Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study

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Summary

Background The level of evidence for HIV transmission risk through condomless sex in serodifferent gay couples with the HIV-positive partner taking virally suppressive antiretroviral therapy (ART) is limited compared with the evidence available for transmission risk in heterosexual couples. The aim of the second phase of the PARTNER study (PARTNER2) was to provide precise estimates of transmission risk in gay serodifferent partnerships.

Methods The PARTNER study was a prospective observational study done at 75 sites in 14 European countries. The first phase of the study (PARTNER1; Sept 15, 2010, to May 31, 2014) recruited and followed up both heterosexual and gay serodifferent couples (HIV-positive partner taking suppressive ART) who reported condomless sex, whereas the PARTNER2 extension (to April 30, 2018) recruited and followed up gay couples only. At study visits, data collection included sexual behaviour questionnaires, HIV testing (HIV-negative partner), and HIV-1 viral load testing (HIV-positive partner). If a seroconversion occurred in the HIV-negative partner, anonymised phylogenetic analysis was done to compare HIV-1 *pol* and *env* sequences in both partners to identify linked transmissions. Couple-years of follow-up were eligible for inclusion if condomless sex was reported, use of pre-exposure prophylaxis or post-exposure prophylaxis was not reported by the HIV-negative partner, and the HIV-positive partner was virally suppressed (plasma HIV-1 RNA <200 copies per mL) at the most recent visit (within the past year). Incidence rate of HIV transmission was calculated as the number of phylogenetically linked HIV infections that occurred during eligible couple-years of follow-up divided by eligible couple-years of follow-up. Two-sided 95% CIs for the incidence rate of transmission were calculated using exact Poisson methods.

Findings Between Sept 15, 2010, and July 31, 2017, 972 gay couples were enrolled, of which 782 provided 1593 eligible couple-years of follow-up with a median follow-up of 2·0 years (IQR 1·1–3·5). At baseline, median age for HIV-positive partners was 40 years (IQR 33–46) and couples reported condomless sex for a median of 1·0 years (IQR 0·4–2·9). During eligible couple-years of follow-up, couples reported condomless anal sex a total of 76 088 times. 288 (37%) of 777 HIV-negative men reported condomless sex with other partners. 15 new HIV infections occurred during eligible couple-years of follow-up, but none were phylogenetically linked within-couple transmissions, resulting in an HIV transmission rate of zero (upper 95% CI 0·23 per 100 couple-years of follow-up).

Interpretation Our results provide a similar level of evidence on viral suppression and HIV transmission risk for gay men to that previously generated for heterosexual couples and suggest that the risk of HIV transmission in gay couples through condomless sex when HIV viral load is suppressed is effectively zero. Our findings support the message of the U=U (undetectable equals untransmittable) campaign, and the benefits of early testing and treatment for HIV.

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Introduction

Early evidence of a strong link between the HIV viral load of an HIV-positive partner and the risk of transmission to an HIV-negative partner came from observational studies in serodifferent heterosexual couples.[1–5] Evidence from a randomised study of risk of HIV transmission in the context of virally suppressive antiretroviral therapy (ART) in heterosexual couples was

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Research in context

Evidence before this study

To review previous evidence on the effect of antiretroviral therapy (ART) on risk of HIV transmission, we searched PubMed for articles published in English from Jan 1, 2000, to Nov 7, 2018, using the MeSH terms "HIV infection" and "transmission" and "antiretroviral therapy" or "ART" and "men who have sex with men" or "gay or heterosexual" or "serodiscordant" or "serodifferent". Previous studies, including one randomised controlled trial and several observational studies, provided estimates of risk of HIV transmission through sexual intercourse in the context of virally suppressive ART. The bulk of the evidence was in heterosexual serodifferent couples and variable levels of condom use were reported in many studies. Some evidence on transmission risk in gay men was provided in the first phase of the PARTNER study and in the Opposites Attract study, but follow-up in these studies was not sufficient to exclude a significant upper limit of risk around the study estimates of zero transmissions in gay men.

Added value of this study

The second phase of the PARTNER study fills the gap in the evidence base for risk of HIV transmission in serodifferent gay couples in which the HIV-positive partner is on virally suppressive ART and condoms are not used. By the end of follow-up, 15 new HIV infections had occurred during eligible couple-years of follow-up, but none were phylogenetically linked within-couple transmissions. Thus, the linked HIV transmission rate during eligible couple-years was zero, despite 76 000 reports of condomless anal sex, with a low upper 95% CI limit of 0·23 per 100 couple-years of follow-up. Our findings provide a level of evidence on viral suppression and HIV transmission risk through condomless sex for gay men similar to that already reported for heterosexual couples.

Implications of all the available evidence

The results from the PARTNER studies in addition to evidence from other studies in serodifferent couples indicate that the risk of transmission of HIV through condomless sex in the context of virally suppressive ART is effectively zero for both gay men and heterosexual couples. These results support the U=U (undetectable equals untransmittable) message, as well as promoting the benefits of early testing and treatment.

provided by the HPTN 052 trial,[6] which reported a 96% reduction in linked transmissions in couples assigned to early (immediate) ART compared with couples assigned to delayed therapy. Continued follow-up in HPTN 052 from 2011 to 2016, after all participants were offered ART, showed durability of the effect of ART; however, only 2% of couples were men who have sex with men (MSM).[7] Self-reported condom use was also high; participants reported not using condoms for a total of only 63·4 couple-years of follow-up.[6]

The first phase of the PARTNER study (PARTNER1) estimated the risks for different types of sex and in a broader population. The study reported no linked transmissions in 888 serodifferent couples (548 heterosexual and 340 gay couples) who reported condomless penetrative sex during 1238 couple-years of follow-up when the HIV-positive partner was on virally suppressive ART.[8] PARTNER1 reported on 439 couple-years of follow-up in serodifferent gay couples, with zero transmissions reported. However, because of the lower number of couple-years of follow-up accumulated for gay couples than for heterosexual couples, the upper 95% CI limit for the transmission rate for gay men was relatively high (0·84 per 100 couple-years of follow-up), almost double that for heterosexual couples (0·46 per 100 couple-years of follow-up). These results equated to an upper limit of risk of one infection per 119 couple-years of follow-up for gay couples compared with one infection per 217 couple-years of follow-up for heterosexual couples and was arguably insufficient to provide the level of evidence required to support ART as a fully effective HIV prevention intervention in MSM.

