Original Investigation

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

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IMPORTANCE A key factor in assessing the effectiveness and cost-effectiveness of antiretroviral therapy (ART) as a prevention strategy is the absolute risk of HIV transmission through condomless sex with suppressed HIV-1 RNA viral load for both anal and vaginal sex.

OBJECTIVE To evaluate the rate of within-couple HIV transmission (heterosexual and men who have sex with men [MSM]) during periods of sex without condoms and when the HIV-positive partner had HIV-1 RNA load less than 200 copies/mL.

DESIGN, SETTING, AND PARTICIPANTS The prospective, observational PARTNER (Partners of People on ART—A New Evaluation of the Risks) study was conducted at 75 clinical sites in 14 European countries and enrolled 1166 HIV serodifferent couples (HIV-positive partner taking suppressive ART) who reported condomless sex (September 2010 to May 2014). Eligibility criteria for inclusion of couple-years of follow-up were condomless sex and HIV-1 RNA load less than 200 copies/mL. Anonymized phylogenetic analysis compared couples' HIV-1 polymerase and envelope sequences if an HIV-negative partner became infected to determine phylogenetically linked transmissions.

EXPOSURES Condomless sexual activity with an HIV-positive partner taking virally suppressive ART.

MAIN OUTCOMES AND MEASURES Risk of within-couple HIV transmission to the HIV-negative partner

RESULTS Among 1166 enrolled couples, 888 (mean age, 42 years [IQR, 35-48]; 548 heterosexual [61.7%] and 340 MSM [38.3%]) provided 1238 eligible couple-years of follow-up (median follow-up, 1.3 years [IQR, 0.8-2.0]). At baseline, couples reported condomless sex for a median of 2 years (IQR, 0.5-6.3). Condomless sex with other partners was reported by 108 HIV-negative MSM (33%) and 21 heterosexuals (4%). During follow-up, couples reported condomless sex a median of 37 times per year (IQR, 15-71), with MSM couples reporting approximately 22 000 condomless sex acts and heterosexuals approximately 36 000. Although 11 HIV-negative partners became HIV-positive (10 MSM; 1 heterosexual; 8 reported condomless sex with other partners), no phylogenetically linked transmissions occurred over eligible couple-years of follow-up, giving a rate of within-couple HIV transmission of zero, with an upper 95% confidence limit of 0.30/100 couple-years of follow-up. The upper 95% confidence limit for condomless anal sex was 0.71 per 100 couple-years of follow-up.

CONCLUSIONS AND RELEVANCE Among serodifferent heterosexual and MSM couples in which the HIV-positive partner was using suppressive ART and who reported condomless sex, during median follow-up of 1.3 years per couple, there were no documented cases of within-couple HIV transmission (upper 95% confidence limit, 0.30/100 couple-years of follow-up). Additional longer-term follow-up is necessary to provide more precise estimates of risk.

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Several studies have demonstrated that HIV-positive people taking antiretroviral therapy (ART) who have low plasma HIV-1 RNA load have markedly reduced infectiousness for sexual transmission.[1-4] In particular, the HPTN 052 study, conducted primarily in heterosexual serodifferent couples, demonstrated a 96% reduction in HIV transmission risk in HIV-positive adults randomized to early ART initiation compared with the group that deferred treatment.[4] As a result, World Health Organization guidelines now recommend that ART should be offered to all HIV-positive people, irrespective of CD4 cell count, to reduce risk of transmission.[5]

There are, however, a number of gaps in currently available evidence. The most significant issue is that no data are available concerning transmission rates for anal sex when the HIV-positive partner is taking suppressive ART, even though per-act estimates of HIV transmissibility without ART are approximately 10 times higher for anal intercourse[6-9] compared with vaginal sex.[10] In addition, in all the transmission studies in heterosexual couples published to date, including HPTN 052, most of the observed couple-years of follow-up have been in the context of reported consistent condom use (up to 93%),[2-4,11-13] which also effectively prevents HIV transmission.[14,15] Study results therefore demonstrate the added benefit of ART in addition to the use of condoms, not just from use of ART alone. Condomless sex (sexual activity in which condoms are not used) was reported for only 330 couple-years of follow-up across all previous studies combined,[2-4,11-13] which is insufficient follow-up to give precise estimates for transmission in the context of ART alone when condoms are not used.[14] The absolute risk of sexual HIV transmission from condomless sex for a person taking stable suppressive ART therefore remains uncertain.

The primary aim of the PARTNER (Partners of People on ART–A New Evaluation of the Risks) study was to follow serodifferent partnerships that have penetrative sex without using condoms in which the HIV-positive partner is taking ART with a plasma HIV-1 RNA load less than 200 copies/mL, to study risk of HIV transmission through anal and vaginal sex in the absence of condom use.

Key Points

Question What is the risk of HIV transmission through condomless sex from an HIV-positive person taking suppressive ART?

Findings In this observational study in HIV-serodifferent heterosexual and MSM couples having ongoing condomless sex over 1238 couple-years of follow-up, there were no cases of within-couple HIV transmission (upper 95% confidence limit of 0.30/100 couple-years of follow-up).

Meaning This study provides estimates of the risk of HIV transmission through condomless anal and vaginal sex with use of suppressive ART.

