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Multiple viral coinfections among HIV/AIDS patients in China

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Summary **A cross-sectional survey was conducted to determine seroprevalence and correlates of coinfections of hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Bar virus (EBV), herpes simplex virus including type 1 (HSV-1) and type 2 (HSV-2) among human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients in China. A total of 1,110 HIV/AIDS patients from Shanxi (Central area, *n* = 287), Zhejiang (Eastern area, *n* = 163), Yunnan (Southwestern area, *n* = 300) and Xinjiang (Northwestern area, *n* = 360) provinces were analyzed. The overall seroprevalence was 6.3% for HBsAg, 59.0% for anti-HCV IgG, 96.6% for anti-EBV IgG, 91.5% for anti-HSV-1 IgG, and 34.1% for anti-HSV-2 IgG. Eleven (1.0%) HIV/AIDS patients were coinfected with all five viruses, 177 (15.9%) with four viruses, 611 (55.0%) with three viruses, 288 (25.9%) with two viruses, 23 (2.1%) with single virus, and 1 (0.1%) with none of the five viruses. Multiple logistic regression analyses indicated that neither HBV, nor EBV and HSV-1 coinfection was associated with sociodemographic characteristics and HIV transmission mode, but HCV coinfection was associated with geographic region, age, gender, ethnicity, marital status, and HIV transmission mode, whereas HSV-2 coinfection was associated with geographic region, ethnicity and HIV transmission mode. This study suggests that HIV/AIDS patients with different regional and sociodemographic backgrounds and HIV transmission mode in China have different profiles of viral coinfections and should be subject to differential considerations in related health care programs.**

Keywords: Coinfection, HSV, EBV, HBV/HCV, HIV, Chinese

1. Introduction

The issue of viral coinfection among human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients represents a growing public health concern worldwide. Viral coinfections among an HIV-infected individual may affect the disease progression of HIV/AIDS and may accelerate the progression of these other viral infections to more severe illness due to HIV coinfection (*1-10*). Among the list of viruses that are likely to be co-infected with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus including type 1 (HSV-1) and type 2 (HSV-2), and the Epstein-Bar virus (EBV) are the most important coinfections among HIV/AIDS patients due to their pathogenicity and relatively high prevalence in populations affected by HIV.

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HBV and HCV are of concerns because both viruses compromise liver function, which may further affect the metabolism and therapeutic effect of antiretroviral drugs (ARV) for AIDS patients (*11-13*). They are also classified as group one causative agents of hepatocellular carcinoma (HCC) by International Agency for Research on Cancer (IARC). Worldwide it is estimated that 10-30% of the 40 million people infected with HIV are co-infected with HCV due to similar transmission routes between HIV and HCV (*14*). In China, high prevalence of HIV and HCV coinfection has been reported among injection drug users (IDU) and plasma/blood donors (*15*,*16*).

HSV also plays an important role in the disease progression of HIV infection. Chronic infection of HSV-1 has been regarded by the World Health Organization (WHO) as an important factor affecting the disease progression of HIV/AIDS. HSV-1 infection is usually transmitted during childhood and adolescence and is most often transmitted *via* nonsexual contact (*17*). On the other hand, HSV-2 is most likely to be sexually transmitted and is the leading cause of the genital ulcer disease. Studies have suggested that there is a strong association between HSV-2 and HIV serostatus and that diagnosis of HSV-2 infection can help to identify individuals at greater risk for contracting HIV (*18*). In China, HSV-2 infection is relatively uncommon in the general population but is very common among female sex workers (*19-24*).

EBV is the causal agent of non-Hodgkin's lymphoma (NHL) which is an AIDS-defining malignancy. It is also the causal agent of Hodgkin's lymphoma (HL) and nasopharyngeal cancer, both of which are non-AIDS defining malignancies but have been increasingly observed among HIV/AIDS patients who have experienced long-term immunodeficiency (*25*,*26*). EBV is also highly prevalent around the world (*27*).

In China, there has been no study specifically designed to examine the seroprevalence of viral coinfections among HIV/AIDS patients. We hypothesize that multiple pathogenic viral coinfections may negatively impact HIV-infected individuals. Therefore, as the first step to test the hypothesis, we conducted a cross-sectional seroprevalence survey of HBV, HCV, HSV-1, HSV-2, and EBV among HIV/AIDS patients from four geographical areas representing different HIV transmission routes in China. The knowledge gained from this study will shed a light on the disease progression of HIV infection in Chinese populations and will be valuable for designing effective antiretroviral treatment (ART) programs for Chinese HIV/AIDS patients.

2. Materials

2.1. *HIV/AIDS reporting and managing system in China*

In China, it is required by law that all newly identified HIV-infected cases must be reported to local centers for disease prevention and control (CDC) first and then to the national CDC through the AIDS Network Direct Reporting Information System. The local CDC is also obligated to conduct a nationwide standardized epidemiological investigation on each newly reported HIV-infected case which ascertains sociodemographic characteristics and HIV-related risky behaviors. Once the HIV-infected cases are registered in the national reporting information system, they will be regularly followed up by local CDC for behavioral interventions, provision of health care services and social support. At each follow-up visit, venous blood is drawn for testing $CD4^+$ cell counts as an index of disease progression. The data obtained from the initial and all follow-up epidemiological investigation, interviews and medical examinations constitute the patient's personal HIV/AIDS file or database, which is located in both local and national CDC.

