Developing a clinical research study: A practical example

Alison Rodger
University College London
Royal Free Hospital

Disclosure slide

Received unrestricted grant funding from Gilead Sciences

Treatment as Prevention (TasP)

- The idea that ART could be used not only to reduce morbidity and mortality amongst HIV-positive people, but also to prevent onwards HIV transmission, by reducing the infectiousness of HIV-positive people, is not new.
- Mother to child transmission an example:
  - If treated early in 2nd trimester virtually eliminates risk to the infant
  - If ART initiated around delivery: cART (<0.5%) vs Single Dose NVP/ZDV (1.8%) vs no ART (25%)
- TasP is the use of ART at any CD4 count to prevent transmission of HIV during sex

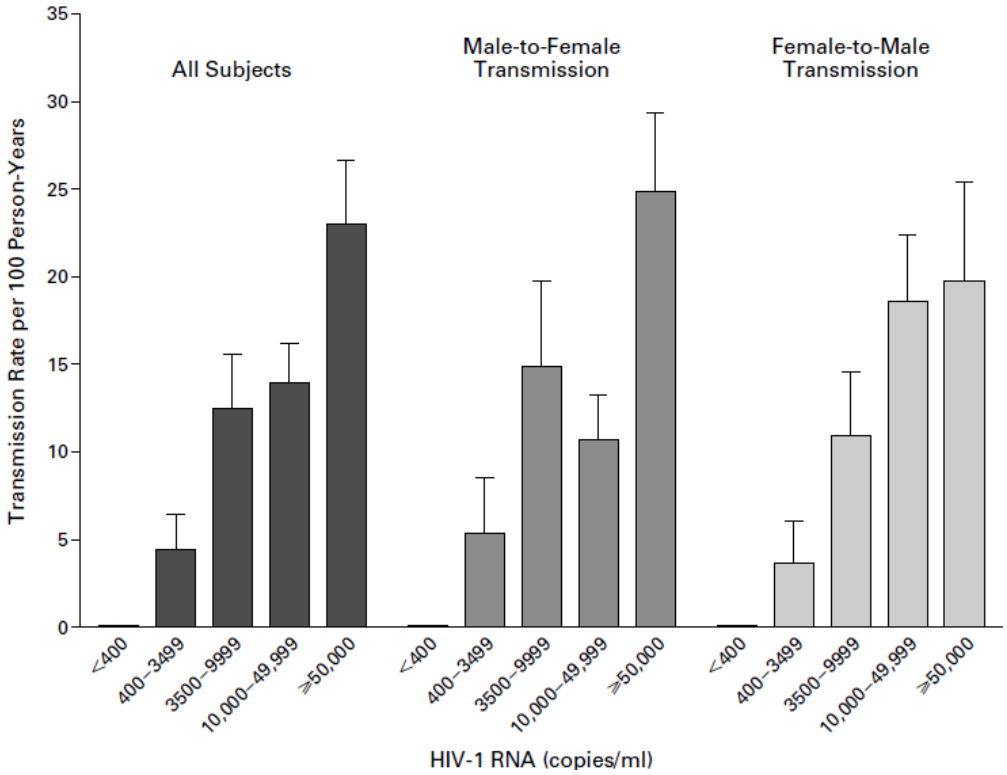
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1

Thomas C. Quinn, M.D., Maria J. Wawer, M.D., Nelson Sewankambo, M.B., David Serwadda, M.B., Chuanjun Li, M.D., Fred Wabwire-Mangen, Ph.D., Mary O. Meehan, B.S., Thomas Lutalo, M.A., and Ronald H. Gray, M.D. for the Rakai Project Study Group

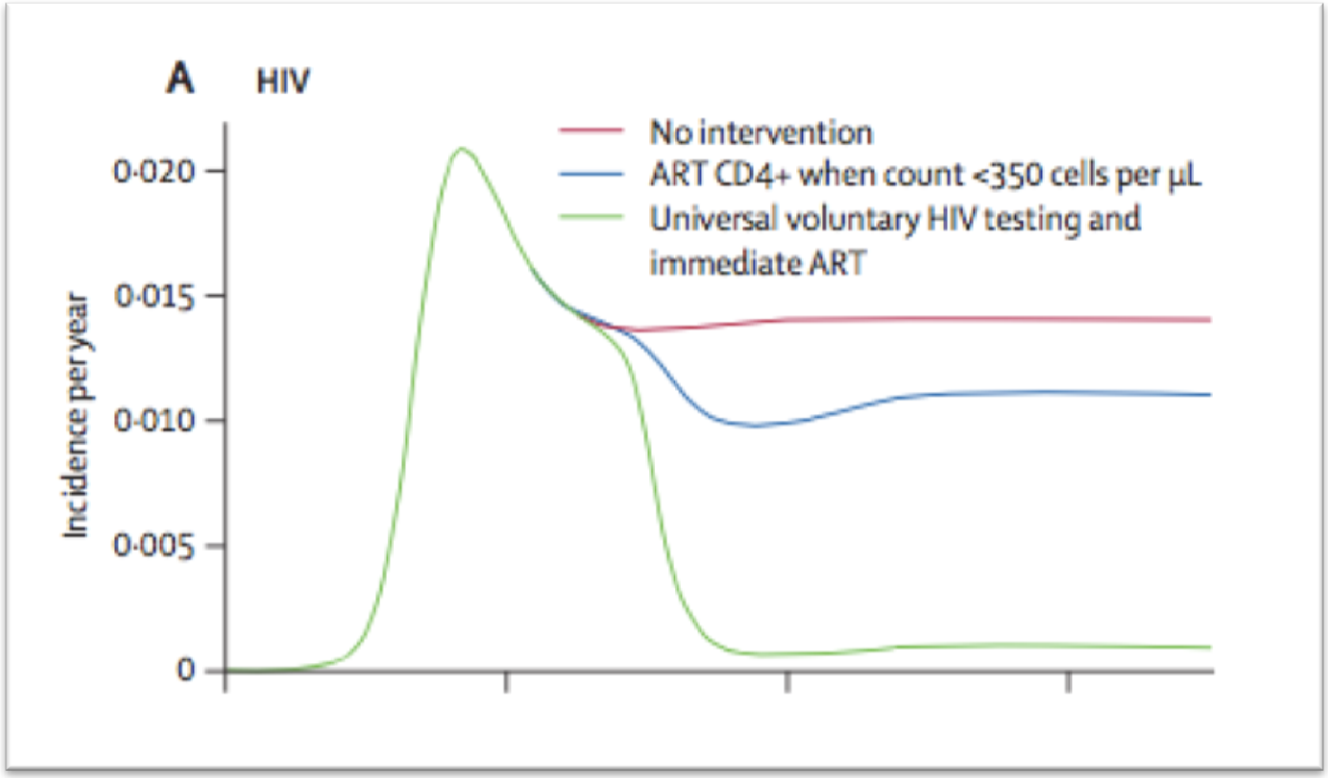
N Engl J Med 2000; 342:921-929 | March 30, 2000 | DOI: 10.1056/NEJM200003303421303



Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

Lancet 2009; 373: 48–57



‘Swiss Statement’

Published in:
Schweizerische Ärztezeitung / Bulletin des médecins suisses / Bollettino dei medici svizzeri / 2008; 89:5

HIV-positive individuals without additional sexually transmitted diseases (STD) and on effective anti-retroviral therapy are sexually non-infectious

Pietro Vernazza, Bernard Hirschel, Enos Bernasconi, Markus Flepp

The Swiss National AIDS Commission, following a proposal of the special commission of the Federal Office of Public Health on HIV/Aids Clinical and Treatment, after a review of the scientific data and after an extensive discussion, resolves that: An HIV-infected individual without additional STD and on an anti-retroviral therapy (ART) with completely suppressed viremia (in the following: “effective ART”) is sexually non-infectious, i.e. he/her cannot pass on the HI-Virus through *sexual contact* as long as the following conditions are fulfilled:

- The HIV-infected individual complies with the anti-retroviral therapy (ART), the effects of which must be evaluated regularly by the treating physician;
- The viral load (VL) has been non-detectable since at least six months (i.e. viremia is suppressed);
- There are no additional sexually transmitted diseases (STD) present.

Research question (2009)

"What further research is needed before a policy of offering ART to all people with diagnosed HIV should be implemented?"

Literature search

- Data from observational studies indicating that suppressive ART markedly reduced infectiousness, but precise estimates of risk of transmission with suppressive ART unknown
- Not clear if risk behaviours change with initiation of early ART which may negate any benefits of reduced infectiousness
- Individual health benefit of early ART is unclear
- Acceptability of early ART in HIV positive people unclear
- Not clear if a policy of offering ART to all diagnosed HIV positive people is cost effective for the UK

Further definition research question/s

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

The ***RESEARCH QUESTIONS*** are:

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 precise transmission risk for individuals on ART with suppressed viral load through condomless sex?

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

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

Workstream 1 (Q: Acceptability of ART in HIV positive people at high CD4 counts?)

- The Antiretrovirals, Sexual Transmission Risk and Attitudes cross sectional study (ASTRA) with linkage to clinical HIV databases for longitudinal follow up
- The Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH)
- [Cognitive Impairment in People with HIV in the European Region (CIPHER) Study]

Workstream 2 (Q: Patterns of sexual risk behaviour on early ART?)

- Transmission risk behaviour of people enrolled in the START (Strategic Timing of Antiretroviral Therapy) Trial

Workstream 3: (Q: Transmission risk with suppressed VL through CL sex?)

- To estimate the rate of transmission of HIV through condomless sex to HIV negative partners of PLWH with plasma viral load < 200 c/ml on ART (PARTNER Study)

Workstream 4: (Q: Would it be cost effective for the UK to offer ART to all those diagnosed with HIV?)

- Modelling of the effectiveness and cost-effectiveness of increased HIV testing and immediate ART at diagnosis in MSM

The team…

Core Group: statistics, epidemiology, clinical, modeling



Data manager

Study Coordinator

HIV virology and sequencing

Community Representation


Clinical Trials


Qualitative, behavioural, health psychology


Clinicians




Expertise in HIV Transmission Law

Health Economics

Cost effectiveness modeling

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		

Write the funding application

BACKGROUND/RATIONALE/IMPORTANCE

AIM AND OBJECTIVES

METHODOLOGY:

- **STUDY DESIGN**
- **SETTING**
- **RECRUITMENT**
- **DATA COLLECTION AND MEASUREMENTS**
- **SAMPLE SIZE**
- **ANALYSIS PLAN**

RELEVANT EXPERTISE AND EXPERIENCE

ANTICIPATED OUTPUTS, OUTCOMES AND IMPACT

DISSEMINATION

MANAGEMENT, TIMELINES & GOVERNANCE

ETHICS

PATIENT & PUBLIC INVOLVEMENT

FINANCES

National Institute for Health Research

PGfAR Competition 14 Stage 2

Peer Review Form

Application Reference RP-PG-1212-20006

- RELEVANCE
- QUALITY OF RESEARCH DESIGN
- MANAGEMENT ARRANGEMENTS
- STRENGTH OF RESEARCH TEAM
- IMPACT OF PROPOSED RESEARCH
- VALUE FOR MONEY
- INVOLVEMENT OF PATIENTS AND PUBLIC

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

Workstream 1 (Q: Acceptability of ART in HIV positive people at high CD4 counts?)

- The Antiretrovirals, Sexual Transmission Risk and Attitudes cross sectional study (ASTRA) with linkage to clinical HIV databases for longitudinal follow up
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Workstream 4: (Q: Would it be cost effective for the UK to offer ART to all those diagnosed with HIV?)

- Modelling of the effectiveness and cost-effectiveness of increased HIV testing and immediate ART at diagnosis in MSM

Protocol

BACKGROUND/RATIONALE/IMPORTANCE

- A proportion of people with diagnosed HIV do not always use a condom when having sex with partners of negative/unknown status.
- Increasingly strong evidence that virally suppressive ART reduces infectiousness of people with HIV through sex
- However, precise estimates of this risk of transmission through condomless sex are not available, particularly for men who have sex with men (MSM).
- It is extremely important that more precise estimates are obtained, both for assessing the effectiveness of ART as a prevention strategy and to inform individual choice on condom use

AIM : To follow serodifferent couples who report recent condomless penetrative sex to assess the risk of HIV transmission in partnerships that do not to use condoms consistently and the HIV-positive partner is on therapy with a viral load < 200 copies/mL

Protocol

STUDY DESIGN:

This is an observational study in which HIV serodifferent partnerships will be followed over time, with 3-6 monthly reporting of transmission risk behaviour and HIV testing for the HIV negative partner.

Eligibility:

- HIV-positive people on ART aged older than 18 years with an HIV negative partner.
- The partnership met the following criteria: (i) reported penetrative sex without using condoms in the month before enrollment, (ii) the partners expected to have sex together again in the coming months, (iii) both partners consent to complete a risk behaviour questionnaire every 6 months, (iv) the HIV negative partner consented to testing for HIV at these visits and (v) both partners consented to provide a separate blood sample if the HIV negative partner should become infected with HIV.

