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HIV transmission risk among serodiscordant couples: a retrospective study of former plasma donors in Henan, China

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Abstract

Objectives—To estimate the HIV incidence and assess the behavioral, clinical, and quality-of-life risk factors for HIV transmission among serodiscordant couples from Henan Province, China.

Methods—Between January 2006 and December 2008, initially seronegative spouses were tested for HIV at six month intervals. Retrospectively identified subjects were interviewed through face-to-face questionnaire. Cox proportional-hazards model was used to assess the relationship between risk factors and HIV seroconversion.

Results—Out of 1927 couples, 84 (4.3%) seroconversions occurred, representing a seroconversion rate of 1.71 per 100 person-years. Seroconversion rates increased over time. Not always using condoms (RR=8.42; 95% CI, 4.83–14.67), sexual activity ≥ 4 times per month (RR=5.24; 95% CI, 2.55–10.77), not switching anti-retroviral treatment regimen (RR=1.99; 95% CI, 0.85–4.65), and a quality of life score <12 on the psychological domain (RR=2.33; 95% CI, 1.21–4.48) were associated with increased risk of seroconversion. Seventy one percent of index spouses were on ART. There was no association between rate of HIV seroconversion and last recorded CD4 cell count level of the index spouse.

Conclusions—Effective HIV prevention interventions targeting discordant couples should focus on sustaining health education, increasing psychosocial support services, and increasing medication adherence monitoring.

Keywords

Serodiscordant couples; Prevention of sexual transmission; Antiretroviral therapy; Sexual behavior; Adherence; China

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INTRODUCTION

The transmission of HIV through heterosexual sex has been one of the primary drivers of the AIDS epidemic world-wide. In China, HIV transmission through heterosexual sex has surpassed that due to either injection drug use (IDU) or homosexual sex and has become the dominant mode of HIV transmission.¹⁻³ Serodiscordant couples, defined as couples in which one partner is HIV-positive and the other HIV-negative, have been used to study heterosexual transmission risk because of the high frequency of sexual acts that occur in stable relationships. Studies from mature epidemics in Sub-Saharan Africa have found that women living with HIV positive partners were 57.9 to 105.8 times more likely to seroconvert than those living in concordant-negative partnerships.⁴⁻⁵

While many studies attempting to quantify HIV incidence among discordant couples have been conducted globally, few have been conducted outside of Africa,⁶⁻⁹ and to our knowledge, none from China have been published in English. The only other Chinese study had a small sample size (22) and was conducted in Xinjiang province, where IDU is the main mode of transmission.¹⁰ According to census statistics, people living with HIV in Zhumadian city account for almost 1/3 of all HIV cases in Henan province. Most became infected through the sale of plasma between 1992 and 1995.¹¹⁻¹³ This cohort is different from those in other serodiscordant couple studies because they are older, live in rural communities, and have low rates of homosexual or extra-marital sex.¹³ In this study we describe the incidence rate, risk factors for HIV transmission, and quality of life indicators in a cohort of serodiscordant couples from Zhumadian City, Henan province.

METHODS

This cohort study followed HIV serodiscordant couples between January 1, 2006 and December 31, 2008 in Zhumadian city, Henan province, China. HIV discordant couples were retrospectively identified from the HIV-positive database administered by Zhumadian city's Center for Disease Control and Prevention (CDC). Local staff enrolled study participants at county hospitals, at community health centers, or at home residences using the following inclusion criteria: 1) HIV-negative living with a HIV-positive partner; 2) in a stable marriage (no separation or divorce); 3) participated voluntarily and provided informed consent.

Study participants had been receiving follow-up every 6 months for HIV testing at the local community health center or county hospital as part of Zhumadian CDC's routine screening programs. Blood specimens were transmitted to county level CDC laboratories and screened for HIV antibodies by enzyme linked immunosorbent assay (ELISA; Wantai, Beijing, China). Positive tests were confirmed by HIV-1 Western blot assay (WB, Wantai, Beijing, China) at Zhumadian city's CDC laboratories.

The primary outcome was HIV seroconversion. We defined seroconverter as an individual who had a negative HIV test before entering the cohort and subsequently had a positive HIV test during follow-up. Time of seroconversion was estimated as the midpoint between the last HIV negative test and the first HIV positive test. The last recorded CD4+ cell counts of index spouses were obtained from the China CDC national case reporting database.