Methods

Study Design

The PARTNER study was an observational multicenter study of serodifferent couples, heterosexual and men who have sex with men (MSM), in which the HIV-positive partner is taking ART. The methods for the PARTNER study have been published.[16]

Ethics Approvals

Prior to the initiation of the study at each clinical research site, the protocol, all informed consent forms, and the participant information materials were submitted to and approved by the site's ethics committee (institutional review board or institutional ethics committee). In the United Kingdom, the study was reviewed and approved by the North West London REC 2 ethics committee (EC reference number 10/H0720/55). Ethics approval was obtained in-country for all other European sites involved in the study. In addition, any amendments to the study protocol were submitted and approved by each site's ethics committee (institutional review board or ethics committee).

Study Population and Eligibility Criteria

From September 2010, we recruited serodifferent couples from 75 clinical sites in 14 European countries. HIV-positive people taking ART and older than 18 years were eligible to take part with their HIV-negative partners. The HIV-positive partner was expected to continue taking ART, and the partnership met the following criteria: (1) the partners reported penetrative sex without using condoms (condomless sex) together in the month before enrollment (during which period the HIV-negative partner was aware of the HIV status of the HIV-positive partner) and (2) the partners expected to have sex together again in the coming months.

Study Procedures

Participating clinics asked HIV-positive patients taking ART about condomless sex with HIV-negative partners and if they wished to take part in an HIV transmission study. If both the positive and the negative partners agreed to take part, they signed separate informed consents, which included partner identification by name. The informed consent also included explicit reference to the fact that HIV-negative partners knew their partner was HIV-positive and that there was a transmission risk from condomless sex. Clinic staff were asked to recommend consistent condom use at each study contact.

Follow-up was stopped if the partnership ended, the partners moved away, or either person in the partnership withdrew consent, but not for changes in sexual behavior or use of ART (although such changes could lead to the follow-up time not being eligible for the main analysis). Follow-up in heterosexual couples ended on May 31, 2014, and remains ongoing for MSM couples. Follow-up in this report was censored on May 31, 2014.

Data Collection

Study data were collected on standardized case report forms after consent at baseline and then every 4 to 6 months. Detailed information was collected on sociodemographics (including participant self-identified race/ethnicity [using fixed

categories defined by the investigators] to consider a possible association between race/ethnicity and transmission rate); self-reported adherence to ART, rated from 0% to 100% over the previous month (positive partner); sexual activity between the partners (since last visit), frequency of intercourse, type of intercourse (receptive or insertive; vaginal or anal) and whether ejaculation occurred; sexually transmitted infections (STIs) and the presence of symptoms suggestive of an STI; and use of preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP). Injection drug use was assessed and if needles, syringes, or any part of injection equipment was shared.

HIV-negative partners were also asked if they had had condomless sex with anyone other than their HIV-positive partner since their last visit, the number of other partners, and if any were HIV-positive or of unknown serostatus. For the HIV-positive partner, data on ART, CD4 cell count, and current and recent plasma HIV-1 RNA load were recorded through a clinical case report form.

Laboratory Testing and Phylogenetic Analysis

The HIV-negative partner was asked to test for evidence of HIV seroconversion every 6 to 12 months. Where possible, a combined antigen/antibody test was used to increase diagnostic sensitivity in early infection. Plasma HIV-1 RNA was measured in the HIV-positive partner according to routine care every 6 to 12 months; testing was undertaken at the local diagnostic laboratory. If at any time the HIV-negative partner was found to have become HIV-positive, a venous blood sample in EDTA was taken from both partners to determine genetic relatedness of HIV-1 *pol* and *env* sequences.

Details of the methodology used for sequencing and analysis are reported in the Supplement. Briefly, following Sanger sequencing of either plasma HIV-1 RNA or cellular HIV-1 DNA,[17] maximum-likelihood and Bayesian Markov Chain Monte-Carlo (MCMC) inferences, as implemented in RAxML-HCP2 v8 and MrBayes v3.2.6, respectively, were determined as previously described.[18] Controls comprised the 10 closest sequences identified through BLAST searches of GenBank (http://blast.ncbi.nlm.nih.gov/Blast.cgi). Replicate partners' sequences (obtained from different sampling points, different specimen types, or repeat testing of the same sample), and sequences from confirmed HIV-transmission pairs obtained in a separate study[18] were included as positive controls. A seroconversion event was to be classed as linked if the partners' sequences grouped together on a monophyletic branch with high support, defined as a bootstrap value of 0.90 or greater (maximum likelihood) or a posterior probability of 0.95 or greater (MCMC), and had a pairwise genetic distance of 0.015 nucleotide substitutions or less per *pol* site, as per published methodology.[19,20] Sequences showing a genetic distance of 0.045 or less were subjected to further inspection, to ensure that potential linkage was not missed.[19,20]

Statistical Analysis

The primary analysis was estimation of the rate of transmission, calculated as the number of HIV infections that occurred during eligible couple-years of follow-up (see definition below) divided by eligible couple-years of follow-up, excluding infections shown to be phylogenetically distinct from the index patient's virus (ie, transmission has not been from the original HIV-positive index partner). Couple-years of follow-up were determined as periods delimited by HIV tests, and corresponding questionnaires on sexual behavior, in the HIV-negative partner. These were eligible for inclusion in this analysis if (1) couples had condomless sex during the period (reported at the end of the period by the HIV-negative partner or, if this partner did not reply, by the positive partner); (2) there was no report of PrEP or PEP use; (3) latest plasma HIV-1 RNA load in the positive partner was less than 200 copies/mL and not dated older than 12 months; and (4) follow-up occurred before May 31, 2014 (ie, the censoring date).

