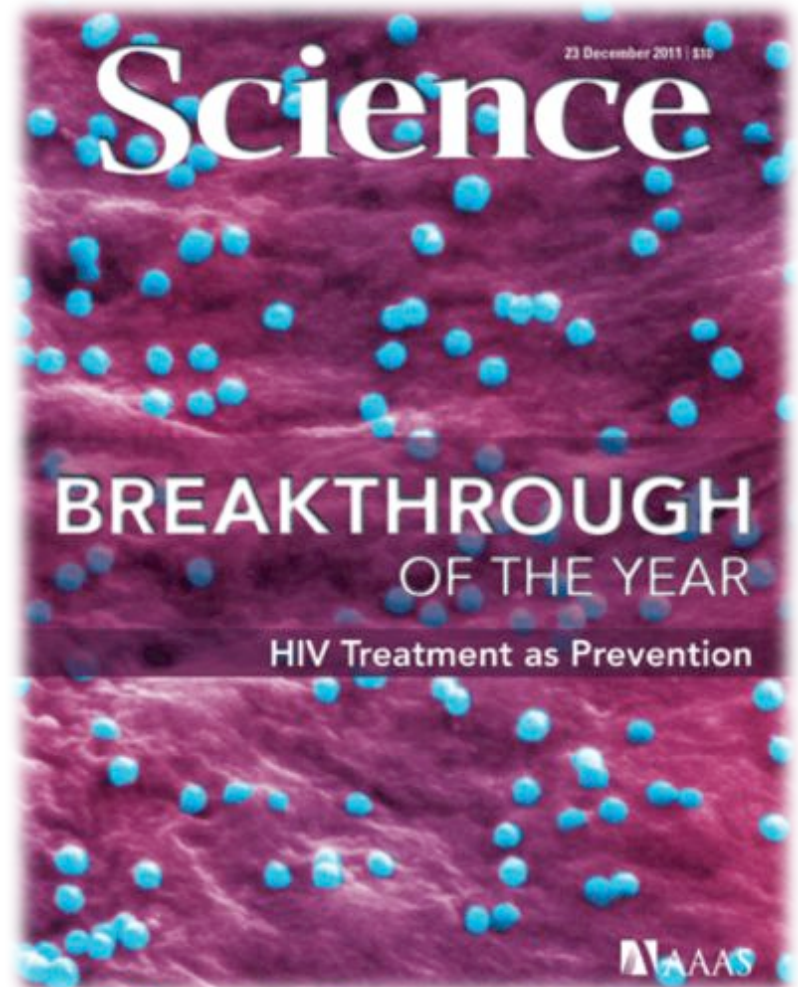
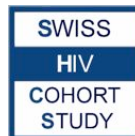


6 ans après "l'avis Suisse": Où en est-on ?

Enos Bernasconi

Service des maladies infectieuses
Département de médecine interne
Lugano et Genève

Mont Saint Michel, 21-02-2014



Disclosure

- Advisory boards and speaker's bureau:
BMS, Boehringer Ingelheim, Gilead, Janssen, MSD, ViiV Healthcare, and Pfizer
- Research grants: Gilead, MSD
- A special thank to Pietro Vernazza who kindly provided several slides

Population des villes de Suisse au 1er janvier 2011

300'001 et +

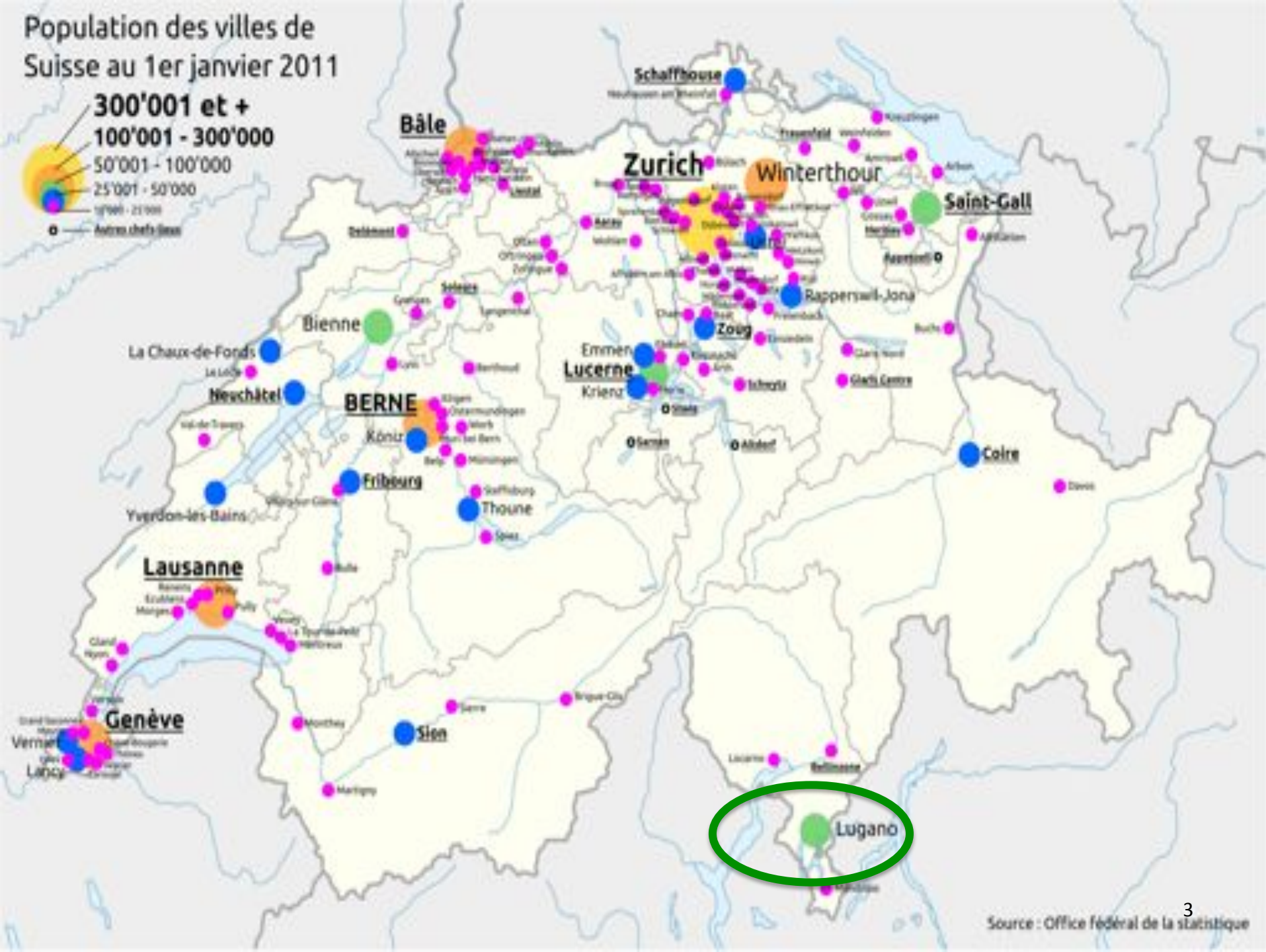
100'001 - 300'000

50'001 - 100'000

25'001 - 50'000

10'001 - 25'000

Autres chefs-lieux



Outline

- A brief recall: The Swiss statement
- Review of the literature after 2008
- Hot (and less hot) topics
 - Procreation without barriers
 - Sex between MSM
 - Break of condom and other accidents



