Published in final edited form as:

Chin Med J (Engl). 2011 June ; 124(12): 1890–1896.

Heterosexual risk of HIV infection in China: systematic review and meta-analysis

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Abstract

Background—Heterosexual sex has become the dominant transmission route in China. Recently studies reported high heterogeneity in heterosexual transmission risk in resource-limited countries. The aim of this study was to summarize the risk of HIV transmission among Chinese serodiscordant couples.

Methods—A systematic review and meta-analysis of observational studies of heterosexual HIV transmission among serodiscordant couples in China was conducted. Two reviewers conducted a literature search using the China National Knowledge Infrastructure (CNKI), Chinese Medical Current Contents (CMCC), and Medline databases. Pooled transmission estimates per 100 person-years (PY) were calculated using a random-effects model. Meta-regression analysis and subgroup

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analysis stratified by study design, transmission direction and period of antiretroviral therapy (ART) availability were conducted to assess the factors associated with transmission.

Results—Eleven eligible studies were identified reporting on 11 984 couples and 405 HIV transmission events. HIV transmission risk from HIV-positive individuals to heterosexual partners was 1.68 (95% *CI* 0.74–2.62) per 100 PY. Study design did not reach statistical significance in meta-regression analysis. The pooled female-to-male transmission estimate was 1.11 (95% *CI* 0.09–2.14) per 100 PY and male-to-female transmission estimate was 1.43 (95% *CI* 0.19–2.68) per 100 PY. The pooled estimate for those before the availability of the Chinese National Free Antiretroviral Therapy Program (2.13 (95% *CI* 0.00–4.63) per 100 PY) was higher than that for those after the implementation of this program (1.44 (95% *CI* 0.62–2.26) per 100 PY).

Conclusions—Transmission estimates in China were lower than other developing countries, but higher than developed countries. Research that better defines HIV secondary transmission rates and the associated behavioral, treatment adherence, and health-related risk factors among heterosexual serodiscordant couples in China is needed.

Keywords

human immunodeficiency virus; heterosexual transmission

Since the beginning of the HIV/AIDS epidemic in China, the Chinese Ministry of Health has taken extensive measures to control the spread of the virus. Illegal blood and plasma stations have been shut down and infection through blood transfusions has been essentially eliminated. Methadone maintenance treatment was scaled-up in 2004 to prevent HIV transmission among injecting drug users (IDUs). Moreover, in 2003 the Chinese government announced the “Four Free One Care” program, which secures free access to voluntary counseling and testing (VCT), free antiretroviral therapy (ART), and free prevention of mother to child transmission (PMTCT).[1–5] In recent years, heterosexual sex has surpassed injection drug use as the primary mode of HIV transmission in China.[6,7]

In 2007, the State Council AIDS Working Committee Office and the United Nations released a report stating that 37.9% of all new infections of HIV/AIDS in China have been transmitted through heterosexual sex. Today, the Chinese HIV epidemic is generally contained to several high-risk groups, including former plasma donors (FPD), men who have sex with men (MSM), and IDUs. Although each group’s defining HIV risk factor is not heterosexual sex, heterosexual sex serve as a bridge to spread HIV from these high risk populations to the general population. Previous studies have found high heterogeneity in heterosexual per-act transmission risk across serodiscordant couples in low-income countries.[8,9] Quantifying the infectivity in resource limited settings is crucial, especially in countries like China, where the large population and limited access to healthcare in some areas could potentially compound the impact of a generalized HIV/AIDS epidemic. To better understand the epidemiology of HIV in China and improve the understanding of epidemiology of HIV/AIDS worldwide, we systematically reviewed the risk of heterosexual HIV transmission among serodiscordant couples in China.

