Partner Protocol

A study in HIV sero-different partnerships to estimate the rate of transmission of HIV and to investigate factors associated with condom use.

Partners of people on ART: a New Evaluation of the Risks
PARTNER study
Version 2.0 16 May 2014
REC ref: 10/H0720/55

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BACKGROUND

Numbers of HIV diagnoses in MSM remain high in Europe despite intensive prevention efforts. Although condom use is advised, it is consistently reported that a proportion of HIV positive MSM have condomless sex. With the publication of the results of the HPTN 052 trial and the interim results from PARTNER Phase 1 study there is now very strong evidence that virally suppressive ART reduces the infectiousness of people with HIV through heterosexual vaginal sex [1,2-4]. However, there remains no reliable data for HIV transmission rates for anal sex with use of ART in MSM which may well be higher than rates for vaginal sex. Studies have documented probable per-act estimates of HIV transmissibility for anal intercourse [5-9], but no data are available from observational cohorts or RCTs in serodifferent MSM couples to determine risk of HIV transmission through anal intercourse with ART. As the risk of HIV transmission in the absence of ART is greater for anal sex than for vaginal sex [10], the degree to which the HPTN 052 results in heterosexual couples can be extrapolated to MSM or to heterosexuals having anal sex is unknown. In 2011, a WHO and NIH working group reviewed what further evidence is required in order to recommend a policy of ART for prevention of HIV transmission in MSM couples. Concern was raised about the external validity of the results of HPTN 052 in MSM and others who engage in anal sex, given that only 2% of the pairs were MSM [1].

Phase 1 of the PARTNER study (RP-PG-0608-10142) will give an overall risk of HIV transmission for condomless vaginal and anal sex combined at study end in mid-2014. The estimated accrual of eligible couple years of follow-up (CYFU) from PARTNER Phase 1 (to April 2014) will be approximately 1150 couple years overall and 397 couple years for MSM couples. The rate of transmission through anal sex will also be reported by the end of phase 1, but even with a zero estimated rate of transmission the upper 95% CI will be too high to resolve the question. In order to increase the precision of the risk assessment for anal sex this second phase of the PARTNER study will continue to follow-up MSM couples for an additional three years in addition to recruit a further 450 MSM couples to achieve a total PYFU of 1986. The table below gives a comparison of the results for HIV transmission through condomless anal sex obtained by HPTN 052 study and PARTNER phase 1, compared to PARTNER phase 2

Table: Comparison of results on anal sex generated by HPTN 052, Partner Phase 1 and PARTNER Phase

Eligibility criteria: HIV negative reporting condom-less sex; HIV+ VL<200 in the last year

	HPTN 052 [3]	PARTNER Phase 1 (by 1st Nov 2013)	PARTNER Phase 2 (by end May 2017)
Number MSM couples	37	436 recruited (342 active)	App .880
Condom-less sex	96% reported regular condom use 5-6% reported having unprotected sex prior to enrolment	Only couple-years in which condomless anal sex is reported will be included in the final analyses.	Only couple-years in which condomless anal sex is reported will be included in the final analyses.
CYFU	Unknown	308	1770
upper 95% confidence limit for Risk of transmissions – condomless sex	Unknown	1/ 83 couple years ** (MSM)	1/480 couple years anal sex** (MSM)
CYFU from couples having condom-less anal sex	Unknown < 100	262	1506
CYFU receptive anal sex with ejaculation	Unknown	93	535
upper 95% confidence limit for risk of transmission – anal sex if 0 transmissions observed	Unknown	1/ 71 couple years anal sex** (MSM)	1/408 couple years anal sex**
upper 95% confidence limit for risk of transmission – receptive anal sex with ejaculation if 0 transmissions observed	Unknown	1/25 couple years ** (MSM)	1/163 couple years **

AIMS

We aim to follow serodifferent men who have sex with men (MSM) partnerships who initially report recently having had condomless sexual intercourse in order to study (i) the risk of HIV transmission to partners, in particular in partnerships that continue not to use condoms consistently and the HIV-positive partner is on therapy with a viral load < 200 copies/mL and (ii) why some partnerships do not use condoms, to describe the proportion who begin to adopt consistent condom use, and factors associated with this.