2.2. *Study sites*

The present study was conducted in four regions which were selected to represent the overall epidemiological pattern of the HIV/AIDS epidemic in China: (*i*) Yuncheng city in Shanxi province in Central China where the HIV epidemic was first reported in 1996 and predominantly transmitted through plasma/blood donation or transfusion. By the end of 2008, 1,436 HIV/AIDS cases had been reported. Among them, 515 died and 715 were alive and traceable. (*ii*) Taizhou city in Zhejiang province in the Eastern coast of China where HIV was primarily transmitted through unprotected sexual behaviors. The first HIV case was reported in 1996. By the end of 2008, 365 HIV/AIDS cases had been reported. Among them, 45 died and 172 were alive and traceable. (*iii*) Urumqi city, the capital city of Xinjiang Uygur Autonomous Region in Northwestern China where drug injection and to a less extent, heterosexual transmission were the two major modes of HIV transmission. The first HIV case was reported in 1995 and by the end of 2008, 9,068 HIV/AIDS cases had been reported. Among them, 258 died and 1,129 were alive and traceable. (*iv*) Yingjiang county in Yunnan province in Southwestern China where HIV was formerly predominantly transmitted through injecting drugs but now is almost equally likely to be transmitted through drug injection or unprotected sexual contacts. The first HIV case in Yingjiang county was reported in 1990. By the end of 2008, 3,335 HIV/AIDS cases had been reported. Among them, 1,069 died and 1,679 were alive and traceable.

Each of the four sites had a qualified laboratory equipped with a flow cytometer for $CD4^+$ cell counting of HIV/AIDS patients.

2.3. *Subject selection*

Due to limited resources and unaffordable expenses for

laboratory tests, we decided not to include all alive and traceable HIV/AIDS patients in these four study sites for this study. Instead, we selected all adult HIV/AIDS patients in these four study sites who visited local CDC for routine follow-up tests of $CD4^+$ cell count during a specified two-week sample collection period for each site from late 2008 through early 2009. The specific two-week sample collection period designated to each site was chosen primarily based on our experience that it would allow for obtaining a reasonable size of the study sample. A total of 1,110 HIV/AIDS patients who visited local CDC during the sample collection period were included in the present study. Among them, 288 HIV/AIDS patients were from Yuncheng city, 163 were from Taizhou, 360 were from Urumqi, and 300 were from Yingjiang. These patients shown up within the two-week sample collection period represented 40% of all alive and traceable HIV patients in Yuncheng, 95% in Taizhou, 32% in Urumqi, and 18% in Yingjiang, respectively. The low representativeness in Yingjiang, Yunnan province, was due to the fact that it had a large number of alive HIV/AIDS patients and the majority of them were living in remote mountainous villages and did not visit the local CDC as often as their counterparts in other areas. Sociodemographic characteristics and HIV transmission route of the study subjects were abstracted from their individual epidemiological HIV/AIDS files. This study was approved by the Institutional Review Board (IRB) of the corresponding institution in China.

2.4. *Blood testing*

To avoid drop of antibody titers due to long distance transportation, all aliquots of serum samples were cryopreserved at −20°C or −70°C and tested in the local CDC. $CD4^+$ cell counts were measured by local CDC laboratory staff using a flow cytometry (BD FACSCount™; BD Biosciences, San Jose, CA, USA), who had been strictly trained and certified following the national guidelines set by the national center for AIDS and sexually transmitted disease (STD) prevention and control (NCAIDS) of China CDC. HBV surface antigen (HBsAg) and anti-HCV IgG antibody were tested using an enzyme-linked immunosorbant assay (ELISA) (Wantai Biological Pharmacy Enterprise Co., Beijing, China). HSV-1- and HSV-2-specific IgG antibodies were tested using the HerpeSelect ELISA Kit (Focus Technologies, Cypress, CA, USA). Anti-EBV nucleic antigen (EBNA) IgG antibody was tested by ELISA (Euroimmun, Lübeck, Germany). All above serological tests were performed by the same two experienced technicians from the key laboratory of the leading institution of this study, according to the manufacturers' standard protocols. Duplicate negative, positive and blank controls were always used.

2.5. *Data analysis*

Seroprevalence of each viral coinfection was tabulated by geographic region and sociodemographic characteristics of study subjects, followed by chi-squared tests to determine statistical significance. Five separate multiple logistic regression analyses were performed to identify independent sociodemographic correlates of HBV, HCV, HSV-1, HSV-2, and EBV infection respectively among HIV/AIDS patients. Their respective odds ratios (ORs) and 95% confidence intervals were calculated. All statistical analyses were carried out using the SAS System for Windows (Cary, NC, USA), version 8.0.

