Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study

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Lancet HIV 2018; 5: e438–47

Published Online July 16, 2018 http://dx.doi.org/10.1016/S2352-3018(18)30132-2

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Summary

Background Evidence on viral load and HIV transmission risk in HIV-serodiscordant male homosexual couples is limited to one published study. We calculated transmission rates in couples reporting condomless anal intercourse (CLAI), when HIV-positive partners were virally suppressed, and daily pre-exposure prophylaxis (PrEP) was not used by HIV-negative partners.

Methods In the Opposites Attract observational cohort study, serodiscordant male homosexual couples were recruited from 13 clinics in Australia, one in Brazil, and one in Thailand. At study visits, HIV-negative partners provided information on sexual behaviour and were tested for HIV and sexually transmitted infections; HIV-positive partners had HIV viral load tests, CD4 cell count, and sexually transmitted infection tests done. Viral suppression was defined as less than 200 copies per mL. Linked within-couple HIV transmissions were identified with phylogenetic analysis. Incidence was calculated per couple-year of follow-up, focusing on periods with CLAI, no use of daily PrEP, and viral suppression. One-sided upper 95% CI limits for HIV transmission rates were calculated with exact Poisson methods.

Findings From May 8, 2012, to March 31, 2016, in Australia, and May 7, 2014, to March 31, 2016, in Brazil and Thailand, 358 couples were enrolled. 343 couples had at least one follow-up visit and were followed up for 588·4 couple-years. 258 (75%) of 343 HIV-positive partners had viral loads consistently less than 200 copies per mL and 115 (34%) of 343 HIV-negative partners used daily PrEP during follow-up. 253 (74%) of 343 couples reported within-couple CLAI during follow-up, with a total of 16 800 CLAI acts. Three new HIV infections occurred but none were phylogenetically linked. There were 232·2 couple-years of follow-up and 12 447 CLAI acts in periods when CLAI was reported, HIV-positive partners were virally suppressed, and HIV-negative partners did not use daily PrEP, resulting in an upper CI limit of 1·59 per 100 couple-years of follow-up for transmission rate.

Interpretation HIV treatment as prevention is effective in men who have sex with men. Increasing HIV testing and linking to immediate treatment is an important strategy in HIV prevention in homosexual men.

Funding National Health and Medical Research Council; amfAR, The Foundation for AIDS Research; ViiV Healthcare; and Gilead Sciences.

Introduction

Studies in HIV serodiscordant couples have provided crucial evidence on the role of antiretroviral therapy (ART) and viral load suppression in reducing the risk of HIV transmission.[1] In 2011, the HPTN 052 trial[2] reported that early ART reduced HIV transmission risk by 96% in heterosexual serodiscordant couples. However, data in male homosexual couples have been scarce. In 2016, the PARTNER study[3] reported no phylogenetically linked HIV transmissions in 415 couple-years of follow-up in male homosexual couples reporting condomless anal intercourse (CLAI), in which HIV-positive partners were virally suppressed and HIV-negative partners reported no use of pre-exposure prophylaxis (PrEP). The upper limit of the CI around this transmission rate of zero was 0·89 per 100 couple-years of follow-up.

Global ART guidelines recommend immediate initiation of ART on HIV diagnosis, in part because of the benefits of ART in preventing transmission.[4] PrEP has also emerged as a highly effective means to reduce HIV acquisition risk in HIV-negative homosexual men,[5,6] and is recommended for serodiscordant couples in some guidelines.[7]

More data on the efficacy of viral suppression to reduce HIV transmission risk in men who have sex with men are required to generate precise estimates of risk. The aim of this study was to determine risk of HIV transmission in serodiscordant male homosexual couples, focusing on periods in which couples reported CLAI, daily PrEP was not used by the HIV-negative partner, and the HIV-positive partner was virally suppressed. We also examined HIV transmission risk in the presence of sexually transmitted

Research in context

Evidence before this study

The role of antiretroviral therapy and viral suppression in reducing the risk of HIV transmission has been proven in heterosexual serodiscordant couples, but such data in serodiscordant homosexual male couples are scarce. The only published study reported no phylogenetically linked transmissions in European male homosexual couples during 415 couple-years of follow-up in which condomless anal intercourse was reported, the HIV-positive partners had viral loads less than 200 copies per mL, and the HIV-negative partner was not taking pre-exposure prophylaxis.

Added value of this study

The Opposites Attract study examined the association between antiretroviral therapy and viral load and HIV transmission in serodiscordant male homosexual couples in Australia, Brazil, and Thailand. The primary aim of this analysis was to measure HIV transmission risk in these couples, focusing on periods in which couples reported condomless anal intercourse, daily pre-exposure prophylaxis was not used by the HIV-negative partner, and the HIV-positive partner was virally suppressed. We also examined transmission risk in the context of concurrent sexually transmitted infections and recent antiretrovial therapy initiation. No cases of linked transmission within couples were reported. Our findings contribute to existing evidence that the risk of onward HIV transmission is very low when viral loads of HIV-positive partners are suppressed. Across studies, no phylogenetically linked transmissions have been reported in serodiscordant couples after nearly 35 000 acts of condomless anal intercourse in homosexual male couples, in whom viral load is suppressed and the HIV-negative partners are not taking daily pre-exposure prophylaxis.

Implications of all the available evidence

The PARTNER and Opposites Attract studies have reported no linked transmissions despite nearly 35 000 acts of condomless anal intercourse in HIV serodiscordant male homosexual couples not using daily pre-exposure prophylaxis. Longer-term follow-up of couples in existing studies will allow for greater certainty and confidence in treatment as prevention as a highly effective HIV prevention strategy in men who have sex with men. Increasing HIV testing and linking to immediate treatment is an important strategy in HIV prevention in homosexual men.