The Opposites Attract observational study[9] also reported zero cases of HIV transmission in MSM couples during 232 couple-years of follow-up when condomless anal intercourse was reported, the HIV-positive partner was virally suppressed, and the HIV-negative partner did not use pre-exposure prophylaxis (PrEP), with a fairly high upper 95% CI limit of 1·59 per 100 couple-years of follow-up for transmission rate.

The primary aim of the second phase of the PARTNER study (PARTNER2) was to produce a similar level of evidence for transmission risk through condomless anal sex between men with suppressive ART (defined as HIV-1 RNA viral load <200 copies per mL) to that generated for heterosexual couples in PARTNER1.

Methods

Study design and participants

The PARTNER study was an observational multicentre study of serodifferent couples who before enrolment were not always using condoms, and in which the HIV-positive partner was on ART. Phase 1 of the study recruited and followed up both heterosexual and gay serodifferent couples from Sept 15, 2010, to May 31, 2014.[8] From June 1, 2014, to July 31, 2017, the second phase of the study recruited gay male serodifferent couples only. The methods for the PARTNER study and results of the first phase have been published previously.[8,10]

From Sept 15, 2010, to July 31, 2017, we recruited serodifferent gay male couples from 75 clinical sites in 14 European countries. Participating clinic staff asked HIV-positive patients on ART if they had recent condomless sex with an HIV-negative partner and if they

wished to take part in a transmission study. Serodifferent couples (HIV-positive men on ART with their HIV-negative male partner) were eligible to take part if both partners were aged 18 years or older; the partners reported having penetrative sex with each other without condoms in the month before enrolment; the HIV-positive partner expected to remain on ART; the partners expected to have sex together again in the coming months; and both partners agreed to take part. Partners signed separate informed consent forms, which included partner identification by name. Follow-up ended on April 30, 2018. Follow-up was stopped if the partnership ended, the couple moved away, or if either partner withdrew consent, but not for changes in use of condoms or ART.

The protocol,[10] all informed consent forms, and participant information materials were submitted to and approved by the ethics committee (institutional review board [IRB] or independent ethics committee [IEC]) at each clinical site. Ethics approval was obtained in-country for all sites involved in the study. Additionally, any amendments to the study protocol were submitted and approved by each site's ethics committee (IRB or IEC).

Procedures

Study procedures have been described previously.[8] Data were collected at baseline and then every 4–6 months during study visits. Detailed information was obtained at baseline and each follow-up visit through self-completed questionnaires on sociodemographics; self-reported adherence to ART; frequency and type of sexual activity between the partners (since last visit); symptoms and diagnoses of other sexually transmitted infections (STIs); use of PrEP or post-exposure prophylaxis (PEP); and injection drug use. HIV-negative partners were asked if they had condomless sex with anyone other than their HIV-positive partner in the study since their last visit and HIV serostatus of other partners if known.

For the HIV-positive partner, ART regimen, CD4 cell count, and current and recent plasma HIV-1 RNA load were recorded on a clinical case report form at baseline and at each visit. The HIV-negative partner was asked to test for HIV every 6–12 months; a combined HIV antigen–antibody test was recommended to increase diagnostic sensitivity in early infection. Plasma HIV-1 RNA viral load was measured in the HIV-positive partner according to routine care every 6–12 months using the local diagnostic laboratory. Results were included in the case report forms and submitted after each partner visit by the study team to the study centre.

If an HIV-negative partner became HIV-positive, HIV-1 *pol* and *env* sequences were obtained from the seroconverted partner's HIV-1 RNA recovered from plasma and from the HIV-positive partner on virally suppressive ART's cellular HIV-1 DNA recovered from peripheral blood mononuclear cells. *Pol* and *env* sequences were generated by Sanger sequencing (on a ABI 3730xl DNA Analyzer, Thermo Fisher, Warrington, UK)[11] complemented by deep sequencing of plasma HIV-1 RNA by Illumina (on a MiSeq, Illumina, Essex, UK) in a subset with available plasma samples.[12] All sequencing testing was done at the University of Liverpool (Liverpool, UK). Maximum likelihood and Bayesian Markov chain Monte Carlo inferences and their relevant statistical support were determined with RAxML-HCP2 version 8 and MrBayes version 3.2.6, respectively, as previously described.[8,13]