At the beginning...
there was the
“Swiss statement”

Background of the Swiss statement

- Increasing evidence for low risk on combined antiretroviral therapy (cART):
 - **Epidemiological data**
 - **Biological plausibility**
 - *Lack of case reports*

Une personne séropositive, suivant un traitement antirétroviral (TAR) et avec une virémie indétectable, ne transmet pas le VIH, par voie sexuelle

Validité de l'affirmation:

- 1) TAR appliqué “à la lettre” et suivi régulier par un médecin;
- 2) Charge virale en dessous du seuil de détection ≥ 6 mois (< 40 cp/ml);
- 3) Aucune autre maladie sexuellement transmissible (urétrite, syphilis...)

What the statement described

- It's ok to talk about risk estimates
- Under optimal conditions, risk is in the range of daily life („negligible“)
 - Long term maximal suppression
 - Perfect adherence, regular checks
 - Absence of STDs
- Only the informed partner can decide on condom use

Other “negligible” risk situations:

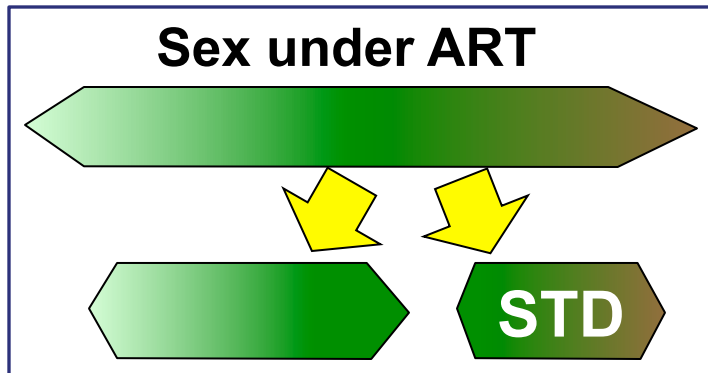
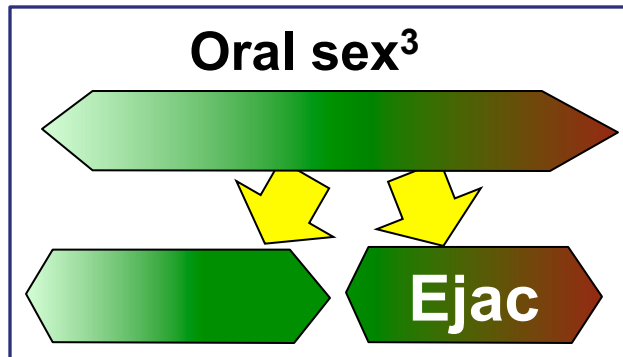
1. Condom-protected vaginal sex:
→ 0.9 / 100 py for always users

Davis, 1999, Fam Plan Perspectives

2. Receptive oral sex (MSM):
→ 0.0004 / act (= 1/2'500)

Vittinghoff, 1999, Am J. Epid

HIV transmission risks are fuzzy



¹Royce RA et al, 1997; ²Davis KR et al, 1999; ³Vittinghoff E et al, 1999

Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis

Deborah Donnell, Jared M Baeten, James Kiarie, Katherine K Thomas, Wendy Stevens, Craig R Cohen, James Mdntyre, Jairam R Lingappa, Connie Celum, for the Partners in Prevention HSV/HIV Transmission Study Team*

	Follow-up during which HIV-1 infected partner had not initiated ART			Follow-up after HIV-1 infected partner initiated ART		
	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)
Overall	102	4558	2.24 (1.84-2.72)	1	273	0.37 (0.09-2.04)
By CD4 cell count†						
<200 cells per µL	8	91	8.79 (4.40-17.58)	0	132	0.00 (0.00-2.80)
200-349 cells per µL	41	1467	2.79 (2.06-3.80)	1*	90	1.11 (0.27-6.19)
350-499 cells per µL	24	1408	1.70 (1.14-2.54)	0	30	0.00 (0.00-12.30)
≥500 cells per µL	29	1592	1.82 (1.27-2.62)	0	21	0.00 (0.00-17.57)

* HIV-neg 18 days after Tx start of index patient, but HIV-pos. at next visit (day 90)

Jorge Del Romero, clinical researcher,¹ Jesús Castilla, consultant medical epidemiologist,² Victoria Hernando, epidemiologist,³ Carmen Rodríguez, research scientist,¹ Soledad García, clinical researcher¹

Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study

Prevalence	Tx Index	
	No ART	cART
Partners (n)	476	149
Partner pos.	9.2%	0%*

*p<0.001

Incidence	Tx Index	
	No ART	cART
Partners (n)	341	144
Sex acts** (n)	11'000	>7000
Pregnancies	50	47
Seroconversions	5	0
s/c per sex act	0.0004	0
Upper 95%-CI	0.001	0.0005

** without condoms

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

AUGUST 11, 2011

VOL. 365 NO. 6

- 1 763 couples, one partner HIV+ and the other HIV negative; HIV+ with CD4+ counts between 350 and 500/ μ L
 - Randomization 1:1 to immediate ART (early) or after CD4+ declined below 250/ μ L
 - After a median follow up of 1.7 years, 38 HIV transmissions, 28 virologically linked to the infected partners
- Only 1 transmission in the early therapy group
= **96% reduction of transmission risk**

HPTN 052: HIV-1 Transmission

>6 Months of therapy

Study Arm	Follow-up (PY)*	Incidence/100PY [95% CI]	
		Linked	> 6 Mth Th
Immediate	1585 / 1145	0.1 [0.0 – 0.4]	0.0 [0.0 – 0.3]
Delayed	1567	1.7 [1.1 – 2.5]	

*Person-years specific for transmission events

Median follow-up: 1.7 (1.1) years

HIV transmission in serodiscordant hetero couples: ART not protective?