3. Results

3.1. *Sociodemographic characteristics*

Table 1 presents sociodemographic characteristics of the study participants. About 45.3% of the study subjects were between 30 to 39 years and 61.5% were males. The majority of them were married and almost a half was either illiterate or educated only at primary schools. All Yuncheng patients and 93.2% of Taizhou patients were ethnic Han, whereas 92.2% of Urumqi patients and 55.7% of Yingjiang patients were ethnic minorities. Table 1 presents a detailed description of their socio-demographic characteristics which varied significantly by geographic region.

3.2. *HIV transmission mode and disease status*

As shown in Table 1, the means of HIV transmission varied widely by geographic region. In Yuncheng the most frequent mode of transmission was through plasma/blood donation or transfusion (85.1%). In Taizhou the majority of transmission was heterosexual (69.9%), however all modes of transmission were reported among the sample. In Urumqi the majority of the transmission reported was through injection drug use (52.8%), however the rate of heterosexual transmission was also relatively high (30.0%). In Yingjiang injection drug use was the most common transmission route (50.0%), which was followed closely by heterosexual transmission (42.0%).

About 42.7% of the patients were receiving ART, and 32.1% had 200-349 $CD4^+$ cells/μL and 23.4% had less than 200 $CD4^+$ cells/μL (Table 1).

3.3. *Prevalence of viral coinfections*

The overall seroprevalence was 6.3% for HBV, 59.0% for HCV, 96.6% for EBV, 91.5% for HSV-1, and 34.1% for HSV-2 (Table 2). The seroprevalence of all five viruses except for HBV varied significantly by geographic region, most sociodemographic

Table 1. Sociodemographic characteristics, transmission modes and current CD4$^+$ T-cell counts of HIV/AIDS patients in four geographical areas in China

	Yuncheng, Central China (n_1 = 287) No. (%)	Taizhou, Eastern China (n_2 = 163) No. (%)	Urumqi, Northwestern China (n_3 = 360) No. (%)	Yingjiang, Southwestern China (n_4 = 300) No. (%)	Total (n = 1,110) No. (%)
Age (years, $p < 0.001$)					
18-29	23 (8.0)	47 (28.8)	75 (20.8)	46 (15.3)	191 (17.2)
30-39	81 (28.2)	68 (41.7)	216 (60.0)	138 (46.0)	503 (45.3)
40-49	117 (40.8)	29 (17.8)	54 (15.0)	90 (30.0)	290 (26.1)
50-59	60 (20.9)	12 (7.4)	3 (0.8)	21 (7.0)	96 (8.6)
60-94	6 (2.1)	7 (4.3)	12 (3.3)	5 (1.7)	30 (2.7)
Gender ($p < 0.001$)					
Male	155 (54.0)	109 (66.9)	188 (52.4)	230 (76.7)	682 (61.5)
Female	132 (46.0)	54 (33.1)	171 (47.6)	70 (23.3)	427 (38.5)
Ethnicity ($p < 0.001$)					
Han	287 (100.0)	152 (93.2)	28 (7.8)	133 (44.3)	600 (54.1)
Uygur	0	1 (0.6)	317 (88.0)	0	318 (28.6)
Dai	0	0	0	112 (37.3)	112 (10.1)
Jingpo	0	1 (0.6)	0	48 (16.0)	49 (4.4)
Other minorities	0	9 (5.5)	15 (4.2)	7 (2.3)	31 (2.8)
Occupation ($p < 0.001$)					
Peasant	282 (98.2)	51 (31.3)	4 (1.1)	245 (81.7)	582 (52.5)
Commercial service	0	73 (44.8)	47 (13.1)	8 (2.7)	128 (11.5)
Other employees	5 (1.8)	39 (23.9)	77 (21.4)	14 (4.7)	135 (12.2)
Unemployed	0	0	232 (64.4)	33 (11.0)	265 (23.8)
Marital status ($p < 0.001$)					
Never married	2 (0.7)	30 (18.9)	65 (18.1)	61 (20.3)	158 (14.3)
Married	275 (95.8)	115 (72.3)	251 (69.9)	180 (60.0)	821 (74.3)
Divorced/Widowed	10 (3.5)	14 (8.8)	43 (12.0)	59 (19.7)	126 (11.4)
Education ($p < 0.001$)					
Illiterate	74 (25.8)	12 (7.4)	10 (2.8)	36 (12.0)	132 (12.0)
Primary school	119 (41.5)	53 (32.9)	62 (17.5)	176 (58.9)	410 (37.3)
Secondary school	83 (28.9)	73 (45.3)	160 (45.1)	67 (22.4)	383 (34.7)
High school or equal	10 (3.5)	17 (10.6)	90 (25.4)	17 (5.7)	134 (12.1)
College/University	1 (0.3)	6 (3.7)	33 (9.3)	3 (1.0)	43 (3.9)
Transmission route ($p < 0.001$)					
Heterosexual	39 (13.6)	114 (69.9)	108 (30.0)	126 (42.0)	387 (34.8)
Injection drugs	0	13 (8.0)	190 (52.8)	150 (50.0)	353 (31.8)
Plasma/blood donation or transfusion	244 (85.0)	10 (6.1)	0	1 (0.3)	255 (23.0)
Homosexual	0	10 (6.1)	3 (0.8)	0	13 (1.2)
Unidentified	4 (1.4)	16 (9.8)	59 (16.4)	23 (7.7)	102 (9.2)
Receiving ART ($p < 0.001$)					
Yes	190 (66.2)	42 (25.8)	89 (24.7)	153 (51.0)	474 (42.7)
No	97 (33.8)	121 (74.2)	271 (75.3)	147 (49.0)	636 (57.3)
CD4$^+$ counts ($p < 0.001$)					
< 200	96 (34.2)	33 (26.0)	62 (17.3)	57 (19.2)	248 (23.4)
200-349	84 (29.9)	39 (30.7)	108 (30.1)	111 (37.4)	342 (32.1)
350-499	53 (18.9)	33 (26.0)	88 (24.5)	68 (22.9)	242 (22.7)
500-749	41 (14.6)	18 (14.2)	64 (17.8)	48 (16.2)	171 (16.0)
750-	7 (2.5)	4 (3.1)	37 (10.3)	13 (4.4)	61 (5.7)