Statistical analysis

The primary analysis was estimation of the incidence rate of HIV transmission through condomless anal sex, calculated as the number of phylogenetically linked HIV infections (ie, transmission from the HIV-positive study index partner) that occurred during eligible couple-years of follow-up divided by eligible couple-years of follow-up. Couple-years of follow-up were periods of time defined by HIV tests and corresponding questionnaires on sexual behaviour in the HIV-negative partner. These couple-years were eligible for inclusion in the analysis for this study if couples had condomless sex during the period (reported at the end of the time period by the HIV-negative partner, or by the HIV-positive partner if the HIV-negative partner did not complete the question); PEP or PrEP was not reported by the HIV-negative partner during the period; the most recent plasma HIV-1 RNA viral load in the HIV-positive partner was measured to be less than 200 copies per mL and within the past 12 months at all points measured in the period; and follow-up occurred before April 30, 2018 (the censoring date). Couple-years of follow-up could be ineligible for one or more reasons; the choice of primary reason for ineligibility was prioritised in the following order: (1) PEP or PrEP used; (2) HIV-negative partner (or the HIV-positive partner if the HIV-negative partner did not reply) reported no condomless sex; (3) most recent viral load of HIV-positive partner more than 200 copies per mL; (4) data on sexual behaviour missing; (5) no viral load available in the past year for each day in the time period; and (6) no HIV test from the HIV-negative partner at the end of the time period or later in time. Two-sided 95% CIs for the incidence rate of transmission were calculated using exact Poisson methods. Missing data were not imputed and the analysis was performed only on the available data. Data were analysed using SAS version 9.4.

In terms of sample size calculation, the PARTNER2 study was designed to assess whether the risk of transmission in the context of virally suppressive ART was below an acceptably low level, defined as one infection per 500 couple-years of follow-up, corresponding to an upper limit for the two-sided 95% CI of the rate of within-couple HIV transmission of 0·2 per 100 couple-years of follow-up. In the absence of linked infections, we determined that we needed 1770 eligible couple-years

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	HIV-positive partner (n=782)	HIV-negative partner (n=782)
Age (years)	40·0 (33·3–46·1)	37·6 (30·9–45·3)
Ethnicity		
White	674/765 (88%)	686/767 (89%)
Black	10/765 (1%)	9/767 (1%)
Asian	14/765 (2%)	14/767 (2%)
Other	67/765 (9%)	58/767 (8%)
Education		
High school or less	143/762 (19%)	144/760 (19%)
Vocational education	191/762 (25%)	176/760 (23%)
College or university	428/762 (56%)	440/760 (58%)
HIV acquisition route		
Heterosexual	2/762 (<1%)	NA
Homosexual	736/762 (97%)	NA
Shared needles or other injection equipment	0/762	NA
Other	24/762 (3%)	NA
Years of condomless sex*	1·0 (0·4–2·9)	1·0 (0·4–2·9)
Years on ART†	4·3 (1·8–9·3)	NA
Self-reported adherence		
≥90%	739/753 (98%)	NA
<90%	14/753 (2%)	NA
Missed ART for more than 4 consecutive days		
Yes	15/762 (2%)	NA
No	747/762 (98%)	NA
Informed their partner if they missed doses of ART		
No	26/765 (3%)	NA
Yes	316/765 (41%)	NA
Did not miss doses	423/765 (55%)	NA
Correctly self-reported HIV load (whether undetectable or not)		
Yes	698/747 (93%)	NA
No	49/747 (7%)	NA
Undetectable viral load (measured, copies per mL)		
<50	754/781 (97%)	NA
≥50	27/781 (3%)	NA
Undetectable viral load (measured, copies per mL)		
<200	774/781 (99%)	NA
≥200	7/781 (<1%)	NA
CD4 count (cells per μL)		
>350	730/781 (93%)	NA
≤350	51/781 (7%)	NA

Data are median (IQR) or n/N (%). NA=not applicable. ART=antiretroviral therapy. Denominators for percentages are all participants in that group who contributed to eligible couple-years of follow-up and provided a response to that question (missing data are excluded). *Data missing for 63 HIV-positive partners and 64 HIV-negative partners. †Data missing for 43 HIV-positive partners.

Table 1: **Baseline characteristics of couples eligible for the primary analysis**

of follow-up to obtain such an upper limit of the two-sided 95% CI. On the basis of findings from PARTNER1, we planned to recruit 450 couples over 27 months in PARTNER2. Assuming a retention rate of 85%, this would have allowed us to accumulate 2082 couple-years of follow-up through PARTNER1 and PARTNER2, of which 85% were predicted to be eligible (based on interim results[14]) for the primary analysis.

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

Between Sept 15, 2010, and July 31, 2017, 972 gay couples were recruited (477 couples during PARTNER1). By the end of follow-up on April 30, 2018, a total of 2072 couple-years of follow-up had been accrued (556 couple-years of follow-up during PARTNER1), with an estimated dropout rate of 25 per 100 couple-years of follow-up. Reasons for dropping out of the study were the couple broke up (213 [43%] of 499 couples), one or both partners moved away (33 [7%]), consent was withdrawn (54 [11%]), the 2-year study consent expired (21 [4%]), or the couple was no longer eligible (ten [2%]). The reason for dropping out of the study was not available for 168 (34%) couples. 479 couple-years of follow-up were ineligible for inclusion in the analysis for the following reasons: no condomless sex reported (153 [32%] of 479 couple-years of follow-up); use of PEP or PrEP (115 [24%]); HIV viral load data not available (86 [18%]); missing data on whether condomless sex was reported (91 [19%]); viral load in the HIV-positive partner more than 200 copies per mL (19 [4%]); or no HIV test available in the HIV-negative partner (15 [3%]).

1593 (77%) couple-years of follow-up were eligible and contributed by 782 couples, with 439 couple-years of follow-up contributed by 340 couples during PARTNER1. Unless otherwise stated, the following results focus on the 782 couples who provided eligible couple-years of follow-up. Median eligible years of follow-up per couple was 2·0 years (IQR 1·1–3·5). 1523 (96%) of the eligible couple-years of follow-up were during periods in which the most recent measure of plasma HIV-1 RNA in the HIV-positive partner was less than 50 copies per mL; the remaining 70 (4%) were during periods in which the most recent measure was between 50 and 200 copies per mL.