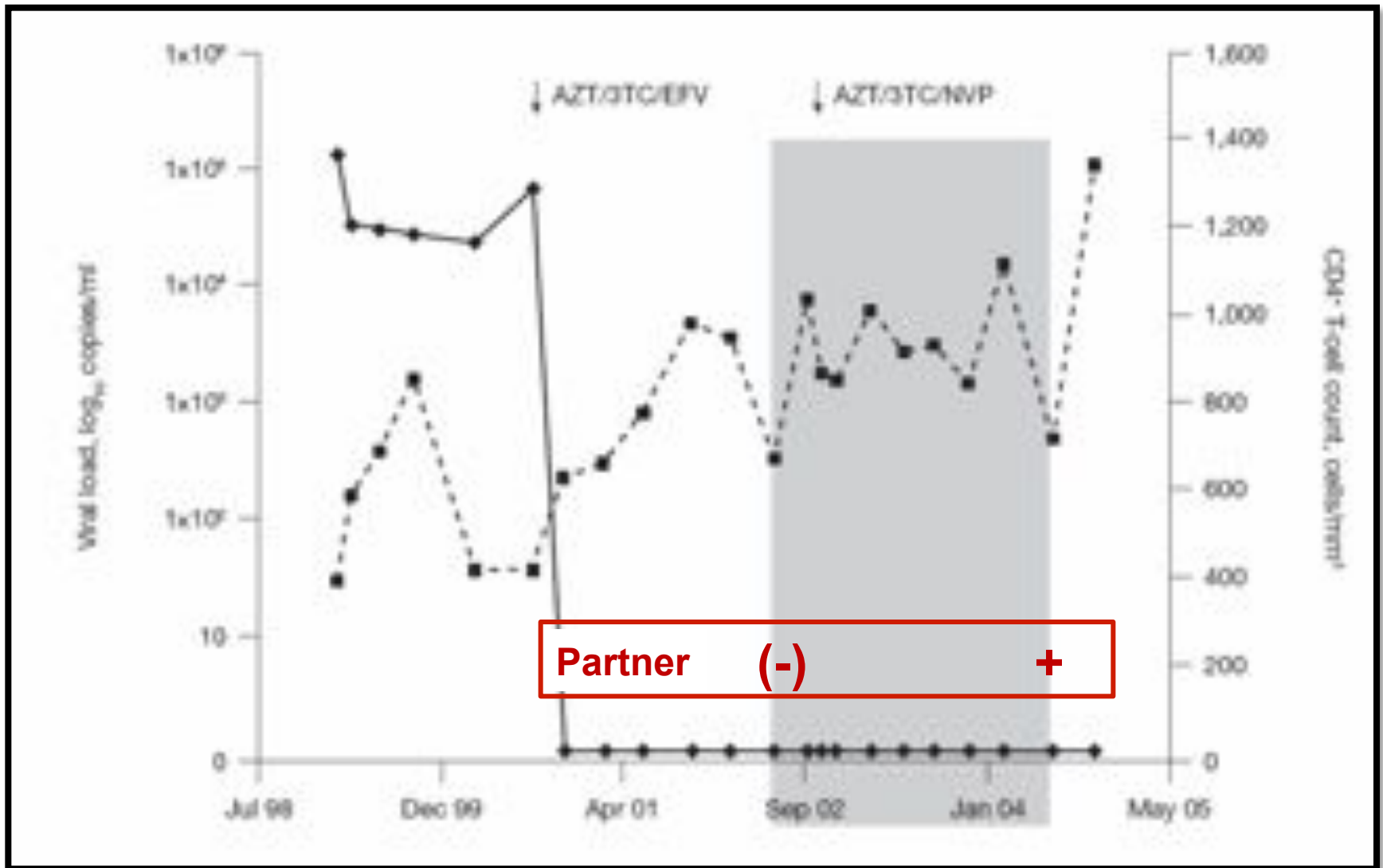
1927 (57% men) initially HIV-negative spouses in Zhumadian city, Henan, China
(Study period: Jan 2006 – Dec 2008; 4918 person-years of follow-up time)

	Did NOT seroconvert	Did seconvert	RR (95%) univariable	RR (95%) multivariable
AIDS diagnosis				
YES	1583	73	1.0 (0.53-1.89)	
NO	260	11	1.0	
On ART				
YES	1303	66 = 4.8 %	1.32 (0.78-2.22)	
NO	540	18 = 3.2 %	1.0	

But: No information on adherence to ART, viremia on treatment, and if HIV transmissions were linked to the stable partner or not

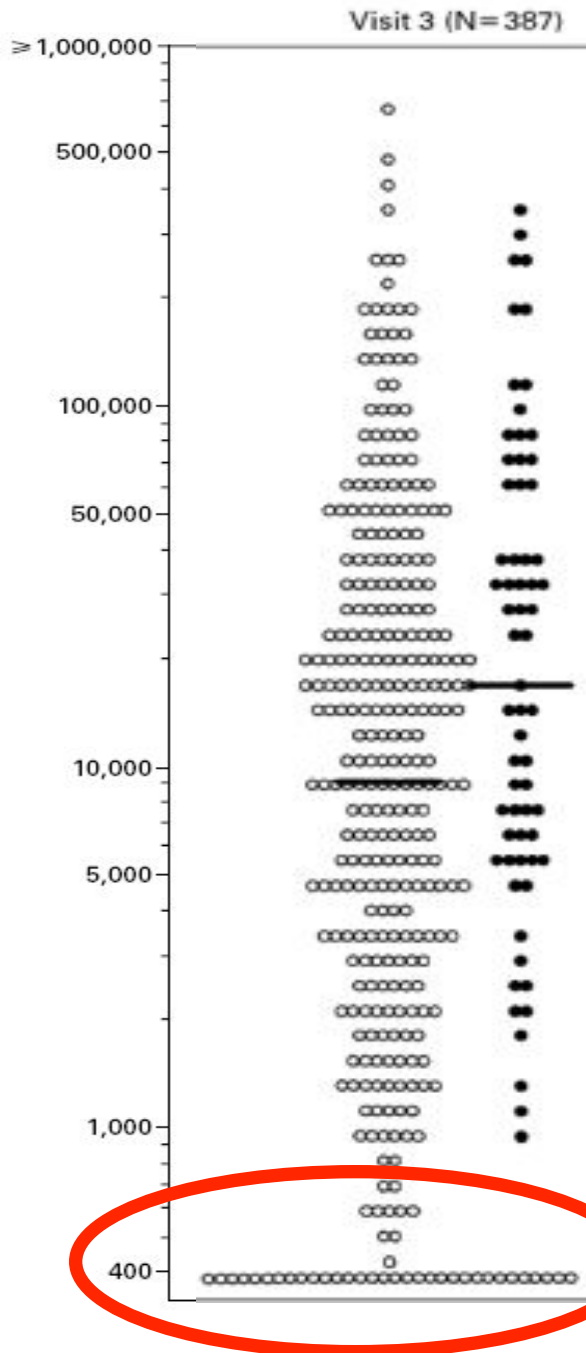
**The ultimate proof: Lack of reported
transmission on cART after 2008**

One swallow does not make a summer



Mr A and Mrs B are married and want to have a child. Mrs B is 35 year old and has an HIV infection stage CDC A1 with CD4+ count of 650/uL, VL 12'350 copies/mL. Because of the high CD4+ count she didn't started a treatment yet.

