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Original Article

HIV transmission in sero-discordant couples with the HIV-positive partner in Xinjiang: incidence and associated predictors

Yongkang Ni[1], Xiaoyuan Hu[2], Zaoling Liu[1], Ning Tao[1], Yuanyuan Ma[2], Zhen Ni[2], Mingjian Ni[2]

[1] *School of public health, Xinjiang Medical University, Urumqi, Xinjiang, China*
[2] *Xinjiang Uighur Autonomous Region Center for Disease Control and Prevention, Urumqi, Xinjiang, China*

Abstract

Introduction: To control the spread of human immunodeficiency virus (HIV) among sero-discordant couples, we explored the HIV seroconversion and its contributing factors.

Methodology: We recruited negative partners in HIV sero-discordant couples to established a prospective cohort between January 2010 and June 2015 from areas with severe HIV epidemic in Xinjiang. Follow up once every 3 months, serological tests and risk behavior surveys every 6 months. Variables were screened by LASSO regression and a Cox proportional hazards model was established.

Results: A total of 1162 negative partners of sero-discordant couples were recruited. The seroconversion occurred in 42 negative partners during follow-up period, with a seroconversion rate of 2/100 (95% CI = 1.21-2.27), and the median time for seroconversion was 0.92 years. The Cox model showed that frequency of sexual behavior for nearly six months, consistent condom use, knowledge of the transmission route for HIV, a history of sexually transmitted diseases, recent CD4 + T lymphocyte count were all significant contributing factors to the seroconversion in negative partner of HIV sero-discordant couples. In addition, the Cox model was used to evaluate the risk factors of seroconversion for HIV negative partners.

Conclusions: The seroconversion rate of HIV negative partners in Xinjiang was lower. The LASSO Cox model may accurately predict the risk of HIV transmission in sero-discordant couples.

Key words: HIV sero-discordant couples; seroconversion; influencing factors; LASSO; Cox multivariate analysis.

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Introduction

Human immunodeficiency virus (HIV) infection causes acquired immunodeficiency syndrome (AIDS) [1]. After decades of research and treatment, HIV / AIDS remains a major challenge to global public health [2]. According to statistics, by the end of 2016, there were 36.7 million people living with HIV and 1.8 million new infections worldwide [3]. It is estimated that there were 758,610 people were cumulatively HIV infected in China by the end of 2017, with continuous increase individuals over the years [4]. Antiretroviral therapy (ART) reduces morbidity and mortality in majority of HIV-1-infected individuals and effectively prevents the progress of HIV-1 disease [5,6]. Early ART for HIV prevention can reduce transmission between HIV sero-discordant couples [7].

Observational studies from different heterosexual couples showed that there was a close relationship between the HIV RNA load of HIV positive partners and the risk of transmission to HIV negative partners [8-11]. In general, couples or stationary partners in sero-discordant couples are considered to be "uninfected but exposed", and various factors may contribute to their seropositive transformation [12]. There is considerable variation in the prevalence of HIV positive conversion rate for negative partners of sero-discordant couples in different regions. A study conducted in 23 sub Saharan countries showed that the positive conversion rate of negative partners in sero-discordant couples varied from 4.2% person years to 47.4/100 person years [13]. Studies in South India demonstrated a seroconversion rate of local negative partners was 6.5/100 person years [14]. The total positive conversion rate of negative partner in sero-discordant couples was 1.2/100 person years in China [15]. Xinjiang is an important city of HIV infection in China, and therefore, it is necessary to screen the seroconversion rate of negative partner in sero-discordant couples in this region.