Protocol

DATA COLLECTION AND MEASUREMENTS

- Study data collected at baseline and then 4 to 6 months
- Self completed paper questionnaires: socio-demographics; self-reported adherence to ART; sexual activity between the partners (since last visit), frequency of intercourse, type of intercourse (receptive or insertive, vaginal or anal) and whether ejaculation occurred; diagnosed STIs; use of condoms, PrEP or PEP.
- Injecting drug use and if needles, syringes or injection equipment was shared.
- HIV-negative partners asked if condomless sex other than their HIV-positive partner, the number of other partners and HIV-positive or unknown serostatus.
- HIV-negative partner tested every 6 months.
- HIV-positive partner: data on ART, CD4 count and current and recent plasma HIV-1 RNA load recorded on CRF

Protocol

DATA COLLECTION AND MEASUREMENTS

Risk behaviour questionnaires:

1. Baseline risk behaviour in HIV positive partner, 3 versions (i) HIV+ male, HIV - male (ii) HIV + male, HIV - female, (iii) HIV + female, HIV - male
2. Baseline risk behaviour in HIV negative partner (self-complete) – 3 versions as above.
3. Follow-up risk behaviour in HIV positive partner (self-complete) – 3 versions as above.
4. Follow-up risk behaviour in HIV negative partner (self-complete) – 3 versions as above.
5. Partner infection form – risk behaviour (to be completed by prev HIV neg partner if becomes infected with HIV) – 3 versions as above.

Case Report Forms (CRFs)

1. Baseline clinical and antiretroviral drug use status on HIV positive partner (clinician/nurse to complete)
2. Follow-up clinical and antiretroviral drug use status on HIV positive partner (clinician/nurse to complete)
3. Partner infection form (to be completed by clinician/ nurse if partner becomes infected)

Questionnaire Design

- What are the research questions to be answered
- Only ask what you really, really need to know
- Think about target audience
- Are instructions, content and wording clear and appropriate
- Question placement, sequence, layout, length
- Response format
- Make sure you pilot it!

AURAH

PREFERENCES FOR HIV TESTING

Version 5 07/08/2013 REC Ref: 13/LO/0246

After completing the main AURAH questionnaire we hope you will answer some additional questions on the other side of this inserted sheet.

There are likely to be many different ways to have an HIV test in the near future and the questions are about your preferences for HIV testing.

Please do NOT write your name on this insert. If you have any questions or need any help, please ask the person who gave you the AURAH questionnaire.

Please place your completed insert in the envelope with the AURAH questionnaire.

Thank you for your help!

Study No. ☐☐☐☐☐ Date: ___ / ___ / ___

J1. How appealing are these ways of getting tested for HIV?

Please rank each of the following four options from 1 (least appealing) to 4 (most appealing)

Way of testing	Explanation	1 Least liked	2	3	4 Most liked
Sexual health clinic	This is testing in a sexual health clinic setting where you can usually get the result in an hour and the test is done by health care staff.	☐	☐	☐	☐
GP surgery	This is having an HIV test through your own GP where the test can be done in the surgery and the results are available in a few days from your GP.	☐	☐	☐	☐
Self sampling	This is where you ask online for a free HIV test kit to be sent to your home. You take a saliva sample or finger prick of blood yourself and send it back to the laboratory where it is tested. The results are almost always accurate. If your result is negative it will be texted to you and if it is positive you would be phoned by a counsellor or health advisor.	☐	☐	☐	☐
Self testing	This is where you ask online for a free HIV test kit to be sent to your home. You take a saliva sample or finger prick of blood and do the test yourself which takes about 5 minutes. The test will tell you if you are HIV negative, but if it says you might have HIV, then would need to go to a clinic for another test. If you needed counselling or clinic referral, phone numbers are provided in the test kit. Only you will know your test result.	☐	☐	☐	☐

If you have a strong preference either way, please write in the reasons below

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J2. What would be your preferred sample type for HIV testing at home?

Please tick one option only

Saliva based test ☐

Finger prick sample of blood ☐

Protocol

Analysis Plan

- **Primary outcome** is rate of transmission of phylogenetically linked HIV infections during eligible CYFU
- **CYFU eligible** if (i) couples had condomless sex during the period (ii) no PEP or PrEP use; (iii) latest HIV-1 VL <200 copies/mL and not older than 12 months; (iv) questionnaires on TRB completed and (v) follow-up before the censoring date.
- **Confidence intervals** for the incidence rate of transmission calculated using exact Poisson methods.
- HIV – and HIV + characteristics compared using Kruskal Wallis test (continuous) and Chi-Square tests for (categorical)
- All tests used $P<0.05$ as the threshold of statistical significance.
- **Missing data** not imputed and the analysis performed only on the available data.
- **Data analysed** using SAS (version 9.3).

Protocol

- **Phylogenetic analysis:** If at any time the HIV-negative partner was found to have become HIV-positive, HIV-1 *pol* and *env* 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 statistical 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.

Sequencing and Phylogenetic Analysis

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Protocol

- **Study Management**: An Executive Committee will oversee the implementation of the study on a day to day basis. Membership will include PIs, study co-ordinator, co-applicants, PPI representation and investigators from participating countries with prior interest.
- To assist the EC, a Steering Committee will be formed of persons in central study functions (i.e. national representatives, statistics, virology, ethics and legal issues). The Steering Committee will be consulted on major study-specific decisions.
- A wider Study Group will be formed. All investigators involved in the study are automatically part of the PARTNER Study Group.
- The Study Group will be kept informed on progress of the study via e-mails, newsletters and investigator meetings at all major conferences.

Protocol

Sample Size

- In planning the sample size it was known that the transmission rate was low and the aim was to generate a more precise estimate of the rate than was available.
- The sample size based on a hypothesized transmission rate of 1 per 1000 couple-years of condomless sex, with the choice of this very low rate based on arguments laid out in the Swiss Statement.
- Under this hypothesis, 2000 couple-years-of-follow-up was required to have an 85% chance that the upper limit of the 95% confidence interval for the transmission rate is < 0.44 per 100 couple-years-of-follow-up (0.2 per 100 couple-years-of-follow-up with a transmission rate of zero).

Sample Size

Recruitment expanded to 75 sites in 14 countries

PARTNER sites and site PIs

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. Mater Misericordiae University Hospital, Dublin, Paddy Mallon

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.

