Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003–11): a national observational cohort study

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Summary

Background On the basis of the results of the randomised clinical trial HPTN 052 and observational studies, WHO has recommended that antiretroviral therapy be offered to all HIV-infected individuals with uninfected partners of the opposite sex (serodiscordant couples) to reduce the risk of transmission. Whether or not such a public health approach is feasible and the outcomes are sustainable at a large scale and in a developing country setting has not previously been assessed.

Methods In this retrospective observational cohort study, we included treated and treatment-naive HIV-positive individuals with HIV-negative partners of the opposite sex who had been added to the national HIV epidemiology and treatment databases between Jan 1, 2003 and Dec 31, 2011. We analysed the annual rate of HIV infection in HIV-negative partners during follow-up, stratified by treatment status of the index partner. Cox proportional hazards analyses were done to examine factors related to HIV transmission.

Findings Based on data from 38 862 serodiscordant couples, with 101 295·1 person-years of follow-up for the seronegative partners, rates of HIV infection were 2·6 per 100 person-years (95% CI 2·4–2·8) among the 14 805 couples in the treatment-naive cohort (median baseline CD4 count for HIV-positive partners 441 cells per µl [IQR 314–590]) and 1·3 per 100 person-years (1·2–1·3) among the 24 057 couples in the treated cohort (median baseline CD4 count for HIV-positive partners 168 cells per µl [62–269]). We calculated a 26% relative reduction in HIV transmission (adjusted hazard ratio 0·74, 95% CI 0·65–0·84) in the treated cohort. The reduction in transmission was seen across almost all demographic subgroups and was significant in the first year (0·64, 0·54–0·76), and among couples in which the HIV-positive partner had been infected by blood or plasma transfusion (0·76, 0·59–0·99) or heterosexual intercourse (0·69, 0·56–0·84), but not among couples in which the HIV-positive partner was infected by injecting drugs (0·98, 0·71–1·36).

Interpretation Antiretroviral therapy for HIV-positive individuals in serodiscordant couples reduced HIV transmission across China, which suggests that the treatment-as-prevention approach is a feasible public health prevention strategy on a national scale in a developing country context. The durability and generalisability of such protection, however, needs to be further studied.

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Introduction

The beneficial role of antiretroviral therapy in reduction of mortality in people infected with HIV has been clearly shown.[1–5] The additional role of antiretroviral therapy in reduction of HIV viral load and thereby prevention of transmission of HIV[6,7] in serodiscordant couples (in which one partner is HIV-positive and the other HIV-negative) was suggested by investigators of several observational studies[8–10] and in 2011 was lent support by the results of the prospective, randomised clinical trial HPTN 052.[11] Because of the strength of these studies, but despite the absence of evidence to show the feasibility and durability of such a public health approach on a national scale, WHO has issued guidelines recommending that antiretroviral therapy be offered to the HIV-positive partner from all serodiscordant couples, irrespective of CD4 cell count, to reduce the risk of HIV transmission.[12]

By the end of 2011, China had an estimated 780 000 people infected with HIV. Since the beginning of the national treatment programme in 2003, a cumulative total of 157 050 individuals have received antiretroviral therapy.[13] One meta-analysis of studies in HIV serodiscordant couples from China reported an overall rate of 1·2 infections per 100 person-years (95% CI 0·9–1·7).[14] However, these individual studies did not measure the effect of antiretroviral treatment on transmission, so the meta-analysis was also unable to analyse the effect of treatment. The investigators did, however, suggest that treatment was beneficial on the basis of a subanalysis

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that showed a decrease in rates of infection in the years after the scale-up of treatment (2005–11), compared with the years before treatment was available (1994–2004). In this study, our aim was to measure the effect of antiretroviral therapy on the transmission of HIV in serodiscordant couples across China, and thereby assess the feasibility and durability of such a treatment-as-prevention approach on a national scale in a developing country context.

Methods

Study design and procedures

All individuals in China who test HIV-positive are reported to the National Center for AIDS/STD Control and Prevention at the Chinese Center for Disease Control and Prevention (China CDC). Baseline data from these individuals, including demographic characteristics, route of infection, and CD4 cell count, are captured in the national HIV epidemiology database. The local CDC follows up individuals who report a spouse or regular sex partner with whom they cohabit, and tests them for HIV, with repeat tests recommended every 6 months for partners who test negative. All HIV-positive individuals are also followed up every 6 months for a repeat CD4 cell count, with the data recorded in the epidemiology database. HIV-positive individuals who meet the Chinese national treatment criteria (WHO stage 3 or 4 disease or CD4 count of 350 cells per μl or less [cutoff increased from 200 cells per μl in 2008]) are referred for treatment with standard three-drug therapy, with subsequent treatment outcomes captured in the national HIV treatment database.[3,4,15,16]

We retrospectively analysed the national HIV epidemiology and treatment databases to identify seroconversion rates over time among HIV serodiscordant, heterosexual couples, stratified by HIV treatment status. Using data downloaded from these databases on