A sensitivity analysis included periods of follow-up time in which the HIV-RNA load was suppressed at the beginning of the period but during which the load became elevated. This allows inclusion of periods during which a couple may continue having condomless sex until they know the HIV RNA load is elevated. Exact Poisson methods were used to calculate confidence intervals for the incidence rate of transmission.

The rate of within-couple transmission was calculated restricting to couple-years of follow-up during which a certain type of sex (eg, receptive anal sex with ejaculation) was reported (note that it was not required that this was the only type of sex the couple was having). However, in sensitivity analysis the rate and confidence interval were calculated taking a hierarchical approach to classifying transmission risk with types of sex. Having defined such a hierarchy of risk, in referring to a specific sex act, the upper limit of the rate was estimated if this type of sex was the highest-risk sex being performed. The hierarchy (from highest to lowest risk) was receptive anal sex with ejaculation, receptive anal sex without ejaculation, insertive anal sex, vaginal sex with ejaculation, and vaginal sex without ejaculation.

To assess whether there were differences in the characteristics among HIV-negative and HIV-positive people across the different groups (heterosexual men, heterosexual women, and MSM), the 2-sided Kruskal-Wallis test was used for continuous variables and 2-sided χ^2 tests for categorical variables.

$P < .05$ was used as the threshold of statistical significance. Missing data were not imputed, and the analysis was performed only on the available data. Data were analyzed using SAS version 9.3 (SAS Institute Inc).

Sample Size Calculation

In planning the sample size it was known that the transmission rate was low,[3] and the aim was to generate a more precise estimate of the rate than was available. The sample size was based on a hypothesized transmission rate of 1 per 1000 couple-years of condomless sex, with the choice of this very low rate based on arguments laid out in the Swiss Statement.[21] Under this hypothesis, 2000 couple-years of follow-up were required to have an 85% chance that the upper limit of the 95% confidence interval for the transmission rate is less than 0.44 per 100 couple-years of follow-up (0.2 per 100 couple-years of follow-up, with a transmission rate of zero). The executive committee stopped follow-up of

heterosexual couples at May 31, 2014, at the end of phase 1 to concentrate resources on MSM couples. Phase 2 with MSM couples only will be continued for a further 4 years to accrue additional data for anal intercourse. It was prespecified that further analysis will not be undertaken until the end of the second phase of the study in 2018.

Results

Eligible Couple-Years of Follow-up Accrued

From the 1166 couples enrolled by May 31, 2014, a total of 1004 couples had at least 1 follow-up visit by the censoring date and 888 couples (548 heterosexual and 340 MSM) contributed 1238 eligible couple-years of follow-up; 1251 when including periods of follow-up time in which the HIV-RNA load was suppressed at the beginning of the period but during which the load became elevated. The main reasons for couples providing no eligible couple-years of follow-up (n = 116) among those with at least 1 follow-up visit were no HIV test in the negative partner (n = 20), use of PEP/PrEP (n = 9), no condomless sex reported (n = 15), plasma HIV-1 RNA load greater than 200 copies/mL (n = 55), and plasma measurement not available (n = 17). Participants who contributed eligible couple-years of follow-up (compared with those who did not) were slightly older, more likely to have undertaken vocational education (among heterosexual participants), more likely to have reported sex with other men rather than "other" as HIV acquisition route (among MSM), had been having condomless sex for longer (among MSM), and more likely to have a CD4 cell count greater than 350/mm^3 (among heterosexuals) (see eTable 5 in the Supplement).

Median eligible years of follow-up per couple was 1.3 years (interquartile range [IQR], 0.8-2.0). The estimated dropout rate was 18 per 100 couple-years of follow-up when considering all the couples enrolled (n = 1166) and 11 per 100 couple-years of follow-up when restricting to the 888 couples who contributed to eligible couple-years of follow-up. The reason for dropping out of the study, among couples who contributed eligible couple-years of follow-up (888 couples) were relationship broke up (n = 69 [41%]), moved away (n = 15 [9%]), consent withdrawn/did not want to continue (n = 18 [11%]), and other/not clear (n = 65 [39%]). Among couples contributing eligible couple-years of follow-up, 340 were MSM, 269 heterosexual in which the male partner was HIV-positive (male positive/female negative) and 279 heterosexual in which the female partner was HIV-positive (male negative/female positive). Overall, 94% of the eligible couple-years of follow-up were during periods of very low plasma HIV-1 RNA load (<50 copies/mL); the other 6% were during periods with HIV-1 RNA loads between 50 and 200 copies/mL.

Baseline Couple Characteristics

Characteristics at baseline of the participants who contributed to eligible couple-years of follow-up are reported in **Table 1**. Median age was 40 to 45 years in all participant groups. HIV-negative MSM reported having condomless sex with their positive partners for a median 1.4 years (IQR, 0.5-3.5 years) prior to enrollment. For heterosexual couples this was 2.8 years (IQR, 0.6-7.5 years) for male-negative/female-positive couples and 3.6 years (IQR, 0.7-11.4 years) for male-positive/female-negative couples.