A standardized questionnaire was administered in Chinese by trained local healthcare workers to initially HIV-negative spouses between October 2008 and May 2009. Survey questions included information on demographic characteristics, sexual activity, condom use, quality of life, STI history, as well as medical history of their HIV positive spouses. If subjects had seroconverted during follow-up, they were asked to report sexual behaviors in the month(s) prior to their first HIV positive test. Quality of life was measured by a Chinese

version of the brief World Health Organization Quality of Life instrument (WHOQOL-BREF). This instrument has been previously described and validated in patients with HIV.¹⁴ Our adapted survey consisted of 29 items, including one item each for general quality of life, health-related quality of life, marital conflict, appetite, self-evaluation, and 24 items belonging to four comprehensive domains (physical, psychological, social and environment). Scores for each domain ranged from 4 to 20, with higher scores indicating better functional status.

The study received approval from the institutional review board of the National Center for AIDS/STD Control & Prevention, China CDC. All participants were given pre-test and post-test counseling and HIV-positive subjects were referred to the Zhumadian CDC for free counseling and evaluation for treatment.

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Illinois, USA). Continuous variables were described using mean and standard deviation. Cox proportional-hazard modeling was used to assess the relationship between seroconversion and potential risk factors. Subjects that never seroconverted or were lost-to-follow-up in December 2008 were censored. Univariate Cox models were run to assess the unadjusted relationship between seroconversion and specified covariates of interest for all subjects. Survival time was defined as the time from baseline to when the initially HIV-negative spouse was confirmed positive or censored. Covariates with a p-value <0.10 from the univariate analysis were entered into a full multivariate Cox model with stepwise selection used to include significant covariates. All hypothesis testing was based on 2-sided tests with alpha level of 0.05.

RESULTS

Demographic Characteristics

According to data from the Zhumadian CDC's database of HIV-positive persons, there were 4348 HIV-negative spouses married to and living with HIV-positive partners in the city in 2006. By December 31, 2008, 238 more serodiscordant couples were identified. Of the 4,301 people who met the study's inclusion criteria, 1,927 (44.8%) completed the questionnaire. Baseline characteristics of study participants and non-participants were comparable in terms of age and sex. Of those who participated, 835 (43.3%) were women and 1092 (56.7%) were men. Their average age was 44.16 ± 7.69 years (range 30–69). One thousand and nineteen were of Han ethnicity (99.6%), 8 were Hui (0.4%). One thousand seven hundred and forty one (90.4%) were farmers, and 186 (9.7%) had other occupations.

HIV Seroconversions

Over 3 years, there were 84 seroconversions among 1,927 serodiscordant couples. The total follow-up time was 4918 person-years (median 2.84 years) and the incidence rate was 1.71 per 100 person-years. There was no statistical difference between the male and female seroconversion rates at 1.75 and 1.66 per 100 person-years, respectively ($p = 0.65$). On average female index cases (1078) were older than males (849) ($t = -6.7$ $p < 0.001$). Female index cases were also more likely to be on ART ($\chi^2 = 0.502$ $p = 0.025$). There was no difference in the mean last recorded CD4 between males and females ($t = 0.10$ $p = 0.93$) or in other variables such as AIDS diagnosis, frequency of sexual intercourse, or whether or not the index case had switched ART regimens. Figure 1 shows the cumulative and interval seroconversion rates expressed as a function of follow-up time. As length of follow-up increases, so does the interval seroconversion rate (Figure 1).

High Risk Behaviors

In the past 3 months, 1,611 (83.6%) reported having sexual intercourse. The reported mean frequency of intercourse was 3.5 times per month (range 1–9). Compared with those who did not seroconvert, those who seroconverted were more likely to have reported having sexual intercourse in the past 3 months (90.5% vs. 83.3%, $p < 0.05$). Seven hundred and thirty-five spouses who were HIV-negative at baseline reported having sex less than 4 times per month and 866 spouses reported having sex 4 times or more per month. Fifteen seroconversions occurred among couples who had less frequent sex (< 4 times per month) and 61 seroconversions occurred in couples who had more frequent sex (≥ 4 times per month). Spouses reporting more frequent sex were 5.13 times more likely to seroconvert than spouses reporting less frequent sex ($RR = 5.13$; 95% CI, 2.76–9.53) and this difference retained significance in multivariate analysis ($RR = 5.24$; 95% CI, 2.55–10.77) (Figure 2, A). Compared with couples who reported always used condoms (93.0%) during the past month, those who did not always use condoms (7.0%) had a 12.64 times higher risk of transmitting HIV in univariate analysis ($RR = 12.64$; 95% CI, 8.18–19.57). This risk remained significant in multivariate analysis ($RR = 8.42$; 95% CI, 4.83 – 14.67) (Figure 2, B). Spouses reported the following reasons for not always using condoms: 1) too expensive (43.8%), 2) not necessary (25.8%), 3) did not want to use (16.8%), 4) forgot (3.4%), or other (10.2%). Among the 54 (3%) HIV-negative spouses who reported having a STI symptom, 33 (61.1%) went to a hospital, 3 (6%) went to a private clinic, and 16 (29.6%) did not seek treatment. Only 7 people reported having extra-marital sexual relationships in the past year and only one of these seroconverted. One person reported a history of drug abuse and this individual did not seroconvert. None of the surveyed men reported ever having sex with another man.