Baseline characteristics of the participants who contributed to eligible couple-years of follow-up are shown in table 1. Median age was 38 years (IQR 31–45) in HIV-negative participants and 40 years (33–46) in HIV-positive partners. Three trans men were included, one HIV negative and two HIV positive. 19 (2%) of 782 HIV-positive and 33 (4%) of 782 HIV-negative men reported that they were bisexual. HIV-negative men reported having condomless sex with their HIV-positive partners for a median 1·0 years (IQR 0·4–2·9) before study enrolment.

At baseline, HIV-positive partners had been on ART for a median of 4·3 years (IQR 1·8–9·3). Self-reported

adherence to ART was high, with 739 (98%) of 753 HIV-positive partners reporting adherence of 90% or more at study entry. 698 [93%] of 747 HIV-positive partners correctly self-reported at baseline whether their viral load was undetectable or not. This was an underestimate by the HIV-positive participants: 97% had undetectable viral load (<50 copies per mL) and 99% had viral load of less than 200 copies per mL. 730 [93%] of 781 HIV-positive partners had a CD4 count of more than 350 cells per µL at baseline.

During all couple-years of follow-up, very few (37 [5%] of 779) of the HIV-positive partners reported that they missed ART for more than four consecutive days. For 1461 (92%) of 1593 eligible couple-years of follow-up, adherence was more than 90% (not reported for 96 [6%] couple-years of follow-up) according to the HIV-positive partner. Most HIV-positive partners were on ART regimens containing three or more drugs (1470 [92%] couple-years of follow-up), with fewer HIV-positive partners taking regimens containing two drugs (73 [5%] couple-years of follow-up), or ART monotherapy (34 [2%] couple-years of follow-up). For the remaining 1% (16 couple-years of follow-up), the HIV-positive partners were either in a blinded clinical trial group or the ART regimen was unknown. For a quarter (396 [25%]) of eligible couple-years of follow-up, the HIV-positive partners were taking protease-inhibitor based regimens, for 47% (754 couple-years of follow-up) they were taking non-nucleoside reverse transcriptase inhibitor-based regimens, for 26% (408 couple-years of follow-up) they were taking integrase inhibitors, and for the remaining 2% (35 couple-years of follow-up) they were taking other or not reported regimens.

During follow-up (table 2), 185 (24%) of 779 HIV-negative men and 214 (27%) of 779 HIV-positive men reported an STI since their last visit. Couples reported having condomless sex 6090 times during eligible periods when an STI was present. 288 (37%) of 777 HIV-negative partners reported condomless sex with other partners. Few HIV-negative partners (28 [4%] of 775) reported injecting drugs during follow-up. In total, couples reported having condomless anal sex approximately 76 088 times during eligible couple-years of follow-up (figure 1). The median number of times couples had condomless sex was 43 times per year (IQR 19–75). Condomless sex was reported 2–10 times per 4-month period in 657 (41%) of 1593 eligible couple-years of follow-up, 21–40 times per 4-month period in 408 (26%) eligible couple-years of follow-up, and between 11 and 20 times per 4-month period in 332 (21%) eligible couple-years of follow-up (appendix).

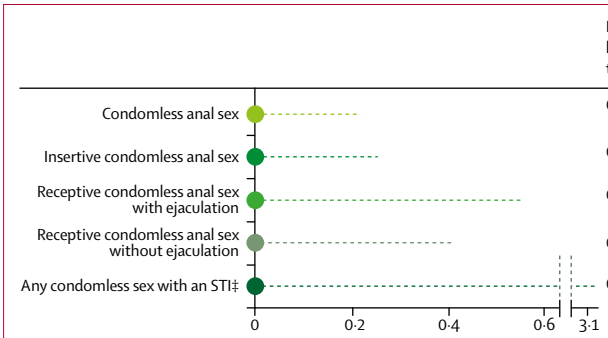
Figure 1 shows data on prevalence of the types of condomless penetrative sex (with the HIV-positive partner) reported by the HIV-negative partner. By definition, couples contributing eligible couple-years of follow-up reported anal sex without condoms during follow-up. Overall, 577 (75%) of 773 HIV-negative partners reported that they had receptive anal sex without ejaculation during follow-up, 436 (56%) of 776 reported receptive anal sex with their partner ejaculating inside, and 709 (91%) of 777 reported insertive anal sex.

	HIV-positive partner (n=782)	HIV-negative partner (n=782)
Time in the study (years)	2·0 (1·1–3·5)	2·0 (1·1–3·5)
STIs*	214/779 (27%)	185/779 (24%)
Syphilis	69/779 (9%)	54/779 (7%)
Gonorrhoea	85/779 (11%)	84/779 (11%)
Chlamydia	79/779 (10%)	66/779 (8%)
Herpes	10/779 (1%)	10/779 (1%)
Chronic herpes	7/779 (1%)	5/779 (1%)
Warts	22/779 (3%)	20/779 (3%)
LGV	9/779 (1%)	4/779 (1%)
Other STI	24/779 (3%)	23/779 (3%)
Not specified	4/779 (1%)	3/779 (<1%)
Condomless sex with other partners		
Yes	NA	288/777 (37%)
No	NA	489/777 (63%)
Condomless sex with other HIV-positive partners†		
Yes	NA	249/777 (32%)
No	NA	528/777 (68%)
Condomless sex acts‡ per year	41·3 (17·6–72·7)	43·4 (19·2–75·1)
Total number of condomless sex acts during eligible CYFU‡	73 674	76 088
Missed ART for more than 4 consecutive days		
Yes	37/779 (5%)	NA
No	742/779 (95%)	NA
Injected non-prescription drugs		
Yes	42/779 (5%)	28/775 (4%)
No	737/779 (95%)	747/775 (96%)
CYFU with reported frequency of condomless sex per month of§		
Less than once	335/1593 (21%)	312/1593 (20%)
1–2 times	222/1593 (14%)	236/1593 (15%)
3–4 times	310/1593 (19%)	329/1593 (21%)
5–8 times	434/1593 (27%)	439/1593 (28%)
More than 8 times	227/1593 (14%)	240/1593 (15%)
Not reported or missing	64/1593 (4%)	38/1593 (2%)