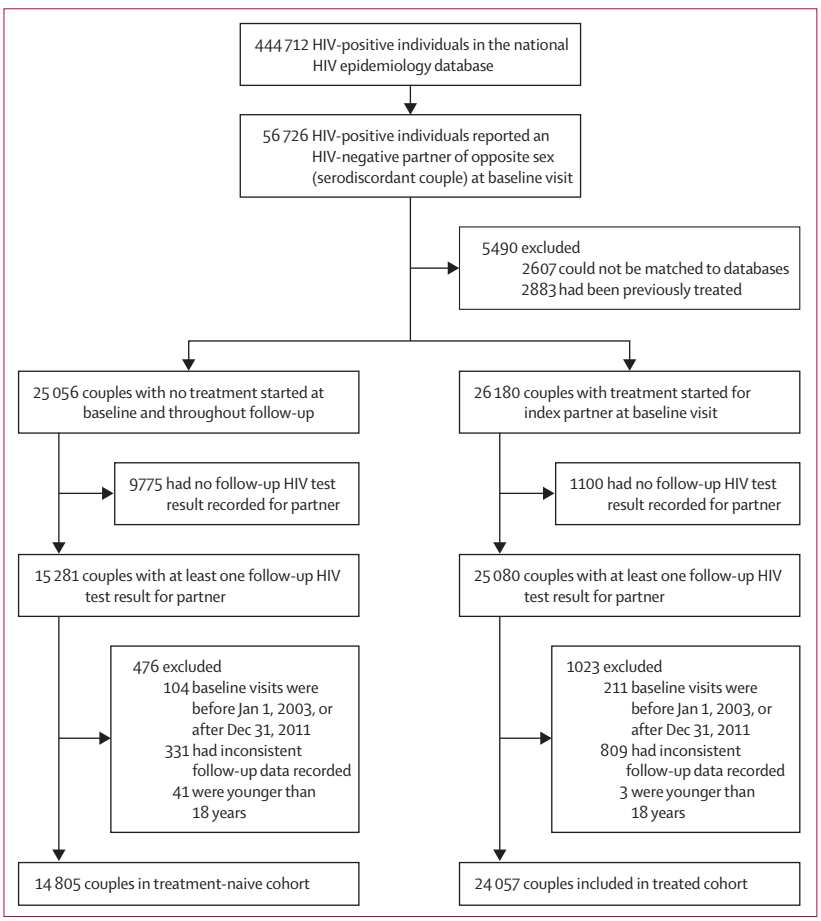

Figure 1: **Study profile**

	On treatment (n=24 057)	Treatment-naive (n=14 805)
Duration of follow-up (years)	2·4 (0·7–5·3)	1·2 (0·5–2·5)
Number of HIV tests for seronegative partner per year	2·6 (1·2)	2·0 (0·9)
Sex		
Male	14 273 (59%)	9685 (65%)
Female	9784 (41%)	5120 (35%)
Age (years)		
18–24	655 (3%)	1754 (12%)
25–44	15 971 (66%)	10 210 (69%)
≥45	7431 (31%)	2841 (19%)
Education		
No schooling	2166 (9%)	1476 (10%)
Primary school	8065 (34%)	4477 (30%)
Secondary school	10 157 (42%)	6317 (43%)
Post-secondary school	3390 (14%)	2305 (16%)
Missing data	279 (1%)	230 (2%)
Marital status		
Living with partner	2233 (9%)	2256 (15%)
Married	21 808 (91%)	12 531 (85%)
Missing data	16 (<1%)	18 (<1%)
Occupation		
Farmer	17 148 (71%)	9026 (61%)
Other	6909 (29%)	5779 (39·0%)
Route of HIV infection		
Blood or plasma transfusion	12 109 (50%)	2302 (16%)
Heterosexual intercourse	8710 (36%)	8163 (55%)
Homosexual intercourse*	929 (4%)	777 (5%)
Injecting drug use	1628 (7%)	2954 (20%)
Other or unknown	681 (3%)	609 (4%)
CD4 cell count (per μL)		
<250	11 006 (46%)	1856 (13%)
250–349	3063 (13%)	1183 (8%)
350–550	1117 (5%)	3977 (27%)
>550	427 (2%)	3098 (21%)
Missing data	8444 (35%)	4691 (32%)

Data are median (IQR), mean (SD), or n (%). *Homosexual intercourse refers to intercourse between two men only.

***Table 1:* Baseline characteristics of index patient (HIV-positive partner) by treatment**

Jan 1, 2012, we assessed serodiscordant couples from across the country reported between Jan 1, 2003 and Dec 31, 2011. A couple was defined as two people of opposite sex who reported a continuing sexual relationship, and who were either married or unmarried but living together. Serodiscordant couples from the databases were included if: at the baseline visit, one partner was HIV-positive (index patient or partner) and the other tested HIV-negative; and at least one additional follow-up HIV test result was recorded for the HIV-negative partner. Individuals in the treatment database were linked to their own records in the epidemiology database by use of their unique treatment identification numbers or national identification numbers.

