Training Course in Sexual and Reproductive Health Research 2013

Module: Principles and Practice of Sexually Transmitted Infections Prevention and Care

The Synergy between HIV and other STIs

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Sexual Transmission of HIV

- Accounts for 75-85% of HIV infections worldwide
- Heterosexual transmission is the major cause in developing nations, and is the most rapidly increasing subset in US and Europe
- Homosexual transmission continues among MSM in developed countries

HIV/STD Connections Background

- Similar behaviors transmit HIV and STIS
- Potential interactions between HIV and STDs are multiple and complex

Source of HIV shedding in the female genital tract

HIV replicates in the genital associated lymphoid tissue consisting of cervical stroma lymphocytes.

And is present in cervical secretions.

Coombs RW, AIDS, 2003; 17:455

Source of HIV shedding in the male genital tract

Sperms considered to be virus free

Virus vehiculated by polinuclear cells, lymphocyte and macrophages, present also in seminal plasma

Very large between and within subject variations in semen composition

Main source seems to be the urethra

Timing of HIV shedding at genital sites

Longitudinal studies ranging from 8 to 10 weeks:

Men

Continuously detected	28 – 37%
Intermittently detected	39 – 44%
Never detected	24 – 28%

Coombs RW, JID, 1998; 177:320
Gupta P, JID 2000; 182: 79

Women

Continuously detected	29%
Intermittently detected	58%
Never detected	13%

Coombs RW, JID, 2001; 184:1187

Determinants of HIV load in genital secretions

Serum HIV viral load

Plasma RNA concentrations, both qualitatively and quantitatively were the most important factor (the only one at significancy level) predicting genital HIV-1 shedding in women

Kovacs A, Lancet 2001; 358: 1593

Sexual Transmission of HIV

- Risk of transmission is low after a single sexual contact
  - Receptive anal intercourse**: 0.8 - 3%**
  - Penile-vaginal intercourse:

    M to F = **0.05 - 0.15%**, F to M = **0.03 - 0.09%**
  - Oral intercourse: unclear, but **~ 10x lower** than vaginal intercourse
- Cofactors important in transmission

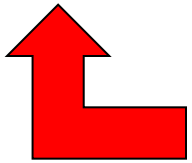
STIs are a cofactor of sexual transmission of HIV