Compared with other diseases, HIV infection has obvious social attributes. Factors influencing HIV transmission not only include biological and behavioral factors, but also sociological factors [16-19]. Some studies suggesting that sexual history is an independent

contributing factor to heterosexual HIV transmission [20]. Studies in Uganda have shown significant difference in the risk of HIV transmission to partners when HIV positive patients are in different course of disease [21]. In addition, in recent years, an increasing number of studies showed that performing circumcision could reduce the risk of HIV infection in male [22]. Lack of knowledge about HIV sero-discordance, transmission and prevention increases the risk of HIV transmission [23]. It is well known that CD4 + T lymphocyte count is closely related to HIV-1 infection [24]. Condom use has been shown to reduce the risk of HIV transmission in sero-discordant couples [25].

Understanding the factors associated with transmission among partners in sero-discordant couples can help to understand the etiology and target interventions, thus reduce the risk of HIV infection among negative partners. Intervention sero-discordant couples and implementation comprehensive prevention and control measures for AIDS are also important factors affecting the transmission of HIV. Unfortunately, to our knowledge, there are too many possible factors affecting the risk of HIV negative partners in sero-discordant couples. Therefore, it is important to find out the important influencing factors of HIV negative partners and predict the risk of positive conversion.

This study is the first to establish a prospective study cohort in Xinjiang. Sero-discordant couples in areas with severe HIV epidemic were selected for follow-up and observation for 5 years. To obtain the HIV seroconversion rate and its influencing factors, an individual risk prediction model was established. This may provide scientific basis for the formulation and optimization of HIV prevention and control strategies for sero-discordant couples in the region.

Methodology

Study design and population

This study included the HIV seroconversion rate of negative partner in sero-discordant couples, the influencing factors of HIV seroconversion for negative partner and the establishment the risk prediction model for HIV seroconversion of negative partner. The study involved areas with more serious HIV epidemic in Xinjiang (Aksu City, Kashi City, Yining City, Yining County, Huocheng County, Kuche County, Tianshan District, Shuimogou District and shayiba District of Urumqi City). Blood samples from HIV negative and positive patients were collected. The information of HIV positive patients and negative partners for 1,162 sero-discordant couples were included in the study, and a prospective cohort was established for observation and follow-up from January 2010 to June 2015. Exclusion criteria: obvious mental illness or mental illness, divorce when investigation or lost visit. All subjects signed an informed consent prior to enrollment. The protocol was submitted and approved by the center for epidemic control of Xinjiang Autonomous Region and the ethics committee of each participating clinical center.

Queue maintenance and follow-up

The subjects were followed up every 3 months, HIV antibody test and risk behaviors were investigated every 6 months. Baseline questionnaire survey of negative partners including gender, nationality, age, education level, income and knowledge of HIV infection. Then, we obtain the information of HIV infection route (injecting drug, heterosexual transmission and others), history of sexually transmitted diseases (STD), ART and the recent CD4 + T lymphocyte count from HIV positive patients.

Laboratory testing

Collected blood samples were sent within 12 hours to HIV screening laboratory for serum isolation. The HIV antibody of couples was screened by enzyme linked immune assay (ELISA) (Beijing Jinhao, China). Those who were positive in the initial screening were retested by ELISA Kit (InTec PRODUCTS, Xiamen, China). The HIV-1 / 2 Blot confirmatory kit (HS1409001) was used for confirmatory test. All samples (including positive and negative samples) shall be stored at least 12 months after the end of the investigation.

Variable selection of HIV seroconversion in negative partners

This study established the LASSO Cox model through glmnet R package. Then, the adjusted hazard ratio (aHR) and its 95% confidence interval (CI) were obtained. The weighted score residual method is used to verify whether the variables in the model and the model as a whole meet the proportional hazards assumption (PH). The test level α was set as 0.05.

Based on the LASSO Cox model, prediction model was established. The prediction equation can be expressed as follows:

$$\hat{P} = 1 - S_0$$

Among them, $S_0(t)$ represents the baseline disease-free probability of the negative partner population for one and two years, which is approximately estimated by Kaplan Meier (KM) method. β is the partial regression

coefficient corresponding to each independent variable in Cox regression model. X is the value of the independent variable. $\bar{X}$ is the mean value of continuous variable or the proportion of classified variable. It can be seen that $S_0(t)$ and $\sum_{i=1}^{p} \beta_i \bar{X}_i$ are common variables and do not need to be calculated according to personal conditions.