Data are median (IQR) or n/N (%), unless othewise specified. Denominators for percentages are all participants in that group who contributed to eligible couple-years of follow-up and provided a response to that question (missing data are excluded), unless otherwise specified. Missing data are less than 1% for all variables. STIs=sexually transmitted infections. LGV=lymphogranuloma venereum. NA=not applicable. CYFU=couple-years of follow-up. ART=antiretroviral therapy. *Participants who reported an STI (excluding HIV) since the last visit were asked whether it was syphilis, gonorrhoea, chlamydia, acute genital herpes, chronic genital herpes, LGV, or other. Participants who replied "yes" to the question "Since your last visit, have you had an STI?" but did not reply to the question "If yes, which STI?" were categorised as "not specified". †Only participants who reported condomless sex with other partners were asked this question. For this variable, missing is treated as "no" and the denominator to calculate the percentages is the number of participants who answered the question on whether they had "condomless sex with other partners" (n=777). ‡Only sex acts within couples are included. §The denominator is the total group-specific eligible CYFU (1593 CYFU). Note numerators and percentages do not add up to 1593 and 100%, respectively, because of rounding.

Table 2: **Characteristics during all follow-up of couples eligible for the primary analysis**

See Online for appendix



	Number of linked transmissions	Upper 95% CI limit*	Couple-years of follow-up	Number of condomless sex acts	HIV-negative men reporting sex act, n/N (%)†
Condomless anal sex	0	0·23	1593	76088	778/779 (99·9%)
Insertive condomless anal sex	0	0·27	1343	52087	709/777 (91·2%)
Receptive condomless anal sex with ejaculation	0	0·57	650	20487	436/776 (56·2%)
Receptive condomless anal sex without ejaculation	0	0·43	865	22995	577/773 (74·6%)
Any condomless sex with an STI‡	0	3·17	116	6090	NA

Figure 1: **Rate of within-couple HIV transmission through condomless sex according to sexual behaviour reported by the HIV-negative partner**
STI=sexually transmitted infection. NA=not applicable. *Estimated using the exact Poisson method. †Numerator is the number of HIV-negative men within the eligible couples ever reporting that specific sexual act and denominator is the group-specific number of HIV-negative participants who contributed eligible couple-years of follow-up. ‡Refers to STIs (excluding HIV) self-reported by the HIV-negative partner.

15 of the initially HIV-negative partners became HIV-1 positive during eligible follow-up, but there were no within-couple phylogenetically linked transmissions. 13 of the 15 individuals provided information about their presumed source of HIV infection, of whom ten (77%) reported recent condomless sex with men other than their study partner. Samples collected from the two partners of each of these 15 couples for sequencing were a median of 0 months apart (IQR 0·0–5·9). Viral sequences were recovered successfully from all couples (15 [100%] of 15 couples for *pol* genes and 13 (87%) of 15 for *env* genes). All new infections were phylogenetically unrelated to the initially HIV-positive partner's virus (figure 2 and appendix). Viral haplotypes derived from deep sequencing data of plasma samples from HIV-negative partners from five (33%) of the 15 couples confirmed the lack of linkage, since all viral haplotypes in the seroconverter samples were phylogenetically unrelated to the virus from their partners. All 15 partners who were the initially HIV-positive partner had subtype B infection according to *pol* gene subtyping; six of the 15 seroconverting partners acquired non-B infections (subtypes C, A1, CRF29_BF, CRF60_BC, and two partners acquired CRF14_BG infections, respectively).

With no linked transmissions, the estimated rate for transmission through condomless anal sex when the positive partner on ART had HIV viral load less than 200 copies per mL was zero, with an upper 95% CI limit of 0·23 per 100 couple-years of follow-up (equivalent to one transmission per 435 years of condomless sex). Figure 1 reports the rates of within-couple HIV transmission per 100 eligible couple-years of follow-up by sexual behaviour reported by the HIV-negative partner. For receptive anal sex with ejaculation the upper 95% CI limit was 0·57 per 100 couple-years of follow-up (equivalent to one transmission per 175 years of condomless sex). Figure 3 gives the upper bounds of the 95% CI around the estimate of zero transmissions for gay men and heterosexual couples achieved by the end of PARTNER1[8] and for gay men by the end of PARTNER2.

There were fewer eligible couple-years of follow-up during periods when the HIV-positive partner (135 couple-years of follow-up) or the HIV-negative partner (116 couple-years of follow-up) reported an STI, but no linked transmissions were reported. The upper 95% CI limit to the transmission estimate for periods with an STI in the HIV-negative partner was 3·17 per 100 couple-years of follow-up. Only 8 couple-years of follow-up of condomless sex were reported when the HIV-positive partner was in the first 6 months of taking ART.

Six additional seroconversions in HIV-negative partners took place outside eligible couple-years of follow-up. Reasons for the ineligibility of the couple-years in which these seroconversions occurred were no questionnaire containing sexual behaviour at the end of the period by the HIV-negative or HIV-positive partner (n=3); HIV-negative partner reported no condomless sex with the HIV-positive partner (n=1); use of PEP reported during the period when the infections occurred (n=1); and no HIV viral load measurement for the HIV-positive partner in the past year (n=1). The six newly infected partners were last seen 2 months, 6 months (n=2), 9 months, 13 months, and 16 months before seroconversion was recorded, respectively. Phylogenetic analysis showed that these transmissions were not linked to the HIV-positive partner on virally suppressive ART.

