Population HIV transmission risk for serodiscordant couples in Guangxi, Southern China

A cohort study

Zhigang Zheng, MPH[a],[*], Yong Li, MD[b], Yi Jiang, MBS[c], Xu Liang, MBS[d], Shanfang Qin, MD[b], Eric J. Nehl, PhD[e]

Abstract

We evaluated the risk of human immunodeficiency virus (HIV) transmission among serodiscordant couples with low adherence to antiretroviral therapy (ART).

Data of heterosexual couples/partners in 2010 were extracted from an Internet-based system. Participants were then followed over the course of a year with 6- and 12-month assessments. Prevalence and density of HIV seroconversion were calculated for spouses/partners who did not have a positive HIV test results at baseline. We calculated the transmission odds ratio (OR) value stratified by personal characteristics and behavioral correlates at 6- and 12-month follow-up, as well as seroconversion in spouses/partners over the year.

A total of 5544 HIV/AIDS patients and their spouses/partners were recruited in this cohort. Incidence of HIV seroconversion among HIV-negative spouse/partner was 63.7/100 person years (PYs) (430/674.9) at the 6-month follow-up and 33.2/100PYs (567/1707.1PYs) at 12 months. The OR value of transmission from female to male was 2.1 times higher than from male to females at 6 months and 2.3 times higher at 12 months ($P < .001$). The 55- to 64-year age group was most likely to transmit HIV to their spouses/partners, 2.2 times greater than the participants who were 65 years and older. Married participants were 2.4 times higher at 6 months and 2.5 times higher at 12 months to transmit HIV than divorced/widowed participants. Lastly, transmission among illiterate participants was 6.7 times higher at 6 months and 2.3 times higher at 12 months than those with an educational attainment of community college or above.

High HIV seroconversion was observed in this cohort. Spouses/partners who were male had the highest risk of HIV acquisition; those aged 55 to 64 years, having married status, and are HIV-positive with less education were more likely to transmit HIV.

Abbreviations: 95% CI = 95% confidence interval, ART = antiretroviral therapy, HIV = human immunodeficiency virus, IQR = interquartile range, M = median, OR = odds ratio, PYs = person years, WHO = World Health Organization.

Keywords: HIV, serodiscordant couples, transmission risk

[a] Department of HIV/AIDS Program, Guangxi Zhuang Autonomous Center for Disease Control and Prevention, Nanning, [b] HIV/AIDS Treatment Center, Long Tan Hospital, Liuzhou, [c] Department of HIV/AIDS Program, Wuzhou Center for Disease Control and Prevention, Wuzhou, [d] Department of HIV/AIDS Program, Baise Center for Disease Control and Prevention, Baise, China, [e] Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, GA.

[*] Correspondence: Zhigang Zheng, Department of HIV/AIDS Program, Guangxi Zhuang Autonomous Center for Disease Control and Prevention, Nanning, China (e-mail: tinygang@hotmail.com).

1. Introduction

A number of studies in developing countries have demonstrated that HIV transmission between serodiscordant couples/partners is a major contributor to new HIV infections, especially in the countries of Sub-Saharan Africa.[1–3] This is concerning as nearly half of HIV-positive individuals in East and Southern Africa have reported being in HIV serodiscordant relationships.[4] For instance, among married couples/partners in the general population in rural Uganda, 5% to 7% were estimated to be HIV serodiscordant.[2,5] HIV transmission rates within serodiscordant couples/partners are typically high, ranging from 3.7 to 19.0 per 100 person years (PYs) at risk.[2,6–11] In China, a meta-analysis reported the overall HIV seroconversion rate among serodiscordant couples in China to be 1.2 per 100 PYs.[12] Previous research in Guangxi Province has demonstrated that the HIV seroconversion rate among serodiscordant couples was 2.5 per 100 PYs,[13] about 2 times higher than the result of the meta-analysis in China, but much lower than the results of the African countries listed above.

Guangxi is a province in Southern China that bears a high disease burden caused by HIV/AIDS. It is a mountainous

province with a large population of ethnic minorities and is bordered by Guangdong province to the east, Yunnan province to the west, Vietnam, and the Gulf of Tonkin to the South. As one of the less developed and more rural provinces in China with the major industry being farming, medical infrastructure and access to care continue to be challenges and result in health disparities between this province and other areas of China. Currently >110,000 people in Guangxi are registered to be living with HIV and >63,000 patients have been treated. As of December 31, 2016, Guangxi was ranked third among all the provinces of China with a general population HIV prevalence rate of 1.30 per 1000. Additionally, compared with the 35.5% of patients presenting late with HIV/AIDS in China, the percentage presenting late in Guangxi has been >51% of total registrations,[14] ranking the province second among the 31 provinces in China. This has been a high public health priority issue in Guangxi, as those with HIV/AIDS who present to care later have worse health outcomes and a higher possibility to spread HIV to others, including their spouses/partners.[15]

Guangxi is also unique in China because the route of transmission is most likely to be reported as heterosexual sexual behavior.[16] Among those who registered in 2016, >92% reported that they were infected by heterosexual sexual transmission, making Guangxi the highest for this reported route of transmission in China. Therefore, the aim of this study was to calculate the incident rate of HIV among serodiscordant couples/partners using data from a cohort of HIV/AIDS patients in Guangxi, and to estimate the population risk of HIV seroconversion among serodiscordant spouses/partners in China. Our findings will provide the HIV incidence rate among serodiscordant spouses/partners and add to the literature of HIV seroconversion in areas where HIV transmission from heterosexual contact is >90%.