Protocol

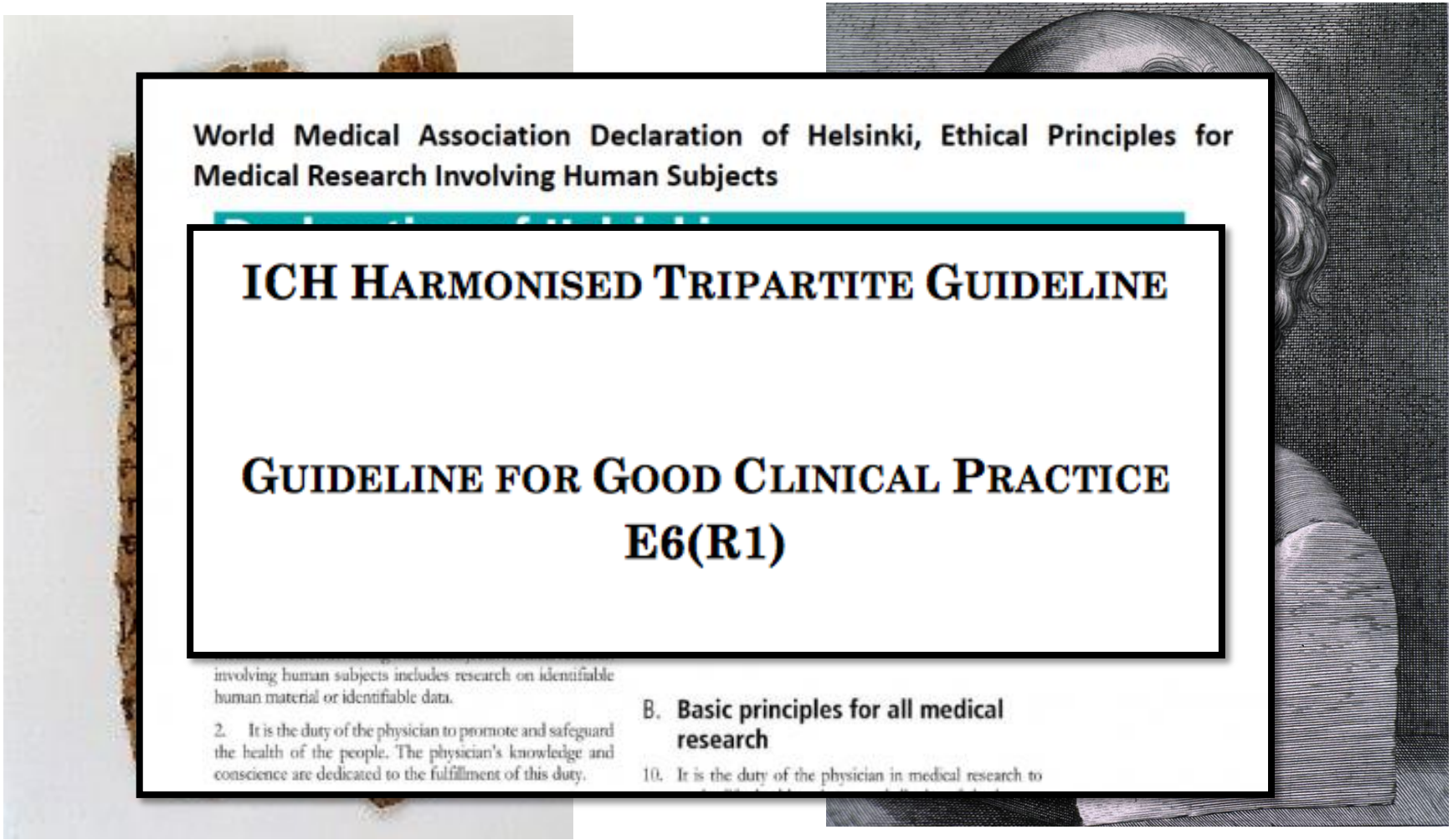
- **Publication Policy:** Publications derived from the study will be authored by the "PARTNER Study Group".
- PARTNER includes >70 clinics, not possible to include all site investigators as co-authors on the first publication.
- Priority will be given to sites that contribute the most, with a balance between number of pairs included per site and the number of couple years of prospective follow-up.
- All named investigators listed as part of the Study Group

Protocol

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
- Data sharing plan
- Confidentiality of Study Participants

Ethics


World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects
ICH HARMONISED TRIPARTITE GUIDELINE
GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)
involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
B. Basic principles for all medical research
10. It is the duty of the physician in medical research to

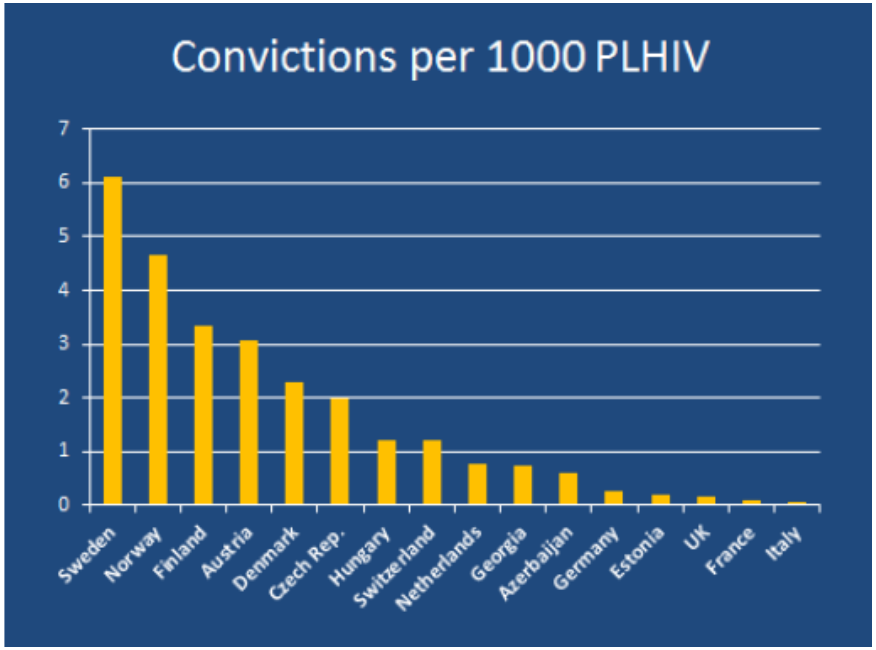
HIV transmission and risk of prosecution

- 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 approvals

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 didn't
- 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



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 is done only after anonymization of samples, and are not linkable to the specific partnership.

Data management/sharing plan

- Taken very seriously by funding agencies - expectation that if a study has received public funding, then any data that derive from the project should be accessible to as wide a group of researchers as possible
- See websites for what should be included and for a template

MRC guidance on data management plans

All applicants submitting funding proposals to the MRC are required to include a Data Management Plan as an integral part of the application. MRC Institutes and Units are required to submit one as part of the Quinquennial Review (QQR) report.

Everyone in a research team should have a clear sense of their responsibilities in ensuring that:

- research data are of the highest quality; have long-term validity; are well documented, so that other researchers can access, understand, use and add value to them over the decades and independently of the original investigators
- research information about people is managed to the highest, most appropriate ethical and best standards.
- Principal investigators and the institutions receiving funding are responsible for planning and executing local policies, systems and standards for how valuable research data are managed.