Effect of ART and Last Recorded CD4 Count on Seroconversion Rate

There were 73 seroconversions among the 1,656 serodiscordant couples that had a spouse with a clinical diagnosis of AIDS. Among the 271 couples that had a HIV-positive spouse without AIDS, there were 11 seroconversions. There was no statistical difference between these seroconversion rates ($p = 0.79$). Most respondents (80.4%) had spouses who were on antiretroviral treatment.¹⁵ There was also no statistical difference in the seroconversion rates between those couples who had a spouse on ART (4.8%) and those couples whose HIV-positive spouse was not on ART (3.2%) ($p = 0.12$). Out of 1,369 individuals receiving ART, 266 had switched regimens and 1103 had never switched. Those on ART who had never switched regimens were significantly more likely to transmit HIV to their spouses than those who did ($RR = 2.66$; 95% CI, 1.15–6.15), but this difference was only marginally significant under multivariate analysis ($p = 0.11$) (Figure 2, C). Clinicians reported that most people switched regimens due to adverse side effects (97.4%) such as severe gastrointestinal symptoms (74/233, 31.8%), skin rash (20/233, 8.6%), anemia (13/233, 5.6%), abnormal liver function tests (11/233, 4.7%), and bone marrow suppression (9/233, 3.9%). Among other reasons for stopping or switching regimens: one voluntarily asked to stop treatment, two became pregnant, and three patients developed resistance.

There was no statistical difference in the median CD4 counts between those index cases who transmitted HIV to their spouses and those index partners who did not transmit HIV ($p = 0.78$). After stratification into three groups based upon last recorded CD4 count level (> 350 , 200–349, 0–199 cells/ μ L), the association remained non-significant (Table 1). Of the 883 patients who did not switch ART and had a recorded CD4 count, the overall transmission rate was 2.64 per 100 person-years. Out of 218 patients who had switched ART and had a CD4 count, the overall rate of transmission was 1.00 per 100-person years.

Quality of Life

HIV-negative spouses had a mean physical domain score of 12.99 ± 1.94 , psychological score of 12.42 ± 1.81 , social score of 13.88 ± 2.41 , and environmental score of 12.47 ± 1.89 . There were no statistical differences in the quality of life scores of those who seroconverted when compared to those who did not seroconvert. However, when divided into two subgroups, those who scored less than 12 points on physical and psychological domains had a significantly higher risk of seroconversion than those who scored 12 or more points (RR=1.67; 95% CI, 1.03–2.72 and RR=2.27; 95% CI, 1.46–3.54 respectively) (Figure 2, D). In multivariate analysis, this association remained significant for the psychological domain but not for the physical domain (Table 1).

DISCUSSIONS

Our study of 1927 HIV discordant couples in Zhumadian city, Henan province is the largest of its kind in China and found an incidence rate of 1.71 per 100 person-years. The only other study of discordant couples in China was conducted in Xinjiang province, but had a sample size of only 22.¹⁰ The incidence rate from our study is similar to the incidence rate of 2.3 per 100 person-years reported among a cohort of injecting drug users from a high prevalence region in southwestern China.¹⁶ This suggests that HIV-negative spouses living in discordant relationships in Zhumadian could be considered one of China's high-risk groups.

The overall seroconversion rate also showed an increasing upward trend as the duration of follow-up lengthened. There are several possibilities for why this occurred. First, chronically-HIV infected patients may undergo immunologic failure, virologic failure, advance to later stages of disease, or acquire resistance, leading to higher rates of transmission over time.^{15, 17–19} Second, couples may engage in riskier behaviors such as increasing the frequency of sex or reducing the percentage of condom use, as knowledge and awareness of self-protection gradually declines.^{20, 21} Third, a desire to have children may be influencing the risk taking behaviors among these couples.⁷ Our findings highlight the importance of strengthening comprehensive HIV prevention interventions such as health education, condom promotion, STI treatment, and psycho-social care and support services.