19·3 couple-years of follow-up were not eligible because of viral load in the HIV-positive partner being higher than 200 copies per mL for at least 1 day during the period (range 202–170 000 copies per mL), but all other criteria were met. During couple-years of follow-up with viral load higher than 200 copies per mL, people reported having condomless sex a total of 810 times with zero phylogenetically linked transmissions. For the

majority of these days, the most recent viral load in the HIV-positive partner was less than 200 copies per mL (12·3 couple-years of follow-up, estimated 513 sex acts), for 4·5 couple-years of follow-up the most recent viral load was between 200 and 1000 copies per mL (estimated 180 sex acts), and only for a minority of days the most recent viral load was higher than 100 000 copies per mL (0·23 couple-years of follow-up, estimated 31 sex acts).

Discussion

Our findings provide conclusive evidence that the risk of HIV transmission through anal sex when HIV viral load is suppressed is effectively zero. Among the 782 serodifferent gay couples followed for almost 1600 eligible couple-years of follow-up, which included more than 76 000 reports of condomless sex, we found zero cases of within-couple HIV transmission. In the absence of ART, on the basis of the frequency and type of sex, for receptive condomless anal sex acts alone approximately 472 transmissions (95% CI 83–714) would have been expected.[15] Our results give equivalence of evidence for gay men as for heterosexual couples and indicate that the risk of HIV transmission when HIV viral load is suppressed is effectively zero for both anal and vaginal sex.

For gay couples at the end of PARTNER1, the rate of within-couple transmission was zero, but this estimate was less precise than that for heterosexual couples because of the lower number of couple-years of follow-up accrued (0·84 per 100 couple-years of follow-up, equivalent to one transmission per 119 years of condomless sex in gay couples *vs* 0·46 per 100 couple-years of follow-up, or one infection per 217 years of condomless sex in heterosexual couples).[8] By extending the study in PARTNER2 and increasing the couple-years of follow-up accumulated in gay men, the upper bound of the 95% CI around the estimate of zero transmissions was reduced compared with that reported by the end of PARTNER1. The upper limit of the 95% CI is now 0·23 for anal sex, which is equivalent to one transmission per 435 years of condomless sex, such that the evidence for gay men is now stronger than that for heterosexual

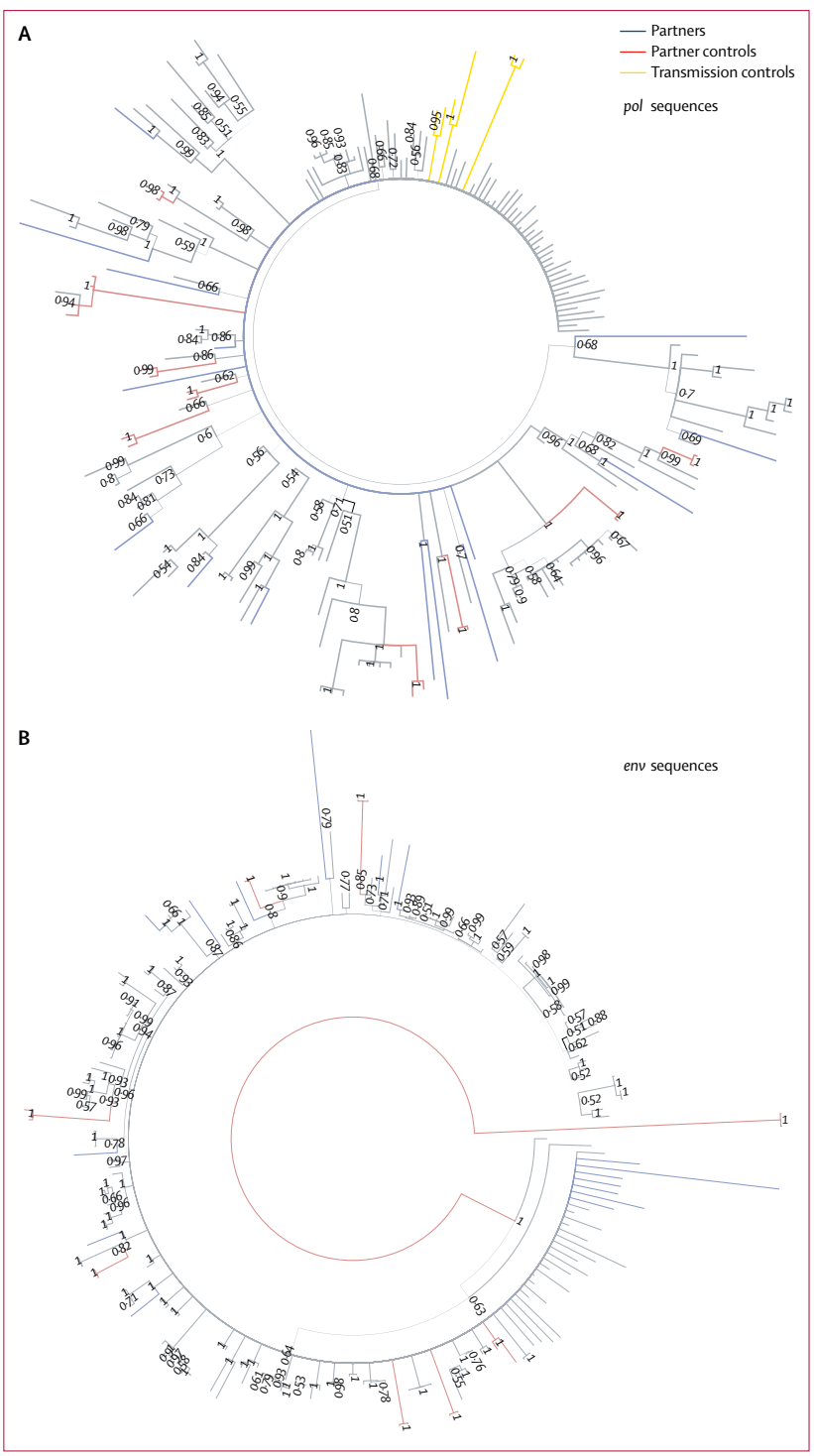


Figure 2: **Phylogenetic tree of *pol* and *env* sequences from nine couples with subtype B infection**