Couples were stratified by treatment status of the index partner at the baseline visit into a treatment-naive (did not yet meet national treatment criteria) and a treated cohort. Baseline characteristics of the index patients were extracted from the databases and rates of HIV seroconversion calculated for the two groups. To ensure no overlap between the cohorts, only couples that were treatment-naive at baseline and throughout follow-up were included in the treatment-naive cohort. Individuals from either cohort for whom key data were missing or inconsistent (seemingly because of errors in data entry) were excluded. The analysis was reviewed and approved by the institutional review board of the National Center for AIDS/STD Control and Prevention at China CDC.

The primary outcome was annual rate of HIV infection in HIV-negative partners during the 9 years of follow-up, stratified by whether or not the index patient was treated. The date of HIV seroconversion was defined as the midway point between the last negative test date and the first positive test date. Rates of infection were also stratified according to the baseline characteristics of the index partner: age, sex, CD4 count (<250, 250–349, 350–550, or >550 cells per μL), route of infection (heterosexual intercourse, male homosexual intercourse, blood or plasma transfusion, or injecting drug use), education status, occupation, and marital status.

Statistical analysis

The rate of HIV infection was calculated by dividing the number of seroconversions each year by the total number of person-years that year. We used Kaplan-Meier analysis to calculate the survival probabilities for the remaining HIV-negative partners by year, and used Cox proportional hazards ratios to compare rates of infection between the two groups. Couples who were lost to follow-up (including couples who separated during the follow-up period) or in which either partner died were right-censored on the date of last contact.

To investigate whether the rate of infection differed by treatment status of the index patient, we compared univariate and multivariate Cox proportional hazards regression analyses, stratified by treatment status, to estimate hazard ratios (HRs; reported with 95% CIs). Factors included in the adjusted models were duration of follow-up, sociodemographic variables (sex, age, education, marital status, and occupation), route of HIV infection, and baseline CD4 cell count of the index patient. For the route of infection, HIV has mainly been transmitted in China through sexual contact, injecting drug use, and, in the early-to-mid-1990s, plasma donation[17] (included in our analysis under the category of index patients infected by blood or plasma transfusion). Each of these three transmission groups has different demographic characteristics and different continuing transmission risks for sexual partners.

Although we were unable to include specific sexual risk variables (frequency of sexual intercourse, number of partners, other sexually transmitted infections, condom use), since these were not captured in the databases, we did compare rates of HIV transmission and adjusted HRs for each transmission group directly between individuals who were treated and those who were not. Additionally, for those HIV-negative partners who became infected, we further examined univariate and multivariate Cox proportional HRs for factors related to infection. This analysis used the same variables as were used to calculate the adjusted HRs and was also stratified by treatment status.

A two-sided p value of 0·05 or less was regarded as significant. The data linkage between the epidemiology and treatment databases was double-checked in both a relational database designed in SQL Server 2008 and in SPSS version 17.0. Statistical analyses were done with SPSS version 17.0.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

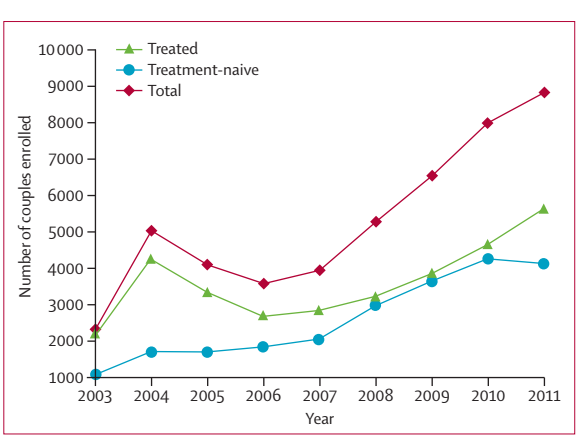

Figure 2: **Serodiscordant couples enrolled, by year**

Results

As of Dec 31, 2011, 444712 HIV-positive individuals were recorded in China's national HIV epidemiology database. 56726 of these individuals were identified as having an HIV serodiscordant spouse or cohabiting partner of the opposite sex at their baseline visit. 2607 couples were excluded because their epidemiology and treatment database records could not be matched, and a further 2883 couples were excluded because they had previously received treatment. Of the remaining couples, 26180 had treatment started for the index patient at the baseline visit and 25056 remained treatment-naive throughout