Communications/dissemination plan

Creating Impact

- How will you ensure that your research findings can be translated into clinical care?
- Who are the key stakeholders in your research?

  - Patient community
  - Academics
  - Clinicians
  - Other healthcare professionals
  - Funders/commissioners
  - Public health professionals
  - Global health leaders

- What are your plans for engaging with each of them outside of the normal academic route?

Other ways to disseminate your findings

- How will you get your research findings out to the HIV community and other audiences (e.g. hospital managers, funders, etc.)

  - Websites (how do people 'find' your website)

  - Study reports

  - Social media

  - Mass media

  - School education

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.

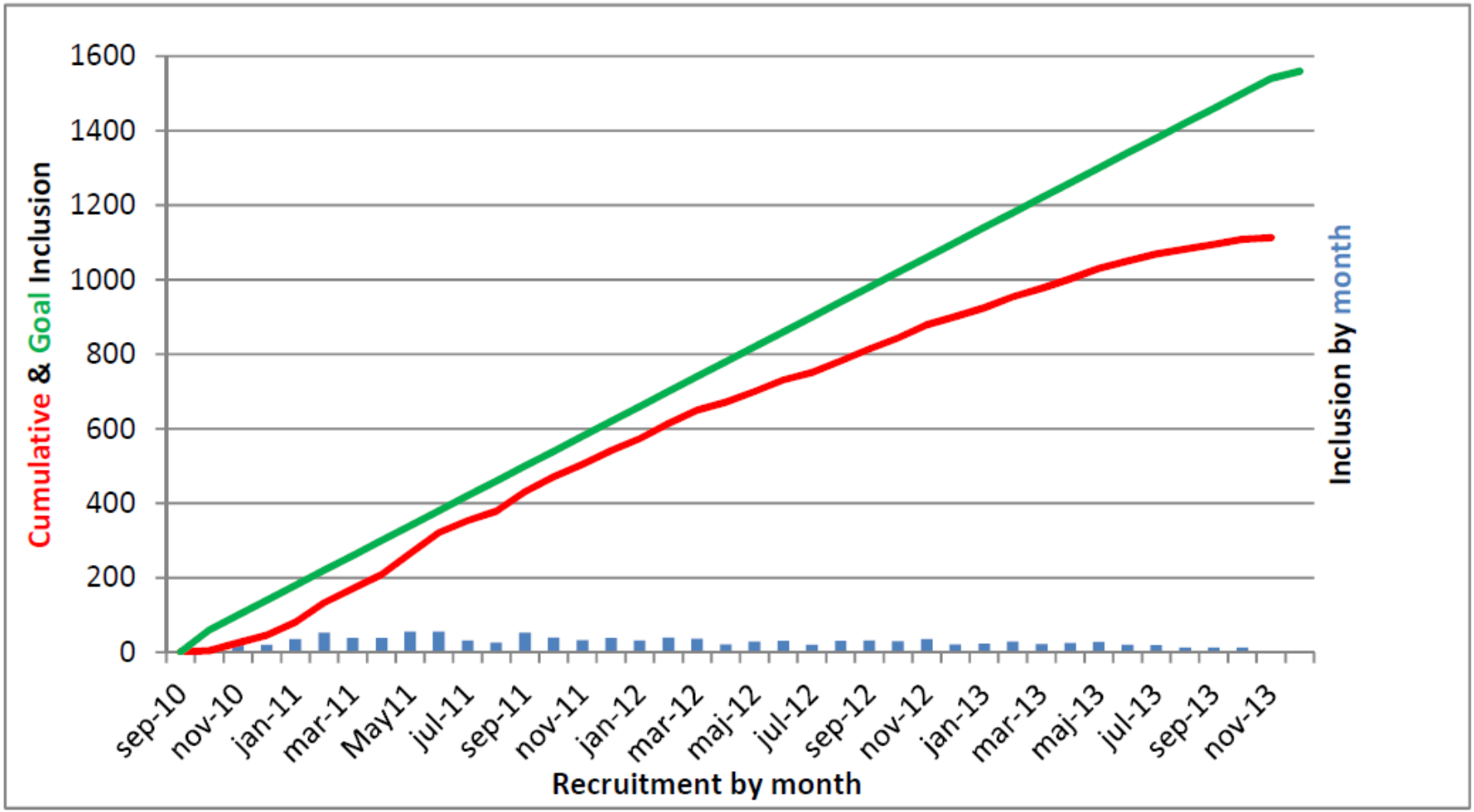
Study Coordinating Centre contact:

Tina Bruun, RN
Study Coordinator
Copenhagen HIV Programme
University of Copenhagen,
Faculty of Health Sciences
The Panum Institute/Building 21.1
Blegdamsvej 3B
2200 Copenhagen N
Denmark
tbr@cphiv.dk
Tel: +45 35 45 57 57
Fax: +45 35 45 57 58

www.partnerstudy.eu

For information in your country, please contact:

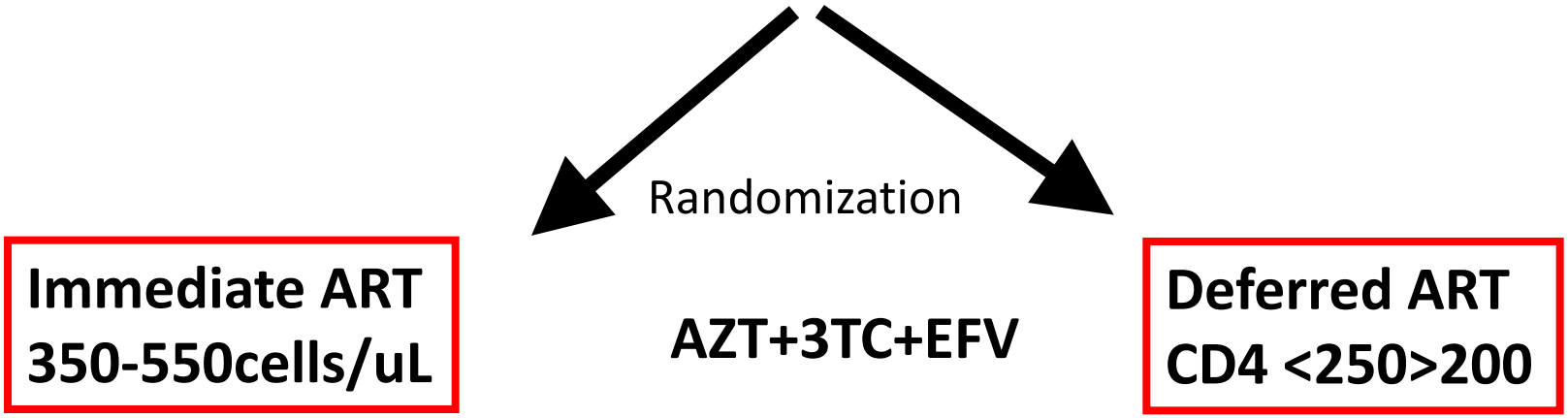
Monitoring Recruitment



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

HIV infected subjects with CD4
350 to 550cells/µL

28th April 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 will continue to follow couples but all participants will be offered ART

iii) ART Toxicity

Is PARTNER still relevant or should we just go home?