Bayesian Markov Chain Monte-Carlo inference (012313+I+G+F). Branch length is proportional to the genetic distance and line weight is proportional to the posterior probability. (A) Partners' (initially HIV-positive partners and seroconverters) sequences are in blue and found phylogenetically unlinked to viruses recovered from their putative transmitters, with a median pairwise genetic distance of 0·069 (IQR 0·057–0·076) and pairwise genetic distances consistently greater than 0·040. Positive control sequences comprised replicate sequences from study partners and sequences from confirmed transmission pairs obtained in a separate study.[13] The positive control sequences show pairwise genetic distance 0·004 (IQR <0·000 to 0·007) and always closely linked on monophyletic clusters with posterior probabilities more than 0·98 (red and orange clusters in the phylogenetic tree). Control sequences comprised the ten closest sequences identified through BLAST searches of GenBank. (B) Partners' (initially HIV-positive partners and seroconverters) sequences are in blue and found phylogenetically unlinked to viruses recovered from their putative transmitters, with a median pairwise genetic distance of 0·14 (IQR 0·125–0·169). Positive control sequences comprised replicate sequences from study partners (in red). The positive control sequences show pairwise genetic distance 0·001 (IQR <0·001 to 0·014) and always linked on monophyletic clusters with posterior probabilities equal to 1·00 (red clusters in the phylogenetic tree). Control sequences comprised the ten closest sequences identified through BLAST searches of GenBank.

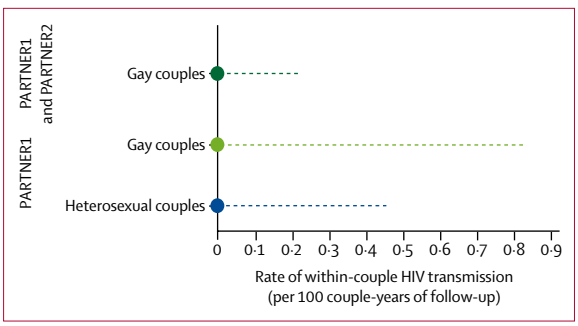


Figure 3: **Upper 95% CI limit around estimated rate of zero HIV transmissions through penetrative sex (vaginal or anal) at the end of PARTNER1[8] and PARTNER2**

couples in PARTNER1, thus achieving the aim of the PARTNER2 study.

Unlike other studies on HIV transmission, we only recruited couples that had already chosen not to use condoms and in the primary analysis we only included periods when condoms were not used and with no use of PrEP or PEP by the HIV-negative partner. We found no linked transmissions across all types of sexual behaviour and during periods when the HIV-positive or HIV-negative partner reported an STI. A quarter of HIV-positive and HIV-negative partners reported having an STI during follow-up, and although there were fewer couple-years of follow-up during these periods (116 couple-years of follow-up), no linked transmissions occurred. Similar to our findings, no HIV transmissions occurred during periods in which STIs were reported (21 couple-years of follow-up) in the Opposites Attract study.[9] We also reported on 19 couple-years of follow-up that were not eligible for inclusion in the primary analysis because the HIV viral load of the HIV-positive partner was higher than 200 copies per mL, but all other criteria for eligibility were met. During this time, no linked transmissions occurred despite couples having sex 810 times without condoms.

One limitation of the study was that most couples had been having sex without condoms for more than 6 months before study entry. Although there is little evidence that some individuals might be more susceptible to early acquisition of HIV infection, we were unable to determine risk of HIV transmission in very new partnerships. We also acknowledge that most HIV transmission is in young people (aged <25 years). In our study, recruited HIV-negative partners were predominantly of white ethnicity (89%), with a median age of 38 years. Most HIV-positive partners had been on virally suppressive ART for several years, so we had limited couple-years of follow-up during the initial months of ART. Data from the Partners PrEP study suggest that a residual risk of HIV transmission persists during the first 6 months of ART because of incomplete viral suppression in blood and genital compartments.[16] However, in that study, all three ART-exposed phylogenetically linked HIV transmission events in the first 6 months occurred before the HIV-positive partner achieved complete HIV viral suppression in blood. This observation suggests that residual transmission risk observed in the first 6 months was related to lack of suppression in blood rather than any genital tract viraemia. It is therefore important after starting ART to use preventive measures such as consistent condom use or PrEP[17] until viral load suppression in blood is fully and sustainably achieved.