2. Methods

2.1. Participants

Participants in this study were registered in an observational cohort in 2010. We collected their spouse/partner information purposely 6 and 12 months from the baseline. To be eligible for the study, participants must have: been 15 years old and above; had a spouse/partner newly registered as HIV positive; not have a positive test for HIV at baseline themselves; and been married, divorced, currently single but married before, or a separated spouse to the newly registered HIV positive spouse/partner. Clinical review for both the patient and their spouse/partner was required every 6 months and blood was sampled to test for HIV antibody and CD4 count simultaneously.

Participants were excluded if: they reported being from Hong Kong, Macaw, other nations, or did not report a permanent address; their spouse/partner tested HIV positive at baseline; their spouse/partner was reported to be dead at baseline; and they reported being single at baseline.

2.2. Data collection

Data were extracted from a HIV serodiscordant couples observation cohort of those who registered from January 1st to December 31, 2010. Standard follow-up information was recorded by program staff and included identification number, spouse/partner HIV testing status, use of antiretroviral therapy (ART), time of follow-up, CD4 cell count, and World Health

Organization (WHO) clinical disease stage. Household information such as demographic characteristics, socioeconomic, and health status were collected at the baseline and follow-ups, and blood samples for HIV testing were collected at all 3 time points. Laboratory testing of blood samples followed the national HIV laboratory testing operational guidelines. A 6-month follow-up period was used during the course of a year. Spouse/partner information and HIV testing were collected during both of these follow-up activities. If a participant was lost to follow-up (3 months' absence from a clinic since last visit), a site visit of the participant's address was conducted by clinic staff to confirm their absence or death, with information collected at the site visit including the date of the last visit to the clinic or date of death. For participants who were missing or reported to have died in the observational period, the date of absence or death was considered the endpoint of the observation.

Written consent for the study was signed by the participants before the initial HIV confirmation testing; spouse/partner' HIV testing and follow-up were included as part of the consent process. To protect participant confidentiality, all data were de-identified by removing names, identification numbers, addresses, and other private information. All analyses were performed using this de-identified dataset.

2.3. Response variable imputation

In this analysis, the dependent variable was "spouse/partner HIV testing status". In certain cases, testing status was missing even though the contact history notes indicated that the participant had a HIV positive spouse/partner, or the participant's "sample source" was from the positive spouse/partner testing. Imputation method has presented a rise trend in medical research recently.[17] Under this circumstance, testing status was imputed as "positive" following the criteria: the "contact history," "notes," or "sample source" noted that the spouse/partner HIV testing result to be positive; the spouse had a HIV-positive card registered "no" in the dataset; previous spouse/partner was HIV-positive (she/he died or was separated) and current spouse/partner was HIV-negative; or spouse/partner was HIV-negative but partner was positive, or spouse/partner was positive but partner was negative.

2.4. Statistical analysis

We used R software (version 3.2.2, R Foundation for statistical Computing, Vienna, Austria) for analysis. Data were stratified and analyzed by sex, age group, ART use, education, and marital status. PYs of follow-up, prevalence of HIV seroconversion based on testing results, and seroconversion density were calculated. Transmission odds ratios (ORs) values were estimated with the Mantel-Haenszel Estimation method, with results compared using χ^2 tests. Finally, HIV transmission risk was estimated for each stratification variable to understand the degree of the HIV transmission risk.

2.5. Calculation of PY of follow-up

We calculated the PYs from baseline to 6 months and from 7 to 12 months separately, and then summed these values for total PYs in the first-year follow-up. The end-point of the study was set to the end of the 12th month with the exception of when a participant was lost to death or was missing. For participants who were missing from baseline to 6 months, but reported for testing in the 7- to 12-month period, the days considered PYs

from baseline to 6 months were imputed to be zero, and follow-up days from 7 to 12 months were considered to be from the first day of 7 months to the end of the year.