Statistical analysis

Mean ± SD / median was used to describe the measurement data of normal distribution / non normal distribution. The counting data were described by composition ratio, frequency, frequency and other indicators. The principle of Poisson distribution was used for comparison of seroconversion rate between different groups, then 95% confidence interval (CI) of serum positive conversion rate was calculated. Statistical processing and analysis were performed using the SPSS 19.0 and "survival", "RMS", "hmisc", "glmnet" and "cschange" packages in R3.3.2. The test level was α = 0.05, and the two-sided test was used.

Ethical Approval

The study was approved by the Xinjiang Medical University and Center for Disease Control and Prevention of Xinjiang Uygur Autonomous Region HIV Research Ethics Board. Written informed consent was obtained from each participant before authors commenced any data collection.

Results

Study Participants

The study flowchart is presented in Figure 1. The average age of negative partners in 1,162 sero-discordant couples was 34.57 ± 7.79 years old, and there were 250 males and 912 females. The ethnic distribution was mainly Uygur of 1,056 cases (Table 1). The average age of the 1,162 HIV positive patients was 36.09 ± 7.61 years. The route of HIV infection for 611 cases were injecting drug, 421 cases were heterosexual transmission. In addition, 22 cases (1%) had history of STD, 721 cases (62%) had no STD, 958 cases (82%) received ART, 153 cases had CD4 + T lymphocyte count less than 200 / μL, 259 cases had 201-349 / μL, and 647 cases had more than 350 / μL. Among 1059 patients with recent CD4 + T lymphocyte count, the median of the last CD4 + T lymphocyte count was 415/ μL (Table 2).

Figure 1. Study flowchart.

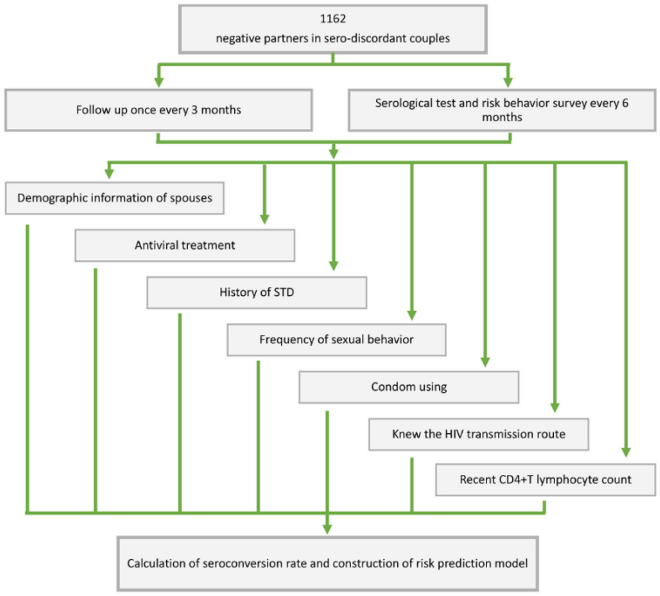


Table 1. The Demographic Information of negative partner in HIV sero-discordant couples.

Characteristic	Number Of Observation (case)	Composition Ratio (%)
Gender		
Male	250	21.51
Female	912	78.49
Age (years)		
≤ 35	653	56.20
＞ 35	509	43.80
Nation		
Uighur	1056	90.88
Other nationalities*	106	9.12
Education level		
Under junior high school	392	33.73
Junior high school and above	770	66.27
Monthly income (yuan)		
＜ 1000	974	83.82
≥ 1000	188	16.18

* Other nationalities include: Han, Hui, Manchu, Mongolian, Dongxiang, Russian, Kazak and Uzbek.

Table 2. The Information of Index Spouses.

