Sexual activity without condoms and risk of HIV transmission when the HIV positive partner is using suppressive ART: The PARTNER study

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AIDS 2016, Durban,19th July, 2016

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Disclosure slide

Alison Rodger has no financial relationships with commercial entities to disclose

Background

- A key factor in assessing the effectiveness of ART as a prevention strategy and to inform individual choice on condom use is the absolute risk of HIV transmission through condomless sex (CL) for a person on ART with undetectable plasma VL
- There are however a number of gaps in currently available evidence
- There is no direct evidence at all for anal sex in men who have sex with men
- In transmission studies in heterosexual (HT) couples most CYFU are in context of reported consistent condom use

Refs: Rodger et al. Antivir Ther. 2013;18(3):285-7, Cohen et al. N Engl J Med. 2011; 365:493–5052.

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PARTNER Study

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

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 and vaginal sex in the absence of condom use

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Study Procedures

- Informed consent included
  - Information on the need for consistent condom use (emphasized at each study contact)
  - Explicit reference, including in consent form, to the fact that HIV negative partners knew their partner is HIV positive and there is a transmission risk
- Study data collected on standardized case report forms after consent at baseline and then every 4 to 6 months
- Included confidential risk behaviour questionnaire and clinical data: HIV viral load (for +ve partner) and HIV test (for -ve partner)

Study Procedures

- Eligible couple years of follow-up (CYFU) formed of periods of time between HIV tests in which:
  - had condomless sex during the time period
  - there was no reported PEP or PrEP use
  - plasma HIV-1 RNA load <200 copies/mL within last 12 months
  - follow-up occurred before 31st May 2014 (censoring date)
- Overall 1,166 couples were recruited by 31st May 2014, of which 888 couples contributed 1238 eligible CYFU
- Reasons couples provide no eligible CYFU (n=116): no HIV test (n=20), use of PEP/PrEP (n=9), no CL sex reported (n=15), VL>200 copies/mL (n=55) or VL not available (n=17)
- We report the rate of within-couple phylogenetically linked transmissions during eligible CYFU

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Sequencing and phylogenetic analysis

- HIV-1 *pol* and sequences were obtained from either plasma or PBMCs and/or both by Sanger sequencing[1]
- 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[2]
- Criteria for linking infections was monophyletic clustering with high support e.g bootstrap value ≥0.90 (ML) or a posterior probability ≥0.95 (MCMC), and a pairwise genetic distance of ≤0.015 nucleotide substitutions per *pol* site[3, 4]

Refs: 1. Geretti AM et al , JAC 2014;69:1090-7; 2. Beloukas A, et al. Virus Res 2012;166:54-60; 3. Hue S, et al. AIDS 2014;28:1967-75; 4. Mbisa JL, et al. CID2015;61:829-36.

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HIV negative partners: Characteristics

	MSM couples (n=340)	Heterosexual couples (n=548)	
		M -ve (n=279)	W -ve (n=269)
At study entry			
Age, median (IQR)	40 (32-47)	45 (37-50)	40 (34-46)
White ethnicity (%)	221 (83%)	229 (85%)	217 (82%)
Yrs CL sex, median (IQR)	1.4 (0.5-3.5)	2.8 (0.6-7.5)	3.6 (0.7-11.4)
During follow up			
Years in the study, median (IQR)	1.4 (0.8-2.1)	1.8 (1.1-2.4)	1.9 (1.1-2.4)
Diagnosed with STI, %	17%	6%	6%
CL sex with other partners, %	33%	4%	4%
CL sex acts/year, median (IQR)	42 (18-75)	35 (14-68)	36 (13-70)
Estimated total number CL sex acts	22,273	18,431	17,509

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HIV positive partners: Characteristics

	MSM couples (n=282)	Heterosexual couples (n=445)	
		W +ve (n=245)	M +ve (n=240)
At study entry			
Age, median (IQR)	42 (36-47)	40 (35-47)	45 (40-49)
Years on ART, median (IQR)	5 (2-11)	8 (3-14)	11 (4-16)
Self-reported adherence >=90%, %	97%	94%	93%
Self report undetectable VL, %	94%	87%	84%
CD4>350 cells/mm^3, %	91%	89%	85%
During follow-up			
Missed ART for more than 4 consecutive days, %	3%	8%	6%
Diagnosed with STI, %	18%	6%	6%

HIV transmissions

- 11 putative transmission events, but there zero phylogenetically linked transmissions.
- Of the 11 people who became infected, 10 were MSM, 1 was heterosexual, 8 (73%) of these reported that they had recent condomless sex with others apart from their study partner.
- Viral sequences were recovered successfully from all couples, comprising 22/22 (100%) subjects for *pol* and 20/22 (91%) subjects for *env*.
- The partners that were initially HIV-positive had subtype B infection in all cases, whereas 2 partner seroconverted during the study acquired non B infections.