At baseline, HIV-positive partners had been taking ART a median of 7.5 years (IQR, 3.3-14.2 years) among heterosexual women, 10.6 years (IQR, 4.3-15.6 years) among heterosexual men, and 4.8 years (IQR, 1.9-11.4 years) among MSM. Self-reported adherence with taking ART was high across all HIV-positive groups, with 93% of heterosexual men, 94% of heterosexual women, and 97% of MSM reporting greater than 90% adherence to ART and very few reporting they missed taking ART for more than 4 consecutive days, although this was more common in heterosexual participants (6% men, 8% women) than in MSM (3%). MSM were also more likely to correctly self-report a suppressed HIV load (94% of MSM, compared with 84% of heterosexual men and 87% of heterosexual women). The majority in all groups had CD4 cell count greater than 350 mm^3 at baseline.

Follow-up Clinical and Behavioral Data

During prospective follow-up, 17% of HIV-negative MSM and 18% of HIV-positive MSM reported being diagnosed with an STI at some point; among both HIV-negative and HIV-positive heterosexual men and women, 6% reported being diagnosed with an STI (**Table 2**).

Thirty-three percent (n = 108) of HIV-negative MSM and 4% of HIV-negative heterosexual men (n = 11) and women (n = 10) reported condomless sex with other partners. Very few HIV-negative partners reported injecting drugs during follow-up (3% [n = 10] MSM, 2% [n = 5] heterosexual men, and 1% [n = 2] heterosexual women).

Couples reported frequent condomless sex during follow-up, as illustrated by the number of condomless sex acts reported during follow-up (**Table 3**). The median number of condomless sex acts per year within the partnership reported by the HIV-negative partner were similar across all groups during eligible couple-years of follow-up, with MSM reporting a median of 42 condomless acts per year (IQR, 18-75) compared with 35 (IQR, 14-68) for heterosexual men and 36 (IQR, 13-71) for heterosexual women. Overall, all groups reported large numbers of condomless sex acts during follow-up, with more than 22 000 condomless sex acts among MSM and 36 000 among heterosexual couples.

Data on prevalence of the type of condomless penetrative sex (with the HIV-positive partner) reported by the HIV-negative partner are shown in **Figure 1**. By definition, couples contributing eligible couple-years of follow-up reported condomless penetrative sex at some point during follow-up. Among heterosexual couples, 99% reported vaginal sex with or without ejaculation and 11.1% reported anal sex. For MSM, 67% of negative partners had receptive anal sex without ejaculation, 45% had receptive anal sex with their partner ejaculating inside them, and 92% reported insertive anal sex.

The main reasons reported by HIV-negative partners for not using a condom were a belief that the risk of HIV transmission was very low (57% heterosexual men, 52% heterosexual women, 63% MSM) and that sex was more enjoyable

Table 1. Characteristics at Baseline of HIV-Positive and HIV-Negative Partners Enrolled in the PARTNER Study and Eligible for the Primary Analysis (N = 888 Couples)

Characteristic	HIV-Positive, No. (%)[a]			HIV-Negative, No. (%)[a]			*P* Value[b]	
	Heterosexual			Heterosexual				
	Men (n = 269)	Women (n = 279)	MSM (n = 340)	Men (n = 279)	Women (n = 269)	MSM (n = 340)	HIV-Positive	HIV-Negative
Age, median (IQR)	44.9 (40.1-48.6)	40.1 (34.6-46.5)	41.7 (35.5-46.8)	44.9 (37.6-50.6)	40.3 (34.3-46.7)	40.1 (31.9-46.5)	<.001	<.001
Race/ethnicity								
White	221 (83)	170 (62)	305 (91)	229 (85)	217 (82)	301 (89)	<.001	<.001
Black	24 (9)	63 (23)	3 (1)	34 (13)	19 (7)	3 (1)		
Asian	4 (2)	27 (10)	9 (3)	1 (<1)	7 (3)	9 (3)		
Other	17 (6)	14 (5)	18 (5)	7 (3)	22 (8)	24 (7)		
Missing	3	5	5	8	4	3		
Education								
High school or less	139 (52)	116 (43)	76 (23)	84 (31)	119 (46)	64 (19)	<.001	<.001
Vocational education	75 (28)	76 (28)	103 (31)	92 (34)	73 (28)	88 (26)		
College or university	51 (19)	77 (29)	156 (47)	93 (35)	69 (26)	183 (55)		
Missing	4	10	5	10	8	5		
HIV acquisition route								
Heterosexual	97 (37)	188 (69)	0				<.001	
MSM	22 (8)	1 (<1)	324 (97)					
Shared needles or other injection equipment	82 (31)	15 (6)	0					
Other	64 (24)	67 (25)	10 (3)					
Missing	4	8	6					
Years of condomless sex, median (IQR)	3.2 (0.7-11.4)	2.9 (0.8-7.8)	1.5 (0.5-4.1)	2.8 (0.6-7.5)	3.6 (0.7-11.4)	1.4 (0.5-3.5)	<.001	<.001
Missing	26	26	21	25	32	23		
Years receiving ART, median (IQR)	10.6 (4.3-15.6)	7.5 (3.3-14.2)	4.8 (1.9-11.4)				<.001	
Missing	31	24	16					
Self-reported ART adherence >90%								
Yes	242 (93)	235 (94)	319 (97)				.10	
Missing	10	29	11					
Informed their partner if they missed doses of ART								
No	23 (9)	17 (6)	13 (4)				.002	
Yes	133 (51)	123 (45)	133 (40)					
Did not miss doses	107 (41)	132 (49)	190 (57)					
Missing	6	7	4					
Self-reported undetectable HIV load								
Yes	220 (84)	231 (87)	309 (94)				<.001	
Missing	8	12	12					
CD4 cell count >350/mm^3								
Yes	229 (85)	249 (89)	309 (91)				.08	

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men.