Characteristic	Number Of Observation (case)	Composition Ratio (%)
Age (years)		
≤ 35	560	48.19
＞ 35	602	51.81
Education level		
Under junior high school	555	47.76
Junior high school and above	607	52.24
Route of infection		
Injection drug abuse	611	52.58
Heterosexual transmission	421	36.23
Other or unknown	130	11.19
History of sexual diseases		
Yes	22	1.89
No	721	62.05
Unknown	419	36.06
Receive antiviral treatment		
Yes	958	82.44
No	204	17.56
Last CD4 + T lymphocyte count (PCS / μL)		
＜ 200	153	13.17
201~349	259	22.29
≥ 350	647	55.68
Deletion	103	8.86

Table 3. The Demographic Information of sero-discordant couples and seroconversion.

Variables	Number of positive conversion (constituent ratio)	Observation Time (year)	Serum Positive Conversion Rate (/ 100 person year)	95% *CI*	Z	*p*
Gender						
Male	8 (19.05)	487.86	1.64	0.71-3.23	0.08	0.935
Female	34 (80.95)	2008.37	1.69	1.17-2.37		
Age (years)						
≤ 35	31 (73.81)	1492.5	2.08	1.41-2.95	-1.82	0.068
＞ 35	11 (26.19)	1003.73	1.1	0.55-1.96		
Nation						
Uighur	41 (97.62)	2292.21	1.79	1.28-2.43	-1.28	0.201
Other nationalities	1 (2.38)	204.02	0.49	0.01-2.73		
Education level						
Under junior high school	20 (47.62)	847.96	2.36	1.44-3.64	-1.84	0.065
Junior high school and above	22 (52.38)	1648.27	1.33	0.83-2.02		
Monthly income (yuan)						
＜ 1000	37 (88.10)	2146.22	1.72	1.21-2.38	-0.39	0.693
≥ 1000	5 (11.90)	350.01	1.43	0.46-3.33		

Seroconversion rate of HIV negative partners

The 1,162 negative partners were followed up for an average of 2.15 years per case. During this period, 42 negative partners had seroconversion, the seroconversion rate was 2/100 person years (95% CI = 1.21-2.27), and the median time of seroconversion was 0.92 years. Among them, the gender distribution was mainly female, accounting for 81% of the total positive conversion population. However, there was no significant difference in seroconversion between male and female (p = 0.94). Besides, there were no statistically significant differences in the effects of age, nationality, education level and income of the negative partner (Table 3).

The influencing factors for the rate of seroconversion in the negative partner

Among the 42 positive partners, 23 were infected by injecting drug, with seroconversion rate of the negative partners was 2/100 person years (95% CI = 1.05-2.48). There was no significant difference in seroconversion rate between negative partners of positive partners with HIV infection through heterosexual transmission and injecting drug. The seroconversion rate of negative partner whose positive partner had history of STD was 6/100 person years (95% CI = 1.29-18.26), which was higher than that of the negative ones (95% CI = 1.03-2.39), and the difference was statistically significant (p = 0.027). For the positive partner with recent CD4 + T lymphocyte count < 200 / μL, the HIV seroconversion rate of the negative partner was 3/100 person years (95% CI = 1.68-6.03). It was higher than 1/100 person years (95% CI = 0.79-2.05) of the negative partner which the positive partner with recent CD4 + T lymphocyte count ≥ 350 / μL (p = 0.013). The HIV seroconversion rate was 2/100 person-years (95% CI = 0.72-3.70) for positive partners who did not received ART, slightly higher than that for negative partners who receive ART (95% CI = 1.16-2.31) (p = 0.851) (Table 4).

On the other hand, 31 of the 42 sero-discordant couples had sex behavior more than twice a month in the recent six months, and the seroconversion rate was 3/100 person years (95% CI = 1.71-3.57). The positive conversion rate who had the frequency of sexual behavior was less than twice a month in the recent six months was 1/100 person years (95% CI = 0.46-1.65), the difference between more than twice and less than twice was statistically significant (p = 0.004). The seroconversion rate of the couples who insisted on

Table 4. The Information of Index Spouses and Seroconversion.