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infections (STIs), recent ART initiation, and combination HIV prevention.

Methods

Study design and participants

Opposites Attract is a prospective, observational, cohort study of serodiscordant male homosexual couples, done in 13 clinics in Australia (Brisbane, Melbourne, and Sydney), one in Rio de Janeiro, Brazil, and one in Bangkok, Thailand. The study protocol is published elsewhere[8] and was approved by institutional human research ethics committees in each country as appropriate.

Homosexual men in sexual partnerships were eligible if both partners were aged at least 18 years, one partner was HIV-positive and the other tested HIV-negative at baseline, partners were having anal sex with each other at least monthly (with or without condoms), partners expected they would still be having anal sex with each other at the HIV-positive partner's next viral load test, and both partners agreed to attend clinic visits at least twice per year. Couples were eligible regardless of ART status in HIV-positive partners and PrEP use by HIV-negative partners.

At enrolment, written informed consent was obtained from all participants.

Procedures

Both partners attended an enrolment visit at the clinic where the study was explained. All couples were assessed on their knowledge about how to reduce the risk of HIV transmission and were provided with education, which included information on postexposure prophylaxis and PrEP. The study did not offer postexposure prophylaxis or PrEP; however, no limitations were placed on clinics for initiating HIV-negative partners on either of these interventions as needed. Testing for HIV viral load and CD4 cell count in HIV-positive partners, and HIV antibodies in HIV-negative partners was done at every visit: blood samples were collected for storage at some visits (at baseline for both partners; once per year during follow-up for HIV-positive partners). Follow-up visits occurred at least twice a year. In Australia, visits were in line with regular viral load monitoring of the HIV-positive partner, commonly 3–6 months apart and had to be at least 1 month apart; in Brazil and Thailand, visits were every 6 months. Partner visits were scheduled within 2 weeks of each other. In case of seroconversion of the initially HIV-negative partner, blood samples were collected from both partners. Blood samples were processed and stored as serum, plasma, and buffy coat. Local diagnostic testing was done according to standardised testing regimens for each site and country. Further laboratory-based testing confirmed HIV-positive test results. In Australia, STI tests were done at most follow-up visits as recommended in Australian guidelines[9] and based on clinic-specific procedures; clinicians decided in consultation with their patients whether STI testing was necessary. In Brazil and Thailand, syphilis testing and urethral and rectal gonorrhoea and chlamydia nucleic acid amplification-based tests were done at every study visit. Both partners in each couple completed online computer-assisted self-interviews at each visit, either in

their homes (Australia) or on a clinic computer in a private area of the clinic (Brazil and Thailand). At follow-up visits, couples stated if they were still having within-couple anal sex at least once per month on average; couples that did not fulfil this criterion, either because of having no or less frequent anal sex or break-up, ceased participation.

Clinical data were collected via electronic case report forms, including ART regimens, HIV viral loads, and CD4 cell counts in the HIV-positive partner, HIV serology results in the HIV-negative partner, and STI test results in both partners. Clinics reported viral load in copies per mL if the test result was detectable, and the test's lower limit of detection if undetectable. Viral suppression was defined as less than 200 copies per mL to allow comparison with other research and ensure consistency across sites.[3] 12 study visits were excluded because results of viral load tests were not available. HIV antibody test results were not available for 30 study visits; however, in 23 cases, these visits were included because of subsequent HIV-negative test results. Testing data for infectious syphilis and urethral and rectal gonorrhoea and chlamydia were included (defined as any STI for this analysis).

Participants completed computer-assisted self-interview questionnaires in English, Brazilian Portuguese, or Thai. Baseline questionnaires covered the 3 months before the visit; follow-up questionnaires covered the period since the previous visit. Participants reported demographic information, sexual identity, and length of time since first having sex together. HIV-positive partners provided self-reported adherence to ART (0–100% of ART pills taken in the previous period). HIV-negative partners reported details of PrEP use and sexual behaviour within the couple and with outside partners (including number of anal intercourse acts, condom use, sexual positioning, and ejaculation or withdrawal before ejaculation during receptive anal intercourse). HIV-negative partners selected the number of acts for each category of anal intercourse (none, one, two, three to five, six to ten, 11 to 30, 31 to 50, and more than 50). For the analysis of ranges, the midpoint was taken as the number of acts; more than 50 was taken as 51 acts. Daily PrEP was defined as the HIV-negative partner reporting PrEP use on all or most days of the previous period.

Phylogenetic analysis in couples who had a seroconversion was done at the prespecified interim analysis in Dec, 2014,[10] and the end of the study, on the basis of blood samples taken from both partners at the time of HIV diagnosis. Frozen EDTA plasma was used to obtain *pol* and *env* sequences from plasma RNA with ViroSeq, version 2.0, (Abbott Laboratories, Lake Bluff, IL, USA) and an in-house tropism RNA assay. Sequences were aligned with MUSCLE (European Bioinformatics Institute, Cambridge, UK) and edited with Geneious, version 9.1.4 (Biomatters Ltd, Auckland, New Zealand). Subtype was determined with REGA, version 3.0 (REGA Institute, Leuven, Belgium). Sequences were obtained from the same laboratory site from newly-diagnosed patients with the same subtype and in the same calendar