Sexual transmission of HIV

$$Ro = \beta cD$$

Basic Reproductive rate

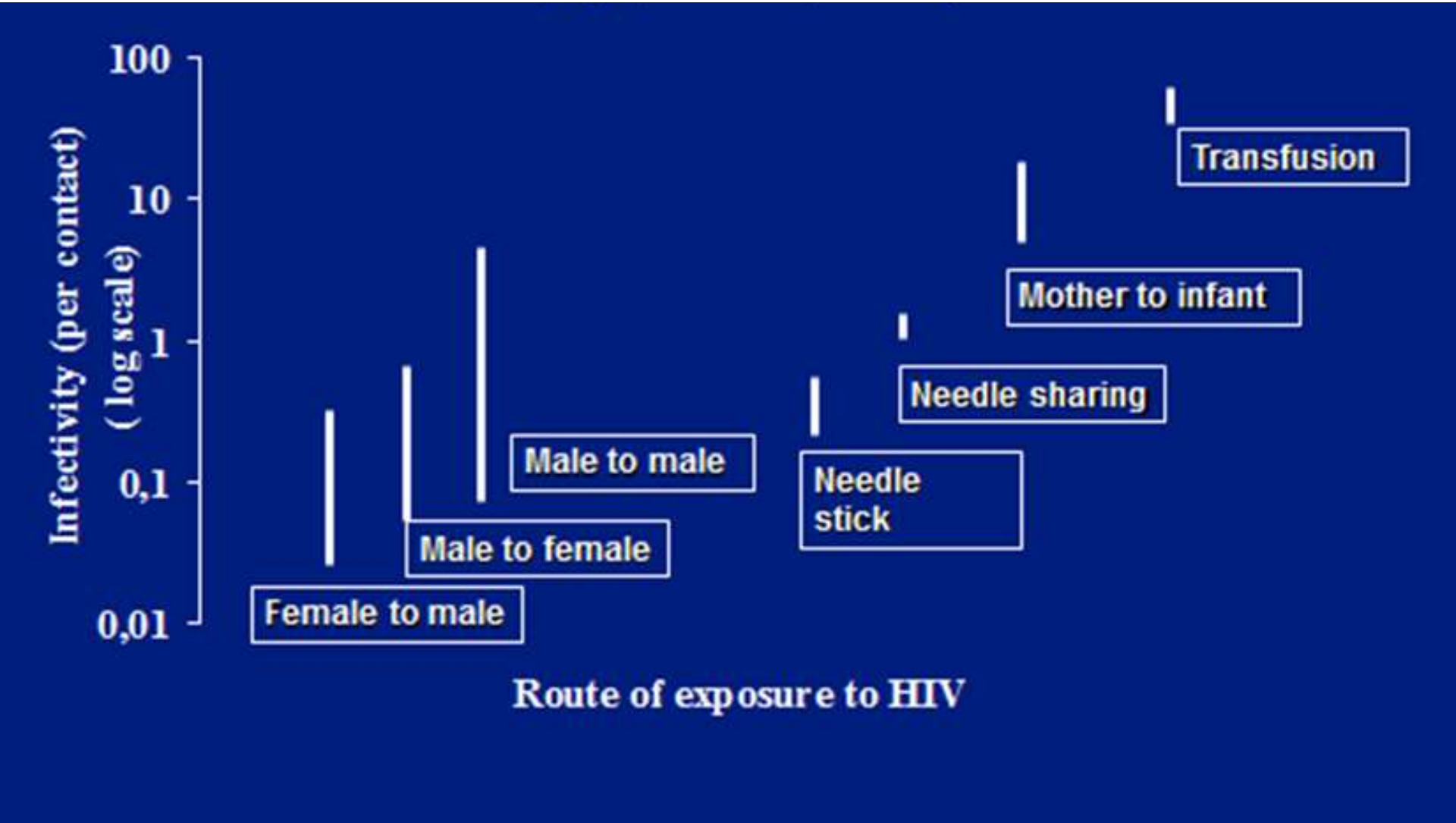
β		c		D
Probability of transmission of infection	X	**Rate of sex partner change**	X	**Duration of infectiousness**



STI as an enhancing co-factor

Per contact probability of HIV transmission

(Royce, NEJM 1997, 336: 1072)



The biological plausibility

Persons with an ulcerative or non-ulcerative STIs more susceptible to the HIV infection

- Disruption of normal epithelial barrier

- Increase in pool of lymphocytes and macrophages

STIs, both ulcerative and non-ulcerative, enhance HIV transmission

- Inflammatory STIs increase the HIV viral load in genital secretions

Biological Mechanisms for the STD Cofactor

Infectiousness:

- Inflammation increases HIV viral load in genital secretions
- HIV can be cultured from genital lesions such as ulcers of syphilis

Susceptibility:

- Breaks in epithelial barrier allow viral access
- Inflammation increases number and/or receptivity of target cells
- Enhancement of viral survival

Epidemiological evidence

Epidemiological evidence from longitudinal studies

Reference	Study population	STD studied	Relative risk
Cameron et al.	Heterosexual men, (Kenya)	Genital ulcer (mainly chancroid)	4.7
Darrow et al.	Homosexual men (U.S.A)	Syphilis	1.5-2.2
Holmberg et al.	Homosexual men (U.S.A)	Herpes	4.4
Laga et al.	Heterosexual women (Zaire)	Gonorrhoea Chlamydia infection Trichomoniasis	3.5 3.2 2.7
Stamm et al.	Homosexual men (U.S.A)	Herpes Syphilis	3.3-8.5 8.4-8.5

Metanalysis of 43 publications of observational studies of the risk of HIV-1 transmission per heterosexual contact

In **high income countries** (and absence of antiretrovirals) **risk is low**:

- female-to-male: 0.04% per act (0.01-0.14)
- male-to-female: 0.08% per act (0.06-0.11)

In **low income countries risk is higher** even in absence of commercial sex:

- female-to-male: 0.38% per act (0.13-1.10)
- male-to-female: 0.30% per act (0.14-0.63)

Boily MC, Lancet Infect Dis 2009; 9:118

Metanalysis of 43 publications of observational studies of the risk of HIV-1 transmission per heterosexual contact

The higher risk of transmission in low-income countries may be justified by the **higher prevalence of STI**

The effect of **gender** is largely counterbalanced by the **geographical setting** (male-to-female risk equal to female-to-male in low-income coutries)