Variables	Number of positive conversion (constituent ratio)	Observation Time (year)	Serum Positive Conversion Rate (/ 100 person year)	95% *CI*	Z	p
Route of infection						
Injection drug abuse	23 (54.76)	1391.94	1.65	1.05-2.48		
Heterosexual transmission	16 (38.10)	839.49	1.91	1.09-3.10	0.44	0.661
Other or unknown	3 (7.14)	264.79	1.13	0.23-3.31	-0.61	0.539
Age (years)						
≤35	25 (59.52)	1264.06	1.98	1.28-2.92	-1.15	0.252
＞35	17 (40.48)	1232.17	1.38	0.80-2.21		
Education level						
Under junior high school	25 (59.52)	1204.81	2.08	1.34-3.06	-1.45	0.148
Junior high school and above	17 (40.48)	1291.42	1.32	0.77-2.11		
History of sexual diseases*						
Yes	3 (7.14)	48.01	6.25	1.29-18.26	2.22	0.027
No	24 (57.14)	1491.38	1.61	1.03-2.39		
Unknown	15 (35.72)	956.84	1.57	0.88-2.59	-0.08	0.937
Receive antiviral treatment						
Yes	35 (83.33)	2106.5	1.66	1.16-2.31	0.19	0.851
No	7 (16.67)	389.73	1.8	0.72-3.70		
Last CD4 + T lymphocyte count (PCS / μL)*						
＜200	11 (26.19)	326.18	3.37	1.68-6.03		
201~349	11 (26.19)	539.36	2.04	1.02-3.65	-1.18	0.238
≥350	19 (45.24)	1447.69	1.31	0.79-2.05	-2.49	0.013
Missing	1 (2.38)	183	0.55	0.01-3.04	—	—

* The infection route of HIV positive patients was heterosexual transmission group, which was not compared with other or unknown groups. The sexual diseases history of HIV positive patients in unknown group and asexual group were not compared. The last CD4 + T lymphocyte count of HIV positive patients was 201-349 / μL group, which was not compared with ≥ 350 / μL group. The deletion group did not participate in the comparison.

Table 5. The Behavior and the Awareness Situation of sero-discordant couples and seroconversion.

Variables	Number of positive conversion (constituent ratio)	Observation Time (year)	Serum Positive Conversion Rate (/ 100 person year)	95%*CI*	Z	p
Frequency of sexual behavior in recent 6 months						
≤2 times / month	11 (26.19)	1190.01	0.92	0.46-1.65	2.85	0.004
＞2 times / month	31 (73.81)	1233.85	2.51	1.71-3.57		
Refuse to answer*	0	72.37	0	—	—	—
Consistent use of condoms						
Yes	27 (64.29)	1980.66	1.36	0.90-1.98	3.56	＜ 0.001
No	14 (33.33)	317.55	4.41	2.41-7.40		
Refuse to answer *	1 (2.38)	198.02	0.5	0.01-2.81		
Knowing the route of HIV transmission						
Yes	38 (90.48)	2450.01	1.55	1.10-2.13	3.27	0.001
No	4 (9.52)	46.22	8.65	2.36-22.16		

* The refusals did not participate in the comparison.