[a] Unless indicated there are no missing values. Percentages are calculated out of all the participants in that group who contributed to eligible couple-years of follow-up and provided a response to that question.

[b] Kruskal-Wallis test for continuous variables, χ^2 test for categorical variable. The comparisons are between all of the HIV-positive groups and then between all of the HIV-negative groups.

without condoms (38% heterosexual men, 41% heterosexual women, 61% MSM). Fifteen percent of HIV-negative women reported not using a condom because they were trying for a pregnancy.

Rates of HIV Transmission Through Condomless Sex

A total of 11 of the originally HIV-negative partners were observed to acquire HIV during eligible follow-up, but there were no phylogenetically linked transmissions. Of the 11 people who

Table 2. Characteristics During Follow-up of HIV-Positive and HIV-Negative Partners Eligible for the Primary Analysis (N = 888)

Characteristic	HIV-Positive, No. (%)[a]			HIV-Negative, No. (%)[a]			P Value[b]	
	Heterosexual			Heterosexual				
	Men (n = 269)	Women (n = 279)	MSM (n = 340)	Men (n = 279)	Women (n = 269)	MSM (n = 340)	HIV-Positive	HIV-Negative
Years in the study, median (IQR)	1.9 (1.1-2.4)	1.8 (1.1-2.4)	1.4 (0.8-2.1)	1.8 (1.1-2.4)	1.9 (1.1-2.4)	1.4 (0.8-2.1)	<.001	<.001
STI[c]	16 (6)	16 (6)	59 (18)	16 (6)	17 (6)	56 (17)	<.001	<.001
Gonorrhea	1 (<1)	0	20 (6)	0	0	0	<.001	
Warts	2 (1)	5 (2)	8 (2)	8 (3)	0	4 (1)	.30	
Other STI	2 (1)	12 (4)	0	0	2 (1)	0	<.001	.09
Not specified	12 (5)	1 (<1)	32 (10)	8 (3)	15 (6)	52 (16)	<.001	<.001
Missing[d]	5	3	11	4	6	10		
Condomless sex with other partners, n (%)				11 (4)	10 (4)	108 (33)		<.001
Missing[d]				7	7	12		
Condomless sex with other positive partners[e]				9 (3)	0	103 (31)		<.001
Condomless sex acts/y, median (IQR)[f]	28.2 (10.5-61.3)	30.1 (11.8-60.6)	33.0 (13.0-64.8)	34.6 (13.7-68.3)	35.6 (13.2-70.7)	41.7 (17.6-74.8)	.24	.05
Estimated total No.condomless sex acts[f]	15 543	16 945	19 685	18 431	17 509	22 273		
Having missed ART for more than 4 consecutive days	15 (6)	21 (8)	11 (3)				.07	
Missing	6	11	3					
Having injected nonprescription drugs	7 (3)	10 (4)	18 (5)	5 (2)	2 (1)	10 (3)	.21	.14
Missing	5	7	11	5	12	14		
Couple-years of follow-up with reported frequency of condomless sex per month[g]								
Less than once	90 (24)	87 (21)	76 (17)	97 (23)	72 (19)	68 (15)		
1-2 times	59 (16)	65 (15)	63 (14)	70 (17)	64 (17)	70 (16)		
3-4 times	54 (14)	85 (20)	80 (18)	76 (18)	72 (19)	88 (20)	.24	.28
5-8 times	93 (24)	95 (23)	103 (24)	105 (25)	93 (24)	121 (27)		
More than 8 times	47 (12)	47 (11)	66 (15)	53 (13)	57 (15)	73 (17)		
Not reported/missing	37 (10)	39 (9)	50 (11)	18 (4)	23 (6)	18 (4)		

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men; STI, sexually transmitted infection.

[a] Unless indicated there are no missing values. Percentages are calculated out of all the participants in that group who contributed to eligible couple-years of follow-up and provided a response to that question. The comparisons are between all of the HIV-positive groups and then between all of the HIV-negative groups.

[b] Kruskal-Wallis test for continuous variables, χ^2 test for categorical variable.

[c] Participants who reported an STI since last visit were asked whether it was syphilis, gonorrhea, chlamydia, acute genital herpes, chronic genital herpes, lymphogranuloma venereum, bacterial vaginosis, or other. None reported being diagnosed with acute genital herpes or syphilis. The following STIs did not have a frequency above 5 and so were grouped together as "Other STI": chlamydia, chronic genital herpes, lymphogranuloma venereum, bacterial vaginosis, and "other." Participants who replied "yes" to the question "Since your last visit, have you had a STI" but did not reply to the question "If yes, which STI?" were categorized as "not specified."

[d] Never replied to this question during follow-up.

[e] Only people that reported condomless sex with other partners were asked this question. For this variable "missing" is treated as "no," and the denominator used to calculate the percentages is the number of participants who reported whether they had "[condomless] sex with other partners."

[f] Only sex acts within couples are included.

[g] The denominator is the total group-specific eligible couple-years of follow-up.

became infected, 10 were MSM and 1 was heterosexual; of these, 8 (73%) reported that they had had recent condomless sex with others apart from their study partner.