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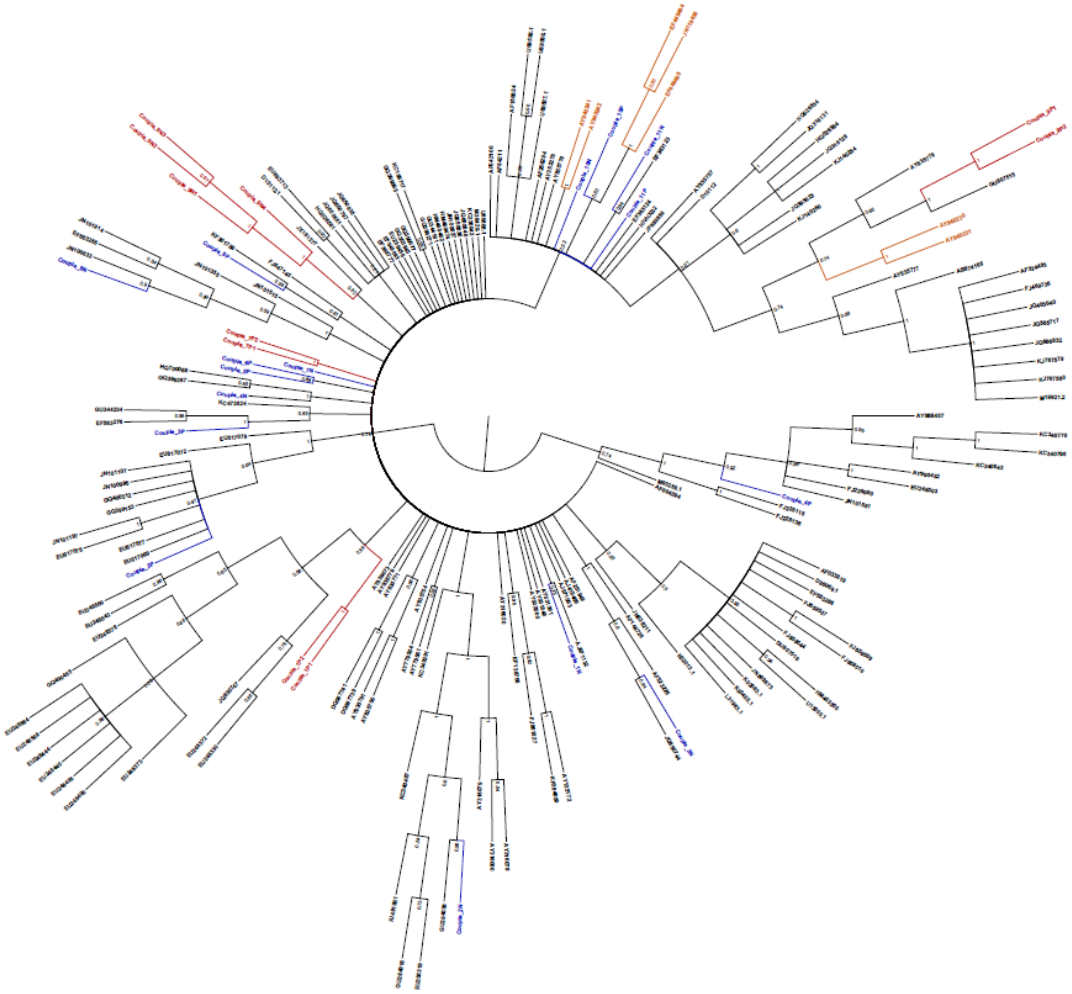
Phylogenetic tree of *pol* sub B sequences

- None of the partners' sequences clustered together, with consistent results observed across analyses (blue).
- The partner controls (red) and the control sequences from epidemiologically confirmed transmission pairs (orange) always clustered together with high supports.
- The partners' sequences showed median pairwise genetic distance 0.070 (IQR: 0.056, 0.079), whilst for the control sequences median genetic distance was 0.004 (IQR: <0.000, 0.008).



