4th ECReCo
Aix en Provence, August 31-September 3, 2014

Plenary 5

Organising a study

Linos Vandekerckhove and Alison Rodger

Outline of Session

- Defining the goal you want to achieve
- Overview of the process from a good idea to conducting the study
  - Developing the research question/s
  - Writing the grant application
  - Conducting the study
- Practical example of the process

Defining the goal/objectives you want to achieve

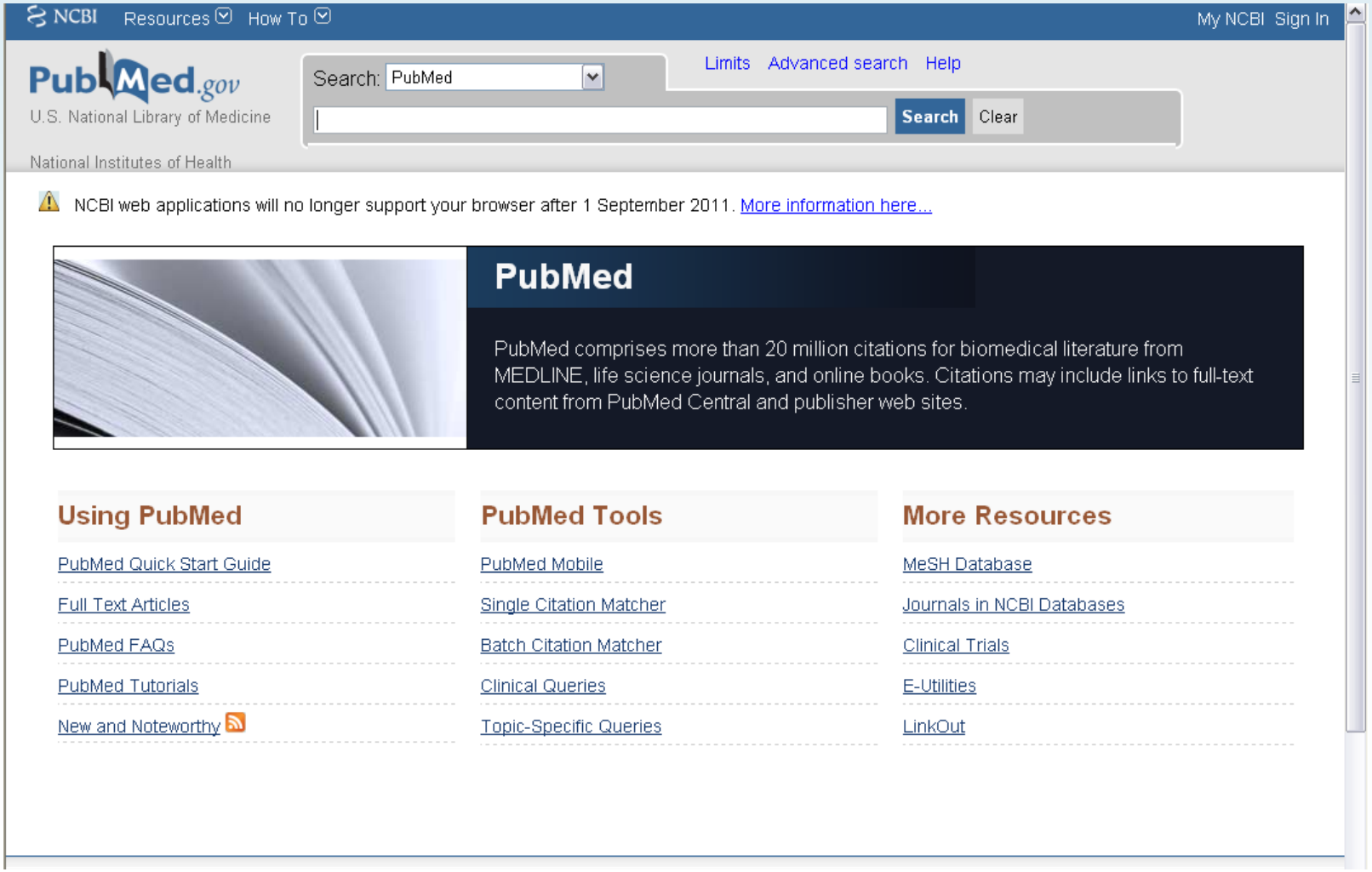
- **S**pecific: is the objective clear
- **M**easurable: are ther clear indicators or parameters
- **A**cceptable: do the objectives provide an acceptable solution to the problem?
- **R**ealistic: is the objective achievable
- **T**imely: when will the objective be achieved?

Clinical trials:From a good idea to the implementation of a clinical trial

- A good idea
- Literature and web search
- Writing the protocol
- Inclusion and exclusion criteria
- Calculation of the sample size
- Feasability assessment
- Administration
- Ethical conduct Safety
- Economics
- Participating in a clinical trial
- Information technology
- Controversy

A good idea

Literature and web search



Writing a protocol

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Goal of the study:

- Primary objective: to evaluate the safety of …..
- Secondary objectives:
  - Inflammation
  - Immunologic endpoints

Inclusion criteria: some examples

1. Male or female, aged 18-60 years

2. Confirmed HIV-1 seropositive documented in the past 6 months (by acute antiretroviral syndrome, p24 antigenemia and/or ELISA seroconversion)

3. Willing and able to give written informed consent for participation in the study

4. Willing and able to adhere to an effective HAART regimen for the duration of the study

5. CD4 cell count > 350 cells/ml at screening and at the preceding clinic visit

6. No new AIDS-defining diagnosis or progression of HIV-related disease.

7. Haematological and biochemical laboratory parameters as follows:
   - Haemoglobin > 10g/dl
   - Platelets < 100,000/dl
   - ALT ≤ 2.5 x ULN
   - Creatinine ≤ 1.3 x ULN

Exclusion criteria: some examples

1. Confirmed HIV-2 seropositive

2. Positive pregnancy test

3. Presence of NRTI mutation in the screening genotype

4. Participation in another clinical trial within 12 weeks of study entry

5. History of autoimmune disease other than HIV-related auto-immune disease.

6. History or clinical manifestations of any physical or psychiatric disorder which could impair the subject‟s ability to complete the study

7. History of anaphylaxis or severe adverse reaction to vaccines

8. Previous immunisation with any experimental immunogens

Subject withdrawal criteria

1) Each participant has the right to withdraw from the study at any time. Any individual for who is being considered for discontinuation or postponement of treatment will be discussed with the trial team.

2) Significant non-compliance with treatment regimen or study requirements.

3) A very severe local or systemic reactogenicity event judged to be possibly, probably or definitely related to the study intervention.

4) A very severe or serious adverse event judged to be possibly, probably or definitely related to the study intervention.

Study procedures: informed consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed

Study procedures: informed consent

- Written and verbal versions of the Participant Information Sheet and Informed Consent should be presented to the participants explaining:
  - the exact nature of the study
  - the implications and constraints of the protocol
  - the known side effects and any risks involved in taking part

- It should be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Trial intervention and study treatment in drug clinical trials

- Trial Schedule
- Description of the study drug and the Placebos
- Packaging, Storage and Shipment
- Dispensing and Handling
- Administration
- Accountability and Disposal

Assessment of efficacy

- *According to the primary endpoints: …*

Safety

- Responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various DSMBs that supervise the study, and (in some cases, if the study involves a marketable drug or device) the regulatory agency for the country where the drug or device will be sold.

Local site investigators

- A physician's first duty is to guarantee safety to his/her patients, and if a physician investigator believes that the study treatment may be harming subjects in the study, the investigator can stop participating at any time.

- The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study.

- The local investigator or his/her study staff are responsible for ensuring that potential subjects in the study understand the risks and potential benefits of participating in the study; in other words, that they (or their legally authorized representatives) give truly informed consent.

- The local investigators are responsible for reviewing all adverse event reports

.

Assessment of safety

Definitions:

- **AE or Adverse Event**
- **SAE or Serious Adverse Event**

Causality and expectedness:

- **Not Related**
- **Unlikely**
- **Possibly**
- **Probably**
- **Definitely**

Randomization and codebreaking

Randomization

Codebreaking

- The blinded treatment assignments will be accessible to the investigator if a subject need to be unblinded in an emergency using the unblinding envelopes

Statistical methods and sample size

- **Statistical analysis**
- **Sample size calculation**
- **Interim analyses and stopping rules**

Ethic, deontological and regulatory considerations

- The Investigator will ensure that the study is conducted in accordance with the principles of the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations.

- The protocol, informed consent form, participant information sheet and any applicable documents should be submitted to an appropriate Ethics Committee (EC) and Regulatory Authority for written approval.

Ethical Conduct

- All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial.

- To be ethical, researchers must obtain the full and informed consent of participating human subjects.

- Informed consent is clearly a necessary condition for ethical conduct but does not ensure ethical conduct.

Administration

- Clinical trials designed by a local investigator and funded clinical trials are almost always administered by the researcher who designed the study (and applied for the grant) (Eudract number).

Data handling and record keeping

- Data will be collected by the site personnel and recorded on the CRFs (case report form's).

- Other source documents include but are not limited to:

  - Documentation of any existing conditions or past conditions relevant to eligibility

  - Signed Informed Consent Forms

  - Reported laboratory results

Information Technology

- The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials.
- Clinical trial management systems (CTMS) are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites.
- Web-based electronic data capture (EDC) and clinical data management systems (CDMS) are used in a majority of clinical trials to collect case report data from sites, manage its quality and prepare it for analysis.
- Interactive voice response systems (IVRS) are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm.
- Patient-reported outcome measures are being increasingly collected using hand-held, sometimes wireless ePRO (or eDiary) devices. .
- Access to many of these applications are increasingly aggregated in web-based clinical trial portals.

Dissemination activities

- Dissemination plan of the results will try to include publications as well as presenting results at international scientific meetings

Final thoughts

1) Avoid me too research
2) Try to be innovative and SMART (see goals)
3) Apply for funding for your research, even small amounts
4) EU, Bill and Melinda Gates, AMFAR, NIH calls prefer partners from Africa, South America, Eastern Europe etc
5) Form networks and collaborations, link with other centres
6) Apply to be sites in larger multicentre studies - Go to conferences and congresses

Organising a study: a practical example

Research question (2009)

“What further research is needed before a policy of treating all people with HIV diagnosed can be implemented?”