METHODS

Search strategy and selection criteria

The China National Knowledge Infrastructure (CNKI), Chinese Medical Current Contents (CMCC), and Medline databases were systematically searched for observational studies of HIV transmission in heterosexual serodiscordant couples in China; CNKI includes conference abstracts and master's and doctoral level dissertations, which were also eligible for inclusion in the meta-analysis. Combinations of the keywords "China" (only used in non-Chinese based database (Medline)) and "HIV" or "AIDS" or "human immunodeficiency virus" or "acquired immunodeficiency syndrome" and "heterosexual transmission" or "secondary transmission" or "couples" or "spouse" or "family transmission" or "discordant" or "transmission" were used to search. Original articles, dissertations, and conference abstracts reporting on observational studies of HIV transmission in serodiscordant couples were included.

Two authors independently reviewed the abstracts and titles of searched articles to determine eligibility. Eligible studies reported heterosexual transmission or had sufficient information to derive an estimate, reported follow-up time, and were conducted between January 1985 and January 2010. The search was updated to December 2010 to include the most recently published research. Case reports, reviews, and modeling papers were excluded and all included papers were restricted to English or Chinese because both reviewers are fluent in these languages. When information in the abstract was not sufficient to determine eligibility, the full text of the article was reviewed. Serodiscordant couples were defined as one HIV positive partner and one HIV negative partner. Included studies must have epidemic evidence that seroconversion was not due to injection drug use, commercial blood plasma donation, blood transfusion, or homosexual sex with a man. A study could only be included if the exposure time to the HIV positive partner could be extracted. A third reviewer (WANG Ning) was consulted when a disagreement between the first two reviewers arose. The reference lists of all articles meeting the exclusion criteria were carefully examined to identify other articles that may meet the inclusion criteria. If multiple publications reported estimates based on the same study population, the largest or most recent sample was used (largest sample size used over the most recent).

Data extraction

The full text of all abstracts meeting the inclusion criteria were retrieved and information was extracted regarding the study design, location and date, as well as the risk of the index group (HIV-positive partners) and transmission data. In prospective studies, serodiscordant couples were followed until seroconversion occurred with exposure time considered the difference between seroconversion date and index partner's diagnosis date. For retrospective studies, the exposure time was calculated as the time between HIV diagnosis date in the first partner and the HIV diagnosis date in the second partner. Since the seroconversion time of prospective studies is more precise than retrospective studies, it was hypothesized that the effect size is varied based on study design. When available, male-to-female and female-to-male transmission estimates, condom use data, and ART data were also extracted. When

additional information was needed, we tried to contact the authors of included studies. We relied solely on the published data when the authors could not be reached.

Statistical analysis

The pooled transmission estimates per 100 person-years (PY) and 95% confidence intervals (95% *CI*) were calculated using a random-effects model based on the DerSimonian-Laird method.[10,11] A value of 0.000001 was substituted for zero transmission.[9] Some studies reported the transmission rate as a percentage, but the transmission rate was calculated in terms of PY using the extracted follow-up time. If the calculated lower limit of the 95% *CI* for transmission rate was less than zero, a zero value was used in its place. I^2 and the Cochran's Q statistic were used to assess the heterogeneity of the included studies overall and within each subgroup. A random effects model was used for the calculation of the pooled estimate to reduce bias caused by heterogeneity. Sensitivity analysis was conducted to assess the individual influence of each study on the pooled transmission estimate. Subgroup analyses were performed to explore differences in transmission risk according to study design, sex, and ART. Finally, univariate meta-regression analysis was conducted to determine other sources of heterogeneity.[12] All analyses were conducted using STATA version 10 (Stata Corporation, College Station, USA).

RESULTS

Literature search

Figure 1 shows the results of the literature search. The search terms yielded 1023 publications, including articles, conference abstracts and theses. In all, 949 publications were excluded because they were not relevant. The abstracts and full texts of 74 publications were thoroughly reviewed and 46 were excluded because of lack of epidemic evidence of infection from heterosexual transmission. Of the 28 remaining articles, another 14 were excluded because exposure time could not be calculated.

Finally, another three studies were excluded because they reported on the same populations as other included studies. We identified 11 eligible studies reporting on 11 984 couples and 405 HIV transmission events in five provinces. The authors of three potentially eligible studies were contacted; one replied and no additional information was provided.