	On treatment (n=24057)			Treatment-naive (n=14805)			HR (95% CI)	Adjusted HR (95% CI)
	Seroconversions	Person-years	Rate* (95% CI)	Seroconversions	Person-years	Rate* (95% CI)		
Total	935	74536·8	1·3 (1·2–1·3)	696	26758·3	2·6 (2·4–2·8)	0·61 (0·55–0·67)	0·74 (0·65–0·84)
Duration of follow-up								
≤1 year	463	19793·8	2·3 (2·1–2·6)	467	11122·3	4·2 (3·8–4·6)	0·56 (0·49–0·63)	0·64 (0·54–0·76)
>1 to ≤2 years	196	14793·7	1·3 (1·1–1·5)	127	6334·1	2·0 (1·7–2·4)	0·66 (0·53–0·82)	0·75 (0·56–1·01)
>2 to ≤3 years	111	11658·1	1·0 (0·8–1·1)	55	3842·3	1·4 (1·1–1·8)	0·67 (0·48–0·92)	0·87 (0·57–1·34)
>3 to ≤4 years	65	9231·4	0·7 (0·5–0·9)	26	2251·4	1·2 (0·7–1·6)	0·61 (0·39–0·96)	0·99 (0·55–1·79)
>4 to ≤5 years	42	7400·7	0·6 (0·4–0·7)	13	1494·2	0·9 (0·4–1·3)	0·65 (0·35–1·21)	0·81 (0·37–1·76)
>5 to ≤6 years	22	5776·1	0·4 (0·2–0·5)	4	1009·0	0·4 (0·0–0·8)	0·96 (0·33–2·79)	1·42 (0·41–4·93)
>6 to ≤7 years	23	4023·3	0·6 (0·3–0·8)	3	572·2	0·5 (0·0–1·1)	1·09 (0·33–3·63)	1·16 (0·24–5·64)
>7 to ≤9 years	13	1859·7	0·7 (0·3–1·1)	1	132·8	0·8 (0·0–2·2)	0·93 (0·12–7·09)	0·17 (0·02–1·67)
Index patient baseline characteristics								
Sex								
Male	498	39665·6	1·3 (1·1–1·4)	393	17170·0	2·3 (2·1–2·5)	0·66 (0·58–0·76)	0·75 (0·63–0·90)
Female	437	34871·1	1·3 (1·1–1·4)	303	9588·3	3·2 (2·8–3·5)	0·53 (0·45–0·61)	0·73 (0·60–0·88)
Age (years)								
18–24	25	1038·5	2·4 (1·5–3·4)	104	2816·9	3·7 (3·0–4·4)	0·67 (0·43–1·04)	0·97 (0·57–1·65)
25–44	635	51621·9	1·2 (1·1–1·3)	478	19781·9	2·4 (2·2–2·6)	0·64 (0·57–0·72)	0·80 (0·69–0·94)
≥45	275	21876·4	1·3 (1·1–1·4)	114	4159·6	2·7 (2·2–3·2)	0·59 (0·47–0·73)	0·60 (0·46–0·78)
Education								
No schooling	104	8636·6	1·2 (1·0–1·4)	69	2681·9	2·6 (2·0–3·2)	0·63 (0·46–0·86)	0·92 (0·61–1·41)
Primary school	360	28652·2	1·3 (1·1–1·4)	242	8843·2	2·7 (2·4–3·1)	0·57 (0·49–0·68)	0·67 (0·55–0·83)
Secondary school	363	29911·2	1·2 (1·1–1·3)	285	11547·9	2·5 (2·2–2·8)	0·61 (0·52–0·71)	0·73 (0·60–0·90)
Post-secondary school	91	6309·0	1·4 (1·1–1·7)	89	3204·8	2·8 (2·2–3·4)	0·62 (0·46–0·83)	0·73 (0·49–1·09)
Missing data	17	1027·7	1·7 (0·9–2·4)	11	480·5	2·3 (0·9–3·6)	0·90 (0·42–1·96)	0·85 (0·34–2·12)
Marital status								
Living with partner	107	5472·5	2·0 (1·6–2·3)	88	3554·7	2·5 (2·0–3·0)	0·87 (0·66–1·16)	1·25 (0·85–1·83)
Married	827	69009·7	1·2 (1·1–1·3)	608	23171·7	2·6 (2·4–2·8)	0·58 (0·52–0·64)	0·68 (0·60–0·79)
Missing data	1	54·6	1·8 (0·0–5·4)	0	31·9	..	..	..
Occupation								
Farmer	705	61904·6	1·1 (1·1–1·2)	450	18532·3	2·4 (2·2–2·7)	0·59 (0·52–0·66)	0·74 (0·63–0·86)
Other	230	12632·1	1·8 (1·6–2·1)	246	8226·0	3·0 (2·6–3·4)	0·68 (0·57–0·82)	0·71 (0·56–0·89)
Route of HIV infection								
Blood or plasma transfusion	495	55794·3	0·9 (0·8–1·0)	86	8463·9	1·0 (0·8–1·2)	0·91 (0·72–1·14)	0·76 (0·59–0·99)
Homosexual intercourse†	9	959·4	0·9 (0·3–1·6)	18	779·5	2·3 (1·2–3·4)	0·39 (0·17–0·88)	0·50 (0·17–1·45)
Heterosexual intercourse	309	12836·9	2·4 (2·1–2·7)	412	10787·3	3·8 (3·5–4·2)	0·67 (0·58–0·78)	0·69 (0·56–0·84)
Injecting drug use	94	3255·3	2·9 (2·3–3·5)	152	5599·5	2·7 (2·3–3·1)	1·11 (0·86–1·43)	0·98 (0·71–1·36)
Other or unknown	28	1690·9	1·7 (1·0–2·3)	28	1128·1	2·5 (1·6–3·4)	0·76 (0·45–1·29)	0·51 (0·27–0·95)
CD4 cell count (per μL)								
<250	394	23630·0	1·7 (1·5–1·9)	83	2460·0	3·4 (2·6–4·1)	0·57 (0·45–0·72)	0·62 (0·49–0·79)
250–349	87	5650·6	1·5 (1·2–1·9)	52	2255·7	2·3 (1·8–2·9)	0·66 (0·47–0·94)	0·69 (0·49–0·98)
350–550	30	3220·2	0·9 (0·6–1·3)	186	6774·9	2·7 (2·4–3·1)	0·45 (0·31–0·67)	0·64 (0·41–0·98)
>550	15	1293·9	1·2 (0·6–1·7)	131	6112·8	2·1 (1·8–2·5)	0·75 (0·44–1·29)	1·52 (0·84–2·74)
Missing data	409	40742·1	1·0 (0·9–1·1)	244	9154·8	2·7 (2·3–3·0)	0·50 (0·42–0·58)	0·80 (0·65–0·99)