3. Results

As can be seen in Table 1, 5544 participants were recruited in the present study, 2731.85 PYs were provided for the cohort in the first-year follow-up period (median [M]: 0.55 PYs, interquartile range [IQR]: 0.29, 0.80). Among them, 659.84 PYs of follow-up were provided for those with HIV/AIDS who had a HIV-tested spouse (M: 0.61 PYs, IQR: 0.35, 0.82); 2072.02 PYs of follow-up were provided for those with HIV/AIDS who had a HIV testing-naïve spouse/partner (M: 0.53 PYs, IQR: 0.28, 0.79). Across age groups, although more HIV/AIDS cases were concentrated from the first quartile to third quartile of PYs at follow-up, the median of PYs of follow-up declined steadily (Fig. 1). Among this cohort, 4095 (73.86%) were males; the 25- to 34- and 35- to 44-year age groups were the majority, 61.81% reported that they were farmers; 87.77% indicated that their educational attainment was

Table 1

Baseline characteristics of HIV patients with serodiscordant spouses/partners.

	All patients, N (%)	Ever tested spouse, N (%)	Testing naïve spouse, N (%)
Total case	5544 (100)	1207 (21.77)	4337 (78.23)
Follow-up year			
Total PY	2731.85	659.84	2072.02
Median (IQR)	0.55 (0.30, 0.80)	0.61 (0.35, 0.82)	0.53 (0.28, 0.79)
Age, y			
15–24	351 (6.33)	134 (11.10)	217 (5.00)
25–34	1398 (25.22)	403 (33.39)	995 (22.94)
35–44	1237 (22.31)	256 (21.21)	981 (22.62)
45–54	774 (13.96)	138 (11.43)	636 (14.66)
55–64	852 (15.37)	136 (11.27)	716 (16.51)
65	927 (16.72)	140 (11.60)	787 (18.15)
Unknown	5 (0.09)	0 (0.00)	5 (0.12)
Sex			
Male	4095 (73.86)	866 (71.75)	3229 (74.45)
Female	1449 (26.14)	341 (28.25)	1108 (25.55)
Ethnics			
Han	3679 (66.36)	726 (60.15)	2953 (68.09)
Zhuang	1644 (29.65)	428 (35.46)	1216 (28.04)
Yao	114 (2.06)	28 (2.32)	86 (1.98)
Others	107 (1.93)	25 (2.07)	82 (1.89)
Occupation			
Farmer	3427 (61.81)	767 (63.55)	2660 (61.33)
Housekeeping	668 (12.05)	134 (11.10)	534 (12.31)
Worker	242 (4.37)	57 (4.72)	185 (4.27)
Government employee	423 (7.63)	83 (6.88)	340 (7.84)
Farmer worker	192 (3.46)	52 (4.31)	140 (3.23)
Business service	135 (2.44)	32 (2.65)	103 (2.37)
Others	457 (8.24)	82 (6.79)	375 (8.65)
Education			
Illiterate	241 (4.35)	39 (3.23)	202 (4.66)
Elementary School	2179 (39.30)	411 (39.57)	1768 (40.77)
Junior High School	2446 (44.12)	587 (48.63)	1859 (42.86)
High School	539 (9.72)	138 (11.43)	401 (9.25)
Community College and Above	135 (2.44)	32 (2.65)	103 (2.37)
Missing	4 (0.07)	0 (0.00)	4 (0.09)
Reported Infection route			
Heterosexual sex	4816 (86.87)	1104 (91.47)	3712 (85.59)
Homosexual sex	54 (0.97)	6 (0.50)	48 (1.11)
IDU	467 (8.42)	69 (5.72)	398 (9.18)
Heterosexual sex and IDU	49 (0.88)	8 (0.66)	41 (0.95)
Other	158 (2.85)	17 (1.41)	138 (3.18)
CD4 cell count, cell/μL			
≤50	179 (3.23)	33 (2.73)	146 (3.37)
51–150	544 (9.81)	123 (10.19)	421 (9.71)
151–250	484 (8.73)	124 (10.27)	360 (8.30)
251–350	446 (8.04)	109 (9.03)	337 (7.77)
351–500	468 (8.44)	134 (11.10)	334 (7.70)
>500	334 (6.02)	109 (9.03)	225 (5.19)
Missing	3084 (55.72)	575 (47.64)	2514 (57.97)

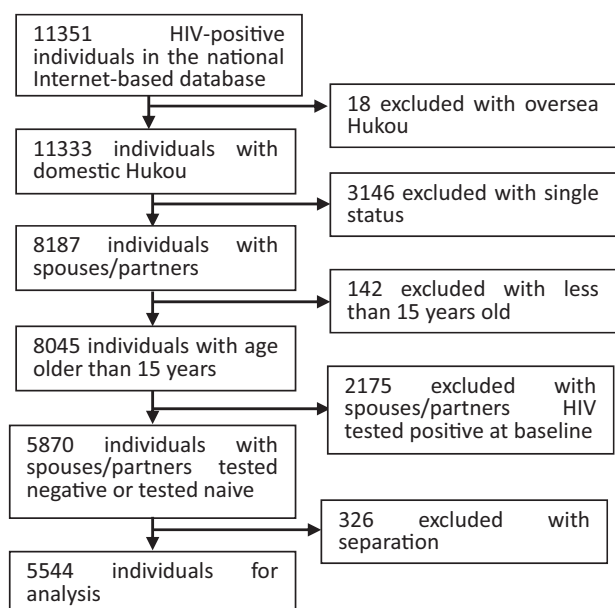IDU = injection drug use, IQR = interquartile range, PY = person-year.