	HIV-positive partner					HIV-negative partner				
	Total (n=343)	Australia (n=153)	Brazil (n=93)	Thailand (n=97)	p value*	Total (n=343)	Australia (n=153)	Brazil (n=93)	Thailand (n=97)	p value*
Age, years	34·4 (27·7–43·9)	39·1 (32·8–48·2)	34·6 (28·0–42·8)	27·9 (23·7–33·7)	<0·0001	34·1 (27·4–43·4)	38·7 (32·2–46·9)	32·7 (26·5–42·1)	29·3 (24·9–36·8)	<0·0001
Ethnicity	..	..	..	..	<0·0001	..	..	..	..	<0·0001
White or Caucasian	167 (49%)	123 (80%)	43 (46%)	1 (1%)	..	170 (50%)	134 (88%)	35 (38%)	1 (1%)	..
Asian	116 (34%)	18 (12%)	2 (2%)	96 (99%)	..	111 (32%)	13 (8%)	2 (2%)	96 (99%)	..
Black	16 (5%)	1 (1%)	15 (16%)	0	..	15 (4%)	0	15 (16%)	0	..
Indigenous	2 (1%)	2 (1%)	0	0	..	3 (1%)	1 (1%)	2 (2%)	0	..
Other or mixed, or both	42 (12%)	9 (6%)	33 (36%)	0	..	44 (13%)	5 (3%)	39 (42%)	0	..
Education	..	..	..	..	<0·0001	..	..	..	..	<0·0001
High school or lower	104 (30%)	28 (18%)	46 (50%)	30 (31%)	..	93 (27%)	29 (19%)	40 (43%)	24 (25%)	..
Vocational education	69 (20%)	54 (35%)	9 (10%)	6 (6%)	..	61 (18%)	41 (27%)	11 (12%)	9 (9%)	..
University	168 (49%)	70 (46%)	38 (41%)	60 (62%)	..	188 (55%)	82 (54%)	42 (45%)	64 (66%)	..
Missing	2 (1%)	1 (1%)	0	1 (1%)	..	1 (<1%)	1 (1%)	0	0	..
Sexual identity	..	..	..	..	0·006	..	..	..	..	<0·0001
Gay	321 (94%)	151 (99%)	81 (87%)	89 (92%)	..	315 (92%)	149 (97%)	83 (89%)	83 (86%)	..
Bisexual	17 (5%)	1 (1%)	9 (10%)	7 (7%)	..	19 (6%)	1 (1%)	5 (5%)	13 (13%)	..
Other	5 (1%)	1 (1%)	3 (3%)	1 (1%)	..	9 (3%)	3 (2%)	5 (5%)	1 (1%)	..

Data are median (IQR) or n (%). *p value for differences between the three countries using χ^2 tests for categorical variables and Kruskal-Wallis test for age. Differences between HIV-positive and HIV-negative partners in these variables were not significant.

Table 1: **Demographic characteristics of couples contributing to the primary endpoint analysis**

year to provide temporally, geographically, and epidemiologically relevant local controls. Local controls for *env* sequences were not available in Thailand so were chosen from the 20 closest sequences by use of a GenBank BLAST search. Positive controls included replicate samples from the same individual. Maximum likelihood and Bayesian Markov Chain Monte-Carlo phylogenetic trees were inferred with IQ-tree, version 1.5.5[11] and BEAST, version 1.8.4.[12] A transmission pair was defined by sequences with a pairwise genetic distance of less than 0·015 substitutions per site, as well as monophyletic branch grouping with a bootstrap value of more than 90 or a posterior probability of more than 0·95.[3,13]

For **GenBank BLAST** see https://blast.ncbi.nlm.nih.gov/Blast.cgi

Statistical analysis

Detailed power calculations have been published previously, and were guided by evidence available in 2011 when the protocol was written.[8] We powered

	Total (n=343)	Australia (n=153)	Brazil (n=93)	Thailand (n=97)	p value*
Time since first sex together (reported by HIV-negative partner)	..	..	..	..	0·001
<6 months	81 (24%)	24 (16%)	27 (29%)	30 (31%)	..
6–12 months	64 (19%)	26 (17%)	23 (25%)	15 (16%)	..
1–5 years	118 (34%)	54 (35%)	29 (31%)	35 (36%)	..
>5 years	80 (23%)	49 (32%)	14 (15%)	17 (18%)	..
CLAI within couples in previous 3 months (reported by HIV-negative partner)	..	..	..	..	<0·0001
Always condom use or no CLAI	156 (45%)	48 (31%)	49 (53%)	59 (61%)	..
Some CLAI, some condom use	126 (37%)	56 (37%)	38 (41%)	32 (33%)	..
Always CLAI	61 (18%)	49 (32%)	6 (6%)	6 (6%)	..
Sex with outside partners (reported by HIV-negative partner)	..	..	..	..	..
Any sex with outside partners	136 (40%)	74 (48%)	18 (19%)	44 (45%)	<0·0001
Any CLAI with outside partners	59 (17%)	42 (27%)	3 (3%)	14 (14%)	<0·0001
HIV-positive partner taking ART at baseline visit	274 (80%)	139 (91%)	79 (85%)	56 (58%)	<0·0001
More than 90% adherence to ART in previous 3 months (reported by HIV-positive partner)†	241 (88%)	121 (87%)	71 (90%)	49 (88%)	0·34
Viral load result of HIV-positive partner	..	..	..	..	<0·0001
<200 copies per mL	267 (78%)	134 (88%)	79 (85%)	54 (56%)	..
200–9999 copies per mL	28 (8%)	9 (6%)	9 (10%)	10 (10%)	..
10 000–99 999 copies per mL	34 (10%)	8 (5%)	3 (3%)	23 (24%)	..
≥100 000 copies per mL	14 (4%)	2 (1%)	2 (2%)	10 (10%)	..
CD4 count of HIV-positive partner	628·8 (292·8)	695·1 (268·6)	693·2 (315·5)	464·6 (239·2)	<0·0001
Daily PrEP use in previous 3 months (reported by HIV-negative partner)	26 (8%)	7 (5%)	12 (13%)	7 (7%)	0·11
STIs diagnosed at baseline visit in HIV-positive partner	..	..	..	..	..
Any STI‡	46 (13%)	12 (8%)	15 (16%)	19 (20%)	0·020
Infectious syphilis	17 (5%)	3 (2%)	11 (12%)	3 (3%)	0·002
Rectal gonorrhoea	9 (3%)	3 (2%)	2 (2%)	4 (4%)	0·55
Urethral gonorrhoea	1 (<1%)	1 (1%)	0	0	0·54
Rectal chlamydia	24 (7%)	6 (4%)	4 (4%)	14 (14%)	0·003
Urethral chlamydia	2 (1%)§	0	0	2 (2%)¶	0·078
STIs diagnosed at baseline visit in HIV-negative partner	..	..	..	..	..
Any STI‡	39 (11%)	9 (6%)	16 (17%)	14 (14%)	0·013
Infectious syphilis	14 (4%)	2 (1%)	10 (11%)	2 (2%)	0·0001
Rectal gonorrhoea	8 (2%)	5 (3%)	2 (2%)	1 (1%)	0·52
Urethral gonorrhoea	1 (<1%)	1 (1%)	0	0	0·54
Rectal chlamydia	14 (4%)	3 (2%)	4 (4%)	7 (7%)	0·12
Urethral chlamydia	9 (3%)§	1 (1%)	1 (1%)	7 (7%)¶	0·004