HR=hazard ratio. *Rate is number of seroconversions per 100 person-years. †Homosexual intercourse refers to intercourse between two men only.

Table 2: **Comparison of seroconversion rates by duration of follow-up and baseline characteristics of the index patient (HIV-positive partner)**

follow-up. After exclusion of couples who had no follow-up visits, did not have their baseline visit between 2003 and 2011, had inconsistent follow-up dates reported, or in which the index partner was younger than 18 years at baseline, 24 057 couples were included in the treated cohort and 14 805 couples were included in the treatment-naive cohort (figure 1). The baseline characteristics of the index patients from the two groups were similar in terms of sex, education, marital status, and occupation, but also had some notable differences (table 1). Treated patients were generally older than treatment-naive patients, were predominantly infected via blood or plasma transfusion, and had a median follow-up of 2·4 years, whereas treatment-naive patients were predominantly infected sexually and had a median follow-up of only 1·2 years. Baseline CD4 cell counts were also significantly lower (p<0·0001) in the treated patients (median 168 cells per µl [IQR 62–269]) than in patients from the treatment-naive cohort (median 441 cells per µl [314–590]). Because of an increased emphasis on early diagnosis and treatment of HIV-infected individuals in China in recent years, 20 412 (53%) couples included in the analysis were enrolled from 2009 to 2011 (figure 2).

From 2003 to 2011, 1631 HIV transmissions were identified, which gives an overall rate of 1·6 per 100 person-years (95% CI 1·5–1·7). The rate of transmission in the treated cohort (1·3 per 100 person-years, 1·2–1·3) was significantly lower (p<0·0001) than that in the treatment-naive cohort (2·6 per 100 person-years, 2·4–2·8), with an overall 26% reduction in risk of HIV transmission from antiretroviral treatment (adjusted HR 0·74, 95% CI 0·65–0·84; table 2). The difference in cumulative probability of infection for the HIV-negative partner was greatest in the first year of follow-up, with this difference maintained fairly stably in the subsequent years (figure 3).

Because some baseline characteristics differed between the treated and untreated cohorts, we also calculated rates of HIV transmission stratified by these baseline characteristics to allow for direct comparisons, and adjusted the HRs to control for confounding (table 2). The adjusted HR for transmission stratified by baseline characteristic was almost always protective for the treated cohort, but the difference was not always significant. With respect to the duration of follow-up, treatment was significantly protective in the first year of follow-up (adjusted HR 0·64, 95% CI 0·54–0·76), but not in the second year (0·75, 0·56–1·01) or in subsequent years. Treatment was significantly protective when the index partner had been infected by blood or plasma transfusion (0·76, 0·59–0·99), or heterosexual intercourse (0·69, 0·56–0·84), but not when they had been infected by male homosexual intercourse (0·50, 0·17–1·45) or by injecting drugs (0·98, 0·71–1·36). Finally, treatment significantly protected the sexual partners of those with baseline CD4 counts of 550 cells per µl or less (table 2).

For seronegative partners who became infected with HIV during follow-up, a Cox proportional hazards analysis was done to identify risk factors for HIV infection, stratified by treatment status (table 3). Women were more likely than men to transmit the virus to their seronegative partner, irrespective of treatment status (treatment-naive adjusted HR 1·45, 95% CI 1·22–1·72; treated 1·18, 1·03–1·36). For the treatment-naive cohort, the partners of patients with baseline CD4 counts of 250 cells per µl or more were significantly protected against HIV transmission compared with those whose partners had baseline counts of less than 250 cells per µl, whereas for those whose partners were on treatment, baseline CD4 counts were no longer a risk factor for infection. Compared with the partners of patients who had been infected via blood or plasma transfusion, those whose partners were infected through heterosexual intercourse or drug injection were at much higher risk of HIV infection, irrespective of treatment status (heterosexual intercourse [treatment-naive], 2·73, 2·11–3·53; heterosexual intercourse [treated], 2·14, 1·78–2·56; injecting drug use [treatment-naive], 2·53, 1·88–3·42; injecting drug use [treated], 2·95, 2·28–3·81). For the treatment-naive cohort, infection of the index partner by male homosexual intercourse was a risk factor for infection of the HIV-negative partner compared with infection of the index partner by blood or plasma transfusion (1·96, 1·13–3·38), whereas infection of the index partner by male homosexual intercourse was no longer a risk factor for patients who were on treatment (0·88, 0·44–1·76). Being married was protective compared with living with a partner for those whose partners were on treatment (0·75, 0·61–0·93), but not for those with treatment-naive partners (1·19, 0·95–1·49).