Your are asked to counsel the pair on the best possible way to obtain a successful pregnancy and on the risk of HIV transmission to the child



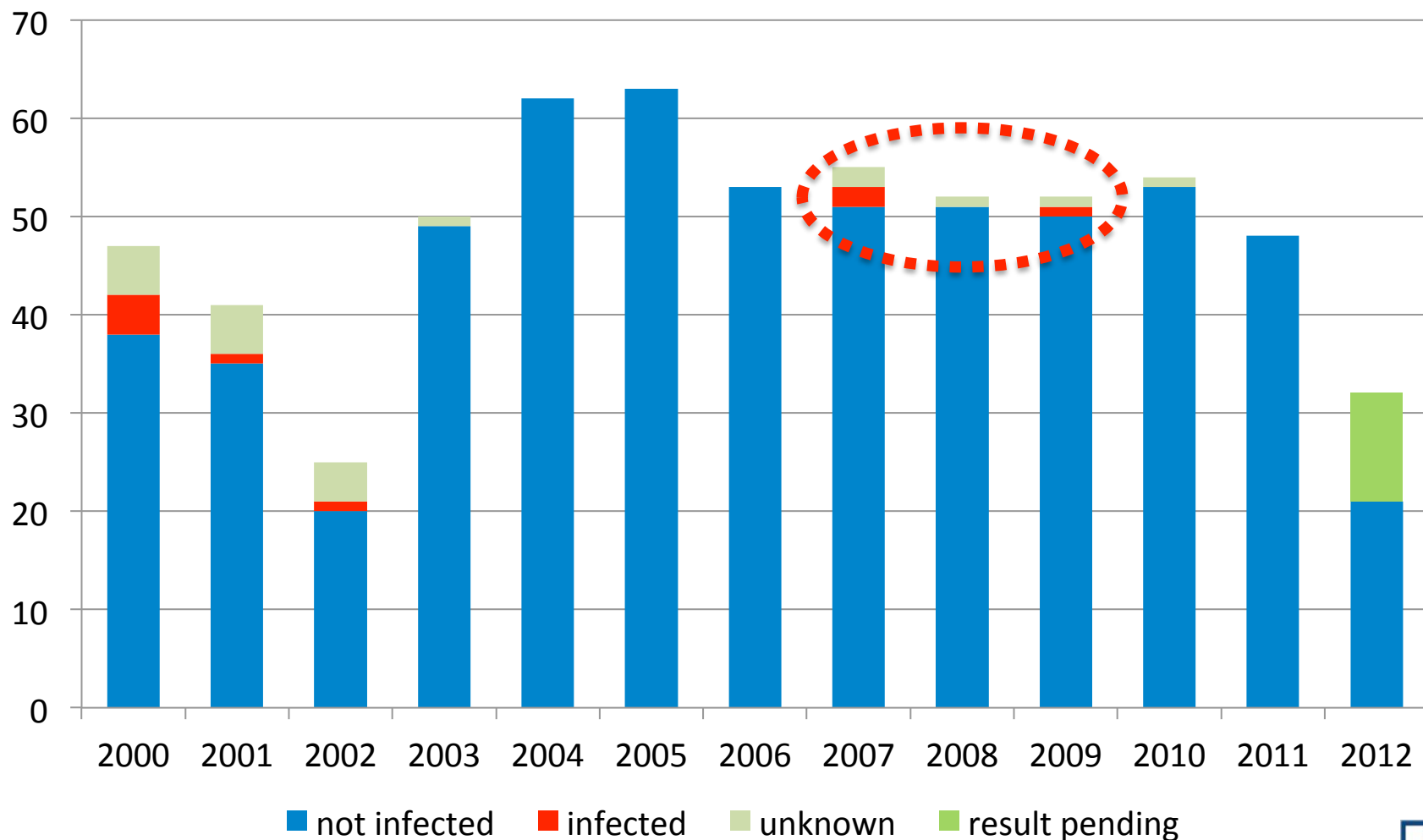
N Engl J Med 1999;341:394-402

Maternal levels of plasma HIV RNA and the risk of perinatal transmission

PATRICIA M. GARCIA, M.D., M.P.H., LESLIE A. KALISH, D.Sc., JANE PITT, M.D., HOWARD MINKOFF, M.D.,
THOMAS C. QUINN, M.D., SANDRA K. BURCHETT, M.D., JANET KORNEGAY, Ph.D., BROOKS JACKSON, M.D.,
JOHN MOYE, M.D., CELINE HANSON, M.D., CARMEN ZORRILLA, M.D., AND JUDY F. LEW, M.D.,
FOR THE WOMEN AND INFANTS TRANSMISSION STUDY GROUP*

No HIV transmission if
VL < 1000/ml
(with or without zidovudine)

Mother to child transmission



MoChiV cohort, 2013

Counselling activity

- The triple value of ART in this situation:
 - Possibility of natural procreation
 - Protection against mother to child transmission of HIV
 - Early ART may be of interest even for the mother's health
- The seronegative husband must be involved in the discussion and he has the last word on natural procreation

