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


Disclosure slide

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
• 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

### Study Procedures

<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>
<td>Demographics</td>
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<td>Sexual behaviour with study partner</td>
<td>Sexual behaviour with study partner</td>
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<td>STI diagnosis</td>
<td>STI diagnosis</td>
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<td>STI symptoms</td>
<td>STI symptoms</td>
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<td>IVDU</td>
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<td>ART adherence</td>
<td>HIV testing history</td>
<td>Knowledge partner VL</td>
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<td></td>
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<td>PEP/PrEP use</td>
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<td></td>
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<td>Sexual behaviour with other partners</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>HIV VL testing</th>
<th>HIV testing</th>
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<tbody>
<tr>
<td>ART use</td>
<td></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>

• 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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Eligible Couple Years of Follow Up

- 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%)

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1. Rodger et al. JAMA, 2016 
2. Geretti et al., JAMA, 2016. 
### HIV negative partner characteristics

**At study entry**
- Age, median (IQR, n=759): 38 (31-45)
- White ethnicity (%), n=768: 687 (89%)
- Years condomless sex, median (IQR): 1.0 (0.4-2.9)

**During follow up**
- Years in the study, median (IQR): 1.6 (0.9-2.9)
- Diagnosed with STI, %: 23%
- Condomless sex with other partners, %: 37%
- Condomless sex acts per year, median (IQR): 43 (19-74)
- Estimated total number condomless sex acts: 76,991

### HIV positive partner characteristics

**At study entry**
- Age, median (IQR; n=758): 40 (33-46)
- Years on ART, median (IQR): 4.0 (2.0-9.0)
- Self-reported adherence >=90%, %: 98%
- Self report undetectable VL, %: 93%

**During follow-up**
- Missed ART for more than 4 consecutive days, %: 2%
- Diagnosed with STI, %: 27%
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

Phylogenetic tree of pol subtype B sequences

- 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

<table>
<thead>
<tr>
<th>Linked transmissions</th>
<th>Upper 95% CL</th>
<th>CYFU</th>
<th>CLS acts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sex</td>
<td>0.23</td>
<td>1596</td>
<td>76091</td>
</tr>
<tr>
<td>Anal sex</td>
<td>0.24</td>
<td>1546</td>
<td>70743</td>
</tr>
<tr>
<td>Inseve anal sex</td>
<td>0.27</td>
<td>1346</td>
<td>52572</td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>0.57</td>
<td>652</td>
<td>20770</td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>0.43</td>
<td>159</td>
<td>233573</td>
</tr>
<tr>
<td>Any sex with a STI</td>
<td>0.27</td>
<td>135</td>
<td>6301</td>
</tr>
</tbody>
</table>

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 = Untransmissible

Acknowledgments

We acknowledge and thank all PARTNER study participants who generously participated in this research.

PARTNER2 Study Sites


Germany: University Clinic, Hamburg Eppendorf: Olaf Degen. University Hospital, Cologne: Tim Kümmerle. University Hospital, Bochum: Norbert H. Brockmeyer. University Hospital, Munich: Johannes Bogner.

Acknowledgments

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PARTNER2 Study Sites

Spain: Hospital Universitari de Bellvitge: BCN Checkpoint, Barcelona: Michael Moultrevi. Hospital Universitario San Carlos, Madrid: Vicente Perez Estrada.

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