Literature search

- 3500 new HIV infections each year in the UK - £1.75 billion in future drug costs
- ART with low viral load leads to markedly reduced infectiousness, but the extent is currently uncertain
- 30% of diagnosed HIV positive people in the UK are not on ART
- Individual health benefit of early ART is unclear
- Acceptability of early ART in HIV positive people unclear
- Not clear if risk behaviours change with initiation of early ART

Further definition research question/s

"What further research is needed before a policy of treating all people with HIV diagnosed can be implemented?"

Q1: What is the acceptability of taking ART In HIV positive people at high CD4 counts?

Q2: What are the patterns of sexual risk behaviour in individuals on early ART?

Q3: What is the transmission risk for individuals on ART with very low viral load through condomless sex?

Q4: Would it be cost effective for the UK to offer ART to all those diagnosed with HIV?

Funding…..

NHS
National Institute for Health Research

PROGRAMME GRANTS FOR APPLIED RESEARCH

Full proposals should observe the maximum text limits as indicated throughout the form. Please note the maximum text limits include spaces and other non-printing characters. The form should be completed using a font size no smaller than 10 (Arial). **Keep the use of acronyms to a minimum**. Only use acronyms where a term is used frequently throughout the proposal. If you do choose to use an acronym, do not assume that the reader knows what it means, and be sure to define it when first used.

You are strongly advised to use spaces, bullet points, subheadings, etc. to structure the longer sections of the application form (particularly the Research Plan) in such a way that they can be read easily by reviewers. **The use of long passages of dense, unstructured text should be avoided.**

Curricula vitae, references, Gantt chart, and supporting information (including diagrams, pictures, charts, letters of support, and papers in press) should be included as annexes to this application form. **Continuation of text is not permitted, however, and applicants should note that any extra pages will be removed upon receipt and therefore not assessed.** All mandatory fields are identified by an asterisk (*). **Failure to complete the form's mandatory fields will result in your application being rejected on the grounds that it is incomplete.**

The completed form must be submitted online by 23 March 2009, 5 PM.

For office use only

Reference Number:

IMPORTANT

Before completing this form, please read the accompanying Guidance Notes.

1. Application

Programme Title*:	Comprehensive Assessment of the Prevention Role of Antiretroviral therapy (CAPRA)		
Programme Duration *: (months)	60.0	**Total funding requested (£'s):**	£1,999,513
Proposed start date if grant awarded *:	01/11/2009 **(dd/mm/yyyy)**		
Lead NHS organisation (which will administer any award) *:	Royal Free Hampstead NHS Trust		

Get the team together

Clinical Trials, Multi-centre Research Studies

insight

chip Centre for Health & Infectious Disease Research

Community Representation

Health Economics

Risk Behavior, Sociology, Psychology

HIV virology and sequencing

HIV Transmission Legal Expertise

Research Methods

Research question 1: What is the acceptability of ART at high CD4 counts?

Study Design:

Multicentre observational cross sectional studies of sexual behaviour, transmission risk beliefs and attitudes to early ART (in those ART naïve) in clinic outpatients with HIV (ASTRA) and HIV negative people attending for STI screening (AURAH)

Research Methods

Research question 2: What are the patterns of sexual risk behaviour in individuals on early ART

Study Design:

Randomized Trial (START) to assess the proportion of patients reporting at least one unprotected sexual partner (anal or vaginal intercourse) of unknown or negative HIV status in the past 2 months at year 1 between patients randomized to immediate initiation of ART and those randomized to deferred ART.

Research Methods

Research Question 3: What is the transmission risk for individuals on ART with very low viral load through condomless sex?

Study Design: Observational multi-centre study to determine rate of HIV transmission in serodifferent partnerships that do not use condoms and the HIV-positive partner is on ART with a viral load < 200 copies/mL (PARTNER study)

Research Methods

Research Question 4: Would it be cost effective for the UK to offer ART to all those with HIV?

Study Design

Transmission modelling study to model the cost effectiveness of provision of ART to all diagnosed HIV positive people using a simulation model to determine the cost effectiveness from an NHS perspective with outcomes as incremental cost per Quality-Adjusted Life-Year gained

Research Methods

Researc smission
risk for i w viral
load?

Study De tre study to
determi
serodiffe use
condom is on ART
with a vi TNER
study)