**CONCEPT OF EQUIPOISE*:
INVOLVE PATIENTS WHEN
RISK IS MARGINAL**

***equilibre clinique**

HC-Provider – Patient relationship

- Knows a lot
- Informs patient



Paternalistic concept



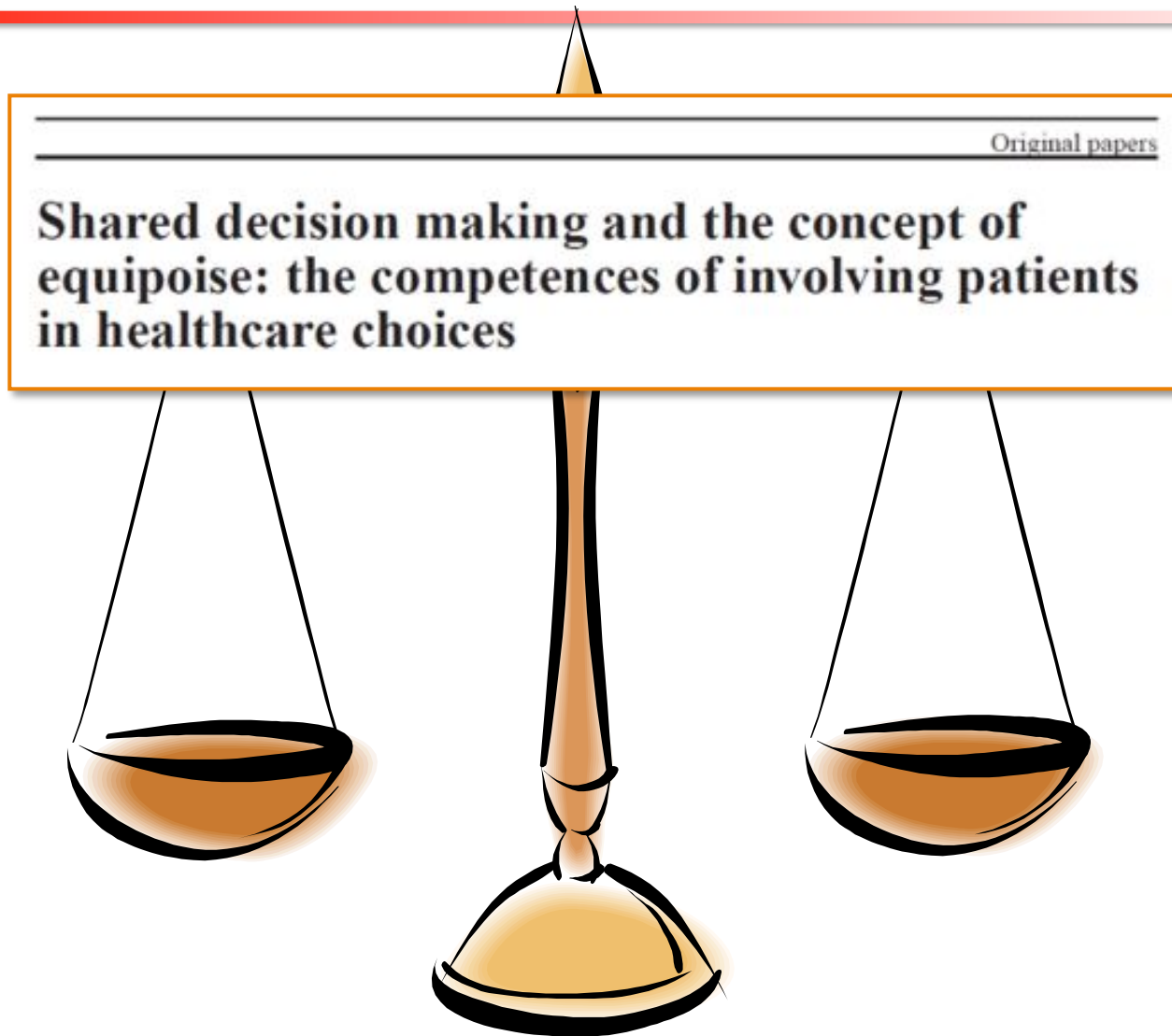
HC-Provider – Patient relationship

I know some, but not
what's best for **you**

→ **Equipoise**



The ethical dilemma of equipoise



HC-Provider – Patient relationship

Equipoise

I know some, but not
what's best for **you**



Shared
decision
making



PRISE EN CHARGE MÉDICALE DES PERSONNES VIVANT AVEC LE VIH

Procréation naturelle

La place de la procréation naturelle a fortement évolué du fait des progrès des traitements antirétroviraux et des données récentes sur les risques de transmission. En pratique, la situation diffère selon que le couple utilise systématiquement ou non les préservatifs et selon le membre du couple qui est infecté par le VIH.

La procréation naturelle est désormais considérée comme une alternative à l'AMP.

...but not all agree with the Swiss and French approach

Future perspective: The combination of SW-IUI and PrEP around the time of the luteinizing hormone surge in well-selected, monogamous HIV-serodiscordant couples is likely to be a less expensive, safe and efficacious alternative to IVF-ICSI in the US

SW-IUI: sperm washing with intrauterine insemination

IVF-ICSI: *in vitro* fertilization with intracytoplasmic sperm injection

Fertility treatment options for HIV-infected individuals

Chantae S Sullivan-Pyke¹, Sahadat K Nurudeen¹, Lisa C Grossman¹, Mark V Sauer¹ & Nataki C Douglas^{*1}

¹Columbia University, Department of OB-GYN, Division of Reproductive Endocrinology & Infertility, 622 W 168th Street, PH-16, New York, NY 10032, USA



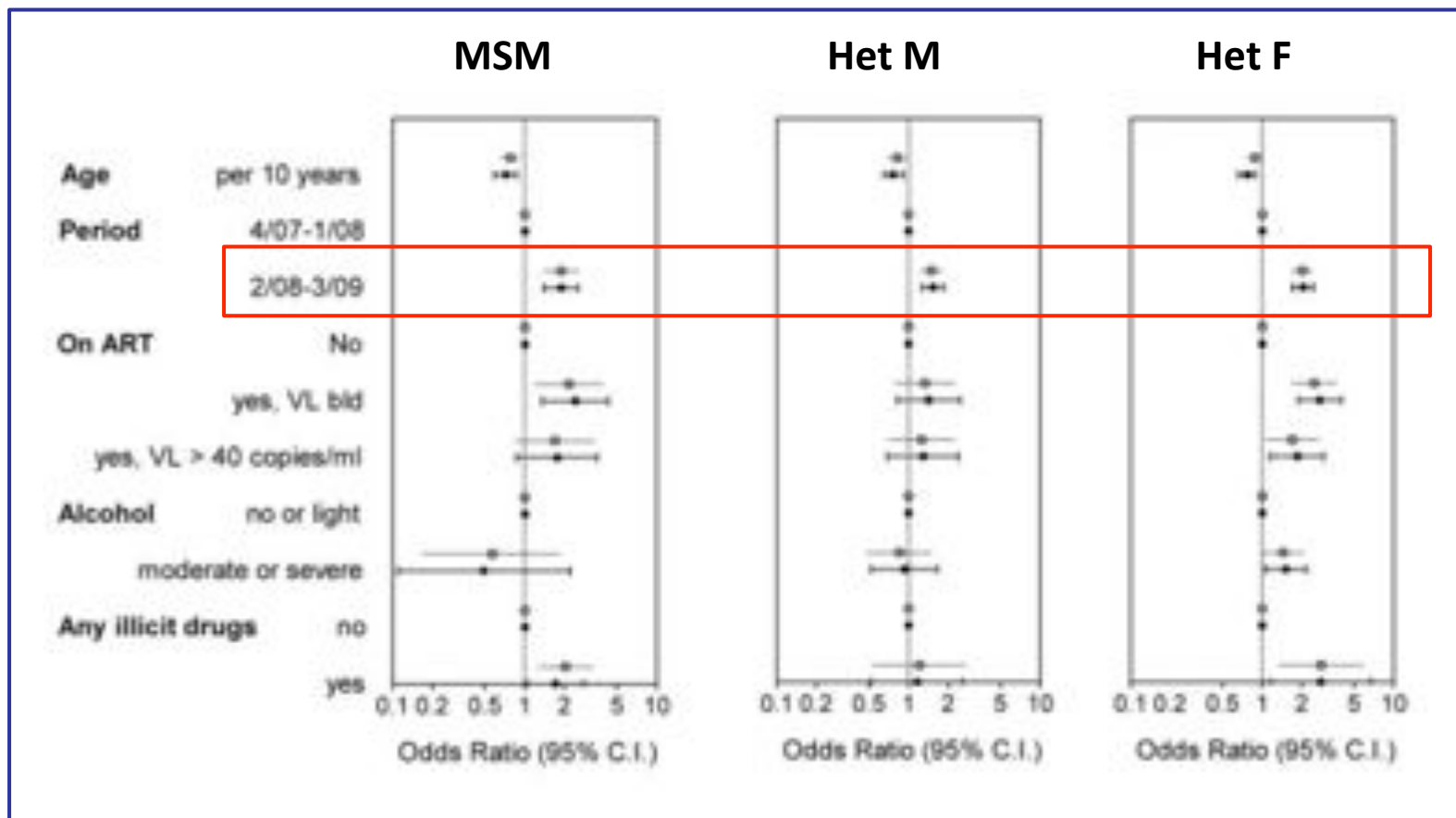
2013 !!