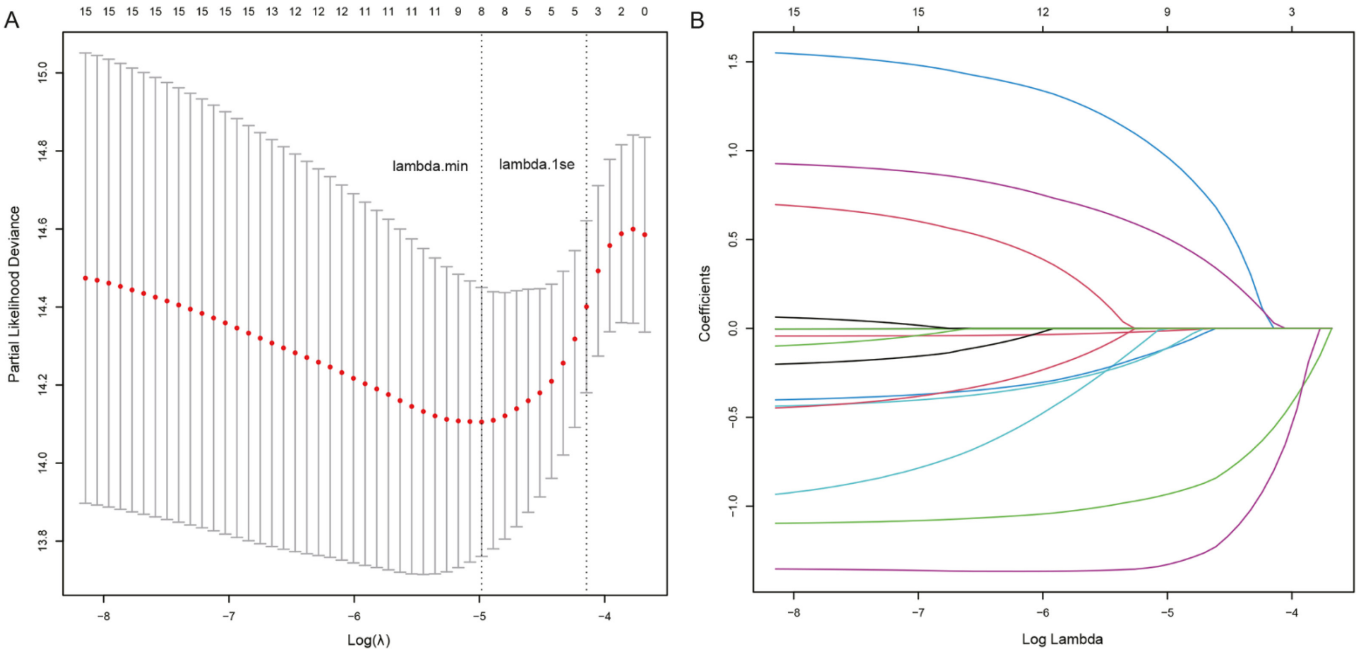
using the condom was 1/100 person years (95% CI = 0.90-1.98), The seroconversion rate who did not insist on using the condom was 4/100 person years (95% CI = 2.41-7.40). The seroconversion rate of the negative partner who knew the HIV transmission route was 2/100 person years (95% CI = 1.10-2.13), lower than 9/100 person years (95% CI = 2.36-22.16) for who unknown, the difference was statistically significant (p = 0.001) (Table 5).

The establishment of LASSO Cox model

During adjustment for the parameter λ, when log (λ) = - 4.15, λ = 0.02 (lambda. 1se), four independent variables were selected (Figure 2A). At this time, the λ value was relatively large value and the number of selected variables was small, which made the model much concise. Therefore, this λ value was taken as the optimal λ value (Figure 2B). The corresponding variables were included in the multivariate Cox regression analysis. All the above variables and the model as a whole meet the PH assumption ($p > 0.05$).

The results showed that the risk of HIV seroconversion was reduced for 0.3% (aHR = 0.99, 95% CI = 0.99-0.99) by every 1 / μL increased in recent CD4 + T lymphocyte count. The risk of HIV seroconversion was 2.49 times higher in the negative partner between who had sex more than and less than twice in a month for recent six months (aHR = 2.5, 95%