Data are n (%) or mean (SD). CLAI=condomless anal intercourse. ART=antiretroviral therapy. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. *p value for differences between the three countries using χ^2 tests for categorical variables and analysis of variance for CD4 cell count. †Among those taking ART, n=274. ‡STIs included were infectious syphilis, rectal and urethral gonorrhoea, and rectal and urethral chlamydia. §Significant differences between HIV-positive and HIV-negative partners on diagnosed STIs at p<0·05. ¶Significant differences between HIV-positive and HIV-negative partners on diagnosed STIs at p<0·01.

Table 2: **Baseline characteristics of couples contributing to the primary endpoint analysis**

the study under two scenarios. First, if at least one phylogenetically linked transmission was seen in couples with detectable viral load, and 40% of HIV-positive men had detectable viral loads, then a study including 640 couple-years had at least 80% power to detect a greater than 75% reduction in the incidence of HIV in the partners, assuming an incidence rate of 5·0 per 100 person-years in those with detectable viral load.[14] Second, to allow for increasing ART levels, if no linked transmissions were seen, we calculated that a study of 640 couple-years of follow-up would lead to a one-sided 95% upper CI limit of the HIV incidence in partnerships with undetectable viral load being 0·64 per 100 person-years, if 90% of HIV-positive participants had undetectable viral load. These power calculations did not account for use of other HIV prevention techniques.

Data were analysed in Stata, version 14.2. Visits for couples were excluded from this analysis if the HIV or viral load test result was not available (n=36). Differences between countries, HIV-positive and HIV-negative partners, and those included and excluded from the primary analysis, were determined by univariable χ^2 tests, *t* tests, analysis of variance tests, or Kruskal-Wallis tests. The primary analysis involved the calculation of incidence rates of phylogenetically linked HIV infection by dividing the number of linked infections by the total number of couple-years of follow-up in various risk strata. Couple-years of follow-up were determined as periods between

	Total (n=343)	Australia (n=153)	Brazil (n=93)	Thailand (n=97)	p value*
Years in study	1·69 (0·88–2·22)	2·01 (1·07–3·18)	1·53 (1·01–2·09)	0·95 (0·68–1·83)	<0·0001
Any CLAI with study partner during follow-up (reported by HIV-negative partner)	253 (74%)	136 (89%)	64 (69%)	53 (55%)	<0·0001
Reported CLAI acts with study partner (reported by HIV-negative partner)	16 800	12 389	3731	681	..
Sex with outside partners (reported by HIV-negative partner)	..	..	..	..	..
Any sex with outside partners	216 (63%)	109 (71%)	47 (51%)	60 (62%)	0·005
Any CLAI with outside partners	132 (39%)	84 (55%)	23 (25%)	25 (26%)	<0·0001
Reported CLAI acts with outside partners	4710	3773	564	373	..
ART in HIV-positive partner during follow-up	..	..	..	..	<0·0001
Never took ART	6 (2%)	1 (1%)	2 (2%)	3 (3%)	..
Started ART during follow-up	85 (25%)	22 (14%)	18 (19%)	45 (46%)	..
Always on ART	252 (73%)	130 (85%)	73 (78%)	49 (51%)	..
Viral load of HIV-positive partner during follow-up	..	..	..	..	<0·0001
Consistently less than 200 copies per mL	258 (75%)	130 (85%)	75 (81%)	53 (55%)	..
Variably less than and more than 200 copies per mL	78 (23%)	22 (14%)	15 (16%)	41 (42%)	..
Consistently at least 200 copies per mL	7 (2%)	1 (1%)	3 (3%)	3 (3%)	..
Daily PrEP use at any time during follow-up (reported by HIV-negative partner)	115 (34%)	41 (27%)	38 (41%)	36 (37%)	0·052
STIs diagnosed during follow-up in HIV-positive partner					
Any STI†	115 (34%)‡	45 (29%)	33 (35%)	37 (38%)‡	0·33
Infectious syphilis	48 (14%)	18 (12%)	18 (19%)	12 (12%)	0·22
Rectal gonorrhoea	22 (6%)	9 (6%)	4 (4%)	9 (9%)	0·35
Urethral gonorrhoea	6 (2%)	2 (1%)	3 (3%)	1 (1%)	0·44
Rectal chlamydia	57 (17%)§	22 (14%)	10 (11%)	25 (26%)‡	0·013
Urethral chlamydia	16 (5%)	11 (7%)	2 (2%)	3 (3%)‡	0·13
STIs diagnosed during follow-up in HIV-negative partner					
Any STI†	85 (25%)‡	37 (24%)	24 (26%)	24 (25%)‡	0·96
Infectious syphilis	33 (10%)	11 (7%)	17 (18%)	5 (5%)	0·004
Rectal gonorrhoea	25 (7%)	18 (12%)	4 (4%)	3 (3%)	0·016
Urethral gonorrhoea	10 (3%)	6 (4%)	2 (2%)	2 (2%)	0·61
Rectal chlamydia	31 (9%)§	15 (10%)	4 (4%)	12 (12%)‡	0·14
Urethral chlamydia	20 (6%)	8 (5%)	1 (1%)	11 (11%)‡	0·010