Boily MC, Lancet Infect Dis 2009; 9:118

Metanalysis of 43 publications of observational studies of the risk of HIV-1 transmission per heterosexual contact

Effect of genital ulcers and circumcision on Relative Risk:

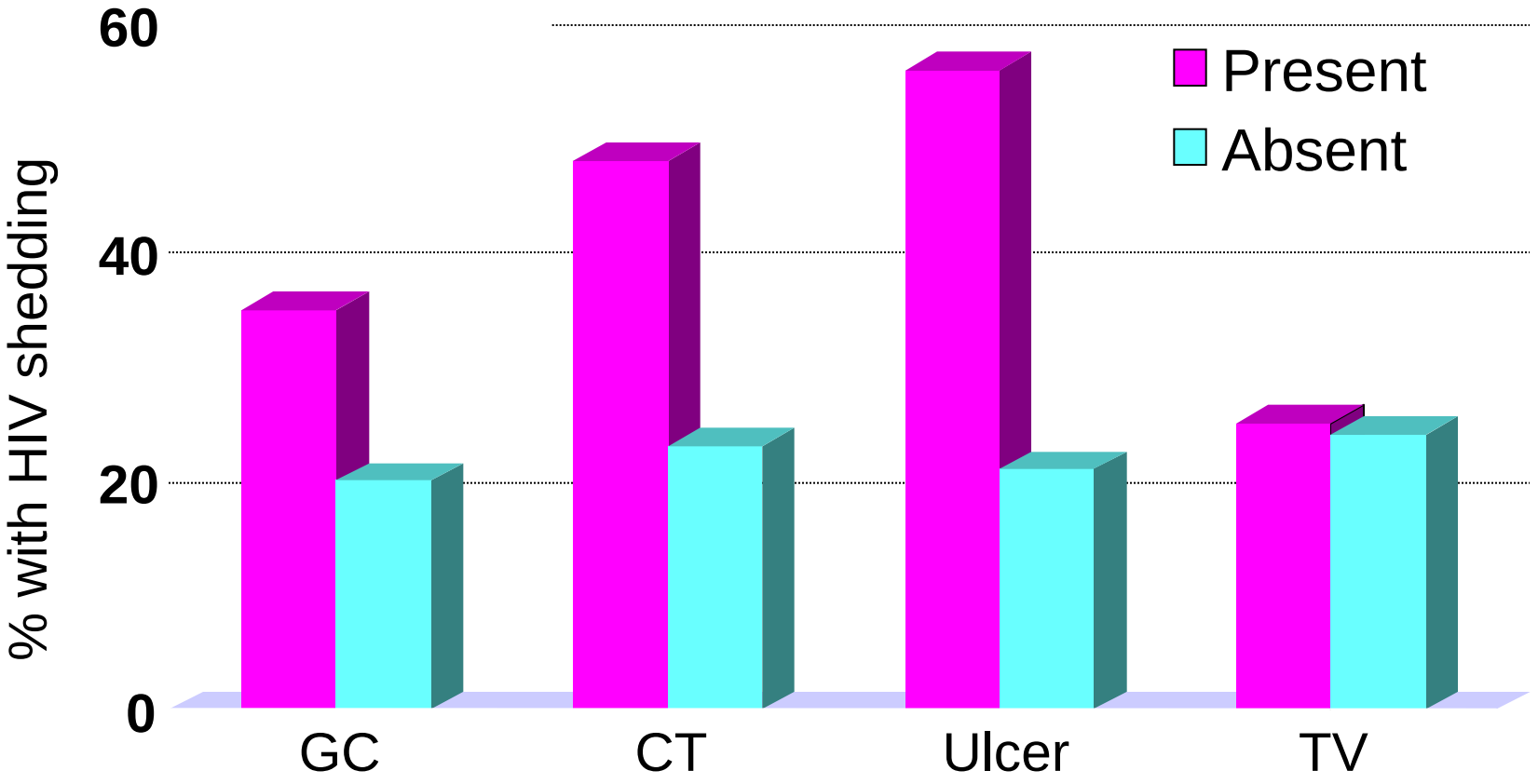
RR for the presence of **ulcers** 5.3 (1.4 – 19.5)