Study characteristics

Table presents the characteristics of all included studies. Reviewed studies were conducted between 1992 and 2009. Six of the included publications were prospective cohort studies of serodiscordant couples and five were retrospective studies of previously serodiscordant couples.[13–23] Among prospective studies, the longest follow-up time was 2.5 years and 11.2 years for retrospective studies. The included studies were conducted in Henan, Yunnan, Hebei and Xinjiang provinces, Beijing municipality, and two studies defined the location as "high-prevalence area," but did not identify the precise locations. Study populations ranged from 22 couples in a study conducted in Xinjiang to 8664 couples in a study conducted in Henan. Transmission estimates extracted from reviewed studies ranged from 0 per 100 PY in both Henan and Beijing to 32.5 per 100 PY in Xinjiang.

Each individual study was also subject to bias. The accuracy of the diagnosis date varied across studies. The infected dates of FPD or blood transmission are more accurate than those who were infected through other routes of transmission. In studies of FPD, the year 1995 was used instead of the diagnosis date since the infection most likely occurred around 1995 due to unsafe plasma donation practices.[2] There were insufficient data to allow estimation of summary rates of transmission through sexual intercourse without condoms or to stratify according to frequency of sex, viral load, and CD4 count.

Figure 2 summarizes the individual and pooled transmission rates of the 11 included studies. The heterogeneity across transmission estimates was significant (P <0.001, I^2=91.7%). The overall HIV transmission risk from HIV positive partners to heterosexual partners, irrespective of other sexually transmitted infections, was 0.19 per 100 PY (95% *CI* 0.10–0.29).

Sensitivity analysis

To evaluate the influence of each study on the overall pooled estimate, sensitivity analysis was performed calculating the overall risk removing one study at a time (Figure 3). Two studies conducted in Henan and one study conducted in Beijing had the greatest influence on the pooled HIV secondary transmission rate. The other eight studies remained within the 95% *CI* of overall pooled estimate. When these three studies were removed from the analysis, the pooled estimate of transmission risk was 1.68 (95% *CI* 0.74–2.62) per 100 PY (Figure 4). Heterogeneity of effects was assessed using I^2 (68.5%) and Q-test (P=0.005).

Subgroup analyses

Figure 5 illustrates the results of subgroup analyses. Of the eight transmission estimates included, five estimates were from retrospective studies and three estimates were from prospective studies. The pooled transmission estimate for prospective studies (4.37 (95% *CI* 0–10.19) per 100 PY) was higher than it was for retrospective studies (1.46 (95% *CI* 0.66–2.26) per 100 PY), but in meta-regression analysis, the difference in study design did not reach statistical significance.

Six studies reported transmission risk by sex and these studies were used to calculate pooled estimates of female-to-male and male-to-female transmission. Pooled male-to-female transmission was 1.43 (95% *CI* 0.19–2.68) per 100 PY and female-to-male transmission was 1.11 (95% *CI* 0.09–2.14) per 100 PY.

China’s National Free Anretrotiviral Therapy Program began in 2003 and has been rapidly expanded to cover the entire country.[24,25] Three studies were conducted before 2003 and five studies were conducted after 2003. Figure 5 shows the individual and pooled estimates of HIV transmission from studies conducted before and after the National Free Anretrotiviral Therapy Program. The pooled estimate for those before the implementation of the National Free Anretrotiviral Therapy Program was 2.13 (95% *CI* 0.00–4.63) per 100 PY. The pooled estimate for those after the implementation of the National Free ART Program was 1.44 (95% *CI* 0.62–2.26) per 100 PY.

Meta-regression

Univariate meta-regression analysis was performed to explore potential cofactors, including study design, direction of transmission (male-to-female vs. female-to-male), sample size (≥100 vs. <100), and ART (before the National Free ART Program vs. after the National Free ART Program) that might influence heterogeneity between studies. None of these factors were found to be statistically significant.