Figure 1. Study flow diagram.

junior high school or below (with junior high school being 44.12%, with elementary school being 39.30%, and illiteracy being 4.35%).

Among spouse/partners at baseline, 48.9% reported that they had ever been tested for HIV and 51.1% tested naïve. Among spouse/partner who had ever tested, the percentage of HIV seroconversion was 23.4% in 6 months and 21.2% at 12 months; with incidence being 63.71/100 PYs (430/674.94) in 6 months and 33.2/100 PYs (567/1707.12 PYs) in 12 months.

As can be seen in Table 2, ORs were calculated to understand risk factors for HIV seroconversion. Compared with males in this cohort, the risk of HIV acquisition was higher among female partners, the OR value was 2.09 (95% confidence interval [CI]: 1.67, 2.63) times higher for females at the 6-month follow-up ($P < 0.0001$). Higher risk for HIV acquisition was observed in the 55- to 64-year age group population with an OR value 2.23 (95% CI: 1.87, 2.66), married HIV individual with 2.45 (95% CI: 1.30, 4.63), and illiterate HIV/AIDS with 6.66 (95% CI: 2.31, 19.24). Compared with those who were taking ART, the OR value in ART-naïve group was 1.14 (95% CI: 0.91, 1.43), there was no significant difference between ART and ART-naïve group. Except for education, the observational results at the 12-month follow-up were consistent with the results of 6-month follow-up including increased risk among females, the 55- to 64-year age group, and for those who were married (Table 2, Figs. 2–4).

4. Discussion

The aim of this study was to estimate the incident rate of HIV among serodiscordant couples/partners using data from a cohort of HIV/AIDS patients in Guangxi. Results from this study indicate that Guangxi has a high rate of HIV seroconversion among serodiscordant spouses/partners after 1 year of follow-up. Additionally, the risk of transmission from female to male spouse/partners was approximately 2 times higher than from male to females, results which are consistent with the findings in the HPTN052 trial.[24] Those in the 55- to 64-year age group, who were married, and who had less education had the highest HIV transmission risk during the first 6 months of the study, and these findings were consistent across the year. Unfortunately, the potentially positive impact of ART to reduce HIV transmission between serodiscordant spouse/partner was not observed in this

Table 2

Seroconversion in HIV serodiscordant couples and odds ratio for testing within 1 year's follow-up.

Patient characteristic	Spouse seroconversion 6-month follow-up				Spouse seroconversion 12 month follow-up			
	No. (%)	OR	95% CI	P	No. (%)	OR	95% CI	P
Sex				<0.0001				<0.0001
Male	254 (19.4)	Ref.			330 (8.1)	Ref.		
Female	176 (33.5)	2.09	(1.67, 2.63)		237 (16.4)	2.23	(1.87, 2.67)	
Age group, y				<0.0001				<0.0001
15–24	28 (20.0)	0.94	(0.61, 1.45)		33 (9.4)	0.36	(0.13, 0.97)	
25–34	108 (20.0)	0.94	(0.77, 1.15)		144 (10.3)	0.64	(0.37, 1.13)	
35–44	89 (21.8)	1.05	0.86, 1.27)		116 (9.4)	0.59	(0.33, 1.07)	
45–54	63 (22.7)	1.10	(0.90, 1.34)		79 (10.2)	0.56	(0.28, 1.09)	
55–64	98 (37.3)	2.23	(1.87, 2.66)		129 (15.1)	1.42	(0.79, 2.55)	
65-	44 (21.1)	Ref.			66 (7.1)	Ref.		
ART				0.25				<0.0001
Yes	278 (24.3)	Ref.			295 (16.1)	Ref.		
No	152 (22.0)	1.14	(0.91, 1.43)		272 (9.1)	0.50	(0.42, 0.60)	
Marital Status				0.005				<0.0001
Married	419 (24.1)	2.45	(1.30, 4.63)		546 (10.7)	2.52	(1.16, 3.94)	
Divorced/widowed	11 (11.5)	Ref.			21 (4.6)	Ref.		
Education				0.001				0.39
Illiterate	22 (38.6)	6.66	(2.31, 19.25)		30 (12.4)	2.34	(0.58, 9.50)	
Elementary School	170 (26.3)	3.78	(1.49, 9.61)		224 (10.3)	1.45	(0.43, 4.86)	
Junior High School	195 (22.0)	2.99	(1.90, 5.55)		249 (10.2)	0.93	(0.28, 3.13)	
High School	38 (20.1)	2.67	(1.00, 7.13)		56 (10.4)	1.28	(0.36, 4.61)	
Community College and Above	5 (8.6)	Ref.			8 (5.9)	Ref.		