characteristics and transmission route but not by CD4$^+$ cell counts, according to chi-squared tests. The HBV prevalence varied only among different ethnicities and occupations.

3.4. *Concurrency of multiple viral coinfections*

Eleven (1.0%) HIV-infected individuals were co-infected with all five viruses, 177 (15.9%) with four viruses, 611 (55.0%) with three viruses, 288 (25.9%) with two viruses, and 23 (2.1%) with a single virus. Only one (0.1%) was not co-infected with any of the five viruses. The most common combination of coinfections was with HCV, EBV, and HSV-1, which accounted for 36.8% of study subjects (Table 3).

3.5. *Correlates of viral coinfections*

The results of multiple logistic regression analyses were shown in Table 4. Sociodemographic characteristics and HIV transmission mode were not significantly correlated with coinfections of HBV, EBV, and HSV-1 among the study subjects (data not shown). However, coinfection with HCV was independently associated

Table 2. Seroprevalence of HBV, HCV, EBV, HSV-1, and HSV-2 among HIV/AIDS patients of four geographical areas in China

	No. of tested	HBV (%)	HCV (%)	EBV (%)	HSV-1 (%)	HSV-2 (%)
Geographic area		$p = 0.210$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Yuncheng, Central China	287	8.0	76.0	93.4	85.8	13.2
Taizhou, Eastern China	163	7.3	21.3	93.9	86.6	53.0
Urumqi, Northwestern China	360	4.2	61.4	98.1	97.5	41.4
YingJiang, Southwestern China	300	6.7	60.3	99.3	92.7	35.0
Age (years)		$p = 0.209$	$p < 0.001$	$p = 0.194$	$p = 0.069$	$p = 0.001$
18-29	191	6.3	37.5	95.3	94.3	43.8
30-39	503	6.4	62.2	97.6	92.6	34.8
40-49	290	4.8	66.3	96.2	89.7	30.2
50-59	96	11.5	67.7	93.8	85.4	20.8
60-94	30	3.3	43.3	100.0	93.3	40.0
Gender		$p = 0.322$	$p < 0.001$	$p < 0.001$	$p = 0.007$	$p < 0.001$
Male	682	6.9	69.6	98.1	89.8	26.5
Female	427	5.4	42.2	94.1	94.4	46.4
Ethnicity		$p = 0.050$	$p < 0.001$	$p = 0.024$	$p < 0.001$	$p < 0.001$
Han (the major ethnic in China)	600	8.0	53.8	95.0	87.5	32.4
Uygur	318	3.8	63.2	97.8	98.4	41.8
Dai	112	3.6	74.1	100.0	95.5	17.9
Jingpo	49	10.2	65.3	98.0	87.8	28.6
Other minorities	31	3.2	51.6	100.0	90.3	54.8
Occupation		$p = 0.058$	$p < 0.001$	$p = 0.327$	$p < 0.001$	$p < 0.001$
Peasant	582	8.1	65.0	96.2	88.7	24.9
Commercial service	128	4.7	37.2	94.6	92.2	48.8
Other employees	135	5.9	47.4	97.8	91.1	39.3
Unemployed	265	3.4	62.3	97.7	97.7	44.5
Marital status		$p = 0.315$	$p = 0.027$	$p = 0.646$	$p = 0.889$	$p = 0.001$
Never married	158	6.3	64.8	95.6	91.8	32.1
Married	821	6.7	59.2	96.6	91.7	32.1
Divorced/Widowed	126	3.2	49.2	97.6	90.5	48.4
Education		$p = 0.364$	$p < 0.001$	$p = 0.025$	$p = 0.040$	$p = 0.009$
Illiterate	132	4.5	66.7	94.7	87.9	25.0
Primary school	410	6.6	64.2	97.1	89.3	32.4
Secondary school	383	7.3	56.5	96.1	93.8	33.9
High school or equal	134	6.0	50.0	100.0	94.8	44.8
College/University	43	0.0	39.5	90.7	95.3	41.9
Transmission route		$p = 0.621$	$p < 0.001$	$p = 0.003$	$p < 0.001$	$p < 0.001$
Heterosexual	387	7.0	23.0	96.6	92.0	49.4
Injection drugs	353	5.4	87.3	99.2	94.3	29.7
Plasma/blood donation or transfusion	255	7.4	84.0	93.4	85.2	11.3
Homosexual	13	0.0	0.0	100.0	100.0	21.4
Unidentified	102	4.9	43.1	95.1	95.1	50.0
Receiving ART		$p = 0.305$	$p = 0.482$	$p = 0.796$	$p = 0.005$	$p = 0.043$
Yes	474	7.2	57.8	96.4	88.8	30.8
No	636	5.7	59.9	96.7	93.6	36.6
$CD4^+$ counts		$p = 0.755$	$p = 0.836$	$p = 0.154$	$p = 0.188$	$p = 0.588$
< 200	248	6.8	61.0	95.6	89.6	29.3
200-349	342	7.6	61.2	98.8	91.5	35.6
350-499	242	5.4	59.1	96.7	93.4	34.3
500-749	171	5.3	58.5	96.5	92.4	32.7
750-	61	4.9	54.1	95.1	98.4	31.1
Total	1,110	6.3	59.0	96.6	91.5	34.1