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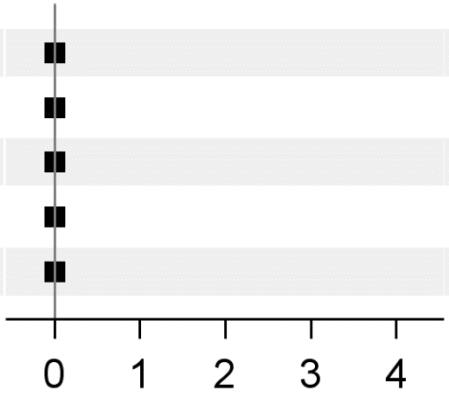
Rate of HIV transmission overall according to sexual behaviour reported by the negative partner – all couples

	% of Eligible Couples Reporting Specific Sex Act	Couple-Years of Follow-up	Upper 95% Confidence Limit
Any sex	99.7	1238	0.30
Vaginal sex	60.6	629	0.59
Anal sex	52.9	522	0.71
Insertive anal sex	42.1	417	0.88
Receptive anal sex with ejaculation	21.4	166	2.23



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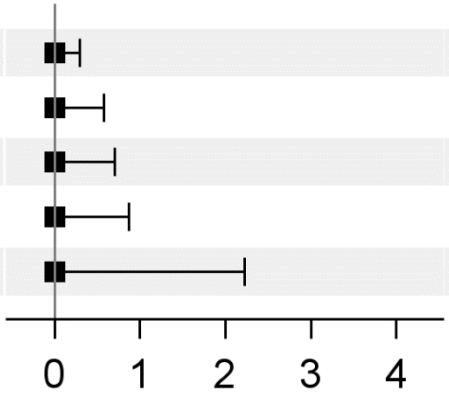

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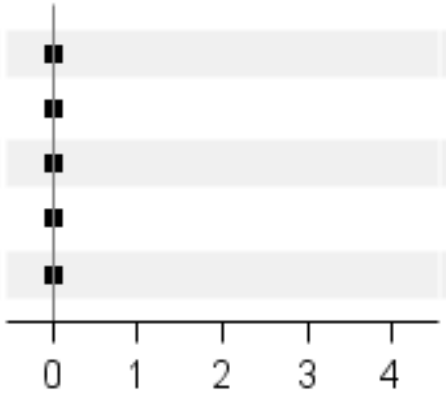
Rate of HIV transmission in MSM according to sexual behaviour reported by the negative partner – MSM couples

	% of Eligible Couples Reporting Specific Sex Act	Couple-Years of Follow-up	Upper 95% Confidence Limit
Any sex	100	439	0.84
Anal sex	99.7	415	0.89
Insertive anal sex	92.1	370	1.00
Receptive anal sex with ejaculation	45.0	137	2.70
Receptive anal sex without ejaculation	67.0	220	1.68



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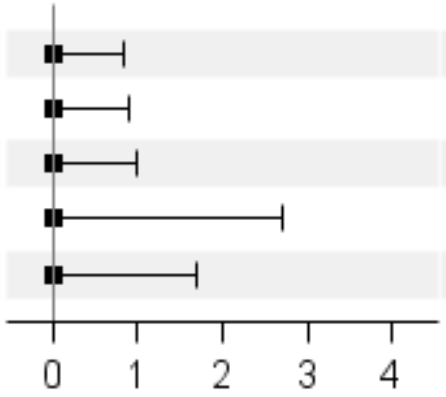

Conclusions

- Among serodifferent heterosexual and MSM couples followed for 1238 couple years in which the HIV-positive partner had viral suppression on ART, during which time there were 58,000 sex acts, there were zero incidences of within-couple HIV transmission.
- The estimated rate of transmission is thus **zero** (upper 95% confidence limit 0.3 / 100 couple years of follow-up)
- This also provides the first estimate (i.e. 0) of HIV transmission risk for MSM through condomless anal sex with suppressed plasma HIV VL.
- Additional longer-term follow-up in MSM is ongoing to 2018 to provide more precise estimates of risk to inform policy and also individual choice on condom use

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Acknowledgments

Thank you to all PARTNER study participants

PARTNER sites

Spain : Hospital Virgen del Rocío, Sevilla, Pompeyo Viciana. Hospital Universitario de Elche, Felix Gutiérrez. Hosp. Universitari Germans Trias i Pujol, Bardalona, Bonaventura Clotet. Hospital La Paz, Madrid, José María Peña. Hospital Universitario San Carlos, Madrid, Vicente Perez Estrada. Hospital Universitario Reina Sofia De Cordoba, Antonio Rivero. Hospital Clínico Universitario de Santiago de Compostela, Antonio Antela. Hospital Clínic de Barcelona, Barcelona, Jose M. Gatell Artigas. Centro Sanitario Sandoval, Madrid, Jorge Del Romero Guerrero. Hospital Ramon y Cajal, Madrid, Fernando Dronda. Hospital Carlos III, Madrid, Vincente Soriano.