METHODS

Study design
This is an observational study in which HIV serodiscordant partnerships will be followed over time, with 6 monthly reporting of transmission risk behaviour and HIV testing for the HIV negative partner.

Inclusion/exclusion criteria:

Inclusion criteria

- Confirmed HIV positive

- On ART (regardless of viral load)

- Age > 18

- Expected to remain under care at the clinic for as long as the participate in the study

- Has a male partner not known to be HIV infected and the following criteria are met:

    - The partners have had condomless penetrative anal together in the past month (during which period the HIV negative partner was aware of the HIV status of the HIV positive partner)
    - The partners expect to have sex together again in the coming months
    - Both partners consent to attend clinic to complete a risk behaviour questionnaire every 6 months for as long as they participate in the study.
    - The HIV negative partner consents to testing for HIV at these visits.
    - Both partners consent to provide a separate blood sample if the HIV negative partner should become infected with HIV (this is for an anonymous comparison of viruses – results will not be linked to the partnership)

Recruitment
HIV clinics in the UK and internationally around 75 clinics will participate. The study will be coordinated by CHIP in collaboration with the HIV Epidemiology & Biostatistic Group at UCL. We will select sites from within this pool of potential sites; probably most sites will be within Europe. The study will last 6,5 years from the start of first recruitment.

Sample size: In studying HIV transmission, the primary aim is the estimation of the transmission rate in partnerships that have unprotected anal sex and where the HIV positive partner has a viral load < 200 copies/mL. It is very difficult to establish what can be considered an acceptable low level. In PARTNER 1, by 1st November 2013, 436 MSM couples had been recruited with 342 still active in the study, for a total of eligible CYFU of 308. The first interim results of PARTNER will be released in March 2014 at the CROI Conference in Boston, USA. As shown in the table below, if 0 linked infections were observed within PARTNER the estimated rate of within-couples HIV transmission per 100 CYFU would be 0 with an upper limit for the 95%CI of 1.2 per 100 CYFU. This corresponds to a 10 year risk within couple HIV transmission of 11.3% and this is of course higher if more phylogenetically linked HIV transmissions are observed. By the end of the study, assuming 450 MSM couples are recruited uniformly over 27 months and assuming a retention rate of 85% per year we estimate to be able to accumulate 2082 CYFU, of which around 85% is

predicted to be eligible for the primary analysis. This corresponds to a total number of eligible CYFU of 1770, more than 5 times the number of eligible CYFU accumulated so far in PARTNER for MSM. With this amount of CYFU more precise estimates of risk are possible (see table) and if 0 linked HIV transmissions are observed by the end of the study, the upper limit of the 95%CI would be 0.2 per 100 CYFU, corresponding to a 10 year risk within couple HIV transmission of 2.1 per 100 CYFU.

# of linked HIV infections	Within couple HIV transmission rate per 100 CYFU if 0 transmissions (95% CI)	
	At 1st Nov 2013 in PARTNER1 (Eligible CYFU=308)	At end of PARTNER2 (Estimated eligible CYFU=1770)
0	0 (0-1.2)	0 (0-0.2)
1	0.3 (0-1.8)	0.1 (0-0.3)
2	0.6 (0.1-2.3)	0.1 (0-0.4)
5	1.6 (0.5-3.8)	0.3 (0.1-0.7)

Analysis Plan:
Eligible person time of follow-up for inclusion in analysis of the transmission rate is defined as time of negative partner follow-up for which there is a subsequent risk behaviour questionnaire from both index MSM patient and partner, the HIV status of the partner is known, and a viral load measure (< 200 copies/mL) within the preceding 6-12 month period for every day in the period. Person time will only be included in the primary analysis if the eligibility criteria as laid out above are fulfilled. We do not impute missing data. The primary analysis will be estimation of the rate of infection in partners per person year of condomless sex partnership where the index patient has a viral load < 200 copies/mL, excluding new infections which are shown to be hylogentically distinct from the index patient's virus; i.e. transmission has not been from the index patient. This will be calculated as the number of infections that occurred during eligible person time divided by the eligible person time.