Is the Question Answered: Are HIV Positive People on Suppressive ART Sexually Non-infectious?

- Condom use also effectively prevents HIV transmission and in HPTN 052 only around 5% reported any condomless sex.
- Cumulative CYFU from all studies during which condomless sex was reported is around 330.
- Uncertainty of upper limit estimates if no transmissions as this is not the same as zero chance of transmission
- In HPTN 052 only 2% (n=37) were MSM couples so along with other studies gave no direct evidence for anal as opposed to vaginal sex

Ref: Rodger et al, Anti-Viral Therapy , 2013

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

Alison Rodger, Valentina Cambiano, Tina Bruun, Pietro Vernazza, Simon Collins, Jan Van Lunzen, Giulio Maria Corbelli, Vicente Estrada, Anna Maria Geretti, Apostolos Beloukas, David Asboe, Pompeyo Viciana, Félix Gutiérrez, Bonaventura Clotet, Christian Pradier, Jan Gerstoft, Rainer Weber, Katarina Westling, Gilles Wandeler, Jan M Prins, Armin Rieger, Marcel Stoeckle, Tim Kümmerle, Teresa Bini, Adriana Ammassari, Richard Gilson, Ivanka Krznaric, Matti Ristola, Robert Zangerle, Pia Handberg, Antonio Antela, Sris Allan, Andrew N Phillips and Jens Lundgren for the PARTNER Study Group

AIDS 2016, Durban, 19th July, 2016

PARTNER

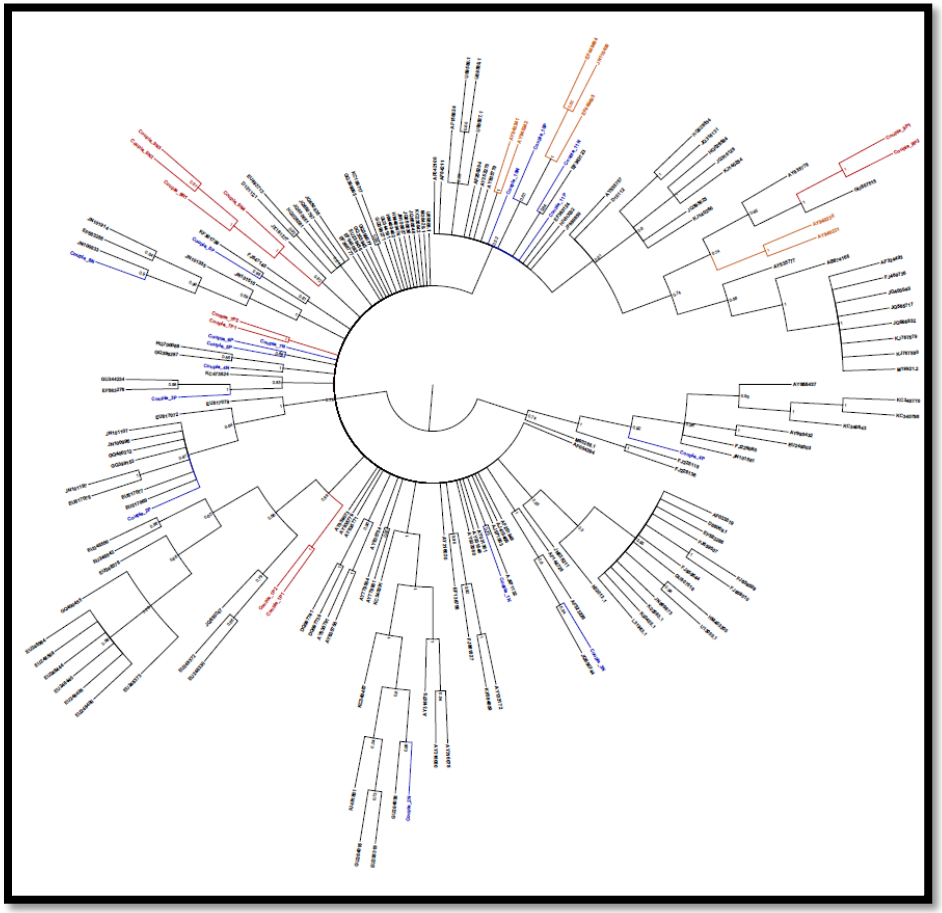
HIV Negative Partners: Characteristics

	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

PARTNER

HIV Transmissions and Phylogenetic Tree of *pol* sub B Sequences

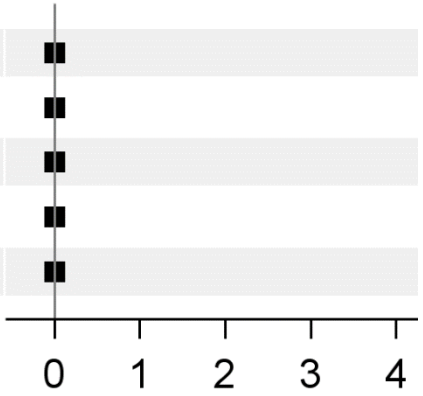
- 11 initially HIV-negative partners (10 MSM) became HIV-1 infected, but **zero** phylogenetically linked transmissions.
- Viral sequences recovered from all couples, comprising 22/22 (100%) for *pol* and 20/22 (91%) for *env*.
- None of the partners' sequences (blue) clustered together.
- The controls (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).