DISCUSSION

The overall pooled estimate of heterosexual HIV transmission was 1.68 (95% *CI* 0.74–2.62) per 100 PY. This estimate is lower than the corresponding rates found in several studies conducted in Africa (5.17–11.80 per 100 PY),[26–30] but similar to India (1.22 per 100 PY).[31] The differences in these transmission estimates may be associated with cofactors such as condom use, ulcerative sexually transmitted infections (STIs), frequency of sexual contact, and ART use.

A previous study that found transmission rates as high as 11.8 per 100 PY also had high rates of unprotected sex (with 89% never using condoms).[30] However, in the studies reviewed in this meta-analysis, condom use varied; in three of the reviewed studies, participants reported never using condoms, while two other studies reported 80% condom use. Ulcerative STIs are of further significance in understanding HIV transmission because they increase the infectivity and susceptibility to transmission. In a recent review of heterosexual transmission, pooled transmission estimates were five times higher when the negative partner had one or more ulcerative STIs.[9] The majority of the index cases in the reviewed studies were originally infected through unsanitary plasma donation, blood transfusion, and IDU, but few were infected through sexual transmission. Their partners, who had not engaged in other risky behavior besides heterosexual sex as defined by the exclusion criteria of the study, may also exhibit few risky behaviors outside of sexual contact with their regular partners. STI prevalence in the populations of the reviewed studies may have been low, which may be reflected in the low HIV transmission rate. STIs are an important risk factor for HIV infectivity and susceptibility,[32–34] Without measure of prevalent STIs, evaluating the accuracy of reported condom use is difficult and future studies of heterosexual transmission need more thorough measures of condom use and STIs.

The prospective study pooled transmission estimate (4.37 per 100 PY) was higher than the retrospective study estimate (1.46 per 100 PY). Any small difference between transmission estimates may be due to differing risk behaviors of these study populations. The three prospective studies were conducted in areas with large injection drug use epidemics and the five retrospective studies were conducted in areas impacted by unsanitary plasma donations and blood transfusions. However, the difference in transmission estimates between study design type did not reach statistical significance in meta-regression analysis and this is consistent with previous findings.[9]

Based on the six studies with sufficient information to extract data on direction of transmission, male-to-female and female-to-male transmission estimates were calculated. The male-to-female pooled estimate was 1.43 (95% *CI* 0.19–2.68) per 100 PY and was

higher than the female-to-male pooled estimate of 1.11 (95% *CI* 0.09–2.14). Both pooled transmission rates are lower than those found in Uganda (male-to-female transmission 12.0 per 100 PY and female-to-male transmission 11.6 per 100 PY)[30] and Tanzania (male-to-female 10 per 100 PY, female-to-male 5 per 100 PY).[27] In this study, direction of transmission was not significant in univariate meta-regression analysis (P=0.11) and this finding is generally inconsistent with previous research that has been conducted in Europe and the United States that has found significantly higher HIV transmission risk in male-to-female transmission in comparison to female-to-male transmission.[35,36] However, transmission estimates from developing countries have generally found a greater female-to-male transmission risk in comparison to that in developed countries[37] and some studies of serodiscordant couples in developing countries have not found significant differences in direction of transmission.[30,33] Some have hypothesized that higher female-to-male infectivity in resource poor countries is related to high female STI prevalence in these settings,[9] but insufficient data in the reviewed studies limit our ability to make the same conclusions.

Subgroup analysis of studies conducted before and after the initiation of the National Free Anretrotiviral Therapy Program indicates that the Chinese National Free Anretrotiviral Therapy Program may have lowered the risk of heterosexual HIV transmission. There was a dramatic decrease from 2.13 (95% *CI* 0–4.63) per 100 PY before 2003 to 1.44 (95% *CI* 0.62–2.26) per 100 PY after 2003. Estimating the transmission risk among ART users was limited by insufficient information in the reviewed studies. Three studies were conducted before 2003 and the participants in these studies were most likely not on ART because prior to this time very few patient had access to ART.[25,38,39] The pooled transmission estimate for those studies conducted prior to 2003 was lower than the corresponding transmission estimate of 5.64 (95% *CI* 3.28–9.70) per 100 PY reported in a recent review.[40] Further research considering ART status and adherence, as well as viral load, is needed to better characterize the HIV epidemic and its transmission among serodiscordant couples.