Study requirements for participants
HIV positive partner
When initially approached about the study
- consider whether they have a male partner for whom all the inclusion criteria above are met
- If so, to invite the partner to attend the clinic to discuss participation in the study
- When the two members of the partnership consent to the study, each should be given a copy of their own and their partner's Informed Consent.

At baseline visit
- To sign a consent for participation in the study, in which the partner is identified by name and date of birth
- To complete a baseline risk behaviour questionnaire (approximately 15 mins)

At each clinic follow-up visit while the partner remains under follow-up
- To complete a follow up risk behaviour questionnaire (approximately 15 mins)

If HIV negative partner becomes infected with HIV:

- To provide an additional blood sample so that virus can be compared anonymously with that of the newly infected HIV negative partner

HIV negative partner

When the two members of the partnership consent to the study, each should be given a copy of their own and their partner's signed Informed Consent.

At baseline visit
- To attend clinic (with or separately from the HIV positive partner) and sign a consent for participation in the study, in which the partner is identified by name and date of birth
- To test for HIV
- To complete a baseline risk behaviour questionnaire (approximately 15 mins)

At 6 monthly intervals after the baseline visit
- To complete a follow up risk behaviour questionnaire (approximately 20 mins)
- To test for HIV
- Note that the HIV negative partner has to fill out the questionnaire before receiving the HIV test result

If becomes infected with HIV:
- To provide an additional blood sample so that virus can be compared anonymously with that of the HIV+ partner

Reasons for ceasing to follow up partnerships
There are only four scenarios that lead to ceasing to follow-up a partnership:
1. If the HIV negative partners becomes HIV positive
2. If one or both partners withdraw their Informed consent
3. If the partnership separates

Participants may withdraw from this observational study at any time at their request or the request of their partner. This will not affect the care of the HIV infected person or any care being received by the negative partner (e.g. for other STI's).

Study requirements for PI/study nurses
Baseline visit

HIV positive partner:
1. Fill out Baseline online CRF for the HIV positive partner
2. Give Baseline Questionnaire to the HIV positive partner to be completed in a private area in the clinic and then to be returned to the clinic staff in sealed envelope.
3. Send HIV positive partner Baseline questionnaire in the sealed envelope to CHIP

HIV negative partner:

1. Before testing for HIV, give the Baseline Questionnaire to the HIV negative partner to be completed in a private area and to be returned to the clinic staff in sealed envelope.
2. HIV test the negative partner after completion of the questionnaire
3. Fill out online CRF for the HIV negative partner
4. Send the HIV negative partner baseline questionnaire in the sealed envelope to CHIP

Follow up visit

HIV positive partner:

1. Fill out the Follow Up online CRF for the HIV positive partner
2. Give the Follow Up Questionnaire to the HIV positive partner to be completed in a private area in the clinic and then to be returned to the clinic staff in sealed envelope.
3. Send the HIV positive partner Follow up questionnaire in the sealed envelope to CHIP

HIV negative partner:

1. Before testing for HIV, give the Follow Up Questionnaire to the HIV negative partner to be completed in a private area and to be returned to the clinic staff in sealed envelope.
2. HIV test the negative partner after completion of the questionnaire
3. Fill out online CRF for the HIV negative partner
4. Send the HIV negative partners follow up questionnaire in the sealed envelope to CHIP

Study requirements if the HIV negative partner becomes infected

Blood sample for comparison of viruses between partners

Blood samples from both partners should be obtained and sent to CHIP. For preparation and storage of samples for sequencing see below in the Data Collection section. After anonymization (see below) the samples will be shipped to the Virology Laboratory, Liverpool University (Dr Anna Maria Geretti). The results of the phylogenetic analysis will allow comparison of the HIV positive partner's virus with that of the newly infected partner, although the specific partnership will not be identifiable (see below). If the viruses are very different by more than a certain percent of 3rd bases (eg 5%) it will be concluded that transmission has not been from the HIV infected partner. The anomymization process means that partnerships cannot be told the results of the virus comparison.