Viral sequences were recovered successfully from all couples, comprising 22 of 22 individuals (100%) for *pol* and 20 of 22 individuals (91%) for *env*. Samples collected from the 2 partners of each couple were a median of 0 months apart (IQR, 0.0-5.9). The partners who were initially HIV-positive had subtype B infection in all cases. The partners who seroconverted during the study acquired subtype B infection in 9 of 11 cases; 1 person (couple 5) acquired subtype A1, and a second person (couple 6) acquired CRF14_BG (eTable 1 in the Supplement). In the phylogenetic analyses, none of the partners' sequences clustered together, with consistent results observed across analyses (**Figure 2**; eFigure 1 and eFigure 2 in the Supplement). The partners' sequences showed pairwise genetic distances consistently greater than 0.040. With couple number 7, the pairwise genetic distances of *pol* sequences were 0.043

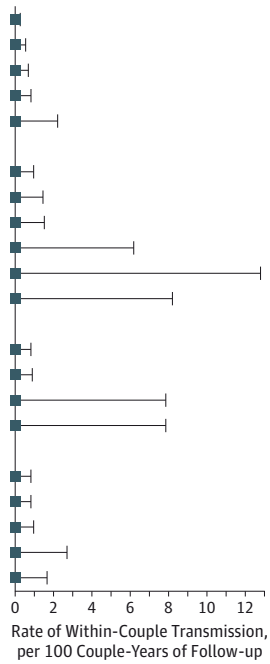
Table 3. Condomless Sex Acts During Follow-up According to Number of Condomless Sex Acts at Baseline[a]

No. of Condomless Sex Acts per 4 Months' Follow-up	No. of Condomless Sex Acts in The Past 4 mo Reported at Baseline by the HIV-Negative Partner						Total Couple-Years of Follow-up
	1 Time (n = 41)	2-10 Times (n = 291)	11-20 Times (n = 178)	21-40 Times (n = 163)	>40 Times (n = 199)	Not Reported (n = 16)	
Less than once	12 (23)	39 (10)	13 (5)	7 (3)	10 (4)	2 (9)	84
1 Time	1 (2)	9 (2)	1 (<1)	2 (1)	0	0	13
2-10 Times	25 (48)	223 (55)	101 (41)	70 (29)	38 (14)	9 (41)	466
11-20 Times	4 (8)	54 (13)	52 (21)	57 (23)	51 (19)	3 (14)	222
21-40 Times	3 (6)	32 (8)	44 (18)	78 (32)	109 (40)	3 (14)	269
>40 Times	1 (2)	3 (1)	6 (2)	13 (5)	35 (13)	0	58
Not reported	6 (12)	41 (10)	29 (12)	17 (7)	29 (11)	4 (18)	126
Total couple-years of follow-up	52	402	245	245	272	22	1238

[a] Table reports total number eligible couple-years of follow-up (one of the main requirements being that condoms are not used) by frequency of condomless sex acts reported at baseline and during follow-up. Values in parentheses represent the number of couples reporting a certain frequency at baseline. The number of couple-years of follow-up have been rounded to the closest integer; thus, some rows and columns do not sum exactly to the column or row total.

Figure 1. Rate of HIV Transmission According to Sexual Behavior Reported by the HIV-Negative Partner

	HIV-Negative Members of Eligible Couples Reporting Specific Sex Act, No./Total (%)	Couple-Years of Follow-up	Upper 95% Confidence Limit
All			
Any sex	863/866 (99.7)	1238	0.30
Vaginal sex	532/878 (60.6)	629	0.59
Anal sex	449/849 (52.9)	522	0.71
Insertive anal sex	363/862 (42.1)	417	0.88
Receptive anal sex with ejaculation	185/864 (21.4)	166	2.23
Heterosexual women			
Any sex	261/262 (99.6)	381	0.97
Vaginal sex with ejaculation	193/259 (74.5)	246	1.50
Vaginal sex without ejaculation	207/257 (80.5)	238	1.55
Anal sex	61/256 (23.8)	60	6.16
Receptive anal sex with ejaculation	37/255 (14.5)	29	12.71
Receptive anal sex without ejaculation	55/253 (21.7)	45	8.14
Heterosexual men			
Any sex	272/274 (99.3)	418	0.88
Vaginal sex	271/275 (98.5)	383	0.96
Anal sex	60/264 (22.7)	47	7.85
Insertive anal sex	60/264 (22.7)	47	7.85
Men who have sex with men			
Any sex	330/330 (100)	439	0.84
Anal sex	328/329 (99.7)	415	0.89
Insertive anal sex	303/329 (92.1)	370	1.00
Receptive anal sex with ejaculation	148/329 (45.0)	137	2.70
Receptive anal sex without ejaculation	217/324 (67.0)	220	1.68