Ref: Rodger et al, JAMA, 2016

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
Any sex	99.7	1238
Vaginal sex	60.6	629
Anal sex	52.9	522
Insertive anal sex	42.1	417
Receptive anal sex with ejaculation	21.4	166



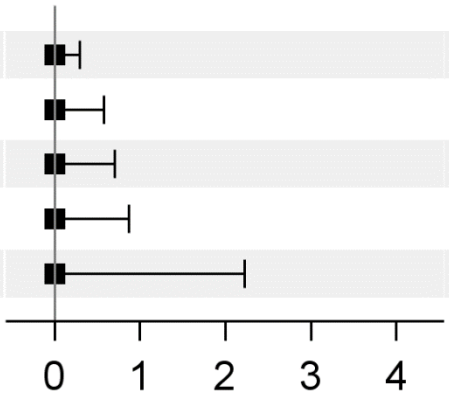
1166 enrolled couples, 888 eligible (548 HT, 340 MSM)
1238 CYFU with >56,000 CL sex acts

- 36,000 Heterosexual CL sex acts
- 22,000 MSM CL sex acts

Ref: Rodger et al, JAMA, 2016

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



Rate of Within-Couple Transmission, per 100 Couple-Years of Follow-up

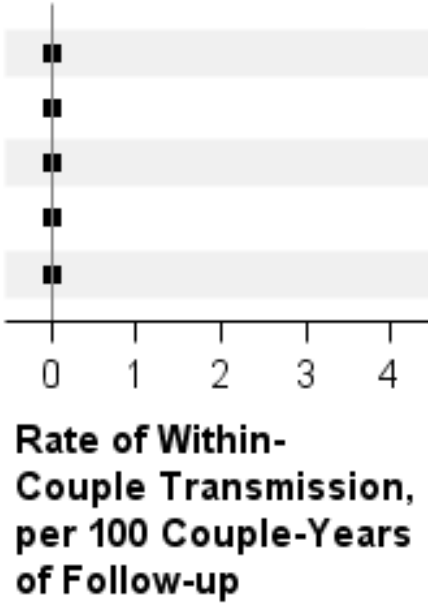
1166 enrolled couples, 888 eligible (548 HT, 340 MSM)
1238 CYFU with >56,000 CL sex acts

- 36,000 HT CL sex acts
- 22,000 MSM CL sex acts

Ref: Rodger et al, JAMA, 2016

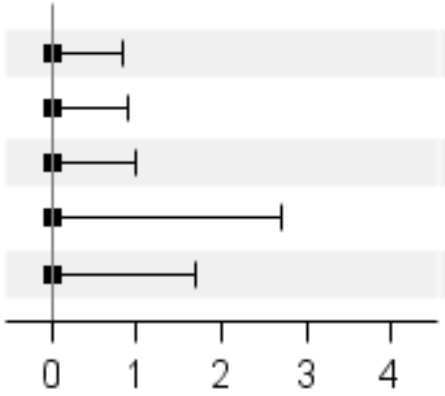
Rate of HIV transmission in MSM according to sexual behaviour reported by the negative partner – MSM couples

	% of Eligible Couples Reporting Specific Sex Act	Couple-Years of Follow-up
Any sex	100	439
Anal sex	99.7	415
Insertive anal sex	92.1	370
Receptive anal sex with ejaculation	45.0	137
Receptive anal sex without ejaculation	67.0	220



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



PARTNER 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 condomless 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 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

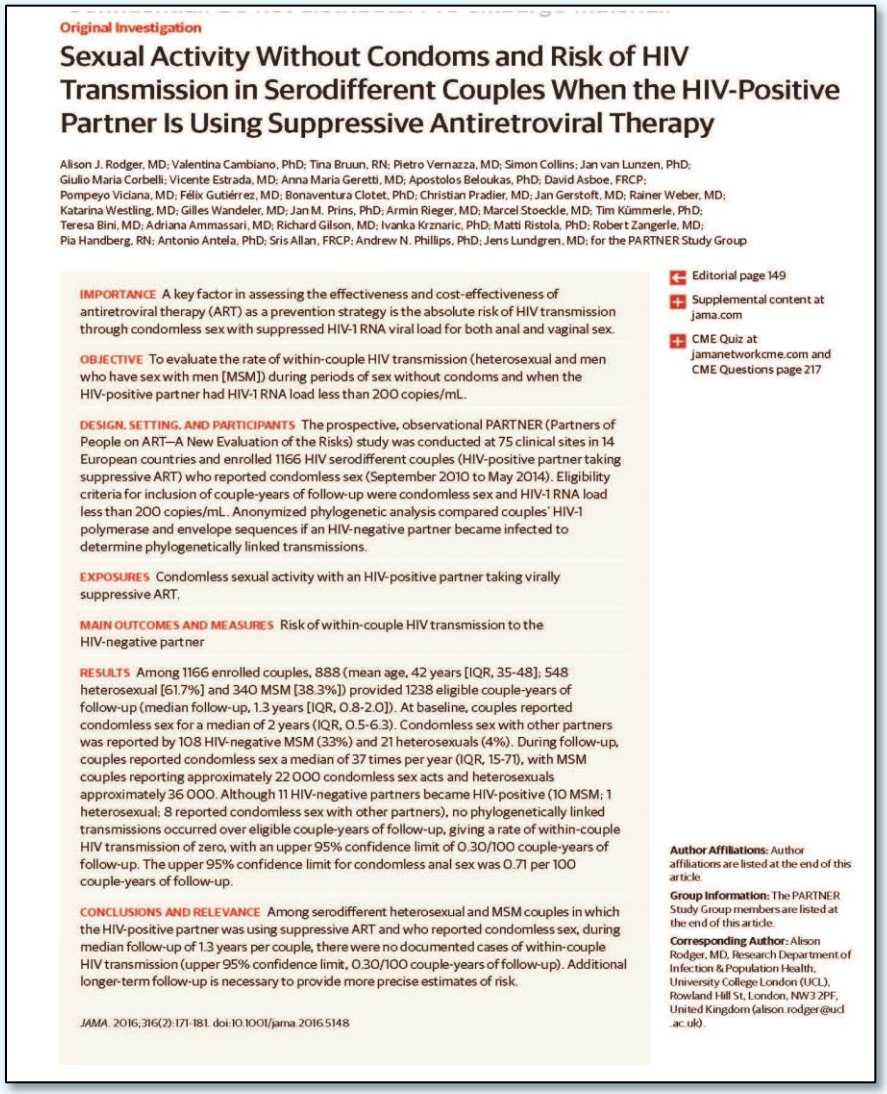
Ref: Rodger et al, JAMA, 2016

What is the Message from PARTNER for PLWH?

- The study message is risk of HIV transmission is, in the worst case scenario, *negligible* via condom-less vaginal sex and is *extremely low* for condom-less anal sex provided the HIV+ person is on fully suppressive ART for >6 months and maintains full adherence.
- The study is ongoing in gay men to improve precision around estimates for the risk from anal sex
- We will never be able to prove the risk is absolutely zero.
- However, the study also demonstrates that if you are HIV negative and have sex without condoms you may become HIV infected if you are unaware of sexual partners HIV and ART status. Condoms or PreP will reduce the risk of this.
- Condoms will also reduce the risk of transmission of other STIs.

Communications/dissemination plan

- Funding agencies EXPECT you to present your data at national/international conferences and publish your findings in peer-reviewed journals… (this is what you are supposed to do as an academic!)
- Identify NOVEL means of disseminating your findings to a wider audience than just your close colleagues
- PPI support for your study invaluable for dissemination i.e. for PARTNER, Simon Collins (iBase), Guilio Corbelli (EATG)
- Opportunities for effective dissemination may come from unlikely places....