Questionnaire

Ask both the HIV positive and the newly HIV infected partner, at a time considered suitable by the clinic staff and the participants, to separately complete the very brief questionnaire. These should be placed by in a sealed envelope prior to handing back to clinic staff. Send the questionnaire and to CHIP.

Data Collection

Questionnaires and clinical CRFs

Data will be collected by means of online case-record-forms (CRF) and self completed paper questionnaires (SCQ) from both HIV positive and HIV negative partners and sent to CHIP for central data-entry. Questionnaire completion should be done in a private place by participants and when completed the questionnaire should be placed in an envelope provided. It should then be

sent to CHIP (the study co-ordinating centre) without being seen by clinic staff. Participants should be informed that clinic staff would not see questionnaires.

These forms will contain the PARTNER study ID and date of birth of the participant. No other patient identifiable information will be included. The clinic will keep a log locally linking participant name and date of birth with study ID. Example of format of a "baseline" CRF, "follow up CRF", "baseline" SCQ and "follow up" SCQ are in Appendix B

On site HIV testing

Sites must use a standard HIV anti-body test and may also choose to use a rapid HIV test as this can minimise the amount of visits for the HIV- partner. Where possible, a 4th generation test which also picks up HIV antigen should be used. The results will be included in the clinical CRFs to be completed and returned by post or fax to the co-ordinating centre at Copenhagen HIV Programme (CHIP) in Copenhagen

EVALUATION

Data Analysis

We will assess the proportion of partnerships that begin to adopt consistent condom use (ie reporting by both partners of 100% of episodes of sexual intercourse in which a condom was used) and assess factors associated with this using logistic regression.

The primary analysis will be estimation of the rate of infection in partners per person year of unprotected sex partnership where the index patient has viral load <200 c/mL, excluding new infections that are shown to be phylogentically distinct from the HIV positive partner's virus; i.e. transmission has not been from the HIV positive partner. This will be calculated as the number of infections identified at the end of eligible periods divided by the sum of the person time over eligible periods (see below for definition of eligible periods).

In secondary analyses we will also estimate (i) the rate of infection in partners *per* condomless *sex act* where index patient has viral load < 200 c/mL, as opposed to per person year (this will be done by summing numbers of acts of anal intercourse over eligible periods) ((iii) the rate of transmission if we insist that the next viral load value in the HIV positive partner after the end of the period is also < 200 copies/mL, (iv) the rate of transmission if we consider periods to be eligible if only oral sex is reported, (v) the rate of transmission if we ignore viral load measures made on the HIV positive partner which are within 4 weeks of the end of the period (because of the lag time in obtaining a result).

Eligibility for periods (between HIV tests in HIV- partner) to be included in analysis

A "period" is defined as the time between HIV tests in the HIV- partner.

For a period to be eligible the following must hold:

For all days in the period, the most recently measured viral load value in the HIV+ partner must be < 200 copies/mL and have been measured no more than 6 months previously

A risk behaviour questionnaire, from the HIV negative partner, reporting condomless anal or sex together with the HIV+ partner *within the period, or the previous period*, must be available.

The entire duration of a period fulfilling these criteria will contribute to define the time spent at risk of transmission.

Examples of periods eligible and not eligible are given in Appendix B.

What to do when an HIV- partner becomes infected and we do not have virus samples to compare viruses?

If the HIV- partner reports no other condomless sex partners in the period then for the main analysis this will be treated as a transmission between partners. If the HIV- partner reports other condomless sex partners then this will not be treated as a transmission between partners in the main analysis.

If there is no completed data on whether the HIV- partner had condomless sex with another partner during the period in which the HIV- partner becomes infected then we would consider the questionnaire (for the HIV- partner) before the infection in the HIV- person and allocate according to the rule above. If there is no data from this questionnaire either then we would assume that it is a transmission between the partners.

Study monitoring

Information on the transmission rate in partnerships will accrue during the study. This is an observational study and the advice on consistent condom use will not change no matter what transmission rate is found. We will release findings on the observed transmission rate (based on the primary analysis) with the 95% confidence interval at the time we have accrued 1000 person years of follow-up, and at each 1000 years thereafter.