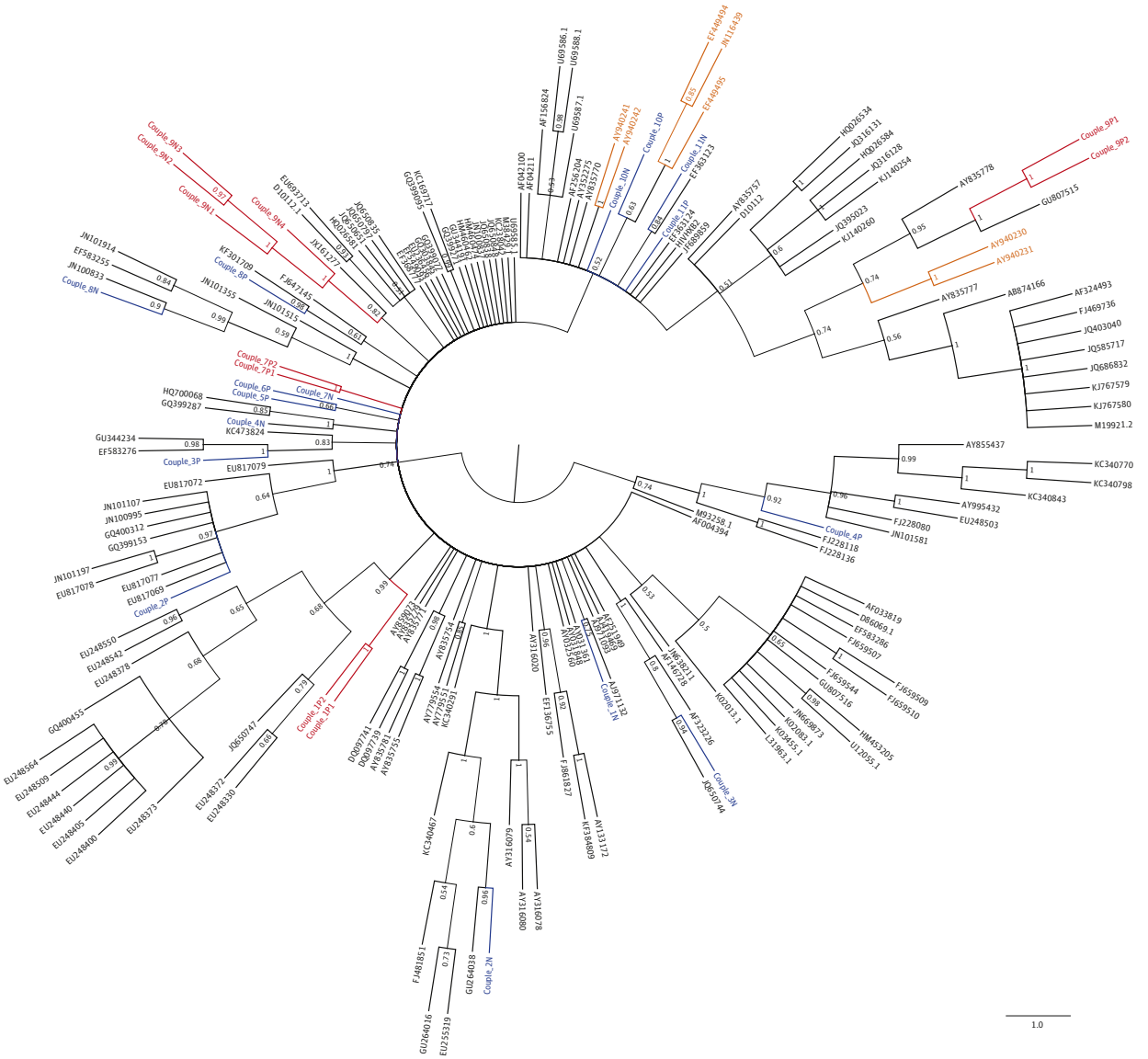


Denominators are the group-specific number of HIV-negative participants who contributed eligible couple-years of follow-up. The upper limit of the 95% confidence interval was estimated using the exact Poisson method.

and 0.040 for different sample types; however, there was no phylogenetic evidence of linked clustering (Figure 2; eFigure 1 and eFigure 2 in the Supplement). Positive control sequences showed median genetic distances of 0.004 (IQR, <0.001-0.008) (eTable 2 in the Supplement) and were closely linked on monophyletic branches with bootstrap values 0.98 or greater and posterior probabilities of 1.00.

Given that there were no linked transmissions (even when considering periods during which the HIV-RNA load became elevated [representing a total of 13 couple-years of follow-up]), the estimated rate for transmission through any condomless sex with the HIV-positive partner taking ART with HIV load less than 200 copies/mL was zero, with an upper 95% confidence limit of 0.30 per 100 couple-years of follow-up (0.29 when including periods of follow-up time in which the HIV-RNA load was suppressed at the beginning of the period but during which the load became elevated). Figure 1 reports the rates of within-couple HIV transmission per 100 eligible couple-years of follow-up by sexual behavior reported by the HIV-negative partner. For all sex in heterosexual couples the upper 95%

Figure 2. Phylogenetic Tree of *Pol* Sequences From 9 Couples With Subtype B Infection



Bayesian Markov Chain Monte-Carlo (MCMC) inference (012212+I+G+F model). Branch length is proportional to the genetic distance and line weight is proportional to the posterior probability. Partners' sequences are in blue; N indicates the initially HIV-negative partner, whereas P indicates the initially HIV-positive partner. Control sequences comprised the 10 closest sequences identified through BLAST searches of GenBank. Positive control sequences comprised replicate sequences from study partners (in red) and sequences from confirmed transmission pairs obtained in a separate study (in orange).[19]

[a] Sequences 9N2 and 9N3 were obtained from the same sample in 2 separate experiments.

confidence limit was 0.97 per 100 couple-years of follow-up for male-positive/female-negative couples, and 0.88 per couple-years for female-positive/male-negative couples. In MSM the upper confidence limit for all sex was 0.84 per 100 couple-years of follow-up. For anal sex, the upper 95% confidence limit was 0.71 per 100 couple-years of follow-up (heterosexual and MSM data combined), and for receptive anal sex with ejaculation it was 2.23 per 100 couple-years of follow-up (heterosexual and MSM data combined) and 2.70 per 100 couple-years of follow-up (MSM only). The upper limit of the 95% CI was higher for anal sex owing to the lower number of couple-years of follow-up accrued to date.