Mr A and Mr B, a homosexual pair for more than 3 years, have always had anal intercourse with condom. In fact, Mr B is HIV positive, on ART for more than 5 years with undetectable viremia at every regular check for at least 4 years. Both guys have sometime other sexual partners (anal sex always with condom).

Your are asked to counsel the pair on the risk of non protected sexual intercourse in their particular situation

Unprotected Sex in SHCS after the Swiss statement

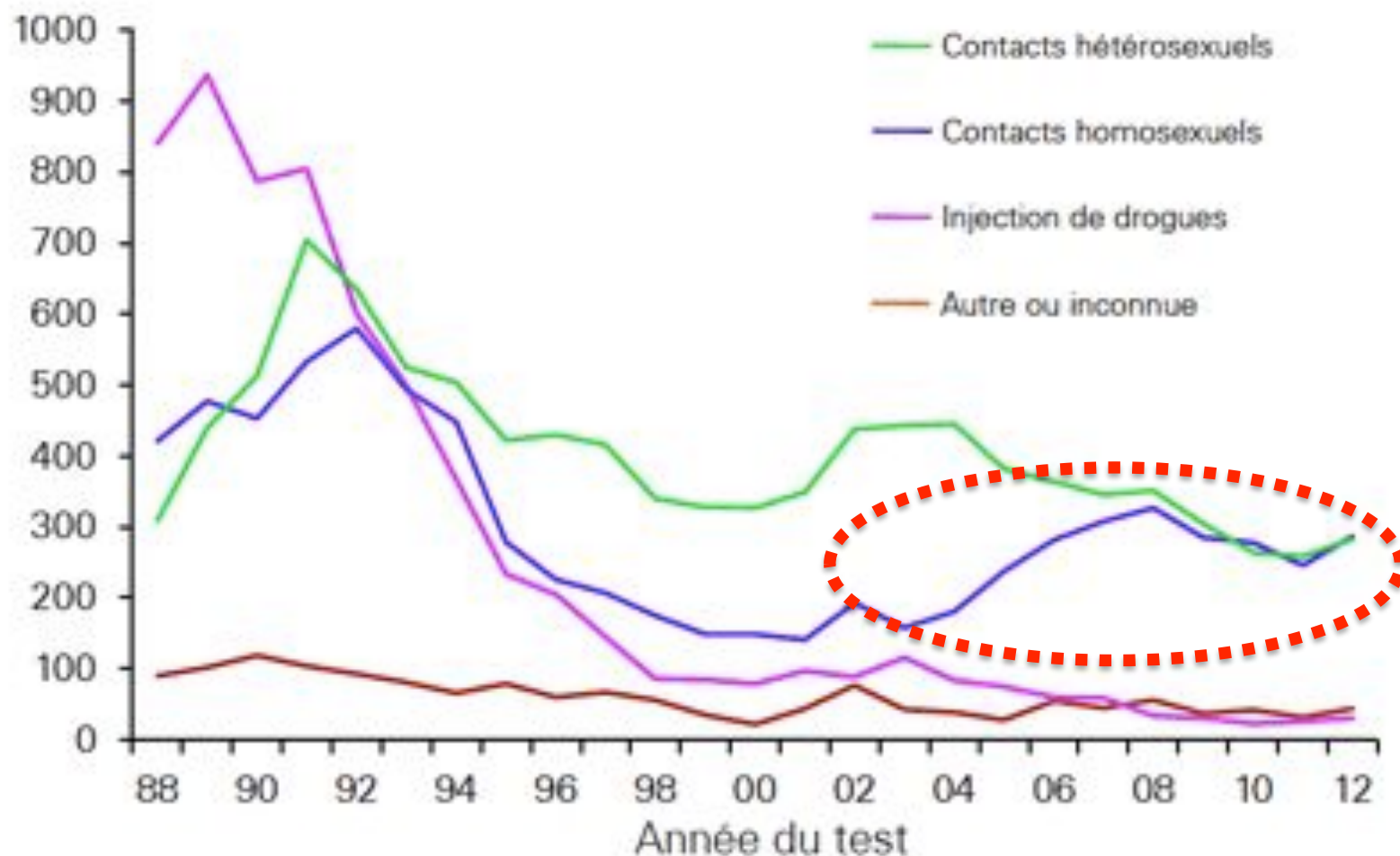
More reports of sex w/o condom



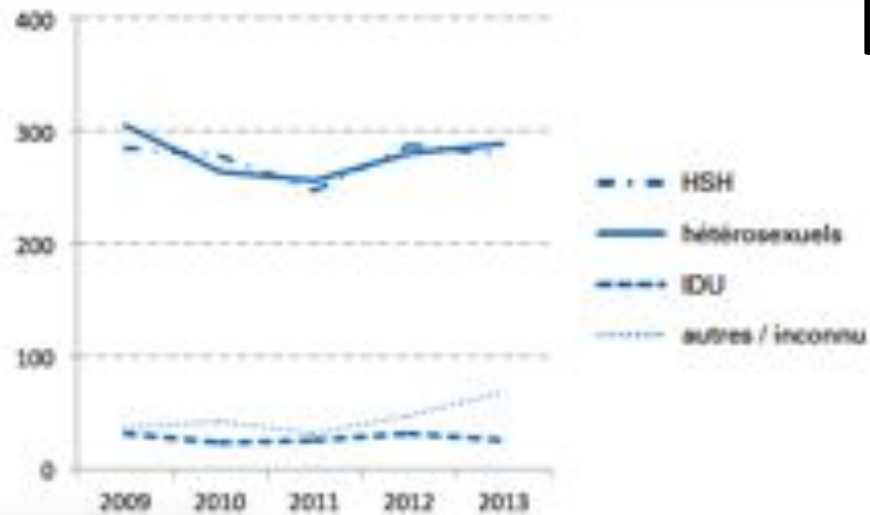


VIH en Suisse

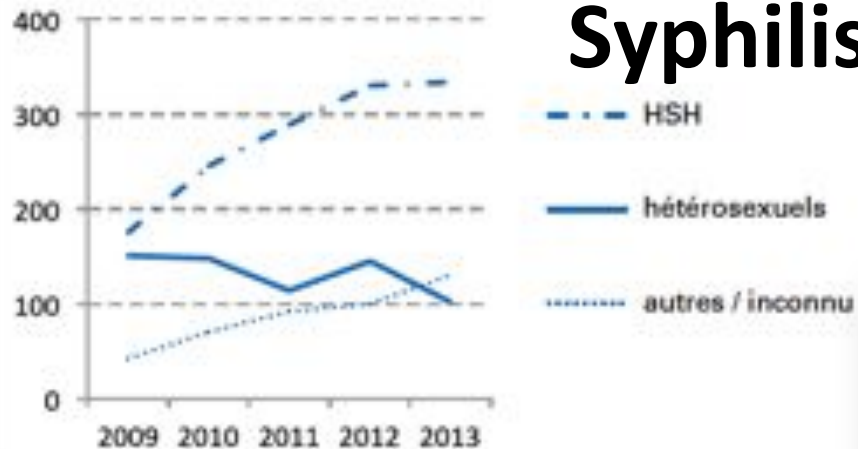
Nombre des nouveaux diagnostics d'infection par le VIH selon la voie d'infection, par année du test (estimation statistique basée sur les déclarations des laboratoires et des médecins)



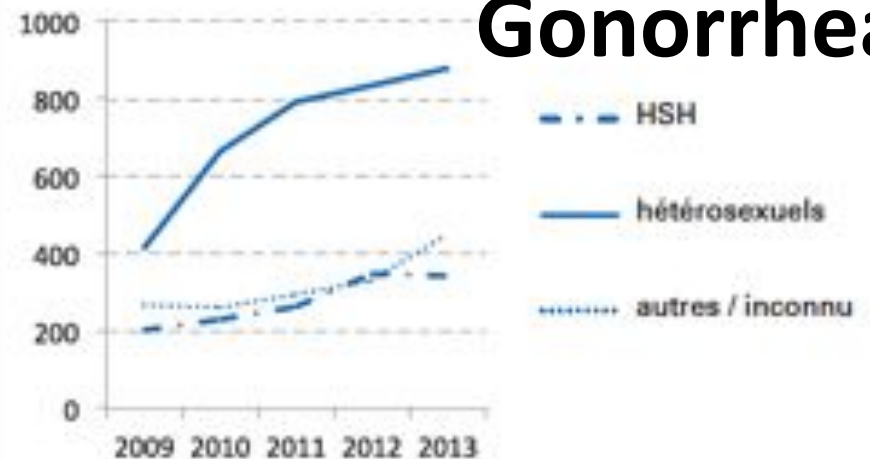
HIV



Syphilis



Gonorrhea



Counselling activity

- Swiss statement does teoretically apply to MSM serodiscordant couple, but risk of other STDs has to be considered in this situation
- Lack of controlled studies and limited number of data from observational studies
- Do not forget to involve the seronegative partner



ORIGINAL RESEARCH

Discordance in HIV-1 concentrations compared to plasma

G Lorello,¹ C la Porte,^{1,2,3} R Pilon,⁴ G Zhang,² T Kan...