ETHICAL CONSIDERATIONS

Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version (2004); the requirements of Good Clinical Practice (GCP) as defined in EU GCP Directive (2005/28/EC); Human Subject Protection and Data Protection Acts or with the local law and regulation, whichever affords greater protection of human subjects.

Ethical Committee Review

Prior to the initiation of the study at each clinical research site, the protocol, all informed consent forms and the participant information materials will be submitted to and approved by the site's Ethics Committee (IRB or IEC). In addition any future amendments to the study protocol will be submitted and approved by each site's Ethics Committee (IRB or IEC). After approval, sites must register for the protocol before screening potential participants, and must also register for any protocol amendments.

Informed Consent of Study Participants

Copies of sample Informed Consent forms are given in Appendix F. Patients and their partner will be informed that the study is aiming to estimate the risk that HIV is transmitted from one partner to the other and why some partnerships do not use condoms, and factors associated with this. The need for consistent condom use to avoid transmission be emphasised at each contact. If the patients and their partner both agree to take part they will sign separate informed consents, which will include identification by name and date of birth of the partner. All study participants must sign all applicable approved informed consent forms (see sample in Appendix F) prior to any study-related processes. The informed consent for HIV negative partners includes explicit reference to the fact that their partner has HIV and there is transmission risk, particularly with condomless sex. Each partner will receive a copy of the other partner's signed Informed Consent, as well as their own.

Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

There have been criminal prosecutions of people with HIV who have unprotected sex with an HIV negative person without having disclosed their HIV status. We will recruit only in countries in which prosecution resulting from unprotected sex or HIV transmission after disclosure of HIV-positive status has not occurred, and is judged very unlikely to ever occur in future.

For all partnerships in which follow-up has discontinued (including those in which the reason for discontinuation of follow-up is infection of the HIV negative partner) identifiers such as study ID, clinic and day/month of birth, will be deleted from the central database, thus anonymizing the data on the partnership. Thus, individuals who may have transmitted HIV to their partners cannot subsequently be identified through the central study database. Should a negative partner become infected with HIV during the study the analysis comparing the HIV positive partner's virus with that of the newly infected partner, will done after anonymization, and hence not linkable to the specific partnership.

Data Storage and Protection

CRFs and questionnaires will contain the study ID and date of birth of the participant. No other patient identifiable information will be included. The clinic will keep a log locally linking participant name with study ID. These forms will be sent to the co-ordinating centre at Copenhagen HIV Programme (CHIP) in Copenhagen. Forms will be stored securely at CHIP. The data will be entered onto a computer and stored securely. Access to the files will be restricted to those who need access. At intervals the files (which will be encrypted) will be sent to the HIV Epidemiology & Biostatistics Group in the Research Department of Infection and Population Health, UCL Royal Free Campus, London. Regarding data security at PCPS, we will follow the principles of Departmental Policy on data security in line with the 1998 Data Protection Act. Specifically for IT, this includes restricting access (through password protection) to the database to personnel working directly with the project and not permitting remote access to the database.

As stated above, for all partnerships in which follow-up has discontinued (including those in which the reason for discontinuation of follow-up is infection of the HIV negative partner) identifiers such as study ID, clinic and day/month of birth, will be deleted from the central database. Thus, individuals who may have transmitted HIV to their partners cannot subsequently be identified through the central study database.

PROJECT MANAGEMENT

Coordination
The study will be coordinated jointly between University College London (UCL), and the Copenhagen HIV Programme. UCL will act as sponsor for the study

Management of the Study
An Executive Committee will oversee the implementation of the study on a day to day basis. Professor Andrew Phillips and Professor Jens Lundgren will co-chair the Executive Committee. Membership of this committee is given in Appendix A.

To assist the Executive Committee in its tasks a Steering Committee will be formed and will include members of the Executive Committee and also encompass persons involved in central functions within the study (i.e. IT, statistics, virology, ethics and legal issues). Additionally, each national representative will be part of the study Steering Committee. The Steering Committee will be consulted on major study-specific decisions by the Executive Committee.