BACKGROUND

OBJECTIVES

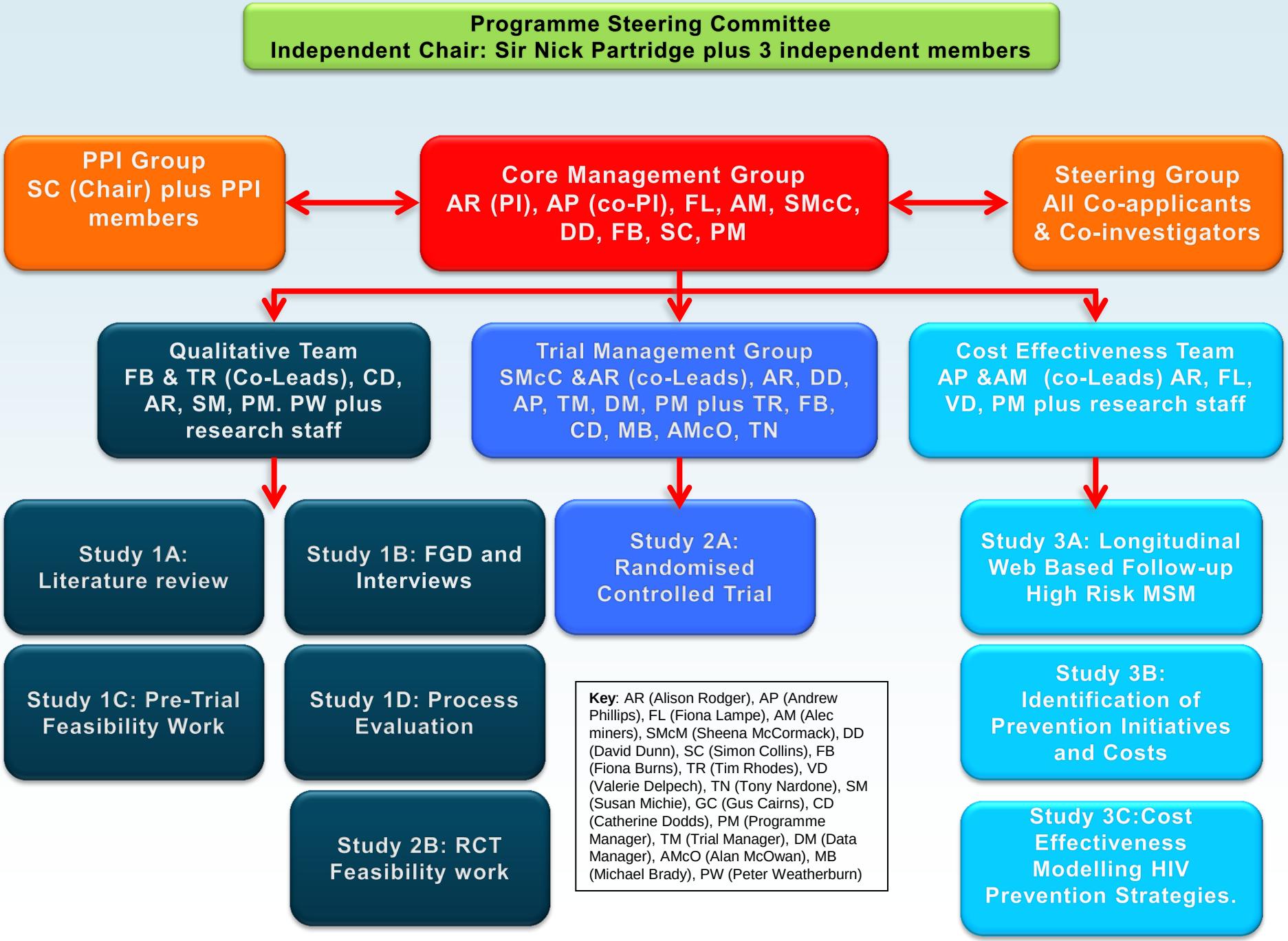
STUDY DESIGN

SETTING

DATA COLLECTION AND MEASUREMENTS

SAMPLE SIZE

ANALYSIS PLAN

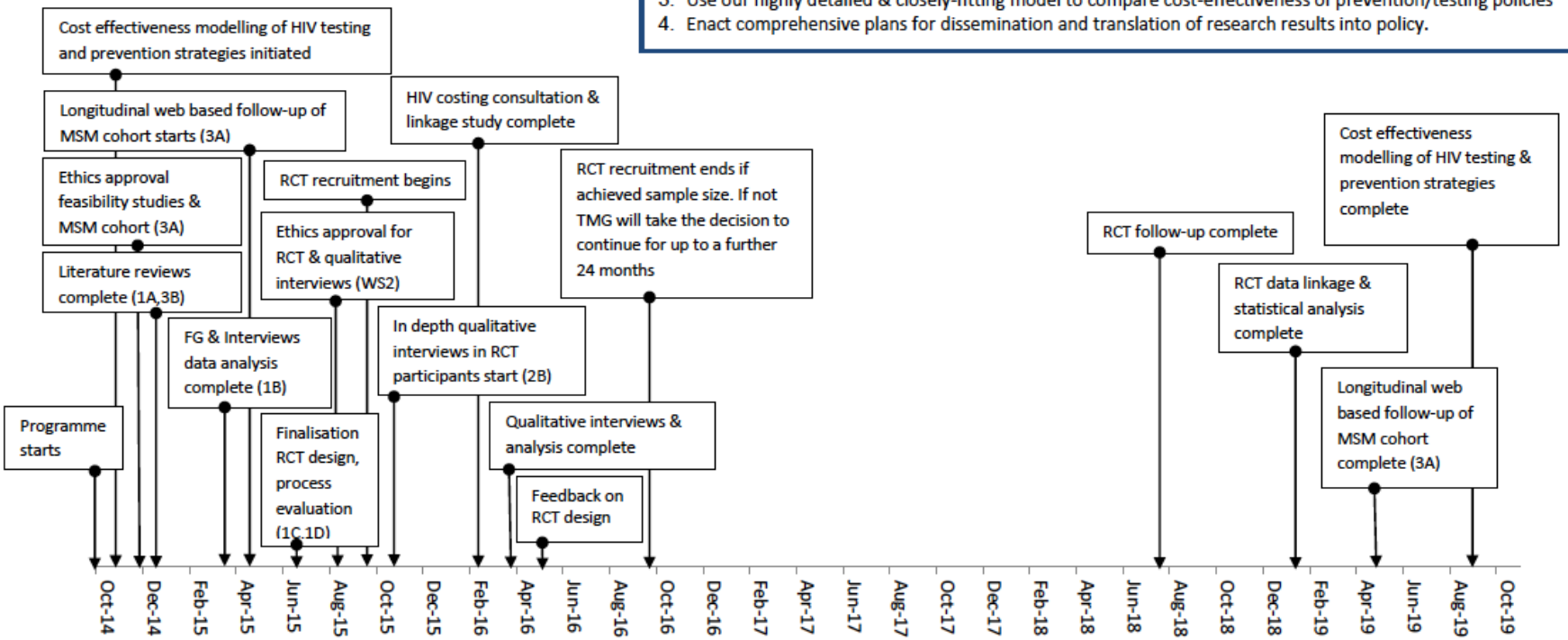

Programme Steering Committee
Independent Chair: Sir Nick Partridge plus 3 independent members
PPI Group
SC (Chair) plus PPI members
Core Management Group
AR (PI), AP (co-PI), FL, AM, SMcC, DD, FB, SC, PM
Steering Group
All Co-applicants & Co-investigators
Qualitative Team
FB & TR (Co-Leads), CD, AR, SM, PM. PW plus research staff
Trial Management Group
SMcC &AR (co-Leads), AR, DD, AP, TM, DM, PM plus TR, FB, CD, MB, AMcO, TN
Cost Effectiveness Team
AP &AM (co-Leads) AR, FL, VD, PM plus research staff
Study 1A: Literature review
Study 1B: FGD and Interviews
Study 2A: Randomised Controlled Trial
Study 3A: Longitudinal Web Based Follow-up High Risk MSM
Study 1C: Pre-Trial Feasibility Work
Study 1D: Process Evaluation
Study 3B: Identification of Prevention Initiatives and Costs
Study 2B: RCT Feasibility work
Study 3C:Cost Effectiveness Modelling HIV Prevention Strategies.
Key: AR (Alison Rodger), AP (Andrew Phillips), FL (Fiona Lampe), AM (Alec miners), SMcM (Sheena McCormack), DD (David Dunn), SC (Simon Collins), FB (Fiona Burns), TR (Tim Rhodes), VD (Valerie Delpech), TN (Tony Nardone), SM (Susan Michie), GC (Gus Cairns), CD (Catherine Dodds), PM (Programme Manager), TM (Trial Manager), DM (Data Manager), AMcO (Alan McOwan), MB (Michael Brady), PW (Peter Weatherburn)

Overview RP-PG-1212-20006: 'A comprehensive assessment of the cost-effectiveness of HIV prevention and testing strategies, including HIV self-testing, among MSM in the UK'

We propose to conduct the research needed to respond to the uncontrolled HIV epidemic in UK MSM.

1. Perform an RCT of a new and potentially highly effective intervention (free online supply of self-testing kits +/- active reminders to test) with a "hard" public health outcome (diagnosis of HIV)
2. Conduct extensive qualitative work both to inform the design of the RCT and to interpret findings
3. Use our highly detailed & closely-fitting model to compare cost-effectiveness of prevention/testing policies
4. Enact comprehensive plans for dissemination and translation of research results into policy.

Programme Grant Milestones



Programme Grant Dissemination, Translation into Policy and Outputs

Engagement, Dissemination &Translation Work Group (EDTWG) (Chair Kevin Fenton) established to enact partner/stakeholder engagement, dissemination of study results and translation into policy

OUTPUTS: (i) Publication of results from studies 1A, 1B, 3B. (ii) RCT intervention manual, process evaluation and monitoring tools

EDTWG strategy enacted, EDTWG input into prevention strategies modelled and how they are parameterized.

OUTPUTS: (i) Publication HIV costing study (3B) & qualitative study 2B (ii) Revised RCT intervention manual produced after WS1 result

EDTWG dissemination and translation strategy fully enacted by 3-5 years of PG end

OUTPUTS: (i) Publication results study (3A) (ii) Cost effectiveness modelling of HIV testing and prevention strategies published (3C)

Date/Year		1	2	3	4	5	Total
Staff	**FTE**						
Alison Rodger	25%						00
Andrew Phillips	20%						00
Fiona Lampe	10%						00
Fiona Burns	10%						00
Richard Gilson	1%						00
Lorraine Sherr	1%						00
Graham Hart	1%						00
Anne Johnson	1%						00
Project manager	100%						00
Statistican	50%						00
Modeller	100%						00
Susan Michie	4%						00
Sheena McCormack	10%						00
David Dunn	10%						00
Trial Coordinator	50%						00
Alec Miners	10%						00
Economic researcher	50%						00
Tim Rhodes	5%						00
Catherine Dodds	20%						00
Qualitative researcher	100%						00
Tony Nardone	2%						00
Kevin Fenton	1%						00
Valerie Delpech	2%						00
Researcher	20%						00
Jonathan Elford	2%						00
Martin Fisher	1%						00
Michael Brady	2%						00
Alan McOwan	2%						00
Katie Donlevy	1%	1,000.00	1,000.00	1,000.00	1,000.00	1,000.00	5,000.00
Staff Totals		**325,592.00**	**331,904.00**	**371,947.00**	**314,616.00**	**321,978.00**	**1,666,038.00**
Non staff costs							
HIV self testing kits		30,016.00	30,016.00	30,016.00	30,016.00	29,936.00	150,000.00
Study website		3,200.00	3,200.00	3,200.00	3,200.00	3,200.00	16,000.00
Focus groups		10,372.00	10,372.00	-	-	-	20,744.00
Stakeholder interviews		500.00	500.00	-	-	-	1,000.00
Computers/software		6,444.00	-	-	-	-	6,444.00
PPI		9,920.00	9,920.00	9,920.00	9,920.00	9,920.00	49,600.00
Online advertising		2,000.00	2,000.00	2,000.00	2,000.00	2,000.00	10,000.00
Incentives		-	2,000.00	2,000.00	2,500.00	2,500.00	9,000.00
Total		**62,452.00**	**58,008.00**	**47,136.00**	**47,636.00**	**47,556.00**	**262,788.00**
LSHTM Non Staff Costs							
Computers		238.00	238.00	238.00	238.00	238.00	1,190.00
Focus groups and transcribing		2,053.00	2,099.00	2,152.00	2,206.00	2,256.00	10,766.00
Rail travel		664.00	679.00	696.00	713.00	729.00	3,481.00
Travel and accommodation		128.00	131.00	134.00	138.00	141.00	672.00
Travel and subsistance		851.00	870.00	891.00	914.00	934.00	4,460.00
Office costs		625.00	640.00	656.00	672.00	687.00	3,280.00
Total		**4,559.00**	**4,657.00**	**4,767.00**	**4,881.00**	**4,985.00**	**23,849.00**
Travel							
Travel/Subsistance		800.00	800.00	800.00	800.00	800.00	4,000.00
Overseas conferences		-	-	-	1,250.00	1,250.00	2,500.00
Total		**800.00**	**800.00**	**800.00**	**2,050.00**	**2,050.00**	**6,500.00**
Grand total		**393,403.00**	**395,369.00**	**424,650.00**	**369,183.00**	**376,569.00**	**1,959,175.00**

NHS
National Institute for Health Research

Programme Grants for Applied Research	**NIHR Number:** RP-PG-0608-10142
Peer Review Form	**Programme Title:** Optimising HIV diagnosis and treatment to reduce morbidity, mortality and ongoing transmission: new approaches for early diagnosis and early use of treatment explicitly to reduce infectivity.
Please return by: 24th April 2009	
If you have any problems submitting this form please contact the CCF on: Tel: 020 8943 8991	**Reviewer Reference Number:** 2

NHS
National Institute for Health Research

NIHR-CCF
PO BOX 407
Teddington
Middlesex
TW11 0XX
UK

Tel: +44 (0)20 8943 8990
Fax: +44(0)20 8943 8972
Web: www.nihr-ccf.org.uk

29 October 2009

NIHR Programme Grants for Applied Research:

Application RP-PG-0608-10142

Thank you for your application to the NIHR Programme Grants for Applied Research funding scheme. This proposal has been assessed by the NIHR Programme Grants for Applied Research Selection Panel and subject to external peer review.

As indicated in the Full Application guidance, the selection criteria at the full application stage were as follows:

- The track-record of the applicants in conducting high-quality applied health research, as judged by publication output and previous research funding;
- The relevance of the proposed research to the priorities and needs of the NHS;
- The likelihood of significant benefit to the NHS and patients within a three to five year timescale;
- The quality of the proposal;
- The value for money provided by the proposal.

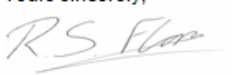
In view of the significant number of full applications submitted, a number of expert Sub-Panels were convened (details of which are available on our website www.nihr-ccf.org.uk) to assist the NIHR Programme Grants for Applied Research Selection Panel by reviewing proposals related to each of the topic areas highlighted in this funding round. The Sub-Panels' recommendations were then reviewed by the main Selection Panel, which made final funding recommendations across all topic areas. These funding recommendations were then considered, and approved, by the DH Director General of Research & Development, Professor Sally Davies.

All Sub-Panels reviewed the full applications against the above criteria. Their decision-making was also guided by, but not entirely dependent upon, comments provided by peer reviewers. Any unduly harsh remarks, bias or misunderstanding in these comments will have been taken into consideration by the Sub-Panels.

I am delighted to be able to confirm, following a suitably robust response to concerns raised by the appropriate Sub-Panel, your award of a Programme Grant for Applied Research.