It is well recognised that HIV-positive people on ART with suppressed viral load in blood can have intermittent shedding and detectable HIV RNA in semen and other genital tract fluids. HIV RNA in semen has been detected in 6–8% of men with suppressed HIV-1 RNA concentrations in blood in the absence of STIs.[18,19] In the Partners PrEP study, seminal HIV-1 RNA was detected in 11%, 5%, and 6% of samples collected after 0–3 months, 4–6 months, and more than 6 months on ART, respectively.[20] However, the scientific detection of small amounts of HIV RNA in semen does not appear to correlate with risk of HIV transmission if plasma viral load is suppressed. This finding might be because the virus present is not whole virus, is not replication competent, or is present at insufficient levels to cause transmission.[21] In the Partners in Prevention study, no transmissions occurred from individuals with detectable HIV genital viral load, but suppressed plasma viral load, to their HIV-negative partners.[22]

The effectiveness of ART in preventing HIV transmission is dependent on maintaining full virological suppression in plasma. In the HPTN 052 trial, the overall risk reduction through ART initiation was 93%,[7] but of the eight linked partner infections diagnosed after the index case started ART, transmissions occurred during a period of detectable HIV viraemia in plasma in index cases.[23] Four transmissions occurred shortly before or after the index case started ART with viral load measurements at the nearest timepoint ranging from 48 316 copies per mL to more than 750 000 copies per mL in the index case. The other four linked transmissions occurred between 1062 and 2162 days after the index case started ART, all of whom had documented ART failure, and in the three cases who remained in follow-up, the last HIV viral load measurement before the estimated infection date was more than 200 copies per mL.[23] These findings emphasise the importance of regular monitoring to ensure HIV viral load remains suppressed and supporting HIV-positive people with long-term adherence. Our study reflected current HIV viral load testing practices in Europe with 6 monthly or even annual viral load testing once individuals are established on ART with good adherence, as in our cohort. Once an individual is virally suppressed on ART, the risk of viral load rebound in the context of good adherence is very low. Data from the large UK CHIC cohort showed that rates of viral rebound in HIV-positive people on ART were low (7·8 per 100 person-years), and that 30% of people with rebound achieved virological

resuppression without a change in ART regimen.[24] In gay men older than 45 years, the rate of viral rebound reached a plateau of 1% per year, suggesting that in high-income settings at least, most people on ART will not have virological failure over their lifetime.[24] In our study, accurate self-knowledge of viral load status was very high, with 93% of HIV-positive partners correctly self-reporting viral load status at baseline. Participants underestimated their suppressed viral load status, however, as 97% actually had a suppressed viral load of less than 50 copies per mL and 99% had a viral load of less than 200 copies per mL.

Despite all the concerns about potential risks, there has not been a single verified case of HIV transmission in the context of complete virally suppressive ART reported in the literature. By contrast, there have been many large prospective studies specifically designed to find cases of HIV transmission when HIV-positive partners were virally suppressed that were unable to do so.[1–4,6–9] A case report of possible HIV transmission in a serodifferent gay couple despite virally suppressive ART in the HIV-positive partner[25] was published in 2008, a few months after the release of the Swiss Statement.[26] However, this case study did not meet the necessary conditions required for establishing that this was a linked transmission in the context of virally suppressive ART. These conditions are documentation of fully virally suppressive ART during which time the couple had condomless sex together, a verifiable negative HIV test in the HIV-negative partner at the start of the documented period of viral load suppression, and phylogenetic linkage of viruses from both partners.[27] In this case report, there was a lack of documentation of a negative HIV test in the HIV-negative partner at the start of the period of viral load suppression in the HIV-positive partner, because the negative result was based only on the participant's recollection of an undocumented, anonymous HIV test obtained 5 years earlier.[27] Because the HIV-negative partner had sex with the index case during the first weeks of ART, it is therefore likely that HIV transmission occurred before viral load was suppressed in the index case.

Knowledge about the impact of viral load suppression on transmissibility has been slow to filter from the scientific community to the wider community. In 2016, Landovitz and colleagues[28] reported that of 1809 participants in the ACTG A5257 study (a drug comparison study) who had been on ART for at least 48 weeks, with 91% with HIV RNA less than 50 copies per mL, 38% thought that they were highly infectious and the majority (90%) thought that they were somewhat infectious. This study was reported 16 years after data from the Rakai Project Study,[1] 5 years after the HPTN 052 trial,[6] and 2 years after the PARTNER1 interim results were released.[14] To improve dissemination of the scientific knowledge in this area, in 2016 the Prevention Access Campaign launched the U=U (undetectable equals untransmittable) campaign, based on the statement: a person living with HIV who has undetectable viral load does not transmit HIV to their partners.[29,30] This statement has been endorsed to date by more than 780 HIV organisations from 96 countries, including by leading scientific and medical organisations.

However, U=U is only easy to apply when HIV-positive people have access to testing, effective treatment, viral load monitoring to levels of less than 200 copies per mL, and support to reach and maintain viral suppression. Even in high-income settings there are differences in rates of viral suppression. For example, the HIV Care Continuum in the USA indicated that of the 1·1 million people living with HIV in 2014, 85% were diagnosed, but only 49% were virologically suppressed.[31] A sustained effort is required to increase rates of testing and HIV diagnosis with early initiation of ART and full support to maintain high levels of adherence.

The results from the PARTNER studies support wider dissemination of the message of the U=U campaign that risk of transmission of HIV in the context of virally suppressive ART is zero. This dissemination is necessary to promote the benefits of early testing and treatment and to tackle stigma, discrimination, and criminalisation laws that continue to affect HIV-positive people.

Contributors

AJR, ANP, and JL conceived the study and obtained funding. AJR drafted the manuscript and wrote the final version of the report. VC analysed the data. TB, PV, SC, GMC, VE, and AMG contributed to the study design, interpretation of the data, and writing of the report. AMG and ABe performed the sequencing and phylogenetic analysis. AJR, PV, OD, VE, NN, PC, AA, JG, JMP, FR, AR, ABl, RW, AVE, JdRG, AC, NHB, AL, MK, HJ, KB, JRB, FG, JL, GW, LO, MR, and H-JS provided data for the study. All authors reviewed and approved the final manuscript.

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Declaration of interests

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