Circumcision reduces by two-fold the risk of infection

Boily MC, Lancet Infect Dis 2009; 9:118

HIV load in genital tract and STI

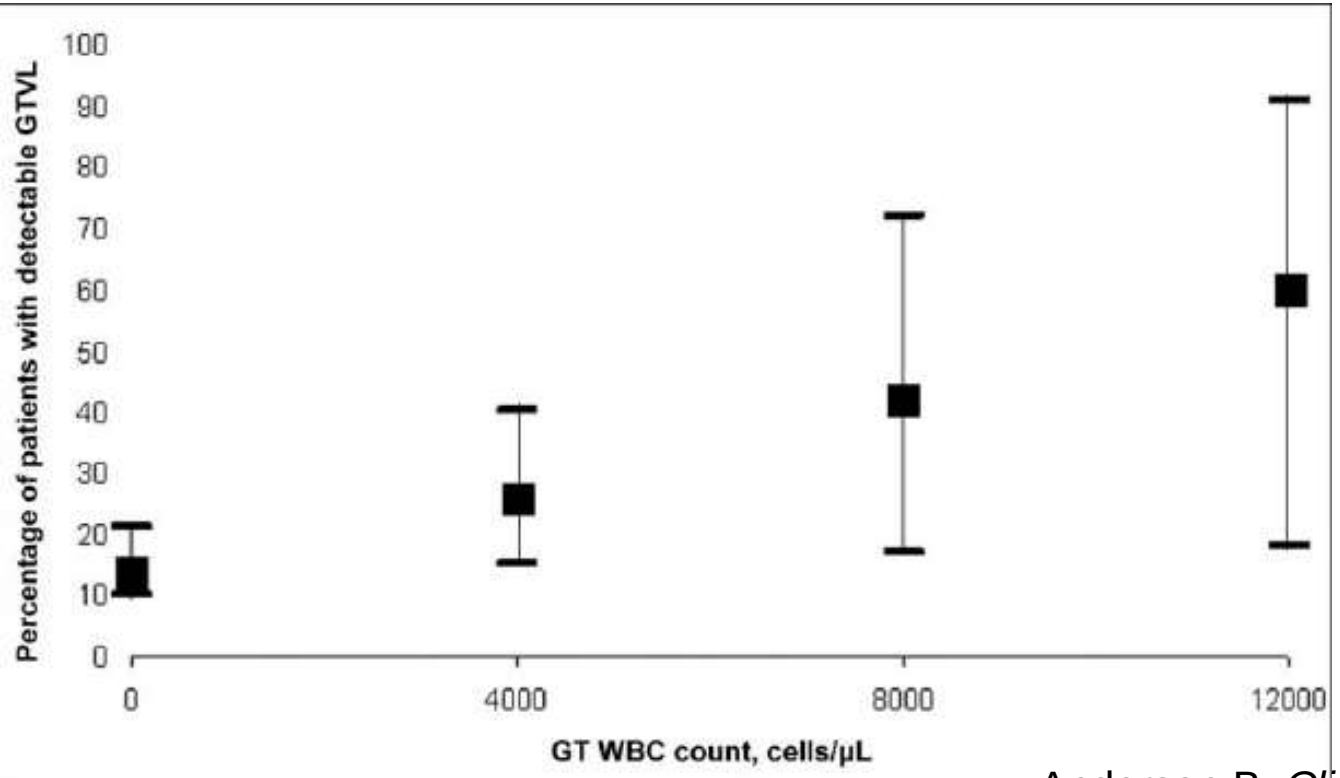
Association between presence of STI and cervico-vaginal shedding of HIV–1