Please note that grant holders should refrain from publicising any programmes until the contracting procedure is complete

Yours sincerely,



Rajinder Flora
Senior Programme Manager, Programme Grants for Applied Research Programme

Research question 3

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)

Design and Methods

- PARTNER recruits serodifferent partnerships (+ve partner on ART) who had condomless (CL) penetrative sex in the past 4 weeks in order to study:

  (i) the risk of HIV transmission to partners, in partnerships that do not use condoms consistently and the HIV positive partner is on therapy with a viral load < 50 copies/mL

  (ii) why some partnerships do not use condoms, the proportion who begin to adopt consistent condom use, and factors associated with this

- Study procedures: 4-6 monthly self completed confidential risk behaviour questionnaire and collection of clinical data including HIV results

Study Processes

Inclusion criteria

1. Confirmed HIV positive, on ART (regardless of viral load)
2. Age > 18
3. Has a partner not known to be HIV infected and following criteria met :
    i. The partners had condomless sex together in the past month (when the HIV negative partner was aware of the HIV status of the HIV positive partner)
    ii. The partners expect to have sex together again
    iii. Both partners consent to attend clinic to complete a risk behaviour questionnaire every 6 months
    iv. The HIV negative partner consents to testing for HIV
    v. Both partners consent to provide a separate blood sample if the HIV negative partner should become infected with HIV (for an anonymous comparison of viruses – results will not be linked to the partnership)

PARTNER

Study Processes

Exclusion criteria

- HIV negative women who are pregnant at baseline are excluded.
- HIV positive women who are pregnant at baseline are eligible for inclusion.
- In addition if a woman (whether the negative or the positive partner) becomes pregnant during the study, then the partnership can continue in the study, if they wish to do so.

Study Processes - Data Collection

The case Report Forms (CRFs) and risk behaviour questionnaires:

1. Baseline risk behaviour in HIV positive partner (self-complete) – 3 versions (i) patient male, partner male (ii) +ve male, -ve female, (iii) +ve female, -ve male
2. Baseline risk behaviour in HIV negative partner (self-complete) – 3 versions as above.
3. Baseline clinical and antiretroviral drug use status on HIV positive partner (clinician/nurse to complete)
4. Follow-up risk behaviour in HIV positive partner (self-complete) – 3 versions as above.
5. Follow-up risk behaviour in HIV negative partner (self-complete) – 3 versions as above.
6. Follow-up clinical and antiretroviral drug use status on HIV positive partner (clinician/nurse to complete)
7. Partner infection form – risk behaviour (to be completed by prev HIV neg partner if becomes infected with HIV) – 3 versions as above.
8. Partner infection form (to be completed by clinician/ nurse if partner becomes infected)

PARTNER

Questionnaire Design

- Research questions to be answered
- Target audience
- Content and wording
- Question placement, sequence, layout, length
- Response format
- Make sure you pilot it!

Baseline Questionnaires for the HIV Positive Partner - Male

PARTNER

BASELINE QUESTIONNAIRE - HIV POSITIVE MAN

ALL PARTICIPANTS SHOULD ANSWER THE FOLLOWING QUESTIONS	
6.5 On the last occasion when you and your HIV negative partner had sex without a condom, what were the main reasons for not using a condom? (Tick more than one box if necessary)	☐1 I believe the risk of HIV transmission is very low ☐2 Trying for pregnancy ☐3 We did not have a condom ☐4 It is more enjoyable without a condom ☐5 I had difficulty maintaining erection and/or ejaculating when using a condom ☐6 Was under the influence of alcohol or recreational drugs ☐7 Partner did not want to use condom ☐8 I did not want/find it difficult to discuss condom use with my partner ☐9 Condoms are too expensive ☐10 I did not think about that ☐11 Other (please specify): _____
6.6 Have you had sex with your HIV negative partner using a condom when the condom broke in the last 4 months?	☐1 Yes ☐0 No
6.7 Have you undertaken any of the following sexual practices with your HIV negative partner in the past 4 months?	Fisting ☐1 Yes ☐0 No Use of sex toys ☐1 Yes ☐0 No If yes to either of the above, did bleeding occur during sex as a result? ☐1 Yes ☐0 No

7. Here is a list of some statements about HIV. Please read each statement carefully and place a tick in the column that is closest to your viewpoint. Give only 1 answer per row.			
	Agree	Neither agree nor disagree	Disagree
Because of the new antiviral drugs, people with HIV/AIDS are living much longer/can have normal life expectancy			
Because HIV therapy is so easy to take with few side effects, people do not need to be concerned about becoming HIV-positive			
If an HIV positive person's viral load is undetectable, condom use during sex with an HIV negative person is not necessary			

PARTNER

CRF - Baseline HIV Positive Partner

PARTNER

CLINIC FORM - BASELINE HIV POSITIVE PARTNER

4.2 Please tick all the ARV drugs that the patient is currently on	
	NUCLEO(T)SIDE REVERSE TRANSCRIPTASE INHIBITORS
	☐ Zidovudine (AZT)
	☐ Didanosine (DDI)
	☐ Stavudine (D4T)
	☐ Abacavir (ABC)
	☐ Emtricitabine (FTC)
	☐ Lamivudine (3TC)
	☐ Tenofovir disoproxil (TDF)
	PROTEASE INHIBITORS
	☐ Atazanavir (ATV)
	☐ Darunavir (DRV)
	☐ Fosamprenavir (FOS)
	☐ Indinavir (IND)
	☐ Ritonavir (RTV)
	☐ Saquinavir (SQV)
	☐ Tipranavir (TPV)
	☐ Lopinavir/Ritonavir (LPV/RTV)
	NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)
	☐ Nevirapine (NVP)
	☐ Efavirenz (EFV)
	☐ Etravirine (ETR)
	INTEGRASE INHIBITORS
	☐ Raltegravir (RAL)
	ENTRY INHIBITORS
	☐ Eufurvitide (T20)
	☐ Maraviroc (MVC)
	☐ Other: _____

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Sample Size

If the true transmission rate is < 1 per 1000 couple years of condomless sex with viral load < 50 copies, then with 2000 CYFU with viral load< 50 cp/ml there is an 85% chance that the upper 95% confidence limit is < 0.0044 (i.e. 1 per 227 person years of condomless sex).

Allowing for periods with VL>50 copies, no risk behavior data available and periods of condom use - estimated 3333 CYFU required from 1666 partnerships

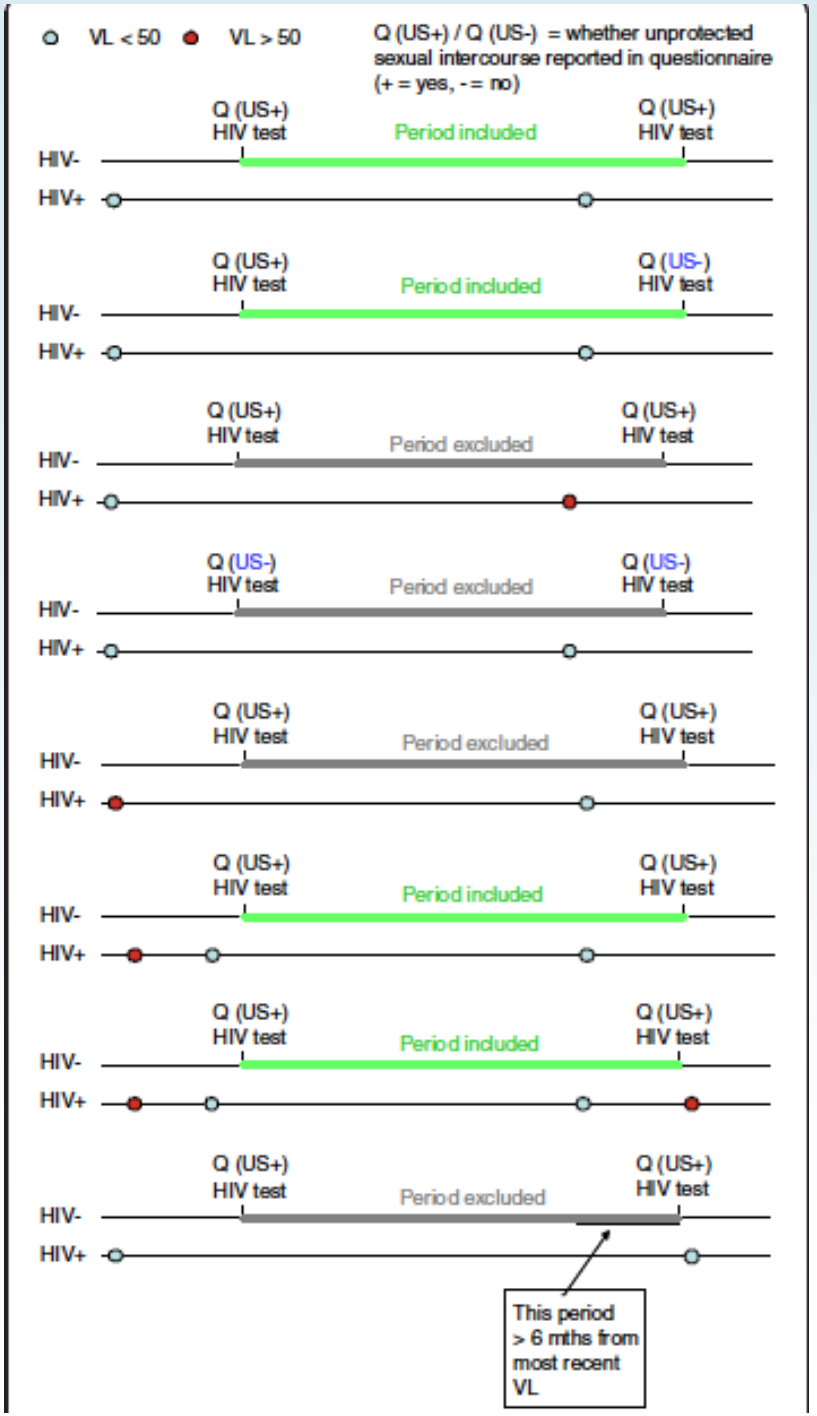
Recruitment expanded to 75 European sites in 12 countries

PARTNER

Analysis Plan

Eligible person time of follow-up for inclusion:
(i) a subsequent risk behaviour questionnaire from both index MSM patient and partner
(ii) the HIV status of the partner is known, and a viral load measure (< 50 copies/mL) within the preceding 6-12 month period for every day in the period.