¹Faculty of Medicine, University of Ottawa, Ottawa, Canada, ²Public Health, Infectious Diseases, Ottawa Hospital, Canada, ³Public Health, Children's Hospital of Eastern Ontario, Ottawa, Canada



MAJOR ARTICLE

Elevated Cervical White Blood Cell Inflammation Is Associated with Cervical Infection



OPEN ACCESS Freely available online



HIV-DNA in the Genital Tract of Women on Long-Term Effective Therapy Is Associated to Residual Viremia and Previous AIDS-Defining Illnesses

Thierry Prazuck^{1,2}, Antoine Collin...



JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2009, p. 2883–2887
0095-1137/09/\$08.00+0 doi:10.1128/JCM.02131-08
Copyright © 2009, American Society for Microbiology. All Rights Reserved.

Determining Seminal Plasma Human Immunodeficiency Virus Type 1 Load in the Context of Efficient Highly Active Antiretroviral Therapy

Christophe Pasquier,^{1,2,3,*} Karine Sauné,^{1,2,3} Stéphanie Raymond,^{1,2,3} Nathalie Moinard,⁴ Myriam Daudin,⁴ Louis Bujan,⁴ and Jacques Izopet^{1,2,3}
Service de Virologie, CHU de Toulouse, Institut Fédératif de Biologie, Toulouse F-31059, France¹; INSERM, U563, Centre de Physiopathologie de Toulouse Purpan, Toulouse F-31300, France²; Facultés de Médecine et de Pharmacie, Université Toulouse III Paul Sabatier, Toulouse F-31400, France³; and Human Fertility Research Group, Université Toulouse III Paul Sabatier (EA 3694) and CECOS Midi-Pyrénées, CHU de Toulouse, Hôpital Paule de Viguier, Toulouse F-31059, France⁴