* All *p*-values in the table were generated from Bivariate chi-squared tests for associations between viral infections and independent variables listed in the table.

with geographic region, age, gender, ethnicity, marital status, and HIV transmission mode. HIV patients who were living in Taizhou, Eastern China, were female or divorced/widowed, were less likely to have an HCV coinfection. Those who aged more than 30 years, were ethnic Jingpo or infected with HIV through drug injection or plasma/blood donation or transfusion were more likely to be co-infected with HCV. On the contrary, coinfection with HSV-2 was significantly higher among those who were living in areas other than Yuncheng city in central China or female. However, those who were ethnic Dai or Jingpo were less likely to have an HSV-2 coinfection than ethnic Han. Those who became infected with HIV through plasma/blood donation or transfusion were less likely to have an HSV-2 coinfection than those who were heterosexually infected with HIV.

Table 3. Combinations of the five viral coinfections among HIV-infected patients in China

No. of virus	HBV	HCV	EBV	HSV-1	HSV-2	No. of patients	Proportion (%)
5	+	+	+	+	+	11	1.0
4	+	+	+	+	–	20	1.8
4	+	+	+	–	+	-	-
4	+	+	–	+	+	-	-
4	+	–	+	+	+	13	1.2
4	–	+	+	+	+	144	13.0
3	+	+	+	–	–	5	0.4
3	+	+	–	+	–	-	-
3	+	+	–	–	+	-	-
3	–	+	+	+	–	408	36.8
3	–	+	+	–	+	13	1.2
3	–	–	+	+	+	163	14.7
3	–	+	–	+	+	4	0.4
3	+	–	–	+	+	-	-
3	+	–	+	+	–	16	1.4
3	+	–	+	–	+	1	0.1
2	+	+	–	–	–	-	-
2	–	+	+	–	–	37	3.3
2	–	–	+	+	–	206	18.5
2	–	–	–	+	+	9	0.8
2	+	–	+	–	–	2	0.2
2	+	–	–	+	–	2	0.2
2	+	–	–	–	+	-	-
2	–	+	–	+	–	12	1.1
2	–	+	–	–	+	1	0.1
2	–	–	+	–	+	19	1.7
1	+	–	–	–	–	-	-
1	–	+	–	–	–	-	-
1	–	–	+	–	–	14	1.3
1	–	–	–	+	–	8	0.7
1	–	–	–	–	+	1	0.1
0	–	–	–	–	–	1	0.1

+, testing positive; –, testing negative.

4. Discussion

The present study, for the first time, examined prevalence and combinations of five pathogenic viral infections amongst Chinese HIV/AIDS patients. The prevalence of coinfections with HBV, HCV, EBV, HSV-1, and HSV-2 amongst HIV/AIDS patients was generally high. About 96% of the study subjects were infected with EBV and more than 90% of them were infected with HSV-1. This might be due to the high background prevalence of EBV and HSV-1 in the general Chinese population (*28-30*). The prevalence of HBsAg among the HIV/AIDS patients was comparable to that in the general Chinese population which was 7.18% for those aged 1-59 years in a nationwide survey completed in 2006 among 81,775 participants (China Ministry of Health, April 21, 2008). Although HCV and HSV-2 are both relatively uncommon in the general Chinese population (*31,19-21*), a high prevalence of HCV coinfection was observed among the study subjects who had contracted HIV through drug injections and plasma/blood donation or transfusion but a high prevalence of HSV-2 coinfection was also observed among those who had become HIV-infected through heterosexual transmission. Previous studies have reported that HCV infection is prevalent among former plasma donors and injection drug users and that HSV-2 infection is prevalent among commercial sex workers in China (*15-16,22-24*).

In this study, geographic region was also independently correlated with HCV and HSV-2 coinfection among HIV/AIDS patients. This may be due to different background levels of HCV and HSV-2 infections in different geographic regions (*14-16,19-24*). Thus HCV and HSV-2 coinfections should be considered in areas where these viruses are common.