ART = antiretroviral therapy, CI = confidential interval, No. = number, OR = odds ratio.
Brief summary of tables: Male had the highest risk of HIV acquisition; those aged 55 to 64, married status, less education had the higher risk of HIV transmission; ART against HIV transmission was not observed.
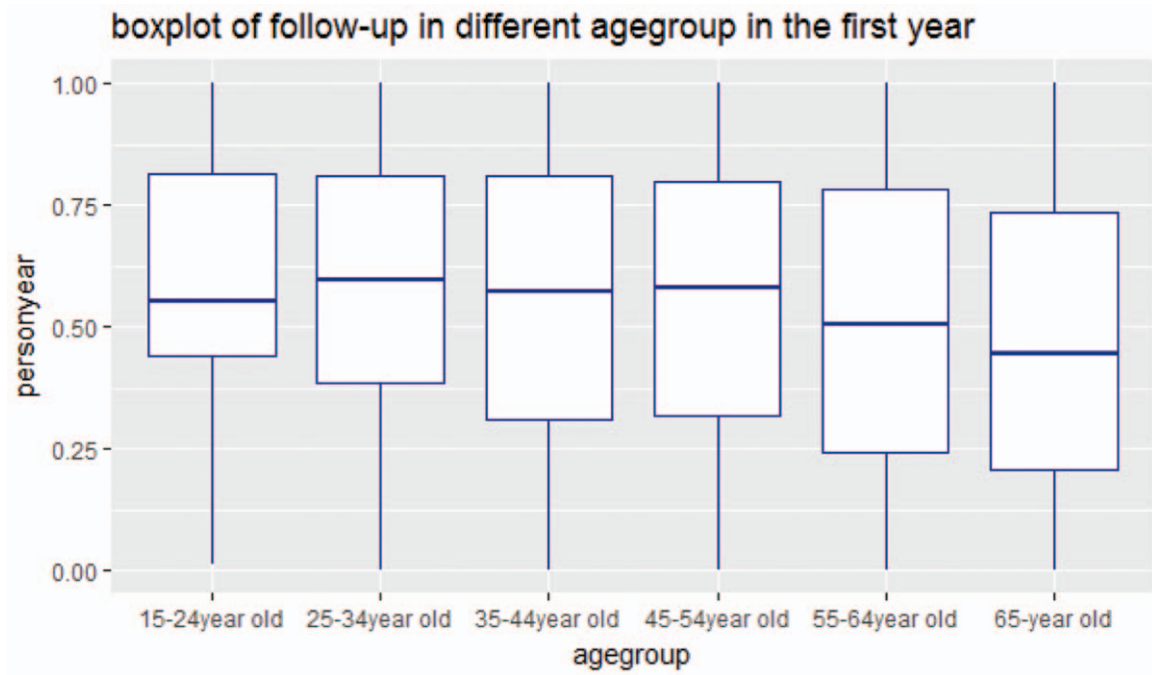
Figure 2. From young to old age groups, the concentrated trend of follow-up has been increased (the length of the box became longer), but the median, the first, and the third point of quartile of follow-up declined steadily. It illustrated that follow-up has been given in the early stage over age groups.

study. It is likely that this finding is a result of low coverage or use of ART in this sample. Similar results have been observed in rural South Africa among HIV-infected people.[25]