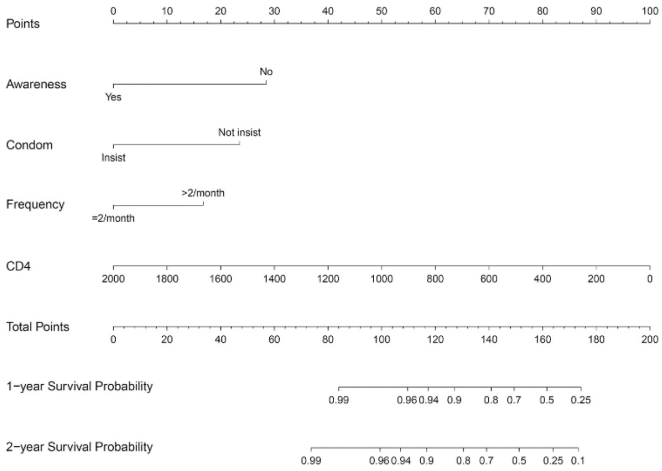
Figure 2. The establishment of LASSO Cox model. A. The process of cross-validation of LASSO.



The horizontal axis represents the logarithm of the adjustment parameter λ, the vertical axis represents the partial likelihood error of the model, and the top number represents the number of variables selected. B. The coefficient solution path of LASSO.

CI = 1.22-5.1). The risk was 0.28 times lower in the negative partner between who insisted on condom use and who had no insistence (aHR = 0.28, 95% CI = 0.14-0.55). The risk was 0.21 times (aHR = 0.21, 95% CI = 0.07-0.64) in the negative partner between who knew the HIV transmission pathway and did not know the pathway (Table 6). Therefore, the influence of risk factors on the seroconversion of HIV negative patients was predicted for one or two years by LASSO Cox model (Figure 3).

Figure 3. The nomogram of LASSO-Cox model.



Discussion

Despite progress in HIV treatment and prevention, the elimination of HIV infection remains an elusive goal [26]. In many high-income countries, the rate of new AIDS diagnosis has not decreased significantly [27,28]. Accurate diagnosis of HIV infection is the key point for infected patients to enter the treatment stage [29]. Serological based incidence rate analysis is widely used in cross-sectional surveys to estimate new infection rates [30]. Therefore, in this study, sero-discordant couples in high HIV incidence areas were selected as subjects to test the positive conversion rate of negative partners. Xinjiang is one of the provinces with the most serious HIV epidemic in China, and more than half of the infected people and patients form families or have fixed sexual partners. The risk prediction model was established to help HIV negative partners in sero-discordant couples understand the risk of disease and prevent it.

The seroconversion rate of negative partners is a key index to reflect the intensity of HIV transmission among couples [31]. The follow-up results of 2,465 sero-discordant couples in Uganda showed that the seroconversion rate of negative partners was 7/100 person years [32]. This study showed that the seroconversion rate of negative partners with HIV sero-discordant couples in Xinjiang was relatively low from January 2010 to June 2015. This may be related to the high proportion of people who insist on using condoms.

Some studies have confirmed that the seroconversion rate of female negative partner is higher than that of male negative partner [33]. However, this study did not find that there was a difference in the rate of seroconversion between them. It may be related to the fact that the gender composition of the negative partner in this study was mainly female (78.49%). In addition, in recent years, the concept of gender has gradually developed with the rise of the feminist movement. The difference of seroconversion rate between men and women in sero-discordant couples may depend on gender to a certain extent, and the seroconversion rate of women with lower sexual relationship power may be higher [34,35]. Both injecting drug users and non-injecting drug users may serve as bridges linking the HIV epidemic between high-risk and low-risk populations [36]. Our findings did not reveal a difference in the effect of injecting drug and sexual transmission on seroprevalence in negative partners.

Table 6. The Result of LASSO-Cox Model.