When considering a hierarchical approach (ie, the act-specific rates were restricted to couple-years of follow-up in which that type of act was the highest-risk type of sex reported), the upper 95% confidence limit was higher: for receptive anal sex without ejaculation, the upper limit increased from 8.14 to 11.95 per 100 couple-years of follow-up for heterosexual women and from 1.68 to 3.06 per 100 couple-years of follow-up for MSM; for vaginal sex, the upper limit increased from 0.59 to 0.69 per 100 couple-years of follow-up (heterosexual men and women combined) (eTable 4 in the Supplement). A table detailing the rates and upper 95% confidence limits using this approach has been included in the

supplementary material (eTable 4 in the Supplement). All but 3 nonlinked HIV-1 infections occurred among partners reporting condomless sex with other partners.

Discussion

This study provides the first estimate to our knowledge of HIV transmission risk through condomless anal sex in which the HIV-positive partner is taking ART with suppressed plasma HIV viral load and also provides an estimate of the absolute rate of HIV transmission through condomless heterosexual sex. The estimate of the overall transmission rate, and the transmission rate for anal sex, was zero. However, 95% confidence limits suggest that with eligible couple-years accrued so far, appreciable levels of risk cannot be excluded, particularly for anal sex and when considered from the perspective of a cumulative risk over several years.

Only couples that continued to have condomless sex were included in this study, to enable focus on situations in which transmission risk without ART is highest. This contrasts with other transmission studies, including HPTN 052, in which reported condom use was high (93%)[4] and the low absolute rate of transmission in the ART group reflects both ART and condom use, thus assessing 2 prevention strategies in combination, not just ART alone. It is important to know how low the risk of transmission was with the use of ART alone without simultaneous use of condoms, and this study contains more than 3 times the couple-years of follow-up for condomless sex than all the other previous studies combined, including more than 500 couple-years of follow-up of condomless anal sex.[14] Both MSM and heterosexual couples in this study reported regularly having sex without a condom during follow-up. Based on the number and type of sex acts and the cumulative probability of HIV transmission, more than 100 transmissions would have been expected in the MSM group alone (see Supplement) if the HIV-positive partner had not been taking ART.[10]

Although these results cannot directly provide an answer to the question of whether it is safe for serodifferent couples to practice condomless sex, this study provides informative data (especially for heterosexuals) for couples to base their personal acceptability of risk on. In the absence of ART, receptive anal sex with ejaculation is recognized as carrying a higher risk than other forms and, despite an observed transmission rate of zero for this risk behavior, a clinically important rate of less than 2.2 per 100 couple-years of follow-up cannot be excluded. This translates into an upper limit estimate of 20% risk over 10 years. Because the upper limit of the 95% confidence interval is a function of the amount of couple-years of follow-up for that sexual act, additional follow-up in MSM is therefore needed through the second phase of the PARTNER study (PARTNER 2) to provide more precise estimates for transmission risk in MSM in the context of ART. These data are needed to provide equality of evidence between MSM and heterosexual couples, to inform both policy and also individual choice on condom use.

Although no linked HIV transmissions within couples were detected, 11 unlinked HIV transmissions occurred during eligible follow-up. One-third of HIV-negative MSM in this study reported having condomless sex concurrently with other partners outside the main relationship. A high prevalence of sexual concurrency and in particular concurrent condomless anal sex has been reported in other studies in MSM.[22,23] Related to this, HIV-negative MSM were also relatively commonly diagnosed with an STI. Acquisition of an STI was not associated with risk of HIV-1 transmission within the couples under study, although power was limited to exclude a possible true effect.

This study has several limitations. The original design aimed to observe 2000 couple-years of follow-up, but only 1238 couple-years were eligible for the primary analysis. Because the primary analysis involves the estimation of a rate with a 95% confidence interval, this does not substantially affect the interpretation. In addition, although there was a moderate degree of dropout of study participants, the reasons for dropout do not suggest that those who dropped out would have experienced a higher transmission rate while virally suppressed when taking ART. The follow-up time was relatively short, although at study entry couples reported having condomless sex with their current partner for several months to years. Direct evidence that some individuals are particularly susceptible to early acquisition of HIV infection is currently lacking, but it remains possible that the transmission rate is higher in the initial period of condomless sex between a couple. Moreover, although the transmission rate was also zero in the 23% of couples in the study in which the partnership was relatively recent (< 6 months), the risk of HIV transmission in very new partnerships could not be determined.

Conclusions

Among serodifferent heterosexual and MSM couples in which the HIV-positive partner was using suppressive ART and who reported condomless sex, during median follow-up of 1.3 years per couple, there were no documented cases of within-couple HIV transmission (upper 95% confidence limit, 0.30/100 couple-years of follow-up). Additional longer-term follow-up is necessary to provide more precise estimates of risk.

ARTICLE INFORMATION

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