Our results provide insight into seroconversion among HIV serodiscordant spouses/partners. This study indicates a much higher seroconversion rate than the results of a previous Meta-analysis in China [12] and previous studies.[13,18] We consider the differences possibly to be related to features of the present study. First, this study used imputation to address missing and inconsistent data and this may have influenced the results.
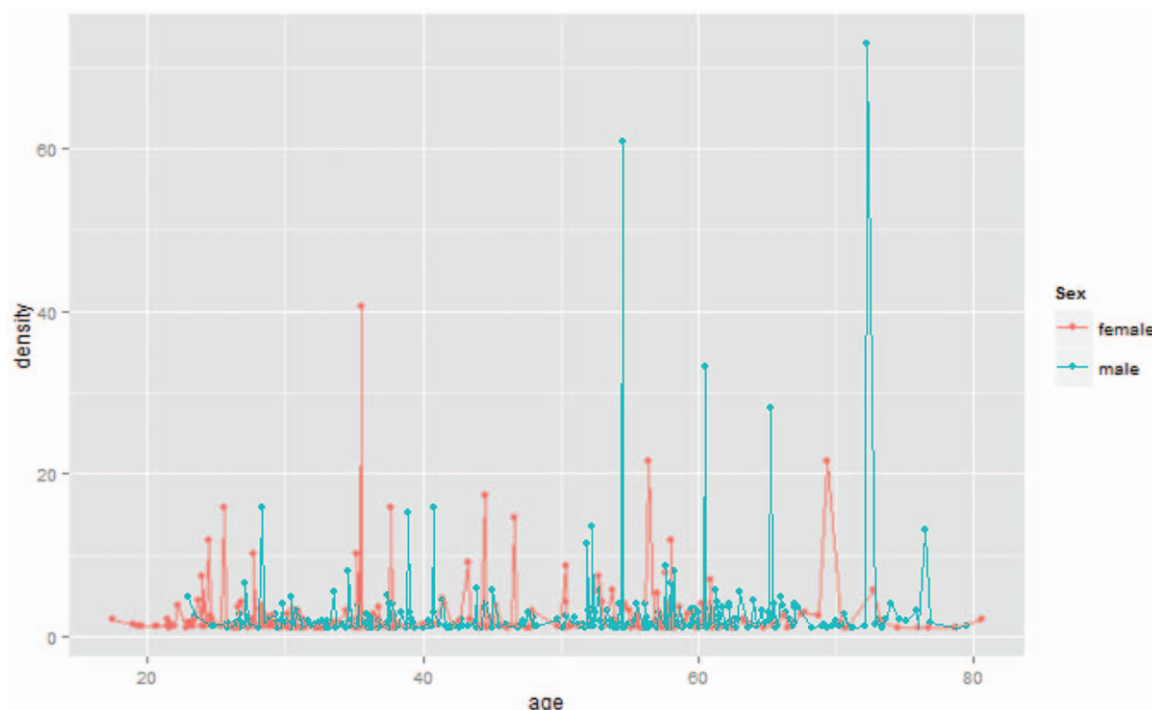
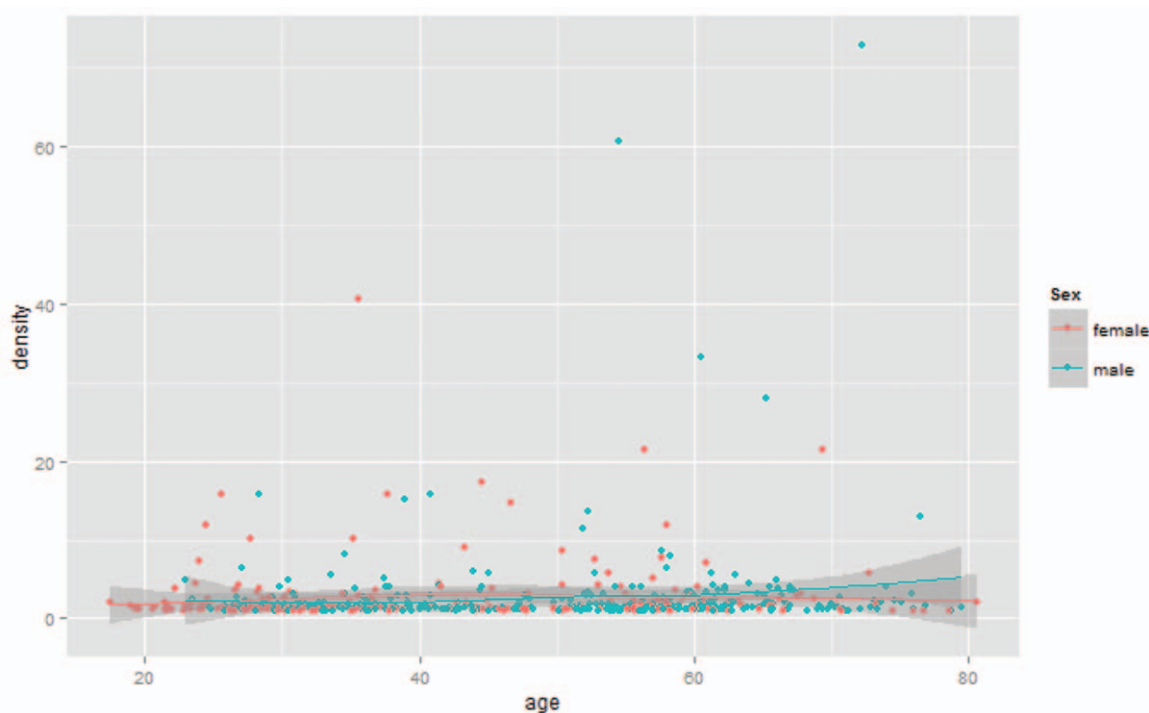**Figure 3.** HIV Seroconversion density by sex and age.

Figure 4. HIV Seroconversion density by sex and age.

However, a standard imputation method was used to impute spouse/partner HIV testing status to adjust for possible reporting bias.[19,20] Second, as compared with other studies, this study included different participant recruitment criteria. The participants of our cohort included any spouse/partner who had not died or did not have a HIV positive test result at baseline. Other studies typically recruit participants whose spouses/partners have negative HIV tests at baseline, ruling out the HIV test naïve individuals which might have a high possibility of HIV seroconversion within the observational period. Third, other studies indicate that those with HIV/AIDS who present for treatment later have a higher possibility of transmitting HIV.[15] Guangxi is ranked second among the 31 provinces in China.[14] Although it did not assess late presentation, the current high seroconversion rate may be a result of the local context of access and use of HIV testing services.