This study was subject to several limitations. There were insufficient data to stratify transmission rates according to STIs, condom use, sexual behaviors, viral load, CD4 count, ART use, adherence to ART, and other factors that may significantly impact the transmission risk associated with heterosexual HIV transmission among serodiscordant couples. In addition, some relevant studies were excluded because they did not have sufficient information to extract exposure time and transmission estimates. The included studies also did not provide sufficient data on frequency of sex. Previous research indicates that frequency of sex varies between countries.[41] This review was also subject to bias due to some of the assumptions used. In retrospective studies, follow-up time was calculated from diagnosis date, but date of infection and diagnosis date likely differ. In this study, we sought to explore the transmission risk associated with heterosexual contact only. However, the reviewed studies were subject to social desirability bias and participants may have been subject to unreported risk factors other than heterosexual with their regular partners that could influence their risk of HIV transmission. The included studies may also not be geographically representative of all serodiscordant couples in China since this analysis depended on available, published studies. This study was also subject to publication bias, as studies with no cases of HIV seroconversion may be less likely to be published.

This meta-analysis summarizes heterosexual transmission among serodiscordant couples in China. The results of this study indicate relatively low transmission among serodiscordant couples in China. This analysis also found high heterogenity across studies. Future research should investigate behavioral, virological, and biological risk factors to better understand and characterize heterosexual transmission of HIV in China.

Acknowledgments

This study was supported by the grants from the Fogarty International Center, National Institutes of Health Office of the Director, Office of AIDS Research, National Cancer Center, National Eye Institute, National Heart, Blood, and Lung Institute, National Institute of Dental & Craniofacial Research, National Institute On Drug Abuse, National Institute of Mental Health, National Institute of Allergy and Infectious Diseases Health, through the International Clinical Research Fellows Program at Vanderbilt (No. R24 TW007988) and the Mega-projects of Chinese National Science Research for the 11th Five-Year Plan (No. 2008ZX10001-003).

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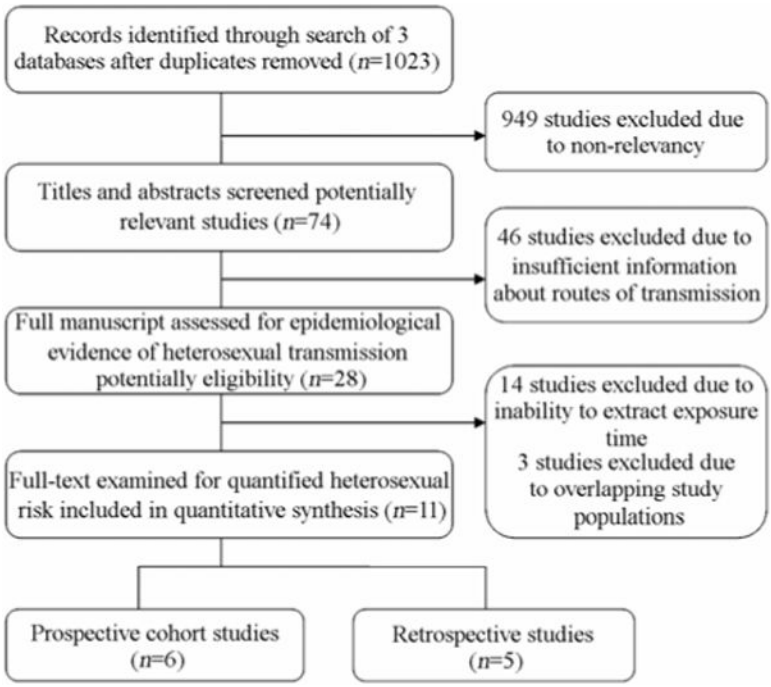

Figure 1.
Identification and selection of eligible studies.