From Ghys *et al.*, *AIDS,* 1997

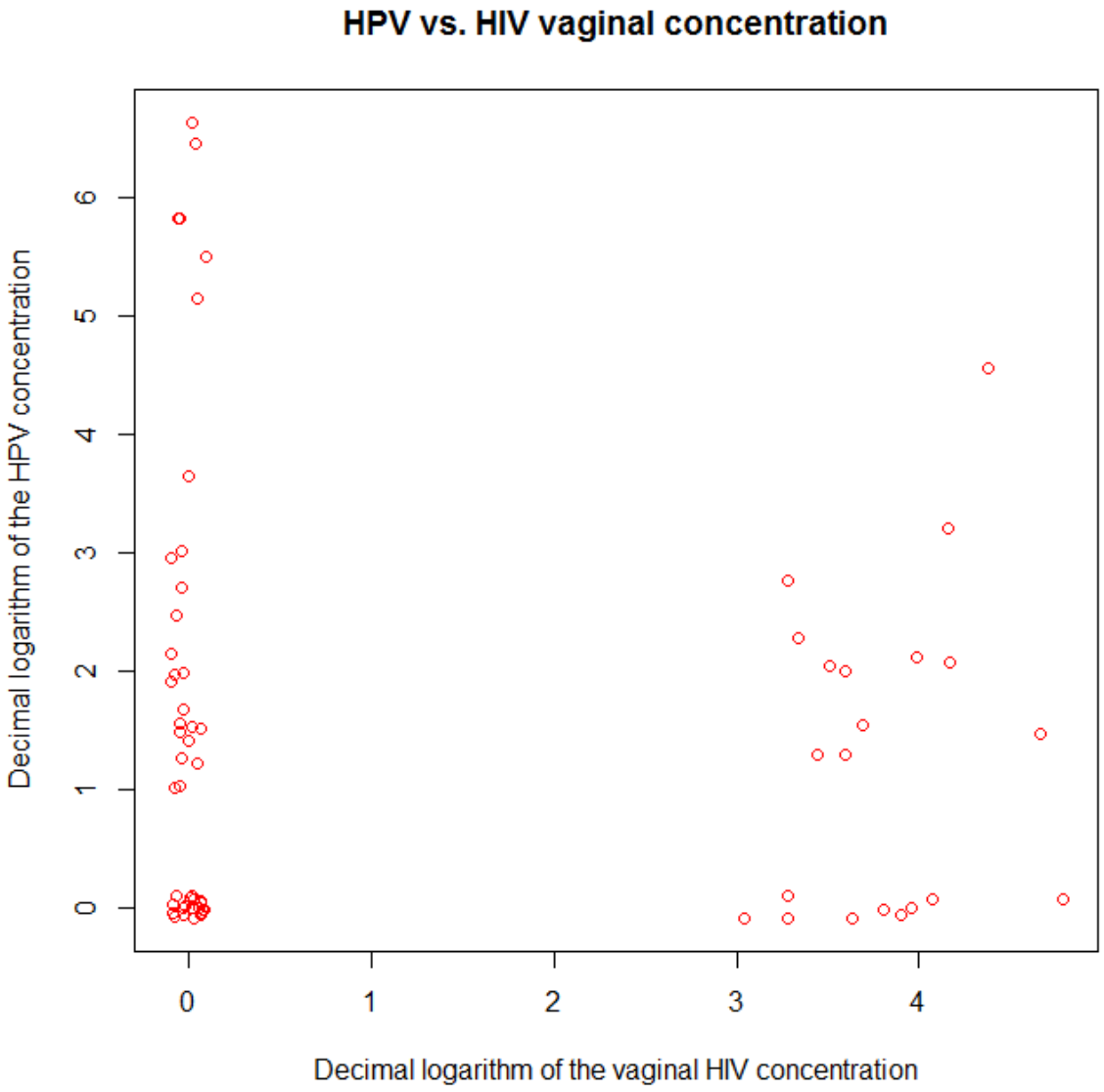
Genital tract leucocytes and shedding of genital HIV type 1 RNA

- The presence of GT WBCs in vaginal secretions predicts viral shedding independent of the presence of infections
- GT WBCs may be a surrogate marker for HIV infectiousness



Anderson B, *Clin Infect Dis* 2008; 47:1216-21

HPV cervical infection does not influence genital HIV shedding



Fornabaio C, et al. J AIDS, 2012

A recent HPV infection is associated with a higher risk of HIV acquisition *(local immune response to HPV may predispose to HIV infection)*

Table 3. Persistent and non-persistent HPV infection as predictors of HIV acquisition.