This study also indicated that the risk of HIV transmission of females was 2 times higher than of males. Similar results have been observed in rural Uganda and in the HPTN 052 trial.[1] The following reasons may explain the result. First, Guangxi is rural area with high levels of poverty in Southern China and females from villages often migrate to larger cities; it is not uncommon for these women to participate in commercial sex. HIV prevalence in female sex workers is high and transmission between sex workers and their clients is a major public health concern.[21,28] Second, HIV prevalence in female sex workers in Guangxi was high.[28] When they return home, we observed transmission from female to male. Based on results of this study, we know that males in this study tended to be older when diagnosed with HIV, with the median age being 51.4 years among males and 38.1 years among females. This may likely reflect the fact that HIV/AIDS is typically diagnosed late in Guangxi. In this cohort, the largest age group for seroconversion among females was 25 to 34 years, whereas in

male was 55 to 64 years. This difference may be attributed to differences in use of medical care, with women in childbearing years visiting clinics more frequently at younger ages. Additionally, the high rate of HIV infection among older participants in this study is of great concern because of the possibility for more rapid disease progression, high mobility, and high mortality in this population.[22] For example, the 55- to 64-year male age group suffered the highest disease burden in this cohort. The reasons may be related to accessing diagnosis and care at a later stage among males than females.[26] Additionally, high seroconversion found in this study among older males may be related to cultural practices of commercial sex activities.[27] The findings in our cohort emphasize that provincial HIV prevention programs should provide more active HIV testing and counseling to the spouses/partners to identify HIV status as early as possible to prevent further transmission.

Research has shown that initiation of ART can reduce HIV transmission, including transmission in serodiscordant couples.[8,23] For instance, the HPTN 052 trial showed that ART could reduce 96% transmission between couples under a strict use conditions.[24] Although ART coverage is now much greater in Guangxi, in the pre-ART period in which data collection for this study was undertaken, coverage in this cohort was 32%, similar to coverage seen in a study of Kenyan serodiscordant couples.[29] Taking this into account, results of this study indicated that ART did not reduce HIV transmission in serodiscordant couples. Other research in this province indicates that barriers to ART use included lower socioeconomic status, ART drugs being out of stock, an insufficient number of HIV treatment facilities, fear of ART side effects, stigma and disclosure, and partner stress to be linked to lower medication adherence.[30] The current findings related to ART in this study may be attributed to low ART coverage and insufficient

adherence to achieve sustained virological suppression in population. It should also be considered that ART initiation may not have been sufficient to prevent HIV transmission. Participants may have acquired HIV acquisition in this study while their HIV-positive spouse/partner was beginning the ART regimen, considering the 51% of patients in Guangxi that present late as HIV-positive.[14] Similarly, a study in Uganda also found that low-population ART coverage was not successful in preventing HIV transmission from HIV-positive individuals to serodiscordant partners.[31] These results indicate that a public health priority in Guangxi should be an expanded HIV testing system and a rapid scale-up of ART coverage among those newly diagnosed with HIV to lower HIV transmission among discordant partners.

This study also has limitations. First, it is probable that HIV acquisition may have been misclassified as transmission between partners, but related to other risk factors such as sex with other men and/or women. Second, some spouses/partners' HIV infection may be obtained before the registration, but were confirmed in the first year of follow-up and this study may be an overestimate of the seroconversion incident rate of HIV in this period. Third, a number of HIV transmissions between discordant couple/partner may have occurred before ART initiation of the first HIV-positive spouse/partner. This might underestimate the protective role of ART in the HIV transmission between discordant couple/partner.

In summary, we have measured HIV incidence among serodiscordant couples/partners in this study, and calculated the risk of HIV transmission among serodiscordant couples/partners according to different population characteristics stratifications. Our study has provided greater insight into HIV serodiscordant transmission rates during 1-year follow-up in Guangxi, Southern China. This study also identified risk factors for HIV transmission, and provided quantitative transmission risk across behavioral risk factors and demographic characteristics. A significantly higher transmission rate was observed in female HIV-positive individuals (OR = 2.3), aged 55 to 64 (OR = 2.2), married status (OR = 2.5), whereas ART as a protective factor against transmission was not observed (OR = 0.5).

Author contributions

Conceptualization: Zhigang Zheng.
Data curation: Yong LI, Shanfang Qin.
Formal analysis: Zhigang Zheng, Yi Jiang, Xu Liang.
Methodology: Zhigang Zheng.
Writing – original draft: Zhigang Zheng.
Writing – review & editing: Eric Nehl.

References

[1] Biraro S, Ruzagira E, Kamali A, et al. HIV-1 transmission within marriage in rural Uganda: a longitudinal study. PLoS One 2013;8: e55060.

[2] Carpenter LM, Kamali A, Ruberantwari A, et al. Rates of HIV-1 transmission within marriage in rural Uganda in relation to the HIV sero-status of the partners. AIDS 1999;13:1083–9.