The primary analysis is rate of infection per person year of condomless sex where the index viral load < 50 copies/mL, excluding new infections which are shown to be phylogentically distinct from the index patient's virus



Phylogenetic analysis if a transmission occurs

- A blood sample will be obtained from both the HIV negative and positive partners (fresh frozen plasma sample if > 500 copies, PMBC if <500 copies) for sequencing
- The samples will be anonymised so the results will not be available to the participants

Sequencing:

- HIV-1 pol and env sequences obtained from plasma and PBMCs by population sequencing
- Maximum likelihood trees constructed using PhyML
- Criteria for clustering was <0.015 nucleotide substitutions per site pairwise genetic distance and >99% bootstrap support

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Ethics

- Ethical committee approval
- Informed Consent of Study Participants
- HIV transmission risks explained in depth in PIS and the need for condom use emphasised
- Data Storage and Protection
- Confidentiality of Study Participants

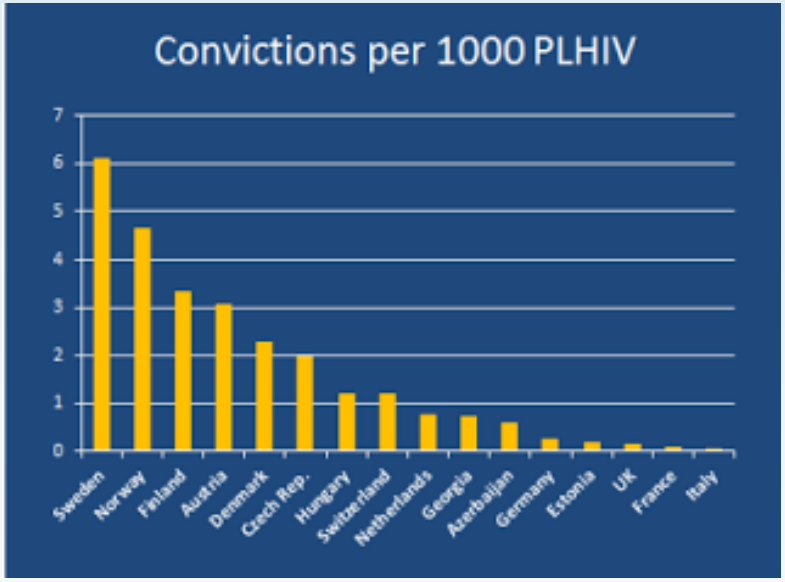
HIV transmission and risk of prosecution

- All countries participating in the PARTNER study have/had, laws which potentially criminalize PLHIV
- Criminalization - transmission, exposure or non-disclosure, and for intentional, reckless or negligent behavior
- People convicted of HIV-related offences often sentenced to custodial punishment.
- That PLHIV may be criminalized in countries participating in PARTNER was a central concern in developing methodology and ethical approval

HIV JUSTICE NETWORK

HIV transmission and risk of prosecution – what did we do…

- The key concern was ‘does informed consent provided a defense?’ e.g. in Norway it did not
- We recruited only in countries in which convictions after disclosure of HIV-positive status had not occurred, and was judged very unlikely to ever occur in future
- Both partners were informed that the study was estimating the risk that HIV is transmitted from one partner to the other



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HIV transmission and risk of prosecution

- The informed consent for HIV negative partners included explicit reference to the fact that they knew their partner has HIV and there is transmission risk
- The need for consistent condom use to avoid transmission was emphasised at each contact
- Once follow-up is discontinued identifiers deleted from the central database.
- The sequencing analysis is done only after anonymization, and not linkable to the specific partnership.

Study Processes Summary

- The protocol (Version 1: 6th May 2010) and a manual of operations were completed.
- Patient information sheets and consent forms, clinical research forms and study questionnaires were developed
- All study documents are available on line on the PARTNER study website in 11 different languages http://www.cphiv.dk/PARTNER/StudyDocuments/tabid/440/Default.aspx)
- Ethical approvals obtained in 12 countries

Recruitment Strategies

What is the PARTNER Study

The PARTNER study is enrolling couples where one partner is HIV-positive and the other is HIV-negative. This new study is looking at the risks of HIV transmission when someone is taking effective HIV treatment.

The PARTNER study particularly focuses on partnerships that do not always use a condom when having sex. The study is also looking at why condoms are not always used.

The PARTNER study is an international collaborative study taking place in several European countries. It is funded by the National Institute for Health Research in England and is coordinated by Copenhagen HIV Programme (CHIP), in collaboration with University College London (the sponsor) and The Royal Free Hampstead NHS Trust, London.

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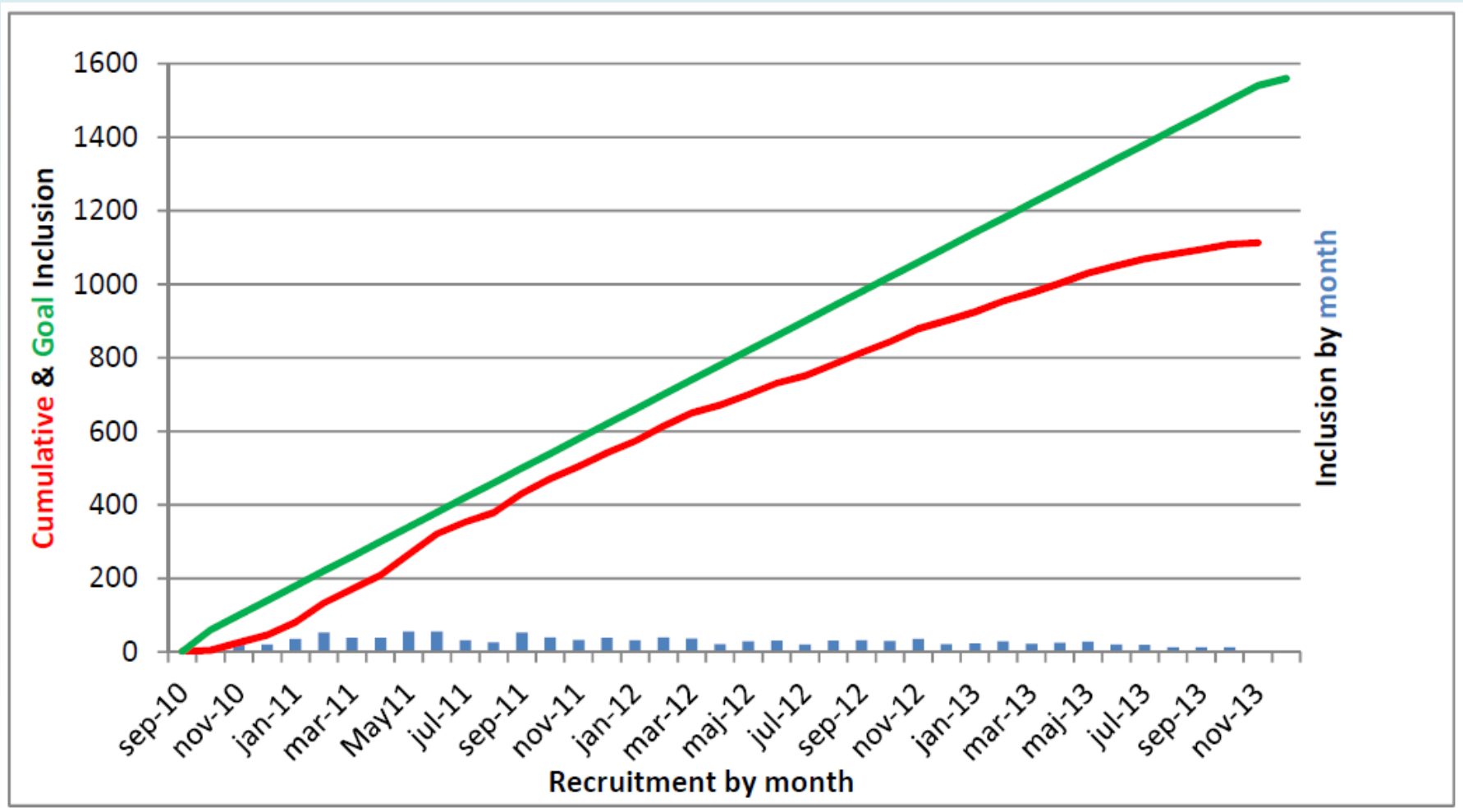
For information in your country, please contact:

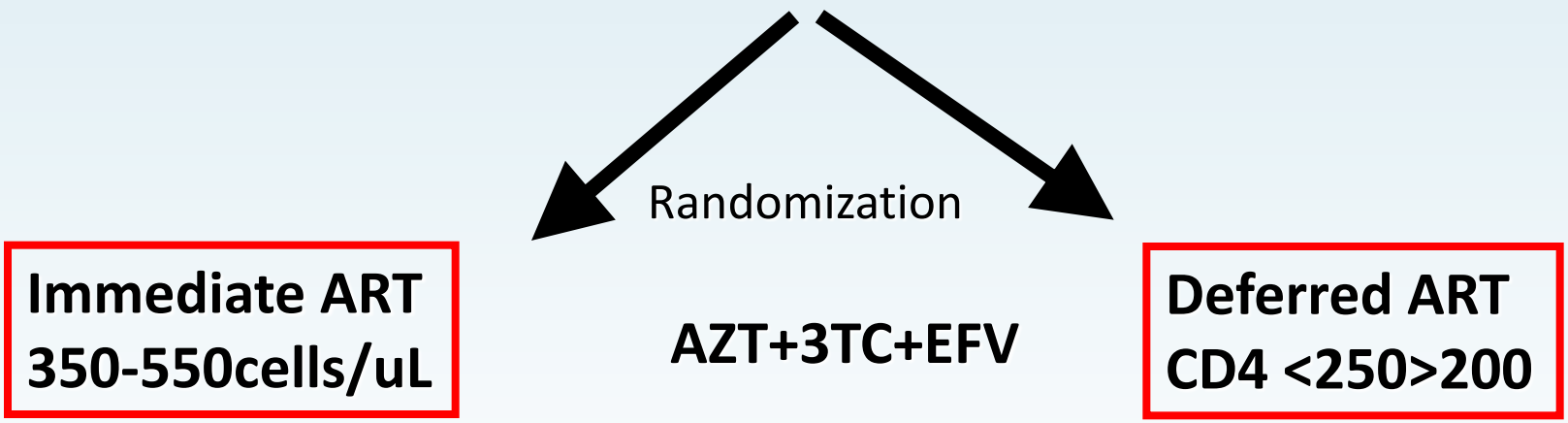
Monitoring Recruitment



Treatment for Prevention
‘Test and Treat’