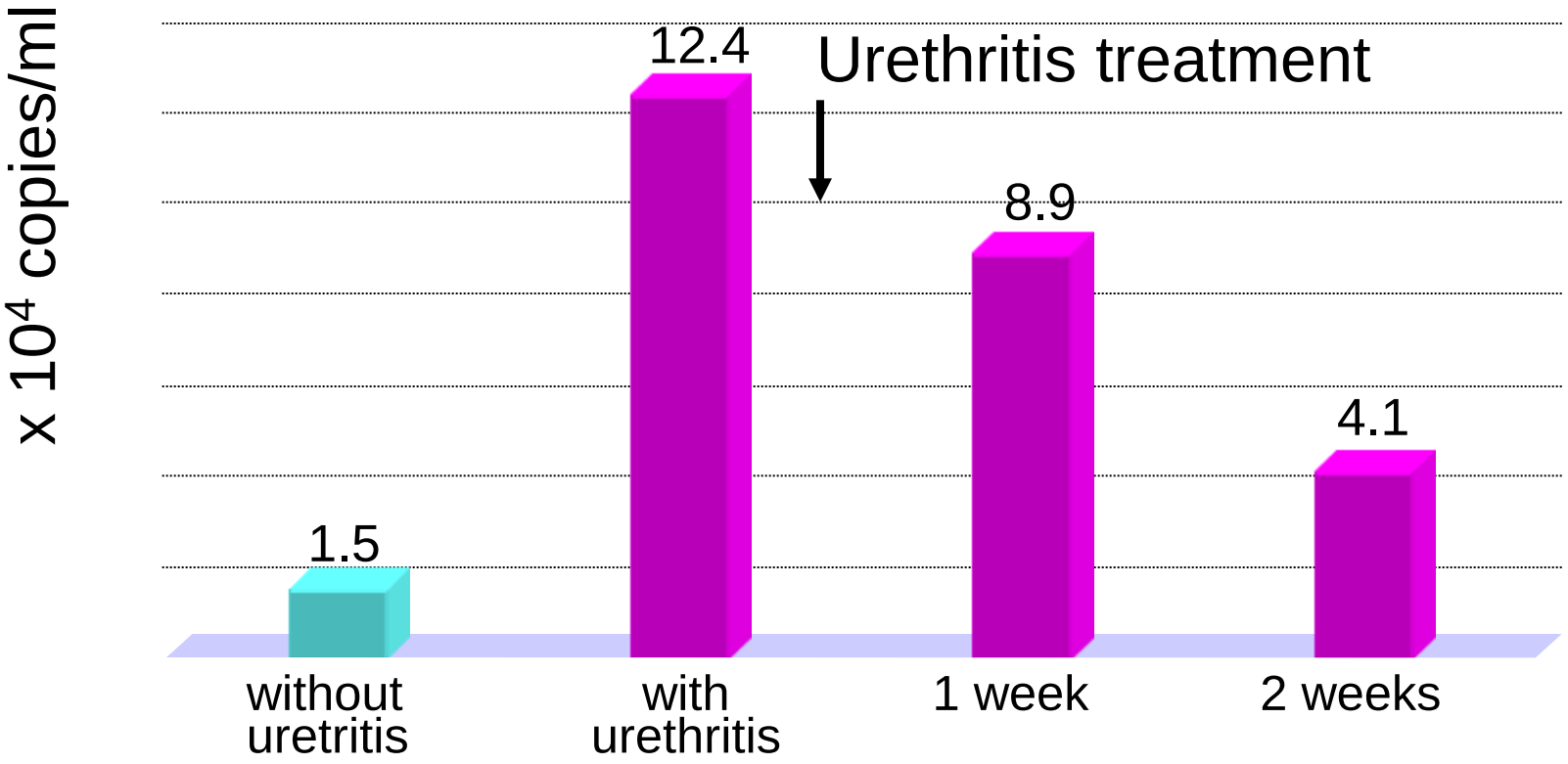
HPV Status	Unadjusted HR	95% confidence interval	P value	Adjusted HR[1]	95% confidence interval	P value
Any non-oncogenic HPV[2]:						
Persistent	1.50	0.56–1.84	0.279	1.24	0.59–2.60	0.574
Non-persistent	2.42	1.26–3.25	<0.001	2.09	1.27–3.44	0.004
Any oncogenic HPV[3]:						
Persistent	1.01	0.72, 3.15	0.969	0.82	0.45–1.50	0.523
Non-persistent	2.02	1.47, 3.98	0.003	1.67	1.03–2.70	0.038

Table 5. Recent HPV infection (within 6 months of HIV acquisition visit) as a predictor of HIV acquisition.