Our study found no statistical difference between the male-to-female transmission and female-to-male transmission rates. These results are consistent with several other studies of discordant couples from Brazil, Haiti, Tanzania, Rwanda, Uganda, and India.^{4, 7–9, 22} It is unclear whether the higher rate of female-to-male transmission (1.75/100py) is a result of a chance or some other unmeasured biological or behavioral characteristic. Although the literature has been inconclusive, one large prospective study from Masaka region Uganda attributed the age-adjusted RR for infection for women of 2.2 (95% CI 0.9 – 5.4) to extra-marital sexual behavior among men and increased biological susceptibility in the female genital tract.⁵ However, in Henan province, the majority of those infected are non-migrant farmers with low rates of STIs, IDU, or extra-marital sex. In our cohort, only 7 out of 1,927 interviewed reported ever engaging in sex outside of marriage. Thus, in this cultural context, it is reasonable to assume that behavioral factors which influence higher HIV transmission in some parts of Africa are different than those of China.²³ Male circumcision was not analyzed as a factor in this study because the prevalence of circumcision is extremely low among ethnic Han Chinese.

As with other studies, we found not always using condoms and a higher frequency of sexual activity to be associated with increased risk of HIV transmission.^{7, 24, 25} Having sex within the past 3 months and extra-marital sex were not statistically significant associations.

Our study also found that ART use in the HIV-positive spouse was associated with a decreased risk of seroconversion, but this result was not statistically significant (RR= 1.32; 95% CI, 0.78–2.22). A meta-analysis of serodiscordant couples studies found that ART reduced heterosexual transmission rates from 5.64 to 0.46 per 100 person-years.²⁶ This suggests that our study may have been subject to misclassification as those who were labeled as on ART may have been non-adherent to treatment. One study of drug resistant HIV-1 variants in Henan found that 66% of patients had low adherence after 6 months of therapy.²⁷ Another possibility is that patients were adherent to ART, but were on regimens that had become suboptimal or acquired drug resistance. This is supported from data from a recently published study which reported immunologic failure rates of 50% by year 5 among patients enrolled in China's free national antiretroviral treatment program, most likely due to the lack of readily available second-line drugs.¹⁸

Furthermore, our data indicates that those who did not switch treatment regimens were more likely to transmit HIV (RR 2.66, 95% CI 1.15–6.15). Although this value became non-significant in multivariate analysis (most likely due to small sample size in those who had switched ART regimens), the data suggests that remaining on an originally prescribed ART regimen may have a detrimental effect on population-level heterosexual transmission dynamics in China because a large proportion of patients may be on ineffective treatment regimens.

As in other studies, we did not find CD4 cell levels to be associated with an increased rate of seroconversion.^{28, 29} Although viral load has been more directly correlated with rate of transmission, we were unable to obtain viral load data from these rural areas because of problems with physical infrastructure and human resource capacity.^{2, 30} The stage of disease has been associated with increased risk of transmission, but we did not find that an association between lower CD4 levels and with higher rates of seroconversion.^{31, 32} One explanation may be that the spouses with late-stage disease in this cohort may have had less frequent sex or used condoms more than those spouses in latency. Our data provides some support to the hypothesis that partners with late-stage disease may have less contribution to the HIV epidemic than early-stage partners or those who are acutely infected and do not know their status.³²

One of the primary limitations of our study is that we were unable to obtain adherence data from those on ART because almost all patients received treatment from local community healthcare centers. Unfortunately, these centers did not reliably track adherence data. To address this limitation, future studies in this cohort will incorporate more detailed questions on drug adherence and attempt to better quantify drug resistance. While the lack of adherence or viral load data is problematic, it reflects real-world challenges associated with ART roll-out in resource-limited settings.³³ Our findings suggest that ART treatment with first line drugs alone may not be sufficient to reduce HIV transmission among discordant couples in China. Another limitation of this study is that our data may be subject to recall bias because some subjects were surveyed at the end of the enrollment period and asked to recall behavior from the month(s) preceding their date of seroconversion. Self-reporting bias may also have resulted in the under-reporting of unprotected sex.³⁴