Gender was also found to be independently associated with HCV and HSV-2 coinfections among HIV/AIDS patients in this study. Females were less likely than males to have a HCV coinfection. This is probably related to the fact that in China females are generally less likely than males to be an IDU. A 2009 meta-analysis found that 84% of all IDU participating in the 1997-2007 studies included in the meta-analysis were men (*32*). The present study found that female HIV patients were more likely than males to have an HSV-2 coinfection. This finding is consistent with a meta-analysis of HSV-1 and HSV-2 infections in regions throughout the globe which indicates that there tend to be a higher HSV-2 seroprevalence among females (*17*). Other studies in China have also suggested that the increased prevalence of

Table 4. Logistic regression analyses for identifying sociodemographic correlates of HCV or HSV-2 coinfection among HIV/AIDS patients in China

	HCV		HSV-2	
	OR* (95% CI**)	*p* value	OR* (95% CI**)	*p* value
Geographic area				
Yuncheng, Central China	1.00		1.00	
Taizhou, Eastern China	0.29 (0.12-0.69)	0.005	4.69 (2.17-10.13)	0.000
Urumqi, Northwestern China	0.71 (0.20-2.44)	0.582	2.18 (0.73-6.49)	0.162
Yingjiang, Southwestern China	0.60 (0.26-1.36)	0.221	4.01 (1.88-8.55)	0.000
Age (years)				
18-29	1.00		1.00	
30-39	2.09 (1.28-3.42)	0.003	0.95 (0.64-1.42)	0.799
40-49	2.30 (1.32-4.03)	0.003	1.10 (0.69-1.75)	0.697
50-59	1.89 (0.88-4.06)	0.102	0.76 (0.37-1.54)	0.442
60-94	2.19 (0.78-6.18)	0.139	0.98 (0.39-2.50)	0.969
Gender				
Male	1.00		1.00	
Female	0.43 (0.30-0.61)	0.000	2.50 (1.79-3.50)	0.000
Ethnicity				
Han (the major ethnic in China)	1.00		1.00	
Uygur	2.23 (0.89-5.59)	0.087	0.97 (0.45-2.13)	0.946
Dai	1.81 (0.88-3.70)	0.107	0.24 (0.12-0.44)	0.000
Jingpo	3.30 (1.35-8.05)	0.009	0.29 (0.14-0.63)	0.002
Other minorities	1.86 (0.67-5.17)	0.234	1.24 (0.52-2.96)	0.623
Occupation				
Peasant	1.00		1.00	
Commercial service	1.28 (0.63-2.60)	0.498	1.08 (0.61-1.90)	0.794
Other employees	1.04 (0.51-2.12)	0.908	0.88 (0.49-1.57)	0.654
Unemployed	0.93 (0.47-1.86)	0.843	1.31 (0.74-2.32)	0.348
Marital status				
Never married	1.00		1.00	
Married	0.67 (0.38-1.16)	0.154	1.15 (0.74-1.79)	0.536
Divorced/Widowed	0.47 (0.24-0.94)	0.033	1.70 (0.97-2.99)	0.063
Education				
Illiterate	1.00		1.00	
Primary school	1.19 (0.66-2.16)	0.566	0.96 (0.56-1.64)	0.881
Secondary school	0.65 (0.35-1.22)	0.184	0.79 (0.44-1.41)	0.422
High school or equal	0.56 (0.26-1.18)	0.128	0.96 (0.50-1.86)	0.912
College/University	0.75 (0.27-2.03)	0.568	0.88 (0.36-2.11)	0.767
Transmission route				
Heterosexual	1.00		1.00	
Injection drugs	13.76 (8.61-22.00)	0.000	0.78 (0.52-1.16)	0.217
Plasma/blood donation or transfusion	12.87 (6.37-25.98)	0.000	0.36 (0.18-0.72)	0.004
Homosexual	0.004 (0.00-N.A)	0.565	0.38 (0.10-1.48)	0.161
Unidentified	2.06 (1.23-3.45)	0.006	1.20 (0.74-1.96)	0.461

* OR: odds ratio, adjusted for potential confounding effects of other variables listed in the table; ** 95% CI: 95% confidence interval.

HSV-2 among women is associated with the growing commercial sex industry (*19,22-24*). Since HSV-2 is the major cause of genital herpes and HSV-2 coinfection can significantly accelerate sexual transmission of HIV, female HIV patients, particularly those who become HIV-infected through heterosexual transmission, should be tested for HSV-2 and treated if infected.

The present study also identified an association between ethnicity and an HCV or HSV-2 coinfection in HIV/AIDS patients. Those of Uygur, Dai and especially Jingpo ethnicities were more likely than ethnic Han to have an HCV coinfection and those of Dai and Jingpo ethnicities were less likely than ethnic Han to have an HSV-2 coinfection. Compared with ethnic Hans, these minorities have a higher percentage infected with HIV through injection drug use but have a lower percentage infected with HIV through sexual transmission. These findings suggest that minority HIV patients are more likely to contract viral coinfections from needle sharing than from heterosexual contacts.