Data are median (IQR) or n (%). CLAI=condomless anal intercourse. ART=antiretroviral therapy. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. *p value for differences between the three countries using χ^2 tests for categorical variables and Kruskal-Wallis test for years in study. †STIs included were infectious syphilis, rectal and urethral gonorrhoea, and rectal and urethral chlamydia. ‡Significant differences between HIV-positive and HIV-negative partners on diagnosed STIs at p<0·05. §Significant differences between HIV-positive and HIV-negative partners on diagnosed STIs at p<0·01.

Table 3: **Follow-up characteristics of couples contributing to the primary endpoint analysis**

clinic visits by the HIV-negative partner where HIV serology was done. CIs around the transmission rate were calculated with exact Poisson methods.[15] Transmission rates were calculated in predefined risk strata including presence of CLAI and sexual position, use of daily PrEP by the HIV-negative partner, viral load result for the HIV-positive partner, STIs diagnosed, and recent ART initiation (defined as initiation since the last study visit) in the HIV-positive partner. For each incidence rate presented, we give the number of linked transmissions, number of couple-years of follow-up, estimated number of CLAI acts, and the 95% CI. For incidence rates of zero, we present one-sided CIs. Incidence rates for STIs were calculated by use of the same method as for HIV.

Role of the funding source

The funders 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 the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were enrolled from May 8, 2012, to March 31, 2016, in Australia, and May 7, 2014, to March 31, 2016, in Brazil and Thailand, and were followed up until Dec 31, 2016. Of 358 couples enrolled, 157 (44%) were enrolled in Australia, 96 (27%) in Brazil, and 105 (29%) in Thailand. 343 (96%) of 358 couples attended at least one follow-up visit and were included in this analysis; 153 (45%) in Australia, 93 (27%) in Brazil, and 97 (28%) in Thailand (table 1). All included couples contributed 588·4 couple-years of follow-up (327·4 years from Australia, 145·1 years from Brazil, and 115·9 years from Thailand). Median per couple follow-up was 1·7 (IQR 0·9–2·2) years and median time between visits was 4·4 (3·2–5·7) months. 230 (67%) of 343 couples participated from enrolment to the end of the study. Of 113 couples who did not continue until the end, 72 (64%) became ineligible for study participation before the end of the study: 60 (83%) ceased within-couple anal intercourse entirely or broke-up, ten (14%) reported anal intercourse less than once per month on average, and two (3%) died in separate couples. The remaining 41 couples (36%) withdrew for other reasons or were lost to-follow-up before the end of the study. Differences were not significant in HIV-positive partner viral load or within-couple CLAI between couples who were enrolled until the end of the study, were no longer eligible, or were lost to follow-up.

Australian participants were older than those from Brazil and Thailand (p<0·0001) and more likely to be white or Caucasian. More than half of the Brazilian participants were not white or Caucasian, and in Thailand, almost all were Thai. About half of the participants were university educated and most identified as gay (table 1).

