time of the survey.

Commercial plasma/blood donation and sexual and drug-using behaviors

Of the 3062 participants, 904 (29.5%) had a history of selling plasma or blood (1.2% plasma only, 21.2% whole blood only, and 7.1% both). Those who had ever sold plasma accounted for 8.3% of all participating villagers. The prevalence of having ever sold plasma or blood was 46.6% in the village where there had been an illegal commercial plasma collection center, and it was 8.5, 15.7, and 35.1% in the other three villages. The prevalence of selling blood/plasma

varied with age ranges: 7.2% in ages < 35 years, 43.5% in ages of 35 to 55 years and 27.8% in ages > 55 years. There was no sex difference (29.0% in males and 30.1% in females).

Among all surveyed villagers, 12.9% (394) reported more than one lifetime sexual partner; however, only 6.4% (196) had ever had extra-marital sex and 0.9% (27) had ever exchanged sex for money. Frequent condom use was reported by 8.6% of villagers in extra-marital sex. Twelve (0.4%) villagers reported having ever used illegal drugs such as marijuana, opiates, but none injected drugs.

HIV and HCV seroprevalence

HIV infection was detected in 40 (1.3%) villagers and HCV infection in 389 (12.7%). Thirty-four (1.1%) villagers were seropositive for both HIV and HCV, whereas 355 (9.9%) had HCV only and 6 (0.2%) had HIV only. Of the 40 HIV-infected villagers; 85.0% were co-infected with HCV, whereas of the 389 HCV-infected villagers, 8.7% were co-infected with HIV. In those who sold blood or plasma, HIV seroprevalence was 31 times higher and HCV infection nearly 10 times higher than in those who did not sell blood ($P < 0.001$ for both comparisons; Table 1).

Risk factors for HIV and HCV seropositivity

As there were only six participants (0.2%) who were only infected with HIV, univariate comparisons were made for HIV–HCV co-infected versus HCV mono-infected and HCV mono-infected versus uninfected subjects (Table 2). In both male and female subjects, selling plasma, older age, spouse's selling plasma/blood, spouse's HCV seropositivity, and residence in the village where a plasma collection center was located were associated with HCV mono-infection (versus absence of infection). In males only, ever having been married, selling whole blood, dental extraction, and receiving blood transfusion were associated with HCV mono-infection; in females only, lower education showed such an association. When combining males and females, male sex appeared to be associated with HCV mono-infection. Analysis comparing HIV–HCV co-infection versus HCV mono-infection found that only selling of plasma was associated with co-infection.

Selling plasma was the only associated factor with both HIV–HCV co-infection (versus HCV mono-infection) and HCV mono-infection (versus absence of infection), and both associations were positive [e.g., among all subjects, HIV–HCV co-infection odds ratio (OR), 4.5; HCV mono-infection OR, 17.6]. Therefore, HIV- and HCV-infected subjects were combined; that is, comparisons were made between those infected with either virus and those uninfected, in multivariate analyses to identify risk factors for either or both of these two infections (Table 3). Selling plasma [OR, 22.5; 95% confidence interval (CI), 16.1–31.7; $P < 0.001$], selling whole blood (OR, 3.1; 95% CI, 2.3–4.2; $P < 0.001$), male sex (OR, 1.5; 95% CI, 1.2–2.0; $P = 0.001$), older age (OR, 4.8; 95% CI, 2.4–10.8; $P < 0.001$), lower education (OR, 1.3; 95% CI, 1.01–1.7; $P = 0.04$) and residence in the village with a former plasma collection center (OR, 2.2; 95% CI, 1.7–2.9; $P < 0.001$) were independently associated with HIV and/or HCV seropositivity (model 1). Subgroup analyses in male and female subjects also found that a spouse's HIV or HCV infection (both OR, 3.2; 95% CI, 2.0–5.2 in men, 2.0–4.9 in women; $P < 0.001$; models 2 and 3) was independently associated with seropositivity of HIV and/or HCV, but a spouse's selling plasma or whole blood was not. There was no interaction between sex and selling plasma or blood in their associations with HIV and/or HCV infections.