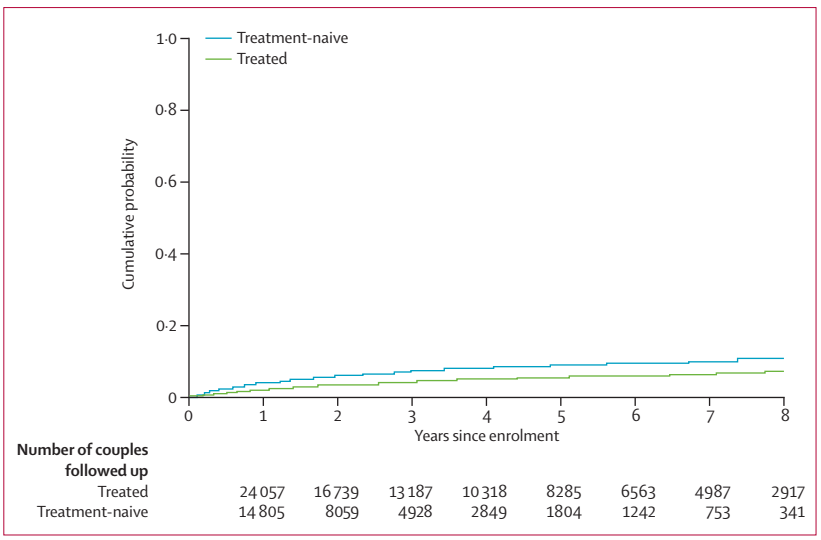

Figure 3: **Cumulative probability of HIV-negative partner in serodiscordant couple becoming infected with HIV, by number of years since enrolment**

Discussion

In this retrospective analysis of China's national HIV epidemiology and treatment databases from 2003 to

	On treatment (n=24 057)		Treatment-naive (n=14 805)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Sex				
Male	1·00	1·00	1·00	1·00
Female	1·09 (0·96–1·24)	1·18 (1·03–1·36)	1·41(1·22–1·64)	1·45 (1·22–1·72)
Age (years)				
18–24	1·00	1·00	1·00	1·00
25–44	0·68 (0·46–1·02)	1·02 (0·67–1·56)	0·74 (0·60–0·91)	0·96 (0·77–1·21)
≥45	0·68 (0·45–1·02)	1·09 (0·71–1·68)	0·78 (0·60–1·02)	1·10 (0·82–1·48)
Education				
No schooling	1·00	1·00	1·00	1·00
Primary school	1·00 (0·81–1·25)	0·98 (0·78–1·23)	1·15 (0·88–1·50)	1·24 (0·95–1·63)
Secondary school	0·90 (0·72–1·12)	0·81 (0·64–1·03)	0·99 (0·76–1·29)	1·03 (0·78–1·36)
Post-secondary school	0·89 (0·67–1·18)	0·72 (0·52–1·00)	0·97 (0·71–1·32)	1·03 (0·72–1·46)
Marital status				
Living with partner	1·00	1·00	1·00	1·00
Married legally	0·69 (0·56–0·85)	0·75 (0·61–0·93)	1·18 (0·95–1·48)	1·19 (0·95–1·49)
Occupation				
Farmer	1·00	1·00	1·00	1·00
Other	1·23 (1·05–1·43)	0·91 (0·75–1·10)	1·02 (0·87–1·19)	0·94 (0·78–1·12)
Transmission route				
Blood or plasma transfusion	1·00	1·00	1·00	1·00
Homosexual intercourse*	0·65 (0·34–1·27)	0·88 (0·44–1·76)	1·36 (0·81–2·28)	1·96 (1·13–3·38)
Heterosexual intercourse	1·88 (1·62–2·19)	2·14 (1·78–2·56)	2·53 (1·98–3·23)	2·73 (2·11–3·53)
Injecting drug use	2·49 (1·99–3·11)	2·95 (2·28–3·81)	2·00 (1·52–2·63)	2·53 (1·88–3·42)
Other or unknown	1·51 (1·03–2·22)	1·50 (0·91–2·46)	1·83 (1·19–2·82)	1·61 (0·96–2·72)
Baseline CD4 cell count (per μL)				
<250	1·00	1·00	1·00	1·00
250–349	0·89 (0·71–1·13)	0·84 (0·66–1·06)	0·74 (0·52–1·05)	0·68 (0·47–0·96)
350–550	0·67 (0·46–0·97)	0·78 (0·54–1·13)	0·83 (0·64–1·07)	0·75 (0·58–0·98)
>550	0·86 (0·52–1·45)	1·03 (0·61–1·73)	0·68 (0·52–0·90)	0·63 (0·47–0·83)
Missing data	0·80 (0·69–0·92)	0·95 (0·81–1·11)	0·81 (0·63–1·04)	0·74 (0·58–0·96)

All characteristics are for the index patient (HIV-positive partner). HR=hazard ratio. *Homosexual intercourse refers to intercourse between two men only.