An important finding of this study is that a combined total of 71.8% of the study subjects were co-infected with at least three other viruses which put them at risk for developing other diseases and malignancies that could significantly reduce their level of general health. The results of the present study also suggest the need to look for coinfections with other viruses such as EBV and HSV-1 which further threat the immune response.

This study has certain limitations. First, the determination of viral coinfections was based on cross-sectional measurement of surface antigen for HBV and IgG antibody for HCV, EBV, HSV-1 and HSV-2 which only reflect historical exposure to the viruses. Thus,

it is difficult to determine the temporal relationship between infections with HIV and the other viruses, limiting our ability to draw causal inferences about these viral coinfections. Second, we only tested for coinfections with HBV, HCV, EBV, HSV-1, and HSV-2. Due to the unavailability of blood-based, type-specific commercial products for testing, we did not test for human papillomavirus (HPV) which is also prevalent in China and is the causal agent of invasive cervical cancer, an important AIDS-defining disease. Also, due to lack of qualified commercial products for testing, we did not test for human herpes virus type 8 (HHV8) which was first identified in 1994 and has been demonstrated to be prevalent in the Mediterranean region and the causal agent of Kaposi's Sarcoma (KS), another important AIDS-defining disease (*33-36*). This limited our ability to draw conclusions with regard to the spectrum of viral coinfections that are of most significance to Chinese HIV/AIDS patients. Third, we only included HIV patients visiting local CDC for follow-up within the specified two-week sample collection period in the study, which compromised the representativeness of the study sample.

In conclusion, this study has demonstrated that most Chinese HIV/AIDS patients are living with multiple pathogenic viruses that may play important roles in their disease progression, responses to antiretroviral treatment and general health. It is foreseeable that the incidence of HIV-related malignancies such as HCC, NHL, HL, and nasopharyngeal cancer in China will increase given the high prevalence of HCV and EBV coinfections among HIV/AIDS patients and their extended lifetime gained from the nationwide antiretroviral treatment campaign. Moreover, Chinese HIV/AIDS patients with different backgrounds in terms of HIV transmission route, residential geographic region, gender and ethnicity may have different profiles of viral coinfections and thus should be subject to differential considerations in designing public health and clinical care programs for both HIV and other co-infected pathogenic viruses.

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References

1. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA. 2002; 288:199-206.
2. Rossi SJ, Volberding PA, Wright TL. Does hepatitis C virus infection increase the risk of HIV disease progression? JAMA. 2002; 288:241-243.
3. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, Moschidis Z, Sypsa V, Zavitsanos X, Kalapothaki V, Hatzakis A. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: A cohort study and meta-analysis. Clin Infect Dis. 2009; 48:1763-1771.
4. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis. Clin Infect Dis. 2001; 33:562-569.
5. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: A meta-analysis. AIDS. 2008; 22:1979-1991.
6. Calistri A, Parolin C, Palù G. Herpes simplex virus type 1 can either suppress or enhance human immunodeficiency virus type 1 replication in CD4-positive T lymphocytes. J Med Virol. 2003; 70:163-170.
7. Kucera LS, Leake E, Iyer N, Raben D, Myrvik QN. Human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 2 (HSV-2) can coinfect and simultaneously replicate in the same human $CD4^+$ cell: Effect of coinfection on infectious HSV-2 and HIV-1 replication. AIDS Res Hum Retroviruses. 1990; 6:641-647.
8. Sheth PM, Sunderji S, Shin LY, Rebbapragada A, Huibner S, Kimani J, Macdonald KS, Ngugi E, Bwayo JJ, Moses S, Kovacs C, Loutfy M, Kaul R. Coinfection with herpes simplex virus type 2 is associated with reduced HIV-specific T cell responses and systemic immune activation. J Infect Dis. 2008; 197:1394-1401.
9. Sculley TB, Apolloni A, Hurren L, Moss DJ, Cooper DA. Coinfection with A- and B-type Epstein-Barr virus in human immunodeficiency virus-positive subjects. J Infect Dis. 1990; 162:643-648.
10. Engels EA, Biggar RJ, Marshall VA, Walters MA, Gamache CJ, Whitby D, Goedert JJ. Detection and quantification of Kaposi's sarcoma-associated herpesvirus to predict AIDS-associated Kaposi's sarcoma. AIDS. 2003; 17:1847-1851.
11. Omland LH, Weis N, Skinhøj P, Laursen A, Christensen PB, Nielsen HI, Møller A, Engsig F, Sørensen HT, Obel N. Impact of hepatitis B virus coinfection on response to highly active antiretroviral treatment and outcome in HIV-infected individuals: A nationwide cohort study. HIV Med. 2008; 9:300-306.
12. Santin M, Mestre M, Shaw E, Barbera MJ, Casanova A, Niubo J, Bolao F, Podzamczer D, Gudiol F. Impact of hepatitis C virus coinfection on immune restoration during successful antiretroviral therapy in chronic human immunodeficiency virus type 1 disease. Eur J Clin Microbiol Infect Dis. 2008; 27:65-73.
13. Weis N, Lindhardt BO, Kronborg G, Hansen AB, Laursen AL, Christensen PB, Nielsen H, Moller A, Sorensen HT, Obel N. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: A nationwide cohort study. Clin Infect Dis. 2006; 42:1481-1487.