Discussion

We conducted our study in rural communities of the southern Shanxi Province where illegal plasma and blood collection was common around 1995. We found a lower prevalence of HIV

infection than observed in other village surveys of Chinese plasma-donating communities [2–4,8], but it is consistent with the findings of our pilot study in a random sample from 12 villages [21]. The possible explanations for the lower prevalence might include a short period of unhygienic plasma collection practices in this particular region (1995 to 1996) and the relatively late introduction of HIV into our study communities. Furthermore, plasma collection and associated HIV infection seem to be distributed in clusters and may vary significantly by area; for example, the prevalence of blood/plasma donors was 46.6% in the village with a history of a plasma collection center, but ranged from 8.5 to 35.1% in the other three neighboring or nearby villages in our study. Overall, our study villages do not represent communities with a severe plasma donation-associated HIV epidemic as is more common in neighboring Henan Province.

Our study indicated that HCV infection is the principal blood-borne viral infection of public health importance in this region given the 12.7% HCV prevalence and the 1.1% prevalence of HIV and HCV co-infection. It is notable that HCV prevalence is higher than HIV in many former plasma/blood donating communities. It is possible that percutaneous exposure during plasma/blood collection and/or red cell re-infusion are more efficient for HCV transmission than for HIV transmission, HCV has been reported to be about 10-fold more easily transmitted via small-volume percutaneous exposure than HIV [22]. In the communities, where injection drug use and risky sexual behavior are rare, we have little evidence from this study of ongoing HIV transmission by sexual or needle routes. Another possibility is that HIV may have been introduced into these communities later than HCV, and HCV baseline rates may have been higher at the time of the unhygienic blood donation practices.

In our whole study sample and in both male and female subgroups, selling plasma/blood showed a consistently strong association with HIV and/or HCV infection; the risk in former plasma donors was 22.5 times higher than that in non-donors and whole blood donation was associated with 3.1 times higher HIV and/or HCV seropositivity. In male subjects, residence in the village where an illegal plasma collection center had operated in around 1995 was independently associated with infections. Age above 30 years was independently associated with infections in female subjects. Due to the cross-sectional nature of this study, we cannot confirm transmission of HIV or HCV through sexual intercourse or other close interpersonal contacts and the transmission direction from husbands to wives or reverse.

HIV infection associated with illegal plasma/blood donation in China has attracted much attention, whereas HCV infection and HCV–HIV co-infection is a neglected topic [21,23]. We found that 85% of HIV-infected villagers were co-infected with HCV and 8.7% of HCV-infected villagers were co-infected with HIV. HCV therapies are unaffordable for Chinese farmers with low incomes and no health insurance. Dual infection in rural residents presents an additional challenge for patient care. HCV may facilitate HIV disease progression, increase the incidence of liver toxicity associated with certain antiretroviral regimens, and represent a leading cause of morbidity and mortality among AIDS patients receiving antiretroviral therapy (ART) [19,20,24]. The Chinese government has initiated free ART programs for the infected rural plasma donors since 2003, but these programs do not provide free HCV screening or interferon-based treatments that are expensive and beyond the affordability of these poor farmers. Laboratory monitoring of virologic and immunologic indicators during ART is necessary but is unavailable in nearly all many rural areas of China. Our study findings underscore the importance of improved HIV treatment and prevention in rural, former plasma-donation communities, including diagnosis and basic care for HCV co-infection.

Our study had several strengths. We invited all villagers age 18 to 64 years to participate in the study, we believe that our Village Health Camps and inviting all villagers to participate have reduced villagers' concern and stigma as there may have been if we had surveyed only a

sample of residents or only former plasma/blood donors. Over 82% of registered villagers participated in the study. While this rate is not very high in the Chinese context, we have ensured that all rural farmers and family members have understood our study and made an informed choice. Our study volunteers included most of the older villagers who might have sold plasma or blood 10 years ago; those younger than 18 years or older than 64 years who were not included among our study subjects are unlikely to have had a history of selling plasma or blood. Strict internal and external quality control ensured the study's compliance with informed consent and other study procedures and increased the validity of questionnaire and laboratory data.