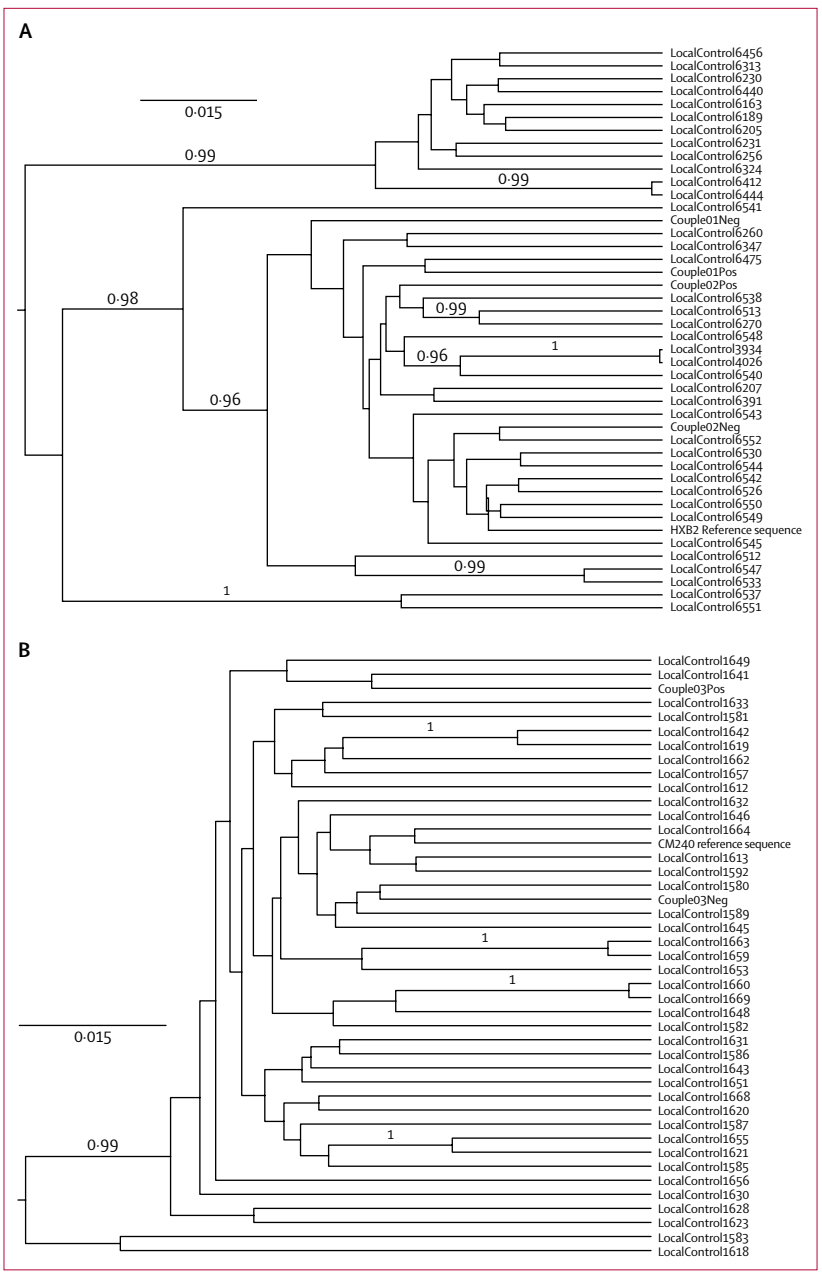

Figure: **Phylogenetic trees of *pol* sequences**
Bayesian Markov Chain Monte-Carlo inference showing couples 1 and 2 with subtype B infection (A) and couple 3 with subtype CRF_AE01 infection (B). Pos and Neg suffix indicates initially HIV-positive and HIV-negative partners. Branch length is proportional to genetic distance. Branches with a posterior probability more than 0·95 are labelled.

145 couples (42%) first had sex with each other within the 12 months before baseline. Australian couples had been together longer than couples from Brazil and Thailand (p=0·003). 187 HIV-negative partners (55%) reported within-couple CLAI in the previous 3 months; Australian couples were more likely to report CLAI than Brazilian or Thai couples (p<0·0001). At baseline, 59 (17%) HIV-negative partners reported CLAI with outside partners. 274 (80%) HIV-positive partners were taking

	Linked transmissions	Couple-years of follow-up	CLAI acts	Upper limit of one-sided 95% CI for HIV incidence
Overall	0	588·4	16 800	0·63
Viral load				
HIV-positive partner viral load more than 200 copies	0	28·4	499	12·99
HIV-positive partner viral load less than 200 copies	0	560·0	16 301	0·66
PrEP				
Any daily PrEP use by HIV-negative partner	0	117·5	4115	3·14
No daily PrEP use by HIV-negative partner	0	440·9	12 685	0·84
CLAI				
No CLAI reported	0	242·3	0	1·52
Any CLAI reported	0	317·0	16 800	1·16
Combination HIV prevention				
Viral load less than 200 copies, daily PrEP use reported, or no CLAI reported, or all these	0	582·5	16 561	0·63
Viral load more than 200 copies, no daily PrEP use, and CLAI reported	0	5·8	239	63·32
Sexual position for CLAI				
Insertive CLAI	0	278·5	10 675	1·32
Receptive CLAI with withdrawal	0	153·8	2939	2·40
Receptive CLAI with ejaculation	0	99·6	3187	3·70
STIs*				
Any STI diagnosed (either partner)	0	76·9	1910	4·80
Any STI diagnosed (HIV-positive partner)	0	56·4	1391	6·55
Urethral STI diagnosed (HIV-positive partner)†	0	8·5	376	43·31
Any STI diagnosed (HIV-negative partner)	0	32·4	975	11·37
Rectal STI diagnosed (HIV-negative partner)‡	0	16·6	428	22·27
Commencement of ART				
Started ART since last visit	0	27·1	221	13·63
Did not start ART since last visit	0	561·3	16 579	0·66

Data are according to sexual behaviour, viral load, diagnosis of sexually transmitted infection (STI), and antiretroviral therapy (ART) during study follow-up. No linked transmissions occurred. CLAI=condomless anal intercourse. PrEP=pre-exposure prophylaxis. *STIs included were active syphilis, rectal and urethral gonorrhoea, and rectal and urethral chlamydia. †Urethral STIs included were urethral gonorrhoea and urethral chlamydia. ‡Rectal STIs included were rectal gonorrhoea and rectal chlamydia.

Table 4: **Linked HIV transmissions within couples and incidence during follow-up**

ART: 91% in Australia, 85% in Brazil, and 58% in Thailand (p<0·0001), and self-reported adherence was high. At baseline, 267 (78%) HIV-positive partners had viral loads less than 200 copies per mL: 88% in Australia, 85% in Brazil, and 56% in Thailand (p<0·0001). 26 (8%) HIV-negative partners reported use of daily PrEP. 46 (13%) HIV-positive and 39 (11%) HIV-negative partners were diagnosed with infectious syphilis, or urethral or rectal gonorrhoea or chlamydia (any STI; p=0·43) at baseline; STIs were more than twice as prevalent in Brazil and Thailand than in Australia in HIV-positive (p=0·020) and HIV-negative partners (p=0·013; table 2).

253 (74%) HIV-negative partners reported some within-couple CLAI during follow-up, totalling 16 800 CLAI acts (53·3% of the total 31 527 within-couple anal intercourse acts). During follow-up, 89% of Australian, 69% of Brazilian, and 55% of Thai couples reported CLAI (p<0·0001); 74% of CLAI acts were in Australian couples. During follow-up, 39% of HIV-negative partners reported CLAI with outside partners (table 3).

Among HIV-positive partners, 73% took ART throughout follow-up, a quarter started ART during follow-up, and 2% did not take ART at any time. Similarly, three quarters had viral loads consistently less than 200 copies per mL, 23% had viral loads variably less and more than 200 copies per mL (67 started at >200 copies per mL then became consistently <200 during the study), and 2% had viral loads consistently 200 copies per mL or more. Thai participants were less likely to have been on ART and have viral loads consistently less than 200 copies per mL for the entirety of follow-up than were Australian or Brazilian participants (p<0·0001), because of the lower proportion being on ART at baseline. 34% of HIV-negative partners took daily PrEP at some point during follow-up.