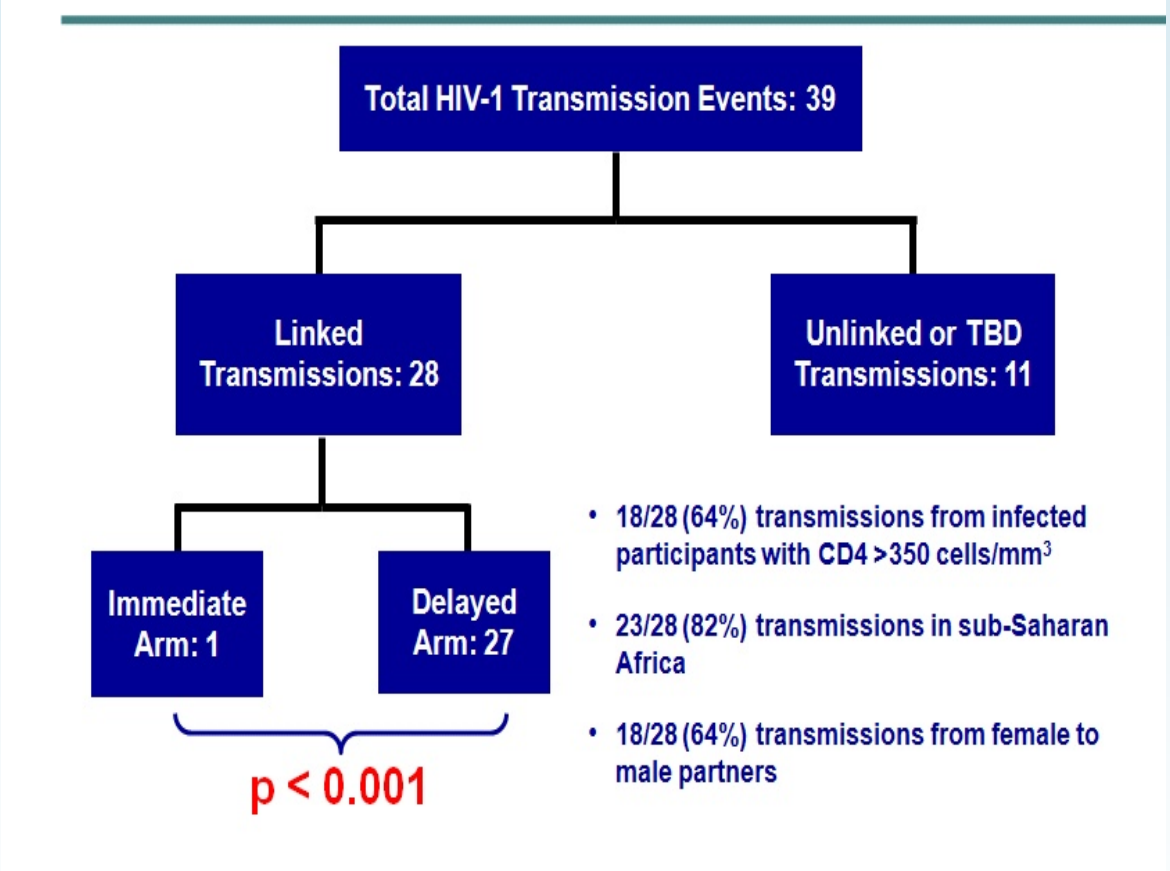
HPTN 052

HIV infected subjects with CD4
350 to 550cells/µL



Endpoints: i) Transmission Events
ii) OIs and Clinical Events
iii) ART Toxicity

HPTN 052 Results



April 28th 2011: DSB recommends that the results of the trial should be announced as soon as possible; 96% reduction in transmission in Immediate arm. HPTN 052 continued to follow couples but all participants were offered ART

Is PARTNER still relevant?

- The results from the HPTN 052 trial were a landmark in informing the debate on use of ART for prevention of HIV transmission
- But, condom use also effectively prevents HIV transmission and the majority of data on transmission risk in heterosexual serodifferent couples is for ART PLUS condoms
- Studies in heterosexual serodifferent couples with viral suppression have so far only reported follow-up data for 330 couple-years when condoms were not being used

- Data are even more limited for anal sex in men who have sex with men

- PARTNER is the only on-going study powered to provide data on HIV transmission risk through condomless sex and anal sex in particular

Comparison of results generated by HPTN 052, and projected for PARTNER phase 1 and 2

	HPTN 052	PARTNER Phase 1 (by March 2014)	PARTNER Phase 2 (by March 2017)
Number serodiscordant couples	1763	App 1350	App. 1780
Number MSM couples	37	App. 500	App .950
Condom-less sex	96% reported regular condom use	Only couples reporting condomless sex included in final analyses	Only couples reporting condomless anal sex included in final analyses
PYFU eligible	1145 *	1753*	3124*
PYFU of condomless sex	Estimated <200 PYFU	1753*	3124*
MSM/Anal sex	2%	48%	100%
PYFU couples who have anal sex	< 50	879	2250
upper 95% confidence limit for risk of transmission – overall	1/54 couple years**	1/474 couple years **	1/847 couple years**
upper 95% confidence limit for risk of transmission – anal sex	Unknown	1/238 couple years anal sex**	1/610 couple years anal sex**
upper 95% confidence limit for risk of transmission – receptive anal sex with ejaculation	Unknown	1/76 couple years **	1/196 couple years **

* Eligibility criteria: HIV negative reporting condom-less sex; HIV+ VL<200

** These numbers will be lower if one or more linked transmissions are observed

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HIV transmission risk through condomless sex if the HIV positive partner is on suppressive ART: PARTNER study

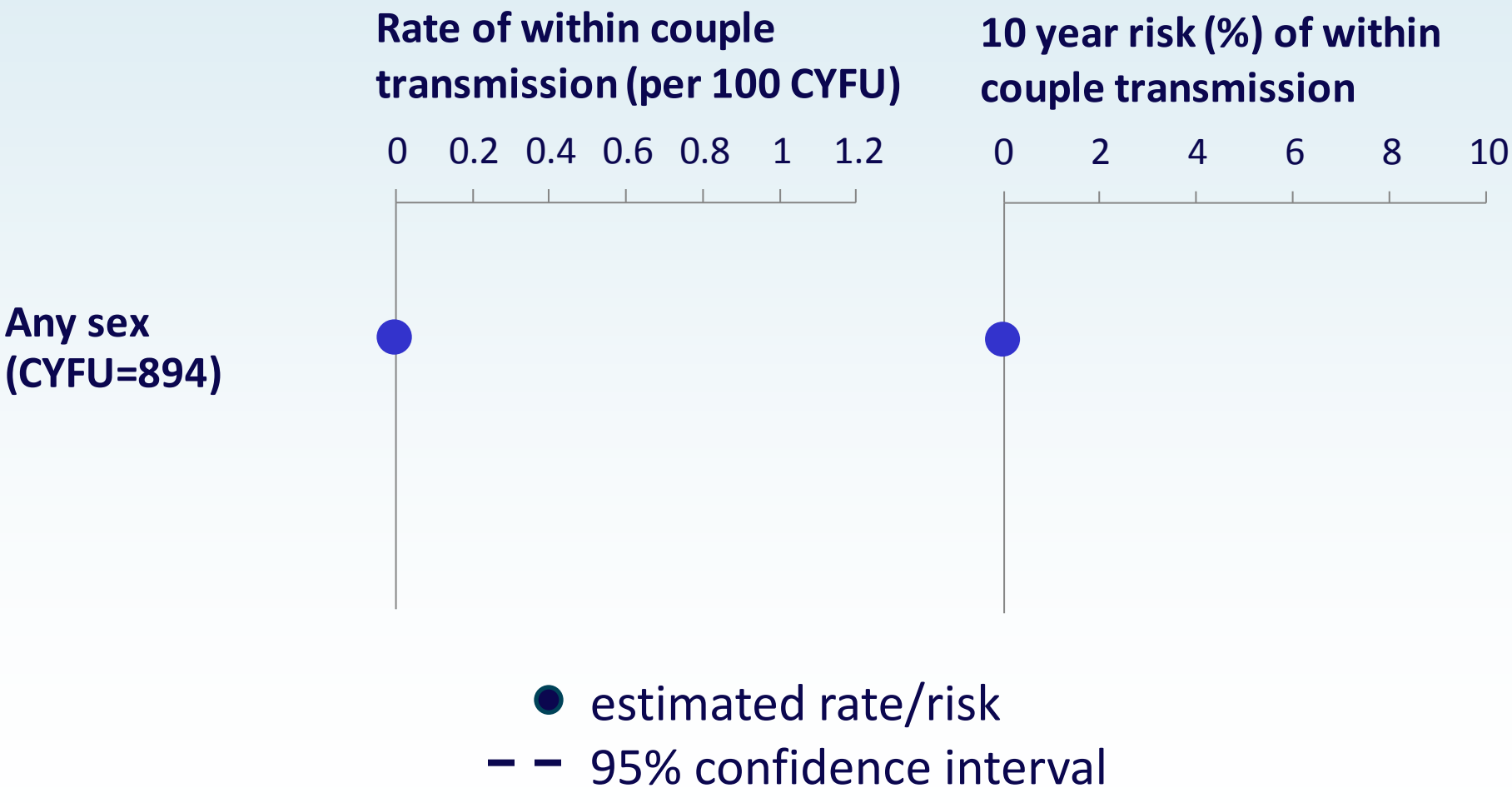
Alison Rodger, Valentina Cambiano, Tina Bruun, Pietro Vernazza , Simon Collins, Vicente Estrada, Jan Van Lunzen, Giulio Maria Corbelli, Anna Maria Geretti, David Asboe, Pompeyo Viciana, Felix Gutiérrez, Christian Pradier, Katarina Westling, Rainer Weber, Hansjakob Furrer, Jan Prins , Jan Gerstoft, Andrew Phillips and Jens Lundgren for the PARTNER Study Group