A wider Study Group will also be formed. All persons centrally involved in the study are automatically part of the PARTNER Study Group (each site can nominate up to 2 persons to become member of the Study Group). The Executive Committee has chosen one national coordinator per country involved. The Study Group will be kept informed on progress of the study via e-mails, newsletters and investigator meetings.

Authorship on Publications.
Publications derived from the study will be authored by the "PARTNER study group". As in other multicentre studies, authorship will include the main participants in the study as well as members of the Executive Committee. The top 20 recruiting sites will be guaranteed to have one person represented on the first major study publication. If the study results in more than one publication, rotation of membership of the writing committee will be made in a fair and geographically balanced way by members of the Study Group in conjunction with the Executive Committee.

Timetable for the study

June 2014 – December 2014. Planning/organisation of the study, recruitment of sites, , obtain ethical permission

June 2014 to December 2016.
Recruitment and follow up of serodiscordant couples

December 2016 to June 2017
Finalisation of the couples follow, analysis, presentation of results and write up

Appendices

A. Study Team
B. Examples of periods eligible
C. Clinical CRFs
D. Questionnaires
E. Introductory letters/leaflets to study participants
F. Forms for informed consent

APPENDIX A: STUDY TEAM

The following teams will oversee the implementation of this observational study:

Executive Committee
Prof Andrew Phillips, University College London (UCL)
Prof Jens Lundgren, CHIP
Dr Alison Rodger, University College London (UCL)
Tina Bruun, CHIP
Simon Collins, HIV i-Base, London
Dothe Raben, CHIP
Prof. Pietro Vernazza, Switzerland
Dr. Vicente Estrada, Spain
Dr. Jan Van Lunzen, Germany
Giulio Maria Corbelli, EATG, Italy