Original Investigation

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

Alison J. Rodger, MD; Valentina Cambiano, PhD; Tina Bruun, RN; Pietro Vernazza, MD; Simon Collins; Jan van Lunzen, PhD; Giulio Maria Corbelli; Vicente Estrada, MD; Anna Maria Geretti, MD; Apostolos Beloukas, PhD; David Asboe, FRCP; Pompeyo Viciana, MD; Félix Gutiérrez, MD; Bonaventura Clotet, PhD; Christian Pradier, MD; Jan Gerstoft, MD; Rainer Weber, MD; Katarina Westling, MD; Gilles Wandeler, MD; Jan M. Prins, PhD; Armin Rieger, MD; Marcel Stoeckle, MD; Tim Kümmerle, PhD; Teresa Bini, MD; Adriana Ammassari, MD; Richard Gilson, MD; Ivanka Krznaric, PhD; Matti Ristola, PhD; Robert Zangerle, MD; Pia Handberg, RN; Antonio Antela, PhD; Sris Allan, FRCP; Andrew N. Phillips, PhD; Jens Lundgren, MD; for the PARTNER Study Group

IMPORTANCE A key factor in assessing the effectiveness and cost-effectiveness of antiretroviral therapy (ART) as a prevention strategy is the absolute risk of HIV transmission through condomless sex with suppressed HIV-1 RNA viral load for both anal and vaginal sex.

OBJECTIVE To evaluate the rate of within-couple HIV transmission (heterosexual and men who have sex with men [MSM]) during periods of sex without condoms and when the HIV-positive partner had HIV-1 RNA load less than 200 copies/mL.

DESIGN, SETTING, AND PARTICIPANTS The prospective, observational PARTNER (Partners of People on ART—A New Evaluation of the Risks) study was conducted at 75 clinical sites in 14 European countries and enrolled 1166 HIV serodifferent couples (HIV-positive partner taking suppressive ART) who reported condomless sex (September 2010 to May 2014). Eligibility criteria for inclusion of couple-years of follow-up were condomless sex and HIV-1 RNA load less than 200 copies/mL. Anonymized phylogenetic analysis compared couples' HIV-1 polymerase and envelope sequences if an HIV-negative partner became infected to determine phylogenetically linked transmissions.

EXPOSURES Condomless sexual activity with an HIV-positive partner taking virally suppressive ART.

MAIN OUTCOMES AND MEASURES Risk of within-couple HIV transmission to the HIV-negative partner

RESULTS Among 1166 enrolled couples, 888 (mean age, 42 years [IQR, 35-48]; 548 heterosexual [61.7%] and 340 MSM [38.3%]) provided 1238 eligible couple-years of follow-up (median follow-up, 1.3 years [IQR, 0.8-2.0]). At baseline, couples reported condomless sex for a median of 2 years (IQR, 0.5-6.3). Condomless sex with other partners was reported by 108 HIV-negative MSM (33%) and 21 heterosexuals (4%). During follow-up, couples reported condomless sex a median of 37 times per year (IQR, 15-71), with MSM couples reporting approximately 22 000 condomless sex acts and heterosexuals approximately 36 000. Although 11 HIV-negative partners became HIV-positive (10 MSM; 1 heterosexual; 8 reported condomless sex with other partners), no phylogenetically linked transmissions occurred over eligible couple-years of follow-up, giving a rate of within-couple HIV transmission of zero, with an upper 95% confidence limit of 0.30/100 couple-years of follow-up. The upper 95% confidence limit for condomless anal sex was 0.71 per 100 couple-years of follow-up.

CONCLUSIONS AND RELEVANCE Among serodifferent heterosexual and MSM couples in which the HIV-positive partner was using suppressive ART and who reported condomless sex, during median follow-up of 1.3 years per couple, there were no documented cases of within-couple HIV transmission (upper 95% confidence limit, 0.30/100 couple-years of follow-up). Additional longer-term follow-up is necessary to provide more precise estimates of risk.

JAMA. 2016;316(2):171-181. doi:10.1001/jama.2016.5148

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Supplemental content at jama.com

CME Quiz at Jamanetworkcme.com and CME Questions page 217

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The PARTNER Study Group members are listed at the end of this article.

Corresponding Author: Alison Rodger, MD, Research Department of Infection & Population Health, University College London (UCL), Rowland Hill St, London, NW3 2PF, United Kingdom (alison.rodger@ucl.ac.uk).

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AJ Rodger and Coauthors

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

Published July 12, 2016

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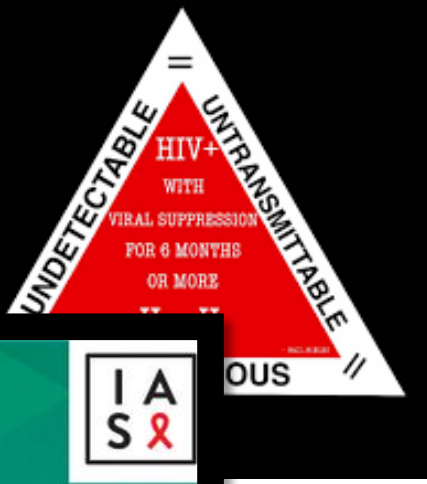
The JAMA Network

"The results provide a dataset to question whether transmission with an undetectable viral load is actually possible. They should help normalise HIV and challenge stigma and discrimination.

The results challenge criminalisation laws that in many countries, including the US, continue to imprison hundreds of people based on assumptions of risk that these results disprove, even when condoms are used and viral load is undetectable.

The results will also have a positive impact on quality of life of both HIV positive and HIV negative individuals who are in serodifferent relationships, irrespective of their choice to use condoms.

This study generated an unprecedented level of interest, the greatest ever for an i-Base report, reflecting the importance of these results to people living with HIV."



"The scientific evidence is clear. Someone whose HIV is undetectable does not pose an infection risk to their sexual partners."

For information on HIV you can rely on: www.aidsmap.com #UequalsU

U=U Undetectable Equals Untransmittable

Final thoughts

- Get involved: network, apply to go to conferences, form collaborations with other centres and investigators, apply to be sites in larger studies.
- When developing your own studies
  - Think about what questions are relevant to you and your clinical practice, read widely, brainstorm with colleagues
  - Get patient and community involvement from the start, think about dissemination
  - You need a team, you can't do it all yourself, but work with people who contribute (and answer emails!)
  - Apply for funding, even small amounts
  - Identify the tasks, the subtasks, the outputs, the timelines - and who is taking responsibility for delivery of each component
- Good communication and good management are key to the successful organisation of your study. It helps if you are good with people, good at motivating a team, can pay attention to detail but also see the bigger picture, can adapt to change, and can work to budgets…. Good Luck!

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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.

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