14. Lu Y, Robinson M, Zhang FJ. Human immunodeficiency virus and hepatitis C virus co-infection: Epidemiology, natural history and the situation in China. Chin Med J (Engl). 2009; 122:93-97.
15. Garten RJ, Zhang J, Lai S, Liu W, Chen J, Yu XF. Coinfection with HIV and hepatitis C virus among injection drug users in southern China. Clin Infect Dis. 2005; 41 (Suppl 1):S18-S24.
16. Qian HZ, Vermund SH, Kaslow RA, Coffey CS, Chamot E, Yang Z, Qiao X, Zhang Y, Shi X, Jiang Y, Shao Y, Wang N. Co-infection with HIV and hepatitis C virus in former plasma/blood donors: Challenge for patient care in rural China. AIDS. 2006; 20:1429-1435.
17. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: A global review. J Infect Dis. 2002; 186 (Suppl 1):S3-S28.
18. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: A meta-analysis. J Infect Dis. 2002; 185:45-52.
19. Detels R, Wu Z, Rotheram MJ, Li L, Guan J, Yin Y, Liang G, Lee M, Hu L; The National Institute of Mental Health (NIMH) Collaborative HIV Prevention Trial Group. Sexually transmitted disease prevalence and characteristics of market vendors in eastern China. Sex Transm Dis. 2003; 30:803-808.
20. Chen XS, Yin YP, Chen LP, Yu YH, Wei WH, Thuy NT, Smith JS. Herpes simplex virus 2 infection in women attending an antenatal clinic in Fuzhou, China. Sex Transm Infect. 2007; 83:369-370.
21. He N, Cao HJ, Yin YP, Gao MY, Zhang T, Detels R. Herpes simplex virus-2 infection in male rural migrants in Shanghai, China. Int J STD AIDS. 2009; 20:112-114.
22. Chen XS, Yin YP, Liang GJ, Gong XD, Li HS, Poumerol G, Thuy N, Shi MQ, Yu YH. Sexually transmitted infections among female sex workers in Yunnan, China. AIDS Patient Care STDS. 2005; 19:853-860.
23. Wang H, Wang N, Chen RY, Sharp GB, Ma Y, Wang G, Ding G, Wu Z. Prevalence and predictors of herpes simplex virus type 2 infection among female sex workers in Yunnan Province, China. Int J STD AIDS. 2008; 19:635-659.
24. Ngo TD, Laeyendecker O, Li C, Tai H, Cui M, Lai S, Quinn TC. Herpes simplex virus type 2 infection among commercial sex workers in Kunming, Yunnan Province, China. Int J STD AIDS. 2008; 19:694-697.
25. Guiguet M, Boué F, Cadranel J, Lang JM, Rosenthal E, Costagliola D; Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): A prospective cohort study. Lancet Oncol. 2009; 10:1152-1159.
26. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. AIDS. 2008; 22:489-496.
27. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer. 2004; 4:757-768.
28. Liu YT. A serological study on anti-CMV and anti-EBV antibodies in population of Beijing, Changzhi Shanxi and Yichang Hubei. Zhonghua Liu Xing Bing Xue Za Zhi. 1989; 10:277-281. (in Chinese)
29. Li YY, Hidaka Y, Kino Y, Mori R. Seroepidemiology of herpes simplex virus type 1 in Yanji, Jilin, China. Microbiol Immunol. 1990; 34:551-555.
30. Dong Z, Li Y, Liu R. IgG and IgM antibodies of Herpes Simplex Virus type-1 and type-2 in 233 maternal and neonatal sera. Int J Gynaecol Obstet. 1998; 63:69-70.
31. Qu JB, Zhang ZW, Shimbo S, Watanabe T, Nakatsuka H, Matsuda-Inoguchi N, Higashikawa K, Ikeda M. Urban-rural comparison of HBV and HCV infection prevalence in eastern China. Biomed Environ Sci. 2000; 13:243-253.
32. Bao YP, Liu ZM. Systematic review of HIV and HCV infection among drug users in China. Int J STD AIDS. 2009; 20:399-405.
33. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994; 266:1865-1869.
34. Serraino D, Toma L, Andreoni M, Buttò S, Tchangmena O, Sarmati L, Monini P, Franceschi S, Ensoli B, Rezza G. A seroprevalence study of human herpesvirus type 8 (HHV8) in eastern and Central Africa and in the Mediterranean area. Eur J Epidemiol. 2001; 17:871-876.
35. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, Hatzioannou T, Suggett FE, Aldam DM, Denton AS, *et al*. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet. 1995; 346:799-802.
36. Min J, Katzenstein DA. Detection of Kaposi's sarcoma-associated herpesvirus in peripheral blood cells in human immunodeficiency virus infection: Association with Kaposi's sarcoma, CD4 cell count, and HIV RNA levels. AIDS Res Hum Retroviruses. 1999; 15:51-55.

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