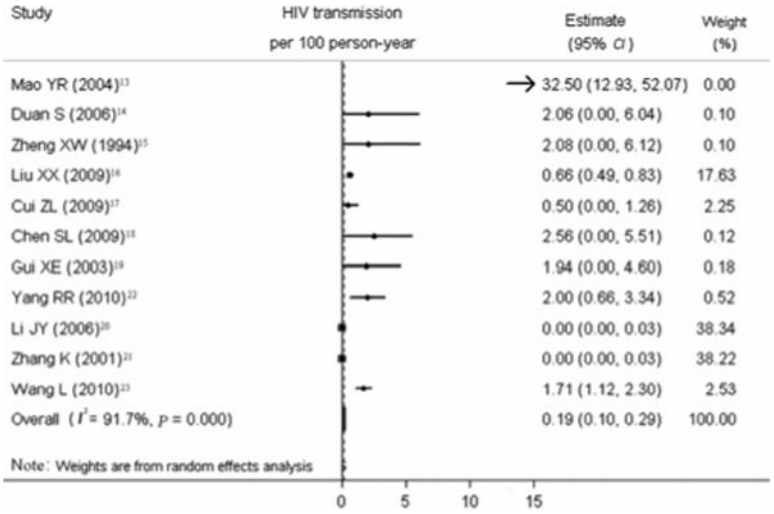

Figure 2.
Forest plot of individual and pooled HIV transmission estimates (per 100 person-years).

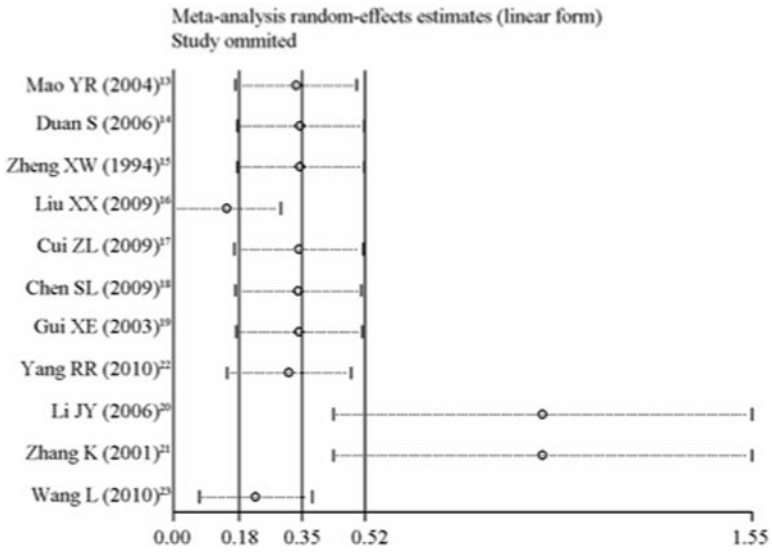

Figure 3.
Sensitivity analysis.

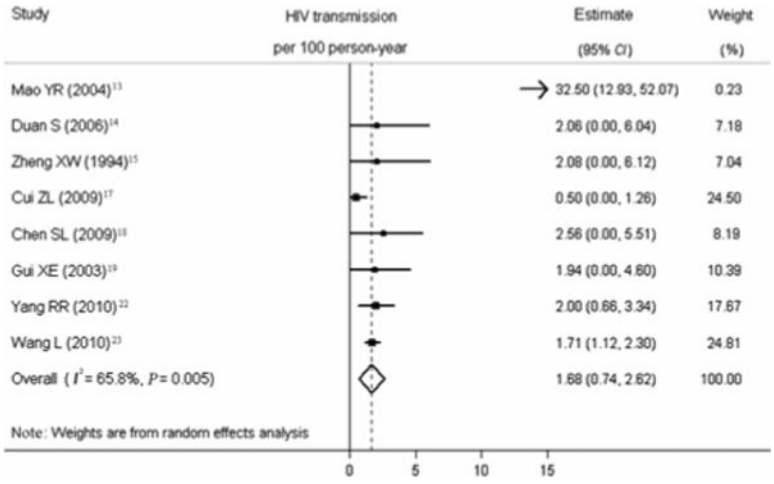

Figure 4.
Forest plot of individual and pooled HIV transmission estimates for included studies.