Table 3: **Risk factors for HIV transmission, stratified by treatment status of HIV-positive partner**

2011, which included 38 862 treatment-naive and treated HIV serodiscordant couples, we noted a 26% relative reduction in HIV infection in couples in which the index patient was treated for HIV (panel). The reduction in transmission was significant in the first year of follow-up and was seen across most baseline demographic characteristics, with a few exceptions.

Antiretroviral treatment as a method of preventing HIV transmission among sexually active, HIV serodiscordant couples was lent substantial support by the prospective, randomised clinical trial HPTN 052,[11] in which early initiation of treatment resulted in an 89% relative reduction in the total number of transmissions (HR 0·11, 95% CI 0·04–0·32) and a 96% relative reduction (0·04, 0·01–0·27) in linked HIV transmissions, under rigorous clinical trial conditions. However, whether or not such a prevention strategy would be feasible under real-world conditions—with treatment non-adherence, resistance, and the potential for more frequent non-linked HIV transmissions—was unknown. That our results show a significant (p<0·0001) 26% reduction in HIV transmission under real-world conditions in a developing country suggests that such a public health prevention strategy is feasible on a national scale and helps to validate the WHO recommendation in support of the treatment-as-prevention approach.[12]

Our results accord with the reduction of HIV transmission shown in previous studies to be associated with antiretroviral treatment, but how durable this protection is remains unclear. In our analysis, protection was only significant in the first year (table 2). The reasons for the absence of statistical significance in our results after that period are not clear from our analysis. On the one hand, a continued protective effect might still exist, but our study might have been underpowered to measure this, particularly because of the falling numbers of seroconversions in the later years of the study. On the other hand, protectiveness might diminish over time, possibly related to factors such as the natural history of HIV transmission in serodiscordant couples or the development of resistance to treatment.[17–19] Among the treatment-naive serodiscordant couples in our analysis (who received no treatment throughout the analysis), the rate of infections fell over the duration of follow-up (table 2). This decrease could reflect the natural history of infection among serodiscordant couples, whereby those susceptible to infection are usually infected within a specific amount of time, irrespective of treatment status.[18,19] Alternatively, the decrease might be a bias of our observational cohort, whereby those individuals with longer follow-up were weighted towards the former plasma donors, who were the first cohort in China to be targeted for HIV surveillance and treatment.[17] The plasma donors were generally poor, rural farmers with more sexually conservative lifestyles than the other groups studied.

Increasing rates of resistance to treatment is another factor that might contribute to the reduction in the protective benefit of treatment over time.[20] Second-line treatment regimens are still not widely available across China, and a previous analysis of the country's national HIV treatment programme identified a cumulative immunological treatment failure proportion of 50% at 5 years on first-line treatment.[16] In a separate analysis, 33% of patients on treatment for 2 years or more in China were in virological treatment failure.[21] Further analyses need to be done on individuals who did and did not transmit the virus, stratified by treatment success or failure. Such analyses would provide a better measure of the durability of the treatment-as-prevention strategy than we have at present and could provide an impetus to rapidly scale up second-line regimens. Durability will also be affected by available resources and drug regimens, and thus could be different for developing

countries and developed countries. Additional studies would therefore help to inform the implementation of WHO's recommendation to offer treatment to all serodiscordant couples.

Treatment reduced transmission in individuals whose partners were infected by blood or plasma transfusion or heterosexual intercourse. HIV-negative individuals whose partners were infected by male homosexual intercourse had a strong protective benefit as well, but the result was not significant, probably because of the small number of infections. Additional analyses need to be done to understand why the partners of people who were infected by injecting drugs were not protected, but potential contributing factors include poor treatment adherence and non-linked HIV transmissions.[5,17,22] Because this was an observational study, HIV transmissions could not be linked to the source partner. Sexual partners of drug users might also inject drugs and therefore could have higher rates of infection than others because of sharing needles with drug users other than their regular sexual partner, thereby negating the preventive effect of the treatment. Non-linked transmissions could also help to account for why couples who were living together but not married were not protected by treatment (1·25, 0·85–1·83), whereas married couples were protected (0·68, 0·60–0·79).

In both the treated and treatment-naive cohorts, female index patients were more likely to transmit HIV to their partners than were male index patients. Several studies,[23–26] but not all,[27,28] have reported that male-to-female transmission of HIV is more efficient than female-to-male transmission. Overall, receptive penile-vaginal intercourse has been estimated to be twice as risky as insertive penile-vaginal intercourse.[29] Our results run contrary to this estimate, but are similar to what was reported in the HPTN 052 study,[11] although that result was not significant. Additional research is needed to understand this discrepancy between the results of different studies.