On quality of life, we found that those who scored lower in the psychological, but not physical, social, or environmental domains was significantly associated with HIV seroconversion (RR=2.33; 95% CI, 1.21–4.48). While the link between HIV transmission and indicators of psychological well-being is not well understood, the WHO quality of life assessment has been previously validated in patients with HIV.¹⁴ A study conducted in Moscow among Tajik migrant workers found that lack of social support and feeling unprotected by law may reduce self efficacy and self-protective behaviors.³⁵ Thus, it is

possible that initially HIV-negative spouses who had lower scores on the psychological domain may be engaging in more risky behaviors, such as having unprotected sex. Our results suggest that psychological assessments may serve as novel indicators of HIV transmission among serodiscordant couples and that interventions aimed at improving quality of life and reducing psychological distress may reduce this risk in China.³⁶ However, more research on the type and effectiveness of these interventions as well as on the appropriateness of the survey instrument is needed for HIV discordant families in China.

Our study found a relatively low rate of HIV transmission among serodiscordant couples in Henan but the rate increased over time. We also found that not always using condoms, more frequent sex, not switching ART regimens, and a lower quality of life score on psychological domains were associated with increased risk of transmission. While adherence to treatment probably played an important factor, ART use and last recorded CD4 count were not found to be associated with HIV transmission. Our study suggests that the use of blanket ART programs alone may not necessarily reduce transmission among rural serodiscordant couples in China. To be most effective, treatment programs in these areas should be combined with HIV prevention interventions that emphasize always using condoms, less frequent sex, switching to more effective ART regimens, and care and support services for those affected by AIDS.

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Figure 1.
Cumulative and interval incidence rate of seroconversion by duration of follow-up.

Figure 2.

Survival Analysis

Cumulative Survival indicates the proportion of people who have not seroconverted. A. Life table survival stratified by frequency of sex in the past month. B. Life table survival stratified by consistency of condom use. C. Life table survival stratified by whether subjects' HIV positive spouse had switched ART regimens. D. Life table survival stratified by quality-of-life score in the psychological domain.

Table 1

Comparison of risk factors associated with HIV seroconversion among 1927 initially HIV-negative spouses in Zhumadian city

Characteristic of the initially HIV-negative partner	Did not seroconvert	Seroconverted	Univariate RR (95% CI)	Multivariate RR (95% CI)
Demographic characteristics				
Sex				
Male	1043	49	0.91(0.59–1.41)	
Female	800	35	1.00	
Age (years)				
<45	1132	45	1.00	
≥ 45	711	39	1.26(0.82–1.94)	
High-risk behaviors				
Sexual Intercourse in past 3 months				
Yes	1535	76	1.90(0.91–3.93)	
No	308	8	1.00	
Frequency of sex in past month				
<4	720	15	1.00	1.00
≥4	805	61	5.13(2.76–9.53)	5.24(2.55–10.77)
Always used condoms in the past month				
Yes	1460	42	1.00	1.00
No	75	34	12.64(8.18–19.57)	8.42(4.83–14.67)
Extra-marital sex				
Yes	6	1	3.22(0.45–23.14)	
No	1828	83	1.00	
No Response	9	0		
Medical history of index spouses				
AIDS diagnosis among those with HIV infection				
Yes	1583	73	1.00(0.53–1.89)	
No	260	11	1.00	
ART				
Yes	1303	66	1.32(0.78–2.22)	
No	540	18	1.00	
Switched ART regimen				
Yes	260	6	1.00	1.00
No	1043	60	2.66(1.15–6.15)	1.99(0.85–4.65)
Last recorded CD4 of index spouse (cells/μL)				
0–199	17	416	1.00	
200–349	21	421	1.20(0.64–2.28)	
≥350	36	639	1.39(0.78–2.48)	
Quality of Life Score (points)				
Physical domain				
<12	357	22	1.67(1.03–2.72)	0.95(0.47–1.94)

Characteristic of the initially HIV-negative partner	Did not seroconvert	Seroconverted	Univariate RR (95% CI)	Multivariate RR (95% CI)
≥12	1486	62	1.00	1.00
Psychological domain				
<12	447	32	2.27(1.46–3.54)	2.33(1.21–4.48)
≥12	1396	52	1.00	1.00
Social domain				
<12	202	12	1.72(0.93–3.17)	
≥12	1641	72	1.00	
Environment domain				
<12	490	27	1.58(0.997–2.50)	
≥12	1353	57	1.00	