HIV transmission risk through condomless sex in gay couples with suppressive ART: The PARTNER2 Study extended results in gay men

No conflicts of interest
Background

• There is clear evidence, particularly in heterosexual couples, of the dramatically reduced risk of HIV transmission from condomless sex with suppressive ART

• Zero cases of HIV transmission in gay male sero-different couples reported in recent observational studies (PARTNER1 and Opposites Attract)

• However with CYFU accumulated in PARTNER1, upper 95% confidence limit of the rate for gay men was 0.84 /100 CYFU (compared to 0.46/100 CYFU in heterosexual couples).

• The aim of PARTNER2 was to provide more precise estimates of transmission risk in gay partnerships in this context

Cohen et al. NEJM, 2016; Rodger et al. JAMA, 2016; Grulich et al. Lancet HIV, 2018
PARTNER Study
(Partners of people on ART: a New Evaluation of the Risks)

Design: observational multi-centre study of HIV serodifferent couples (MSM and HT) in which the positive partner is on ART in 75 European clinical sites:

- **Phase 1:** 2010-2014 (HT+MSM)
- **Phase 2:** 2014-2018 (MSM only)

Primary Aim

- To follow serodifferent partnerships that have penetrative sex without using condoms where the HIV-positive partner is on ART with a plasma HIV-1 RNA load <200 copies/mL to study risk of HIV transmission through anal sex in the absence of condom use.
Study Procedures

- Informed consent included explicit reference to the fact that HIV negative men knew their partner is HIV positive
- Study data collected at baseline and every 6-12 months,
  - Confidential sexual behaviour questionnaires completed by each partner
  - HIV testing for the negative partner
  - HIV viral load measurement for the positive partner

<table>
<thead>
<tr>
<th>Questionnaire data</th>
<th>HIV Positive Partner</th>
<th>HIV Negative Partner</th>
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<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Sexual behaviour with study partner</td>
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<td>STI diagnosis</td>
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<td>IVDU</td>
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<td>ART adherence</td>
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<td>HIV testing history</td>
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<td>Knowledge partner VL</td>
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<td>PEP/PrEP use</td>
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<td>Sexual behaviour with other partners</td>
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<tr>
<th>Clinical Data</th>
<th>HIV VL testing</th>
<th>HIV testing</th>
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<tr>
<td>ART use</td>
<td></td>
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<tr>
<td>STI diagnosis</td>
<td></td>
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<tr>
<td>CD4 count</td>
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</table>
Study Procedures

- Eligible couple years of follow-up (CYFU) formed of periods of time between HIV tests in which:
  - Couples had condomless sex together during the time period
  - No reported PEP or PrEP use by the HIV negative partner
  - Plasma HIV-1 RNA load <200 copies/mL in HIV positive partner within last 12 months at all points in the period
  - Follow-up occurred before 30th April 2018 (censoring date)

- We report the rate of within-couple phylogenetically linked transmissions during eligible CYFU
Sequencing and Phylogenetic Analysis

• HIV-1 pol and env sequences were obtained from either plasma or PBMCs by Sanger sequencing,\(^1\) complemented by deep sequencing by Illumina in a subset\(^2\)

• Maximum likelihood (ML) and Bayesian Markov Chain Monte-Carlo (MCMC) inferences were determined with RAxML-HCP2 v8 and Mr Bayes v3.2.6, respectively

• Controls: i) the 10 closest GenBank sequences, ii) replicate partners’ sequences, and iii) sequences from confirmed HIV-transmission pairs\(^3\)

• Criteria for linking infections was monophyletic clustering with high statistical support e.g. bootstrap value $\geq 0.90$ (ML) or a posterior probability $\geq 0.95$ (MCMC), and a pairwise genetic distance of $\leq 0.015$ nucleotide substitutions per pol site\(^1\)

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Overall 972 gay couples were recruited, of which 783 couples contributed 1596 eligible CYFU.