A third of HIV-positive and a quarter of HIV-negative partners were diagnosed with an STI during follow-up (p=0·012); STI incidence was 22·8 (95% CI 19·3–27·0) per 100 person-years in HIV-positive partners and 15·1 (12·3–18·6) per 100 person-years in HIV-negative partners (p=0·003). HIV-positive partners had a higher incidence of rectal chlamydia than HIV-negative partners (p=0·003). Concerning the STIs most important for potential HIV transmission, incidence of urethral STIs in the HIV-positive partners was 3·9 (95% CI 2·6–5·9) per 100 person-years and incidence of a rectal STI in HIV-negative partners was 7·6 (5·7–10·2) per 100 person-years. A higher proportion of HIV-positive partners in Thailand were diagnosed with rectal chlamydia than in Australia and Brazil (p=0·013). In HIV-negative partners, the most common STI was infectious syphilis in Brazil (p=0·004), rectal gonorrhoea in Australia (p=0·016), and urethral chlamydia in Thailand (p=0·010).

Three incident HIV infections occurred; an incidence rate of 0·51 (95% CI 0·16–1·58) per 100 person-years. All partners who seroconverted reported CLAI with at least one outside partner in the period before diagnosis. The incidence rate in HIV-negative partners who reported CLAI with outside partners was 2·35 (0·76–7·30) per 100 person-years. Partners who seroconverted acquired HIV subtype B in couples 1 and 2, and subtype CRF_01AE in couple 3. Blood samples for phylogenetic analysis were collected at a median of 6 (range 0–12) days after diagnosis. No samples clustered together on phylogenetic analysis of either *pol* or *env* sequences. Pairwise genetic distance was more than 0·015 in each couple; therefore, no transmissions were phylogenetically linked (figure).

The incidence rate of within-couple HIV transmission was zero, with an overall upper limit of the 95% CI of 0·63 per 100 couple-years of follow-up (table 4). HIV-positive partners had viral loads less than 200 copies per mL in 95·2% of the total couple-years of follow-up. HIV-negative partners reported use of daily PrEP in

20·0% of the couple-years of follow-up. Within-couple CLAI was reported in 53·9% of the couple-years of follow-up and the upper CI limit for within-couple transmission for these periods was 1·16 per 100 couple-years of follow-up. Only 5·8 couple-years of follow-up and 239 CLAI acts were not protected by condoms, daily PrEP, or viral suppression (1·0% of the total couple-years of follow-up). Of 239 CLAI acts reported, 219 were when viral loads of HIV-positive partners were more than 1000 copies per mL. Periods before an STI was diagnosed in either partner accounted for 13·1% of couple-years of follow-up, whereas periods in which the HIV-positive partner commenced ART since the last visit accounted for 4·6% of couple-years of follow-up.

Periods when within-couple CLAI was reported, viral loads of HIV-positive partners were less than 200 copies per mL, and daily PrEP was not used by HIV-negative partners accounted for 232·2 couple-years of follow-up (39·5% of the total couple-years of follow-up). No linked HIV transmissions were reported (table 5).

	Linked transmissions	Couple-years of follow-up	CLAI acts	Upper limit of one-sided 95% CI for HIV incidence
Overall	0	232·2	12 447	1·59
Sexual position for CLAI				
Insertive CLAI	0	202·2	8081	1·82
Receptive CLAI with withdrawal	0	102·6	1958	3·60
Receptive CLAI with ejaculation	0	66·7	2408	5·53
STIs*				
Any STI diagnosed (either partner)	0	21·1	948	17·48
Any STI diagnosed (HIV-positive partner)	0	15·4	745	23·97
Urethral STI diagnosed (HIV-positive partner)†	0	2·4	90	155·94
Any STI diagnosed (HIV-negative partner)	0	8·95	381	41·23
Rectal STI diagnosed (HIV-negative partner)‡	0	5·3	162	69·27
Commencement of ART				
Started ART since last visit	0	6·1	145	60·07
Did not start ART since last visit	0	226·1	12 302	1·63

Data are according to sexual behaviour, diagnosis of sexually transmitted infection (STI), and antiretroviral therapy (ART). No linked transmissions occurred. CLAI=condomless anal intercourse. *STIs included were active syphilis, rectal and urethral gonorrhoea, and rectal and urethral chlamydia. †Urethral STIs included were urethral gonorrhoea and urethral chlamydia. ‡Rectal STIs included were rectal gonorrhoea and rectal chlamydia.

Table 5: **Linked HIV transmissions and incidence during periods when CLAI was reported, viral load less than 200 copies per mL and PrEP not used**

Discussion

In this cohort study of serodiscordant male homosexual couples, we found no phylogenetically linked HIV transmissions. In periods when HIV-positive partners were virally suppressed, HIV-negative partners did not use daily PrEP, and when couples reported CLAI, the HIV transmission rate was zero. The upper limit of the 95% CI around zero was 1·59 per 100 couple-years of follow-up, with a total of 232·2 couple-years of follow-up and 12 447 reported CLAI acts in these periods. Three unlinked infections were reported, giving an overall incidence rate of 0·51 per 100 person-years. This study provides evidence that HIV transmission in the context of viral suppression is very low, although we cannot exclude higher levels of risk based on the upper CI limit.