Variables	β	aHR	95% *CI*	*Wald*χ^2	*p*
Last CD4 + T lymphocyte count (PCS / μL)					
	-0.003	0.997	0.997-0.999	11.932	0.001
Frequency of sexual behavior in recent 6 months					
≤ 2 times / month		1			
＞ 2 times / month	0.914	2.494	1.218-5.104	6.253	0.012
Consistent use of condoms					
Yes	-1.284	0.277	0.139-0.552	13.336	＜ 0.001
No		1			
Knowing the route of HIV transmission					
Yes	-1.555	0.211	0.070-0.641	7.544	0.006
No		1			

ART reduced 96% of the risk of HIV transmission among couples in sero-discordant couples, thus the concept of "treatment is prevention" was proposed [37]. In this study, we did not find the protective effect of ART on HIV seroconversion of negative partners. Virological suppression resulting from continued ART use has been shown to substantially reduce the risk of sexually transmitted HIV [38]. However, viral load is not the only factor determining the risk of HIV transmission [39]. The preventive effect of ART on seroconversion of negative partners in sero-discordant couples still needs to be analyzed in the follow-up cohort data and further study in a wider range. Due to HIV infection and destruction of CD4 + T cells, the immune system is damaged [40]. The risk of HIV transmission between couples decreased with the increase of CD4 + T lymphocyte count [41]. In this study, by LASSO Cox model, we found that with the increase of CD4 + T lymphocyte count, the risk of HIV seroconversion in the negative partner decreased gradually. CD4 + T cells count decline over time and are the best predictor of disease progression and risk of death, especially in patients with advanced HIV [42]. CD4 + T cells counts are used to guide some preventive and diagnostic interventions, including prioritizing detection of opportunistic infections [43].

In patients with sexually transmitted diseases, the risk of seroconversion in the negative partner was significantly increased [44,45]. In the study, whether positive or negative partners were infected with sexually transmitted diseases, the risk of HIV seroconversion in negative partners will increase. On the other hand, through the risk prediction model, we found that the higher the frequency of sexual behavior between couples, the higher the risk of HIV exposure of negative partner. Sticking to the correct use of condoms is one of the most effective measures to reduce the sexual transmission of HIV [46,47]. However, it must be taken into account that many sero-discordant couples may have the desire to have children, which leads to their unwillingness or failure to take safety measures when they have sex [48,49]. Therefore, pre exposure prophylaxis (PrEP) may be considered to reduce the risk of transmission in HIV families [50].

In this study, LASSO regression was used to screen variables for predicting the risk factors of HIV seroconversion in sero-discordant couples in Xinjiang.

The results of the risk model suggested that the frequency of sexual behavior of negative couples in the recent six months, whether they knew the transmission route of HIV, whether they insisted on using condoms, and the CD4 + T lymphocytes count in positive patients were the risk factors influencing the conversion of negative partners in sero-discordant couples. According to the analysis results, the LASSO Cox model would be widely used as a risk prediction model of seroconversion in the negative partner of sero-discordant couples in Xinjiang.

Conclusions

From January 2010 to June 2015, the seroconversion rate of negative partners in HIV sero-discordant couples was 2/100 person years, and the median time of seroconversion was 0.92 years. The model analysis indicated that the main influencing factors of HIV seroconversion were the frequency of sexual behavior in recent six months, whether to insist on using condom, whether to know the transmission route of HIV, and the level of CD4 + T lymphocyte count of positive partners. The LASSO Cox model can be used as a risk prediction model of HIV seroconversion for the negative partner of sero-discordant couples in Xinjiang.

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Authors' contributions

Yongkang Ni and Xiaoyuan Hu contributed equally to the manuscript preparation, supervised the experimental work, data analysis and interpretation. Zaoling Liu coordinated the experimental work and contributed to data and manuscript preparation. Ning Tao contributed to the clinical study management and manuscript preparation. Yuanyuan Ma supervised the experimental work and contributed to data. Mingjian Ni conceived and designed the study, supervised the experimental work, data analysis and interpretation, and manuscript critical review.

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Corresponding author

Mingjian Ni, phD,
Xinjiang Uighur Autonomous Region Center for Disease Control and Prevention, No. 380 Jianquan 1 road, Tianshan District, Urumqi, Xinjiang, 830001, China.
Phone: 13369690879
Fax: 0991-3812633
Email: li316896857@163.com

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