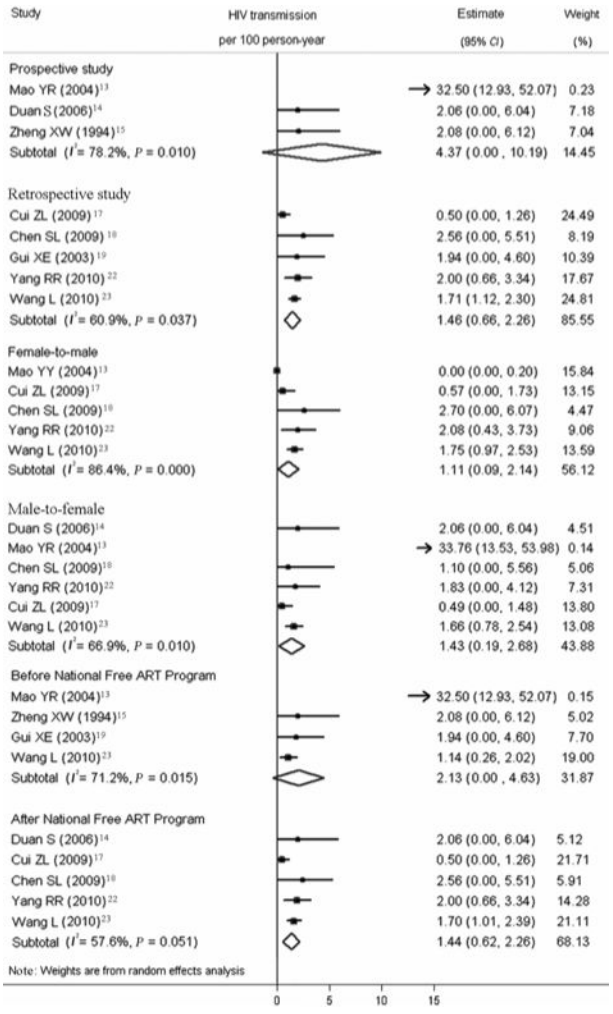

Figure 5.
Forest plot of transmission estimates stratified by study design, sex, and ART use.

Table

Characteristics of eligible studies

Studies	Location	Study design	Risk group of index case	Frequency of HIV tests (per year)	Index case	Total enrolled	Total follow-up (person years)	Study date	Chinese National ART Program	Female/male transmission	Male/female transmission
Chen SL[18]	Hebei	Retrospective	Blood recipient	N/A	19	110	741	2008	After	17/89	2/21
Cui ZL[17]	Henan	Retrospective	FPD	N/A	22	350	4200	2007	After	11/161	11/189
Duan S[14]	Yunnan	Prospective	IDU	1	2	49	97	2002–2005	After	N/A	2/49
Gui XE[19]	High-prevalence area	Retrospective	FPD Blood recipient	N/A	10	103	515	2002	Before	N/A	N/A
Li JY[20]	Henan	Prospective	FPD	0.5, 1.0, 2.5	0	52	66	2002–2005	After	N/A	N/A
Mao YR[13]	Xinjiang	Prospective	General population	0.5	8	22	24.6	1997–2000	Before	0/1	8/21
Liu XX[16]	Henan	Prospective	FPD	0.5	165	8664	24 998	2005–2008	After	N/A	N/A
Wang L[23]	Henan	Retrospective	FPD	N/A	84	1927	4918	2006–2008	After	49/1092	35/835
Yang RR[22]	High-prevalence area	Retrospective	FPD Blood recipient	N/A	94	420	4704	2005–2009	After	67/288	27/132
Zhang K[21]	Beijing	Prospective	Sexual transmission and Blood recipient	0.5	0	37	18.5	2000	Before	N/A	N/A
Zheng XW[15]	Yunnan	Prospective	IDU	1	1	48	48	1992–1993	Before	N/A	N/A

FPD: former plasma donor; IDU: injecting drug user.