The study also has limitations. Some villagers were reluctant to participate in the study, often because of their expressed fears of receiving positive test results. We conducted the study nearly a decade after the illegal plasma collection practices were widespread in these communities. These factors may have led to underestimation of the prevalence due to differential non-participation, out-migration or death. However, about half of non-participants were < 35 years old and were unlikely to have sold plasma/blood 10 years ago (7.2% participants in age < 35 years sold blood/plasma versus 43.5% in age 35–55 years and 27.8% in age > 55 years). We did not collect mortality data in our study. Though AIDS-mortality data is very valuable for public health programs, it is almost impossible to collect in this context as a majority of infected villagers had never received a test and therefore did not know their positive status. There is a possibility that those suspecting that they were infected or knowing that they were former plasma donors declined to participate, and this type of non-participation and AIDS-related deaths would lead to an underestimation of the prevalence. We did not perform HCV RNA tests or recombinant immunoblot tests; HCV-antibody-negative but HCV-RNA-positive cases may exist in patients with severe cellular immune suppression as a result of HIV [25,26], and thus our estimate of HIV–HCV co-infection rate may be a slight underestimate. We also believe that while recall bias is unlikely as to blood product donation *per se*, we assume that some respondents may misreport blood versus plasma donation. Donating blood products is a memorable event for local residents as it was associated with HIV/AIDS in these communities and because Chinese people are often reluctant to donate blood voluntarily.

In summary, HCV is more common than HIV in these rural communities in central China, and is largely associated with past illegal plasma or blood donation activities. HCV is an increasingly important cause of mortality and morbidity as ART reduces death and secondary opportunistic infections among AIDS patients in care. While providing free HIV testing and treatment in these rural communities, Chinese government should make HCV testing available and affordable to these rural residents and consider HCV co-infection in training and patient care.

Acknowledgments

We are grateful to the entire China Integrated Programs for Research on AIDS team and participating staff at the Shanxi Province Center for Disease Control and the Wenxi County Center for Disease Control for their contribution to data collection and data management, and laboratory testing. We thank Drs Rod Hoff, Mary Fanning and Ray Chen (National Institute of Allergy and Infectious Diseases, Bethesda, Maryland) and Judith Chamberlin and Jinhua Jiao (Westat Company, Rockville, Maryland), for their generous help in many areas; two anonymous reviewers, for their critical review of the manuscript; and the study participants, for their participation in the study.

Sponsorship: This work was supported by grants from the National Institute of Allergy and Infectious Diseases (U19 AI51915-04 to Y.S.) and, in part, from the Fogarty International Center (D43 TW010035-07 to S.H.V).

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Table 1

Association of plasma/blood donation and HIV, hepatitis C virus (HCV), or dual infection in residents of rural Shanxi Province, China

Infection	Donors (*n* = 904, %)	Non-donors (*n* = 2158, %)	Crude OR (95% CI)	*P*
HIV	37 (4.1)	3 (0.1)	30.7 (11.1–127.2)	< 0.001
HCV	288 (31.9)	101 (4.7)	9.5 (7.5–12.2)	< 0.001
Co-infection	34 (3.8)	0 (0.0)	ND	< 0.001[a]

OR, odds ratio; CI, confidence interval; ND, not defined.

[a]Fisher's exact test.

Table 2

Univariate analysis of factors associated with HIV–hepatitis C virus (HCV) co-infection and HCV mono-infection in residents of rural Shanxi Province, China