National Coordinators

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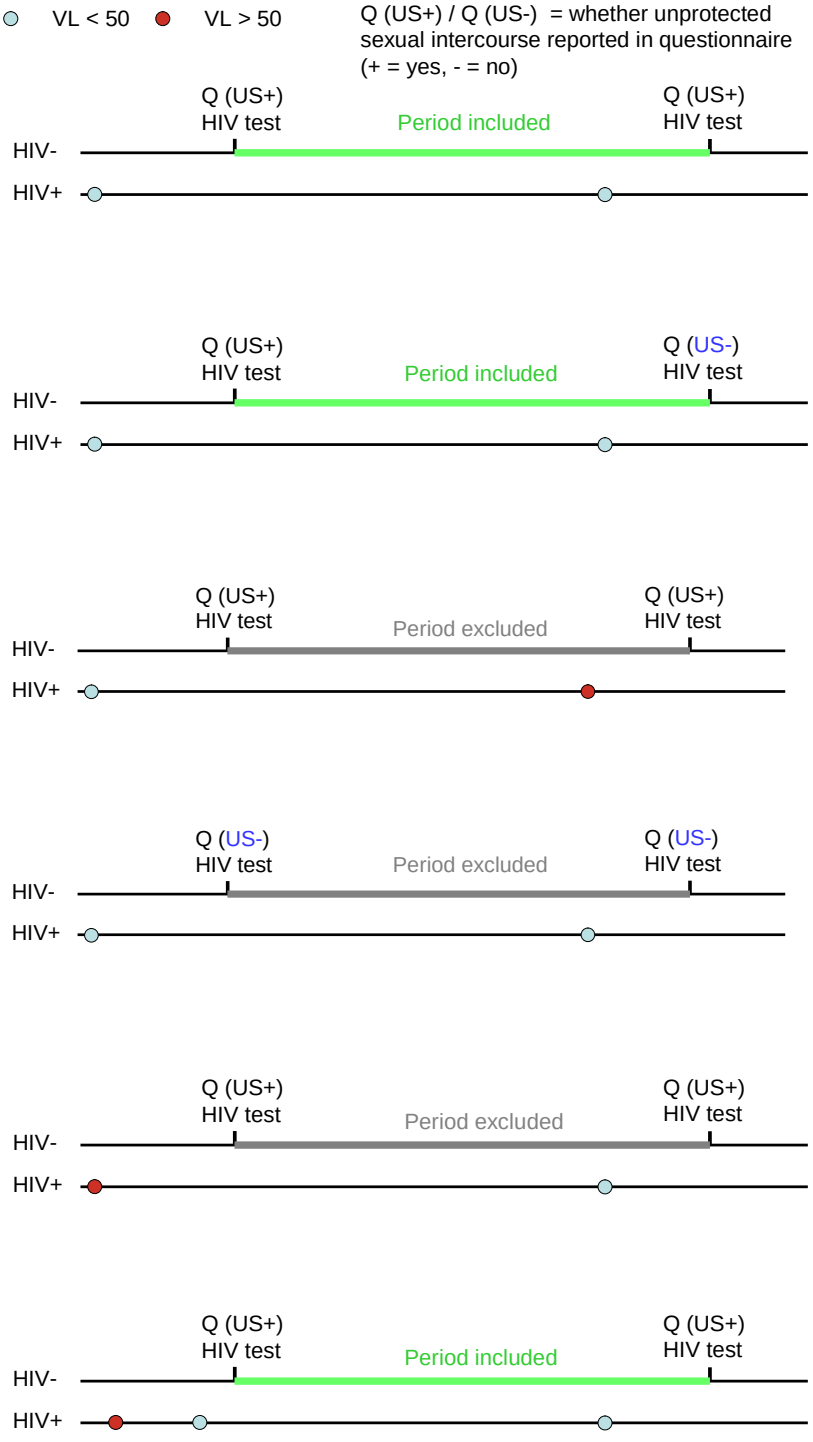
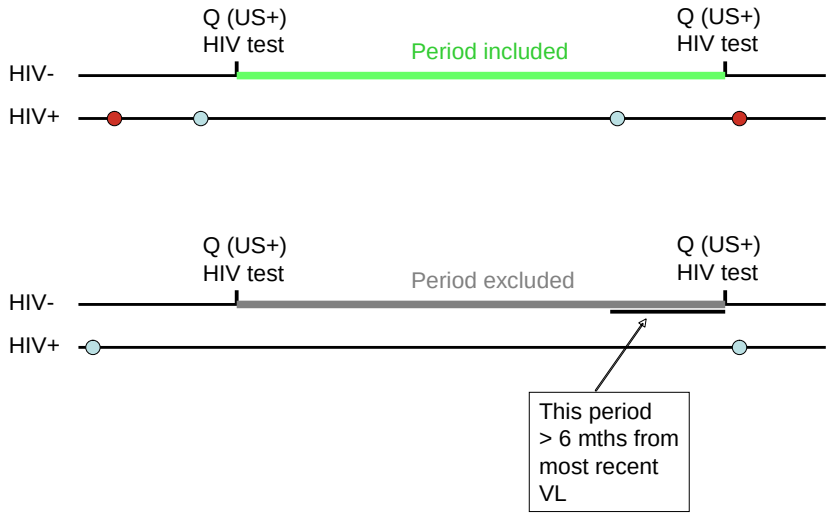
Dr Lars Mathiesen, Denmark
Dr Matti Ristola, Finland
Dr Christian Pradier, France
Dr Jan Van Lunzen, Germany
Dr Gráinne Courtney, Ireland
Prof Antonella d'Arminio Monforte, Italy
Prof Francisco Antunes, Portugal
Dr Vincente Estrada, Spain
Dr Katarina Westling, Sweden
Prof Pietro Vernazza, Switzerland
Prof JM Prins, The Netherlands
Dr Alison Rodger, UK

Study Group
All persons centrally involved in the study will automatically be part of the wider study group. Each site can nominate up to 2 persons to become member of the study group

Appendix B. Examples of periods included and excluded for primary analysis




Q (US+)
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Q (US+)
HIV test
HIV-
HIV+
Q (US+)
HIV test
Period excluded
Q (US+)
HIV test
HIV-
HIV+
This period
> 6 mths from
most recent
VL

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