CROI, Boston, March 3 to March 6, 2014

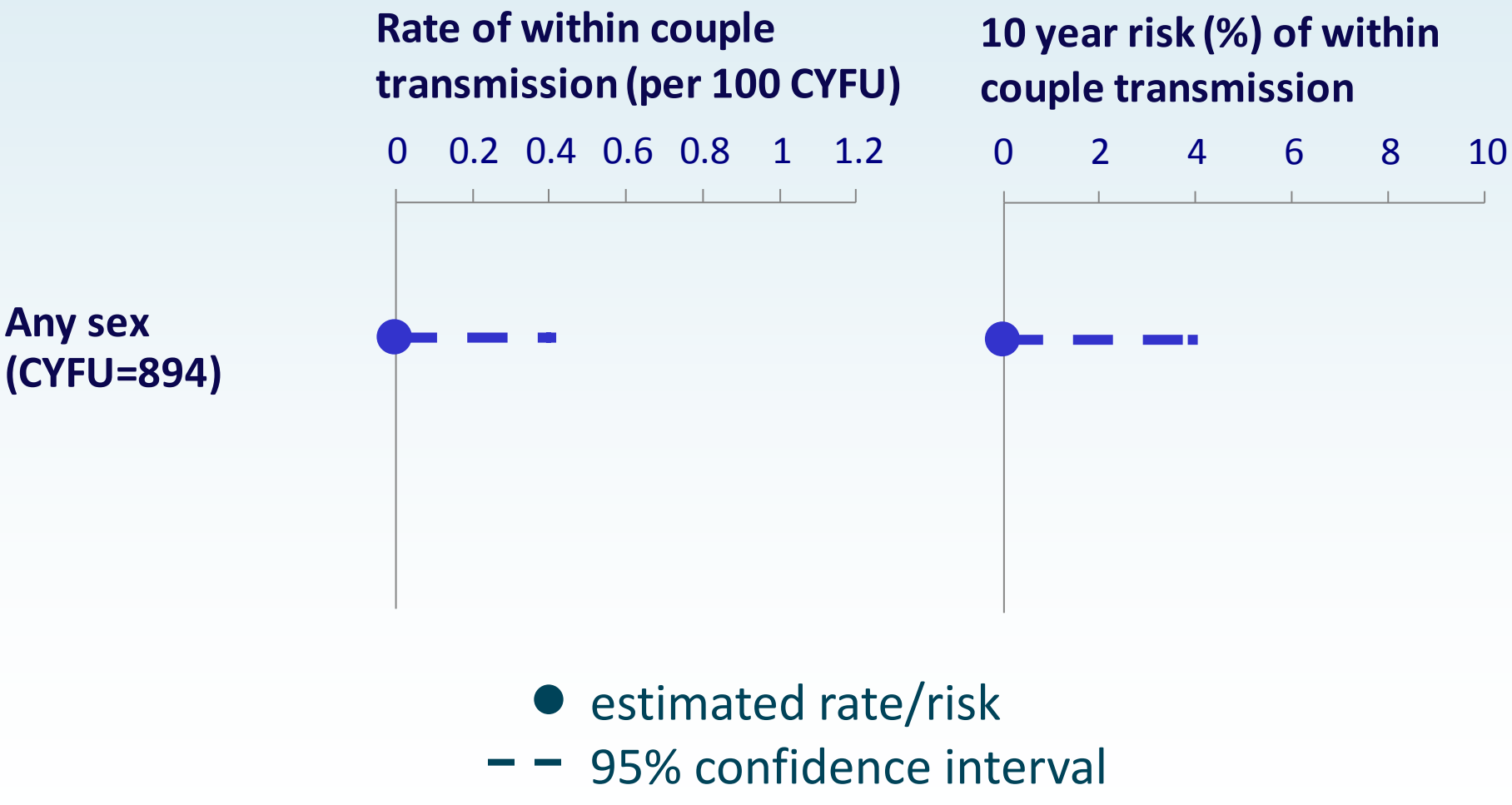
HIV negative partners: Characteristics

	MSM couples (n=282)	Heterosexual couples (n=445)	
		M -ve (n=245)	W -ve (n=240)
At study entry			
Age, median (IQR)	40 (32-47)	45 (37-50)	40 (34-46)
Yrs CL sex, median (IQR)	1.5 (0.5-3.5)	2.7 (0.6-6.9)	3.5 (0.7-10.6)
During follow up			
Years in the study, median (IQR)	1.1 (0.7-1.9)	1.5 (1.0-2.0)	1.5 (0.9-2.0)
Diagnosed with STI, %	16%	5%	6%
CL sex with other partners, %	34%	3%	4%
CL sex acts/year, median (IQR)	43 (18-79)	37 (14-77)	38 (14-71)
Estimated total number CL sex acts	16,400	14,000	14,000

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



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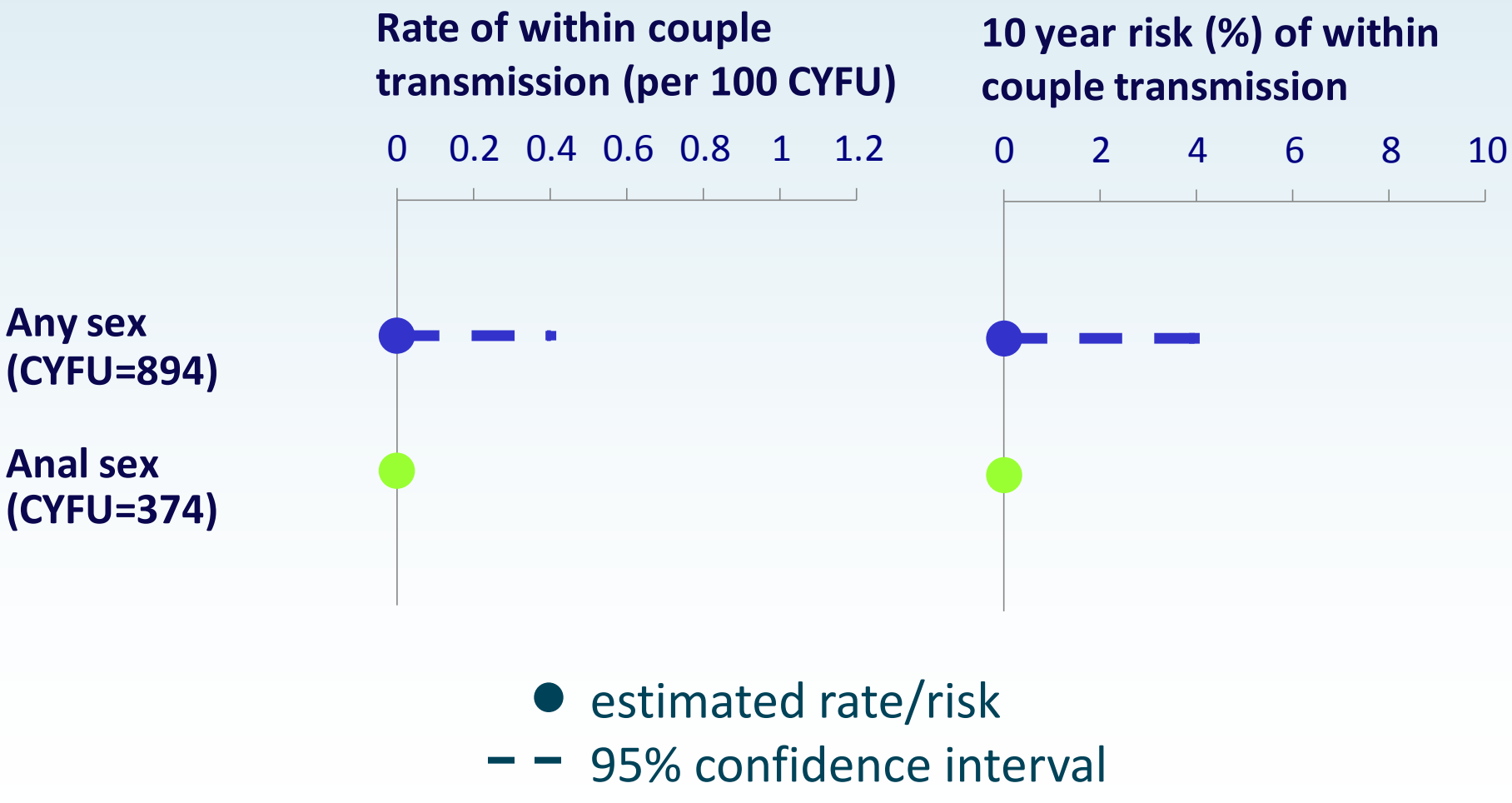