Factor	All subjects		Male subjects		Female subjects	
	Co-infected (*n* = 34) vs. HCV mono-infected (*n* = 355)	HCV mono-infected (*n* = 355) vs. non-infected (*n* = 2667)	Co-infected (*n* = 24) vs. HCV mono-infected (*n* = 198)	HCV mono-infected (*n* = 198) vs. non-infected (*n* = 1306)	Co-infected (*n* = 10) vs. HCV mono-infected (*n* = 157)	HCV mono-infected (*n* = 157) vs. non-infected (*n* = 1361)
Residing in a village with a plasma collection center	1.1 (0.6–2.3)	3.1 (2.5–3.9)***	1.2 (0.5–2.9)	3.9 (2.9–5.3)	0.9 (0.3–3.4)	2.4 (1.7–3.4)***
Male	1.9 (0.9–4.3)	1.3 (1.05–1.6)*	NA	NA	NA	NA
Education (≤ 6 years)	1.9 (0.9–3.8)	1.8 (1.5–2.3)***	1.9 (0.8–4.5)	2.3 (1.7–3.2)	2.5 (0.7–11.9)	1.7 (1.2–2.4)**
Age (≥ 30 years)	ND	11.1 (5.8–24.5)***	ND	19.0 (7.2–77.0)***	ND	6.7 (3.0–19.1)***
Marriage (ever married)	0.4 (0.05–7.5)	3.8 (1.6–12.5)**	0.5 (0.07–9.5)	3.8 (1.6–12.4)*	ND	ND
History of selling plasma	4.5 (2.1–10.4)***	17.6 (13.1–23.8)***	4.4 (1.8–12.6)**	22.0 (14.5–34.0)***	4.2 (1.1–20.1)*	14.0 (9.1–21.5)***
History of selling whole blood only	0.7 (0.3–1.6)	2.1 (1.6–2.6)***	0.6 (0.2–1.4)	3.0 (2.1–4.1)**	1.1 (0.2–4.3)	1.3 (0.9–1.9)
More than one lifetime sexual partner	0.7 (0.2–1.9)	1.3 (0.95–1.8)	0.8 (0.2–2.2)	1.2 (0.8–1.7)	ND	1.2 (0.7–2.1)
Illicit drug use	ND	2.5 (0.6–8.5)	ND	2.2 (0.5–7.5)	ND	ND
History of dental extraction	1.1 (0.5–2.1)	1.4 (1.1–1.8)**	0.96 (0.4–2.3)	1.5 (1.1–2.1)**	1.2 (0.3–4.4)	1.3 (0.9–1.8)
History of acupuncture	0.9 (0.1–3.3)	1.3 (0.8–2.1)	0.8 (0.04–4.6)	0.98 (0.5–1.9)	1.2 (0.06–7.4)	1.8 (0.9–3.3)
History of surgical operation	ND	1.2 (0.8–1.8)	ND	1.5 (0.8–2.5)	ND	1.04 (0.6–1.8)
History of blood transfusion	ND	2.1 (0.9–4.2)	ND	4.2 (1.3–12.7)*	ND	1.4 (0.4–3.7)
History of medical injection	1.2 (0.6–2.6)	0.8 (0.6–1.02)	1.2 (0.5–3.6)	0.8 (0.6–1.1)	0.9 (0.2–3.6)	0.8 (0.6–1.1)
Spouses' history of selling plasma or blood	NA	NA	1.0 (0.4–3.0)	5.6 (4.0–8.0)***	3.9 (0.6–74.7)	3.6 (2.5–5.4)***
Spouse's HCV status (+)	NA	NA	NA	5.1 (3.4–7.7)***	NA	5.2 (3.4–7.7)**

Data in the table are odds ratios and 95% confidence intervals (in parentheses). NA, not applicable; ND, not defined due to zero observation in one or more cells.

*$P < 0.05$;

**$P < 0.01$;

***$P < 0.001$.

Table 3

Multivariate analysis of factors associated with infection of HIV and/or hepatitis C virus (HCV) in residents of rural Shanxi Province, China

	Adjusted OR (95% CI)		
Factors	**Model 1: among all subjects**	**Model 2: among males**	**Model 3: among females**
Residing in a village with an illegal plasma collection center			
No	1.0	1.0	–
Yes	2.2 (1.7–2.9)***	2.5 (1.7–3.7)***	
Sex			
Female	1.0		
Male	1.5 (1.2–2.0)**	NA	NA
Age			
< 30 years	1.0		1.0
≥ 30 years	4.8 (2.4–10.8)***	–	3.4 (1.2–14.0)*
Education			
> 6 years	1.0		
≤ 6 years	1.3 (1.01–1.7)*	–	–
History of selling plasma			
No	1.0	1.0	1.0
Yes	22.5 (16.1–31.7)***	39.4 (23.0–69.5)***	12.4 (7.3–21.4)***
History of selling whole blood			
No	1.0	1.0	1.0
Yes	3.1 (2.3–4.2)***	5.6 (3.6–9.0)***	2.0 (1.2–3.3)**
Spouse's history of selling plasma or blood			
No	NA	–	–
Yes			
Spouse's HCV and HIV status			
Both negative		1.0	1.0
Either positive	NA	3.2 (2.0–5.2)***	3.2 (2.0–4.9)***

OR, odd ratio; CI, confidence interval; NA, not applicable.

*$P < 0.05$;

**$P < 0.01$;

***$P < 0.001$.