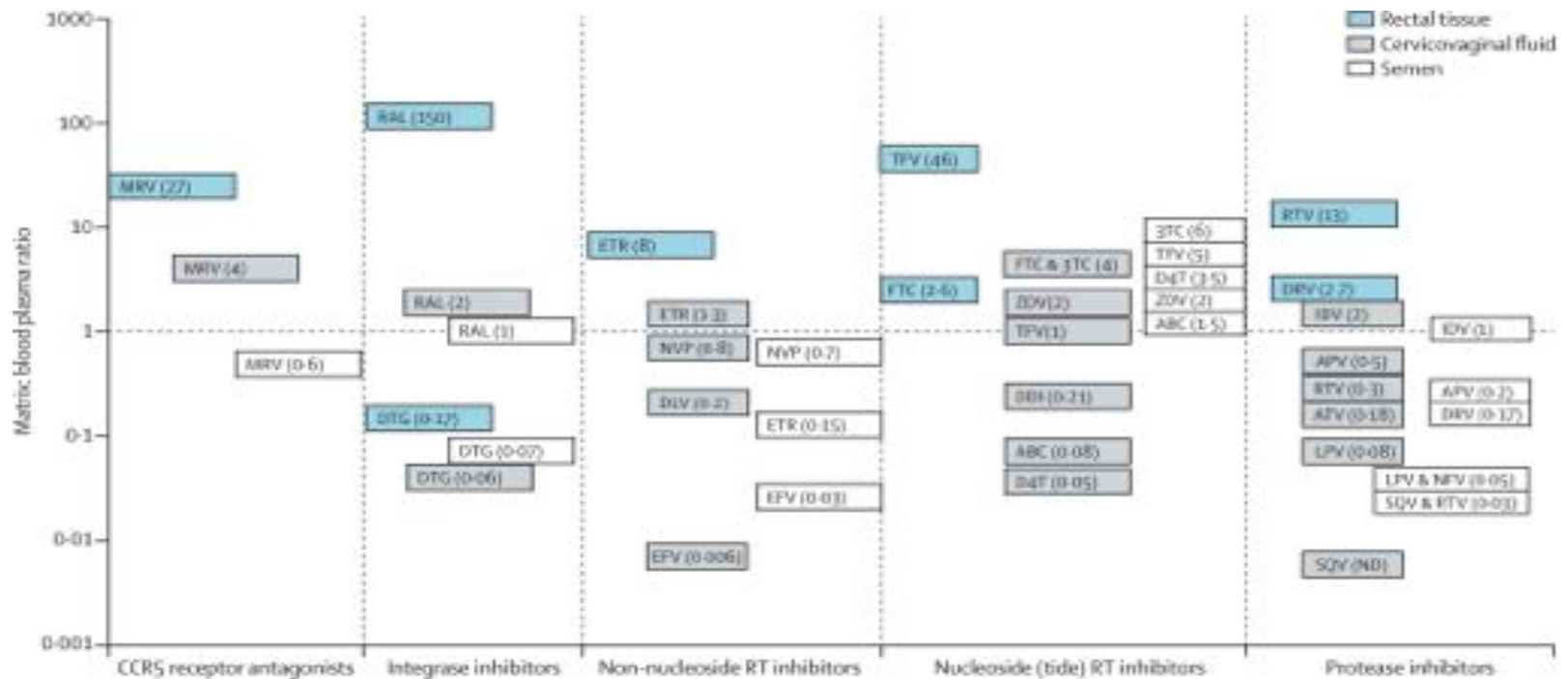


Figure 2 Comparison of antiretroviral exposure at mucosal surfaces
 Seminal plasma, cervicovaginal fluid, and colorectal tissue exposure is plotted as a ratio relative to matched blood plasma exposure. The Y axis is on a log scale.

Facts on HIV in genital fluids on ART

- Methods for the measurement of viral load in semen, vaginal, cervical, and rectal fluids are not standardised
- Most persons on fully suppressive ART have undetectable HIV-RNA in genital fluids (GF)
- HIV RNA and DNA found in GF on ART is usually at low level (cut off for transmission unknown)
- Risk factors for positive HIV RNA/DNA in GF: Inflammation, presence of Lc; drug penetration in genital fluids?
- Presence of replication competent and infectious virus not demonstrated

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.

We know that condoms are the safest and most effective way of protecting against transmission. But we also know that not everyone uses a condom every time.

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 (CHP), in collaboration with University College London (the sponsor) and The Royal Free Hampstead NHS Trust, London.

Study Coordinating Centre contact:

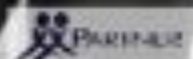
Tina Bruun, RN
Study Coordinator
Copenhagen HIV Programme
University of Copenhagen,
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Fax: +45 35 45 57 58

www.partnerstudy.eu

For information in your country,
please contact:

HIV Treatment
Sexual
Transmission
Condom
Use

The PARTNER
Study:
a new study for
sero-discordant
couples



www.partnerstudy.eu

Kindly provided by P. Vernazza

Mr A comes to the emergency room at 02.30. Two hours before he had receptive anal intercourse with Mr B with condom, but at the end of intercourse the condom broke with probable exposure to seminal fluid. Mr B is well known at the outpatient clinic of your hospital: He has been on ART for more than 10 years. As you can verify online, his viremia was always undetectable (last check 6 weeks before).

You must decide on providing or not Mr A with postexposure prophylaxis for HIV

Risk for acquiring HIV infection: occupational vs. sexual exposure

- Occupational (needle stick injury) 0.3%
- **Unprotected receptive anal intercourse 0.8-3.2%**
- Unprotected receptive vaginal intercourse 0.05-0.15%
- Unprotected insertive anal intercourse 0.03-0.09%
- Use of a contaminated needle (IVDU) 0.67%

- Patient source VIH+ , non traité ou traité de manière inefficace, lors que:
 - Rapport sexuel vaginal/anal non protégé (p.ex. rupture d'un préservatif)
 - Fellation avec éjaculation dans la bouche
 - Recours au matériel d'injection déjà utilisé par une personne VIH+
- Exposition potentielle dans le cadre d'un viol (jusqu'à l'examen chez l'auteur du délit)
- Statut sérologique du patient source inconnu, mais la personne appartient à une région ou un groupe à haute prévalence d'infection par le VIH (p.ex. des personnes provenant de l'Afrique sous-saharienne, MSM, toxicomanes i.v.)

En général il n’y a pas d’indication pour une nPEP si:

- Statut sérologique du patient source inconnu (à l’exception des situations mentionnées plus haut)
- Patient **source infecté par le VIH, mais suivant une ART stable et efficace** (virémie indetectable)
- Morsure par une personne infectée par le VIH
- Blessure par une aiguille qui traîne

Swiss guidelines on non-oPEP

Publication year	1997	2006	2014
Interval (up to)	72h	72h	48h
How long	4 weeks	4 weeks	4 weeks
Drug(s)	AZT + 3TC +/- Indinavir	Lopinavir/rtv + AZT + 3TC	*Raltegravir + Tenofovir + FTC
Publisher	FKT (FOPH) > Bulletin	FKT (FOPH) > Bulletin	"AG1" (FOPH) > soon in Forum

***= Isentress 1-0-1, Truvada 1-0-0**

ORIGINAL RESEARCH

Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence* N = 86

J McAllister,¹ P Read,^{2,3} A McNulty,^{2,4} WWY Tong,¹ A Ingersoll¹ and A Carr¹

¹HIV, Immunology & Infectious Diseases Unit, St Vincent's Hospital, Sydney, Australia, ²Sydney Sexual Health Centre, Sydney Hospital, Sydney, Australia, ³The Kirby Institute, University of New South Wales, Sydney, Australia and

⁴School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia

- **92% completion rate**
- **89% adherence rate**
- **Avoidance of potential DDI**



Merci pour l'attention!