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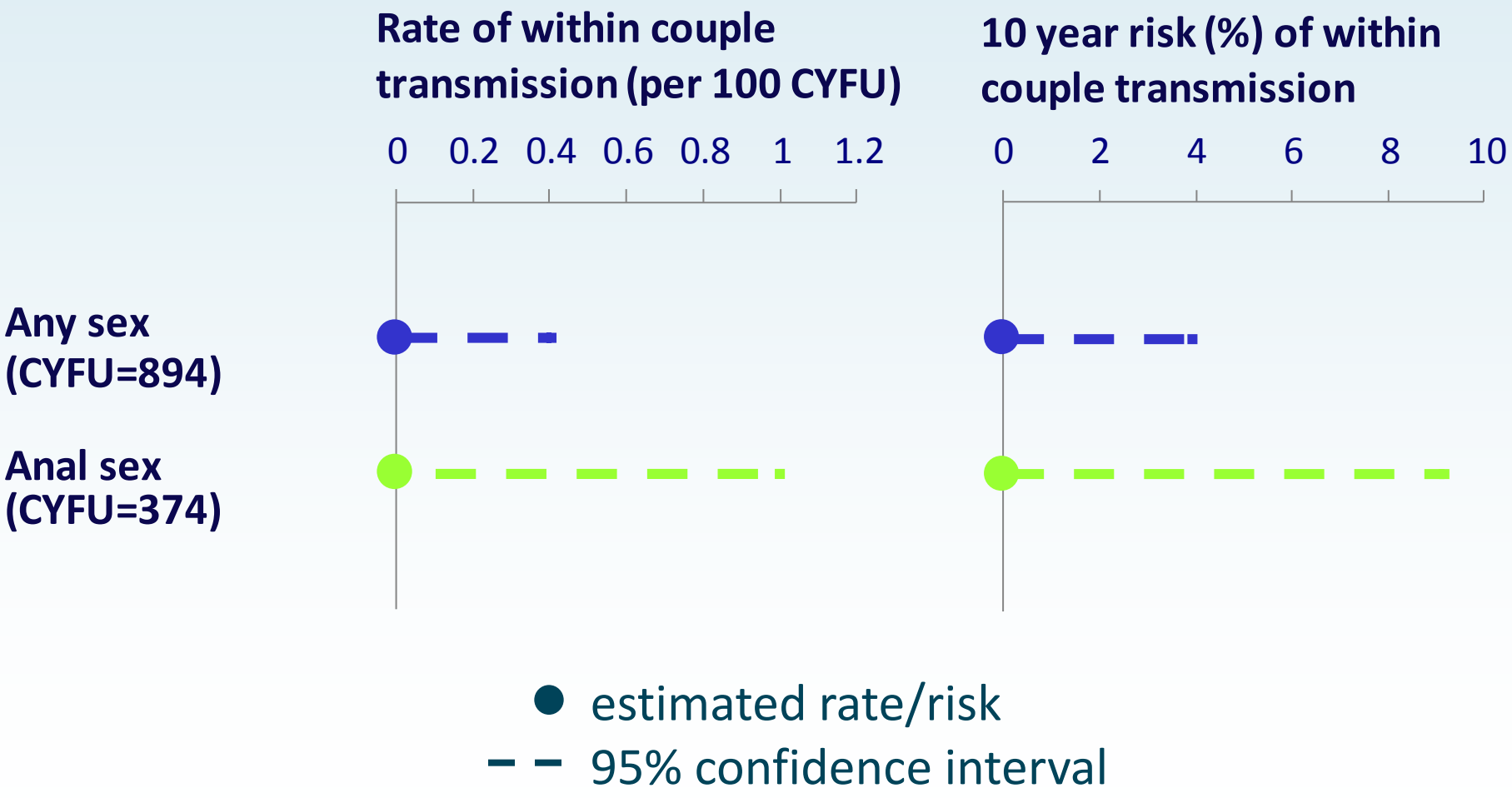

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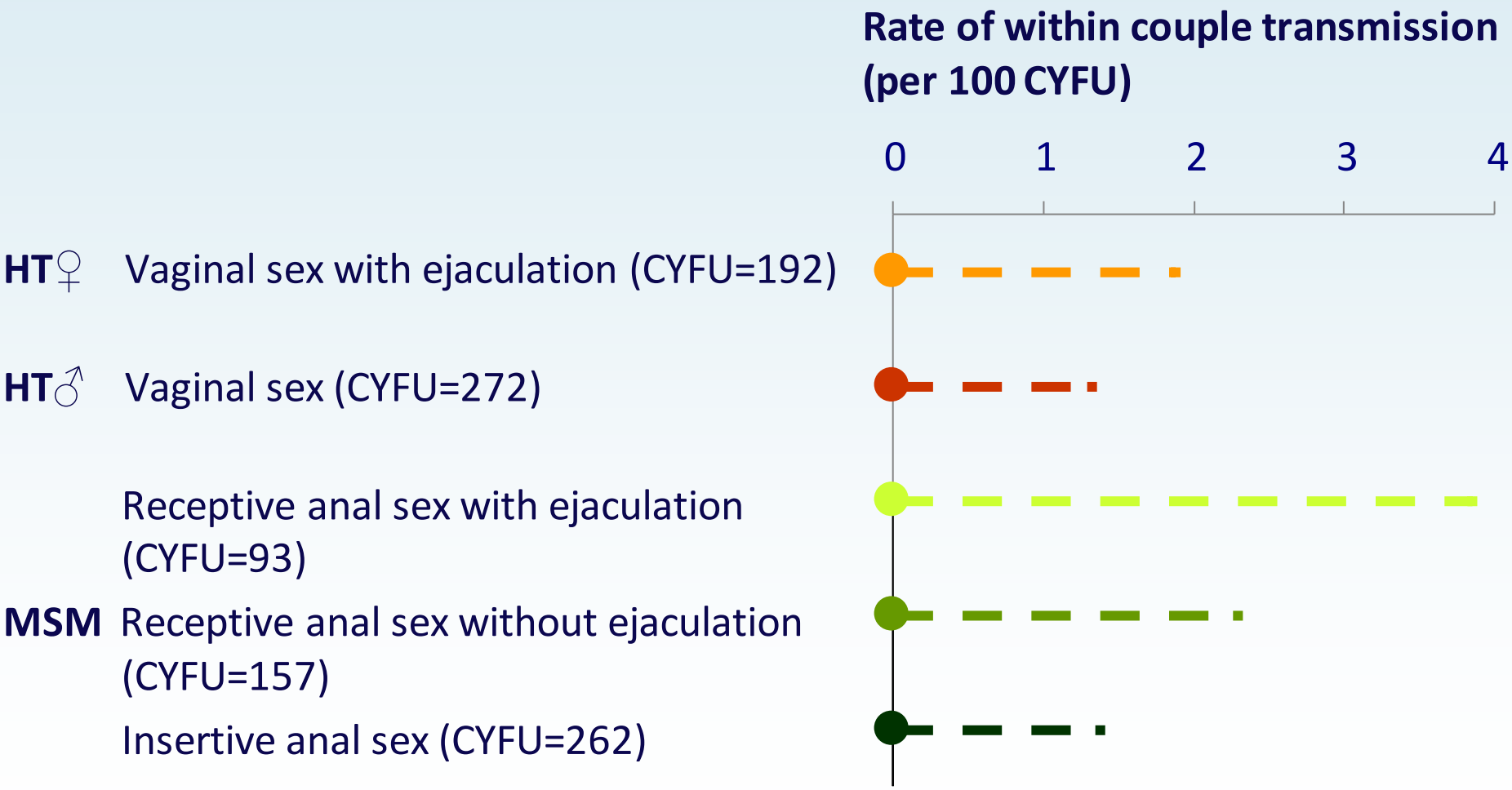
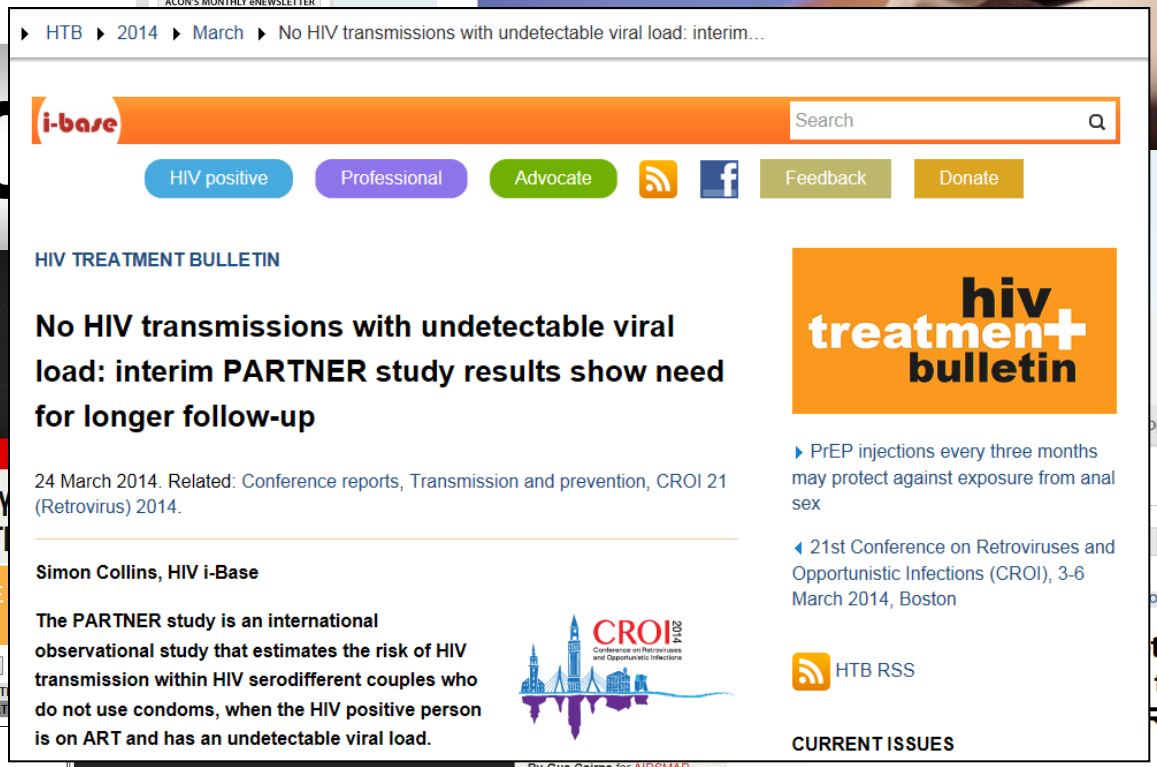


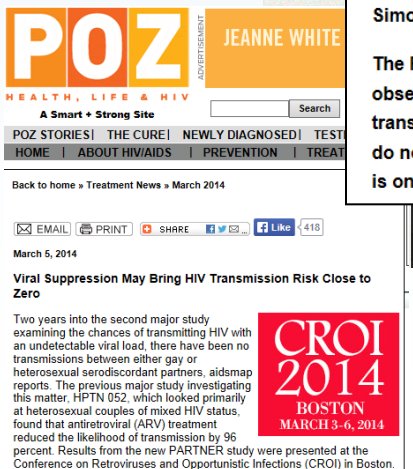
Conclusions

- Interim results after 894 eligible CYFU report an overall HIV transmission rate of zero through condomless sex with a plasma VL < 200 copies/mL on ART, despite a significant number of sexual acts.
- However uncertainty over the upper limit of risk remains, particularly over receptive anal sex with ejaculation
- Additional follow-up in MSM is needed through PARTNER2 (2014-2017) to provide more precise estimates for transmission risk to inform policy and also individual choice on condom use

Community Press

HUFFPOST GAY VOICES





Acknowledgments

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PARTNER sites

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Portugal: Hospital Santa Maria, Lisabon, Nuno Janerio.

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