[3] Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. Lancet 2008;371:2183–91.

[4] Lingappa JR, Lambdin B, Bukusi EA, et al. Regional differences in prevalence of HIV-1 discordance in Africa and enrollment of HIV-1 discordant couples into an HIV-1 prevention trial. PLoS One 2008;3: e1411.

[5] Ministry of Health Uganda and ORC Macro (2006) Uganda HIV/AIDS Serobehavioural Survey 2004–2005. Ministry of Health Uganda.

[6] Guthrie BL, de Bruyn G, Farquhar C. HIV-1-discordant couples in subSaharan Africa: explanations and implications for high rates of discordancy. Curr HIV Res 2007;5:416–29.

[7] Allen S, Tice J, Van de Perre P, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. BMJ 1992;304:1605–9.

[8] Fideli US, Allen SA, Musonda R, et al. Virologic and immunologic determinants of heterosexual transmission of human immuno-deficiency virus type 1 in Africa. AIDS Res Hum Retroviruses 2001;17:901–10.

[9] Hugonnet S, Mosha F, Todd J, et al. Incidence of HIV infection in stable sexual partnerships: a retrospective cohort study of 1802 couples in Mwanza Region, Tanzania. J Acquir Immune DeficSyndr 2002;30: 73–80.

[10] Kamenga M, Ryder RW, Jingu M, et al. Evidence of marked sexual behavior change associated with low HIV-1 seroconversion in 149 married couples with discordant HIV-1 serostatus: experience at an HIV counselling center in Zaire. AIDS 1991;5:61–7.

[11] Serwadda D, Gray RH, Wawer MJ, et al. The social dynamics of HIV transmission as reflected through discordant couples in rural Uganda. AIDS 1995;9:745–50.

[12] Wang L, Pens ZH, Li LM, et al. HIV seroconversion and prevalence rates in heterosexual discordant couples in China:a systematic review and meta-analysis [J]. AIDS Care 2012;24:1059–70.

[13] Zhu QY, Yang XY, Jiang H, et al. Efficacy of antiviral therapy on prevention of HIV transmission among serodiscordant couples in Guangxi Zhuang autonomous region[J]. Chin J Epidemiol 2015;36: 1401–5.

[14] Jin X, Xiong R, Wang LY, et al. Analysis on the 'late diagnosis' (LD) phenomena among newly identified HIV/AIDS cases in China, 2010-2014[J]. Chin J Epidemiol 2016;37:218–21.

[15] Mark G, Crepaz N, Senterfitt JW, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005;342:921–9.

[16] National Health and Family Planning Commission of the People's Republic of China. 2014 China AIDS Response Progress Report. Beijing, China, November, 2014.

[17] Rezvan PH, Lee KJ, Simpson JA. The rise of multiple imputation: a review of the reporting and implementation of the method in medical research. BMC Med Res Methodol 2015;15:30.

[18] Yang YC, Zhang YC, Cao YF, et al. Incidence and risk factors of HIV infections among sero-negative spouses of people living with HIV/AIDS in Dehong prefecture, Yunnan province[J]. Chin J Epidemiol 2016;37: 512–6.

[19] Rubin DB. Multiple Imputation for Non Response in Surveys /Donald B. Rubin. 1987;Wiley, New York:c1987.

[20] Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. Am J Epidemiol 2010;171:624–32.

[21] Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet 2002;359:1896–903.

[22] Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. BMC Infect Dis 2006;6:159.

[23] Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med 2000;342:921–9.

[24] Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365: 493–505.

[25] Tanser F, Bärnighausen T, Grapsa E, et al. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science 2013;339:966–71.

[26] Mills EJ, Bakanda C, Birungi J, et al. Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda. AIDS 2011;25:851–5.

[27] Lu H, Tang Z, Shen Z, et al. Sildenafil use and relevant risk factors among middle-aged or elderly male clients of female commercial sex workers in the central areas of Guangxi, China. Chin J Epidemiol 2014;35:1218–22.

[28] Li J, Zhang H, Shen Z, et al. Screening for acute HIV infections and estimating HIV incidence among female sex workers from low-grade venues in Guangxi, China. PLoS One 2014;9: e99522.

[29] Guthrie BL, Choi RY, Liu AY, et al. Barriers to antiretroviral initiation in HIV-1-discordant couples. J Acquir Immune Defic Syndr 2011;58:e87–93. [PubMed: 21826010].

[30] Molloy GJ, Perkins-Porras L, Strike PC, et al. Social networks and partner stress as predictors of adherence to medication, rehabilitation attendance, and quality of life following acute coronary syndrome. Health Psychol 2008;27:52–8.

[31] Birungi J, Min JE, Muldoon KA, et al. Lack of effectiveness of antiretroviral therapy in preventing HIV infection in serodiscordant couples in Uganda: an observational study. PLoS One 2015;10:e0132182.