Several potential caveats to the effectiveness of treatment as prevention in serodiscordant couples have been raised in medical literature. First, STIs have the potential to increase HIV transmission risk,[16,17] but evidence for the context of viral suppression is scarce.[18] Despite a baseline STI prevalence of more than 10%, and an incidence of about 15–20 per 100 person-years within Opposites Attract, no linked transmissions were observed. PARTNER also showed no transmissions in the presence of self-reported STIs.[3] However, the conclusions that can be drawn from both studies are limited given the small number of couple-years of follow-up under observation (21·7 couple-years of follow-up in our study). Second, early relationships have been identified as a time of potential high risk for HIV-negative partners in male serodiscordant partnerships.[3] In an Australian cohort that did not do phylogenetic analysis, we previously reported HIV incidence of about 6 per 100 person-years in the first year of the partnership, decreasing to about 1 per 100 person-years thereafter.[19] More than 40% of couples in the Opposites Attract study were in their first year of having sex together when enrolled. Third, in HPTN 052, four transmissions occurred in heterosexual couples who were not virally suppressed because of being in the first 6 months of ART initiation.[20] Opposites Attract found no such transmissions, despite a quarter of the HIV-positive partners initiating ART during study follow-up. However, the small number of couple-years of follow-up (6·1 couple-years of follow-up) observed in periods after recent ART initiation limit the conclusions that can be drawn. Given the findings from the Partners PrEP Study showing residual risk in the first 6 months of ART,[21] the most appropriate policy and community education response might be to suggest use of condoms or PrEP in the first 6 months and until viral suppression is certain. After this period, viral suppression alone is likely to be sufficient, as articulated in some PrEP guidelines.[22] However, HIV-negative men in non-monogamous serodiscordant couples should be considered for PrEP initiation, given the high HIV incidence among these men and that CLAI with outside partners was not uncommon.

Condom use remained a key prevention strategy against HIV for some couples, especially in Thailand. During most couple-years of follow-up HIV-negative participants were protected by their partners' viral suppression, and the uptake of daily PrEP in HIV-negative partners increased during the study. Few CLAI acts and couple-years of follow-up were not protected by condoms, daily PrEP, or viral suppression; the upper

CI limit of the transmission rate was 0·63 per 100 couple-years of follow-up for the 582·5 couple-years of follow-up where one or more strategies were used.

This study has several limitations. Our sample might not be representative of male serodiscordant couples in the three participating countries: couples were drawn from urban locations and were recruited through clinics and as such were connected to care. Recall bias might have occurred in the self-reported survey data, especially for periods between study visits of longer than a few months. The number of CLAI acts was estimated as the midpoint of a range, whereas, for some participants having more than 50 acts, the number is likely to have been underestimated. 41 couples were lost to follow-up. If these couples continued having anal sex with each other, the initially HIV-negative partner might have acquired HIV from his study partner, thus risk of transmission might be underestimated. However, testing confirmed that HIV-negative partners were HIV-negative for all couple-years of follow-up included in this analysis. The median follow-up time of 1·7 years per couple was short and the total number of 588·4 couple-years of follow-up accrued was lower than the projected 640 couple-years of follow-up. Recruitment was slower and more challenging than expected, thus, follow-up was extended for 1 year. Study funds were exhausted, precluding the possibility of further follow-up. However, as only one published study exists in this population,[3] our study adds substantially to the available couple-years of follow-up globally. The small number of couple-years of follow-up for periods before diagnosed STIs and after ART initiation resulted in large CIs and limited the conclusions that can be drawn in these scenarios.

This study contributes important further evidence that the transmission risk in the context of viral suppression in men who have sex with men is very low. The PARTNER and Opposites Attract studies have reported no linked transmissions despite nearly 35 000 acts of CLAI in serodiscordant male homosexual couples not using daily PrEP. Longer-term follow-up of couples in existing studies[3] will allow for greater certainty and confidence in treatment as prevention as a highly effective HIV prevention strategy.

Contributors

AEG, GPP, FJ, and IBZ-M conceived of the study with input from DAC, CKF, AK, and SE. BRB, AEG, GPP, FJ, and IBZ-M designed the study and wrote the protocol with input from all authors. FJ did the sample size calculations. BRB, GPP, AEG, IBZ-M, and FJ designed the surveys and data collection tools. NP, BG, RM, CKF, MB, NR, CP, AMM, DB, DJT, JH, BKT, and DAC oversaw recruitment of couples at clinical sites. BRB analysed the data and prepared the manuscript. ANP did the phylogenetic analysis with input from AK. All authors contributed to the interpretation of results and draft manuscripts, and approved the final draft for submission.

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Declaration of interests

BRB reports grants from the Australian National Health and Medical Research Council (NHMRC), amfAR, ViiV Healthcare, and Gilead Sciences during the conduct of the study. MB reports grants from the Kirby Institute during the conduct of the study, and grants, personal fees and other from Gilead Sciences, ViiV Healthcare, MSD, Abbvie, Bristol-Myers Squibb, and Atomo Diagnostics outside the submitted work. JH reports other advisory board participation and reimbursement to institution from Gilead Sciences, ViiV Healthcare, and MSD outside the submitted work. AK reports grants from the NHMRC, European Union H2020, National Institutes of Health (USA), funding of immunogenicity assays in gene therapy trial from Calimmune, grants and non-financial support from Cellgene, grants and non-financial support from Merck, recompense for conduct of assays from VIIV outside the submitted work. AEG reports grants from the NHMRC, amfAR, ViiV Healthcare, and Gilead Sciences during the conduct of the study, and personal fees from Merck, ViiV Healthcare, Gilead Sciences, and Sequirus outside the submitted work. DB reports funds for clinical trials, board membership, and conference scholarships from Gilead Sciences and ViiV Healthcare outside the submitted work. All other authors declare no competing interests.

Acknowledgments

We thank all participants in the study, staff in the participating clinics, laboratory staff, and staff in gay and HIV community organisations for supporting this research.

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