Reasons CYFU are not eligible (n=477):
- Reported no CL sex (32%)
- Use of PEP/PrEP (24%)
- VL not available (18%)
- Missing data on whether CL sex reported (18%)
- VL>200 copies/mL (5%)
- No HIV test in negative partner (3%)
## HIV negative partner characteristics

### At study entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age, median (IQR, n=759)</td>
<td>38 (31-45)</td>
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<tr>
<td>White ethnicity (%, n=768)</td>
<td>687 (89%)</td>
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<tr>
<td>Years condomless sex, median (IQR)</td>
<td>1.0 (0.4-2.9)</td>
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</table>

### During follow up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Years in the study, median (IQR)</td>
<td>1.6 (0.9-2.9)</td>
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<tr>
<td>Diagnosed with STI, %</td>
<td>23%</td>
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<tr>
<td>Condomless sex with other partners, %</td>
<td>37%</td>
</tr>
<tr>
<td>Condomless sex acts per year, median (IQR)</td>
<td>43 (19-74)</td>
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<tr>
<td>Estimated total number condomless sex acts</td>
<td>76,991</td>
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# HIV positive partner characteristics

<table>
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<tr>
<th>At study entry</th>
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<tbody>
<tr>
<td>Age, median (IQR; n=758)</td>
<td>40 (33-46)</td>
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<tr>
<td>Years on ART, median (IQR)</td>
<td>4.0 (2.0-9.0)</td>
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<tr>
<td>Self-reported adherence &gt;=90%, %</td>
<td>98%</td>
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<tr>
<td>Self report undetectable VL, %</td>
<td>93%</td>
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<tr>
<th>During follow-up</th>
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<tbody>
<tr>
<td>Missed ART for more than 4 consecutive days, %</td>
<td>2%</td>
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<tr>
<td>Diagnosed with STI, %</td>
<td>27%</td>
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New HIV infections in negative partners

- 15 initially HIV-negative MSM partners became HIV-positive
  - 11 reported recent condomless sex with others
- Samples collected from partners in each couple a median of 0 months’ apart (IQR 0.0-5.9)
- Viral sequences recovered successfully from all couples: 15/15 (100%) for pol and 13/15 (87%) for env
- All new infections phylogenetically NOT related to the initially positive partner’s virus
The 15 HIV-positive partners all had subtype B infection; 6 of the 15 seroconverting partners acquired non-B infections.

None of the partners’ sequences (blue) clustered together.

The study partner controls (red) and the control sequences from confirmed transmission pairs (orange) always clustered together with high supports.

The controls pairwise genetic distance was 0.004 (IQR: <0.001, 0.007), whilst the partners’ pol sequences showed a median pairwise genetic distance of 0.068 (IQR: 0.060, 0.086).
Rate of HIV transmission according to sexual behaviour reported by the negative partner
Rate of HIV transmission according to sexual behaviour reported by the negative partner

- Any sex
  - Rate: 0
  - 95% CI: 0.23
  - CYFU: 1596
  - CLS acts: 76991
- Anal sex
  - Rate: 0
  - 95% CI: 0.24
  - CYFU: 1546
  - CLS acts: 70743
- Insertive anal sex
  - Rate: 0
  - 95% CI: 0.27
  - CYFU: 1345
  - CLS acts: 52572
- Receptive anal sex with ejaculation
  - Rate: 0
  - 95% CI: 0.57
  - CYFU: 652
  - CLS acts: 20770
- Receptive anal sex without ejaculation
  - Rate: 0
  - 95% CI: 0.43
  - CYFU: 867
  - CLS acts: 23153
- Any sex with a STI
  - Rate: 0
  - 95% CI: 2.74
  - CYFU: 135
  - CLS acts: 6301

Rate of within couple transmission (per 100 CYFU)
Upper 95% CI around estimated rate of zero HIV transmissions: PARTNER 1 compared to PARTNER 1&2

Rate of within couple transmission (per 100 CYFU)
Upper 95% CI around estimated rate of zero HIV transmissions: PARTNER 1 compared to PARTNER 1&2

Rate of within couple transmission (per 100 CYFU)
Conclusions

• Among serodifferent gay couples who had sex 77,000 times without condoms with undetectable viral load, we found zero linked transmissions during almost 1600 CYFU

• 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

• Undetectable = Untransmissable
Acknowledgments

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PARTNER2 Study Sites


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Portugal: Hospital Santa Maria, Lisbon: Nuno Janeiro

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