United Kingdom: Chelsea & Westminster, London: David Asboe. Dean Street Clinic, London: Nneka Nwokolo. Mortimer Market Centre, London: Richard Gilson. Southmead Hospital, Bristol: Mark Gompels. Coventry and Warwickshire Hospital: Sris Allan. King's College Hospital: Michael Brady. Brighton and Sussex: Martin Fisher. Leicester Royal Infirmary: Jyoti Dhar. Newham : Rebecca O'Connell. Birmingham Heartlands : David White. St Thomas's Hospital, London: Julie Fox. St Mary's Hospital, London: Sarah Fidler,.Bradford: Phillip Stanley, Earnsdale Clinic, Redhill: Usha Natarajan. Northampton: Mohamed Ghanem. North Middlesex University Hospital, London : Jonathan Ainsworth. North Manchester General Hospital: Ed Wilkins. St James's, Leeds: Jane Minton. Hastings: Harish Patel. Whipps Cross Hospital, London: Monica Lascar.

Germany: University Clinic, Hamburg Eppendorf: Jan van Lunzen. University Hospital, Cologne Gerd Fätkenheuer. Praxis Driesener Straße, Berlin Ivanka Krznaric. Medizinische Poliklinik, Munich, Johannes Bogner. Universitäts-Hautklinik, Bochum, Norbert H. Brockmeyer. ICH Study Center, Hamburg, Hans-Jürgen Stellbrink. Gemeinschaftpraxis Jessen-Jessen-Stein, Berlin, Heiko Jessen. University Hospital, Bonn, Jürgen Rockstroh.

Switzerland: University Hospital Zürich, Rainer Weber. University Hospital Bern, Hansjakob Furrer. University Hospital Basel, Marcel Stoeckle, Kantonsspital, St. Gallen, Pietro Vernazza. Ospedale Regionale Di Lugano, Enso Bernasconi.

Denmark: Rigshospitalet, Copenhagen, Jan Gerstoft. Hvidovre Universitets Hospital, Lars Mathiesen. Aarhus universitetshospital, Skejby Lars Oestergaard. Odense Universitetshospital, Svend Stenvang.

Finland: Helsinki University Central Hospital, Matti Ristola.

Sweden: Karolinska University Hospital Huddinge, Stockholm, Katarina Westling. Södersjukhuset, Venhälsan, Stockholm, Anders Blaxhult.

Ireland: St. James' Hospital, Dublin Gráinne Cortney.

Belgium: CHU Saint-Pierre, Bruxelles , Nathan Clumeck. University Ziekenhuis, Gent, Linos Vandekerckhove

The Netherlands: AMC. Amsterdam, Jan Prins. OLVG, Amsterdam, Kees Brinkman. Medisch Centrum Jan van Goyen, Amsterdam, Dominique Verhagen. DC Klinieken, Amsterdam, Arne van Eeden.

France: Hopital de l' Archet 1, Nice, Christian Pradier. CHU Hotel-Dieu, Nantes, Francois Raffi. Hopital Tenon, Paris, Gilles Pialoux. "190", Paris, Michel Ohayon. AIDES, Vincent COQUELIN.

Austria: Medical University of Vienna, Armin Rieger. Medical University Innsbruck, Robert Zangerle. FA für Dermatologie/Venerologie, Linz, Maria Geit

Italy: San Paolo Hospital, Milna,Terease Bini. Ospedale Spallanzani, Roma Adriana Ammassari. Malattie Infettive Università di Catania, Maurizio Celesia.Università degli Studi di Modena Cristina Mussini. Universitaria San Martino, Genova,Antonio Di Biagio.

Portugal: Hospital Santa Maria, Lisabon, Nuno Janerio.

The PARTNER study presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG-0608-10142) . The views expressed in this presentation are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health

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