Our study has several limitations. First, as we have already mentioned, we had no genotypic data to link HIV transmissions with the source patient. Treatment would obviously not be expected to prevent HIV transmission from someone other than the treated sexual partner, and the extent of outside relationships can affect rates of infection substantially.[30] However, even without this information, the 26% relative reduction in HIV infections in this study reassures that the treatment-as-prevention strategy is still effective at a population level in a real-world setting. Second, the median duration of follow-up was fairly short—1·2 years for treatment-naive patients and 2·4 years for treated patients—because more than half of the couples included were identified in the past 2 years (2009–11). As such, the long-term durability of the protectiveness of treatment needs to be confirmed with additional studies. Third, because the route of infection of the index patient was self-reported, some misreporting could have taken place, particularly for the sexual and injecting drug-use routes of transmission. Finally, because this was a retrospective observational cohort study and not prospectively randomised, rates of infection might be underestimated and biases such as differences in the baseline characteristics between the two groups might account for some of the prevention effect. Some partners who became infected probably never returned for repeat HIV tests, which possibly means that we have underestimated the rates of infection. However, with means of 2·0 HIV tests per year for the partners of the treatment-naive patients and 2·6 tests per year for the partners of the treated patients, the potential underestimation should not be large. Additionally, with more frequent tests on average done in the partners of the treated patients, infections in that cohort were more likely to be identified than in the partners of the treatment-naive patients, which would narrow the difference between the two groups. Thus, the 26% relative reduction in transmission could be an underestimate of the true value.

Since the patients in the treated cohort had much lower baseline CD4 cell counts than did the treatment-naive patients, which is often associated with higher viral loads, the protective effect seen in our study might be a low estimate of the efficacy of the treatment-as-prevention approach, which is more precisely measured by clinical trials such as HPTN 052 than by an observational study.[11] On the other hand, the untreated cohort of patients was younger, more sexually active, and had higher CD4 cell counts than the treated cohort—differences that bias away from the null and challenge the inferences from our analysis. In view of the results of our multivariate

Panel: Research in context

Systematic review

We searched Web of Science with the terms "HIV-1", "discordant couples", and "treatment" for articles published in English up to June 1, 2012. Several observational studies and one randomised controlled trial were identified, with the data summarised in a Cochrane Review.[8] Additionally, we reviewed the references from the WHO report[12] that recommended that antiretroviral therapy be offered to all serodiscordant couples, which was published on April 1, 2012.

Interpretation

Antiretroviral therapy for HIV serodiscordant couples reduced HIV transmission across China. These results substantiate the previous evidence from smaller observational studies and one randomised clinical trial that the treatment-as-prevention approach is a feasible public health prevention strategy on a national scale and in a developing country context. The durability and generalisability of such protection, however, needs to be further investigated.

model and the cofactors that we took into account, we believe that overall HIV transmission was reduced by antiretroviral treatment, even when adjusted for potential confounding factors such as age, duration of follow-up, route of transmission, and baseline CD4 cell count. Unfortunately, because the data were not available, we were unable to adjust for individual sexual risk factors, adherence to antiretroviral treatment, or virological treatment outcome measures.

Our results strongly support the population-wide, real-world feasibility of treating HIV-positive individuals in serodiscordant couples to prevent HIV transmission in a developing country setting, as has already been shown to be effective in a randomised clinical trial.[11] How durable this protection is over time and whether or not these results are generalisable to other risk groups, such as injecting drug users,[31] are not clear from our analysis and need to be further studied to establish how widely such a treatment-as-prevention public health approach can be implemented.

Contributors

ZJ and YS were responsible for study design and planning; ZJ, RYC, and YS contributed to writing the report; ZJ, YR, QL, PX, and YS contributed to data analysis; ZJ, YR, RYC, and YS contributed to interpretation; QL, PX, PL, and XW contributed to data cleaning. YMao designed the discordant couples programme and helped to facilitate the recruitment of couples to the national cohort, contributed to data collection, management, and maintenance of the programme database. FZ was responsible for the planning and study design of the national antiviral treatment programme and contributed to data analysis and interpretation of the programme database. ZL oversees the management of the national antiviral treatment programme and was responsible for the planning and study design of the programme. YMa was responsible for the data management of the national free antiretroviral treatment programme. YZ helped to implement the strategy for antiretroviral therapy in serodiscordant couples. LuW manages the national HIV epidemiology database; ZDo and DZ contributed to data collection and cleaning of the national treatment database. JL, HT, JH, XJ, JX, EL, and RX contributed to data cleaning and on-site data correction to ensure data quality for the national HIV follow-up database. WG, ZDi, QQ, LiW contributed to data collection and cleaning of the national HIV epidemiology database.

Conflicts of interest

We declare that we have no conflicts of interest.

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