Infection with:	Including current visit Adjusted Hazards Ratio[1]	95% confidence interval	p- value	Excluding current visit Adjusted Hazards Ratio[1]	95% confidence interval	p-value
Any HPV	1.63	1.00–2.66	0.052	1.59	0.97–2.58	0.063
Any Non-oncogenic HPV[2]	1.50	0.92–2.43	0.104	1.70	1.02–2.85	0.042
Any Oncogenic HPV[3]	1.95	1.19–3.21	0.008	1.96	1.16–3.30	0.012

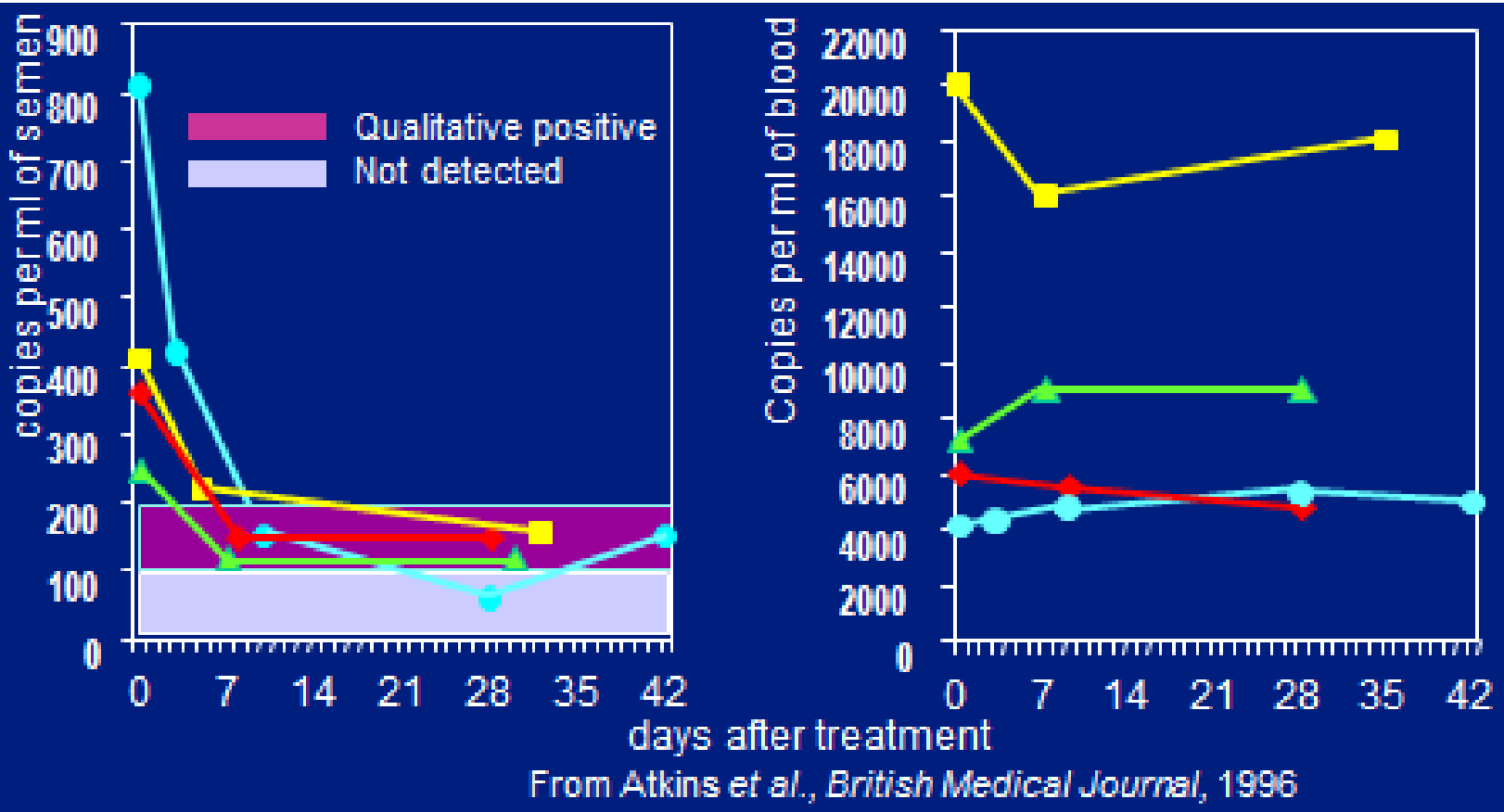
Smith Mc-Cune KK, et al Plos one 2010; 4, e10094

Median concentration of HIV-1 RNA in semen among 104 men with and without urethritis in Malawi



Cohen *et al., Lancet,* 1997

Impact of HIV load in semen and blood in 4 patients receiving treatment for urethral discharge



From Atkins *et al.*, *British Medical Journal*, 1996

HSV-2 valacyclovir suppressive therapy reduces HIV genital levels

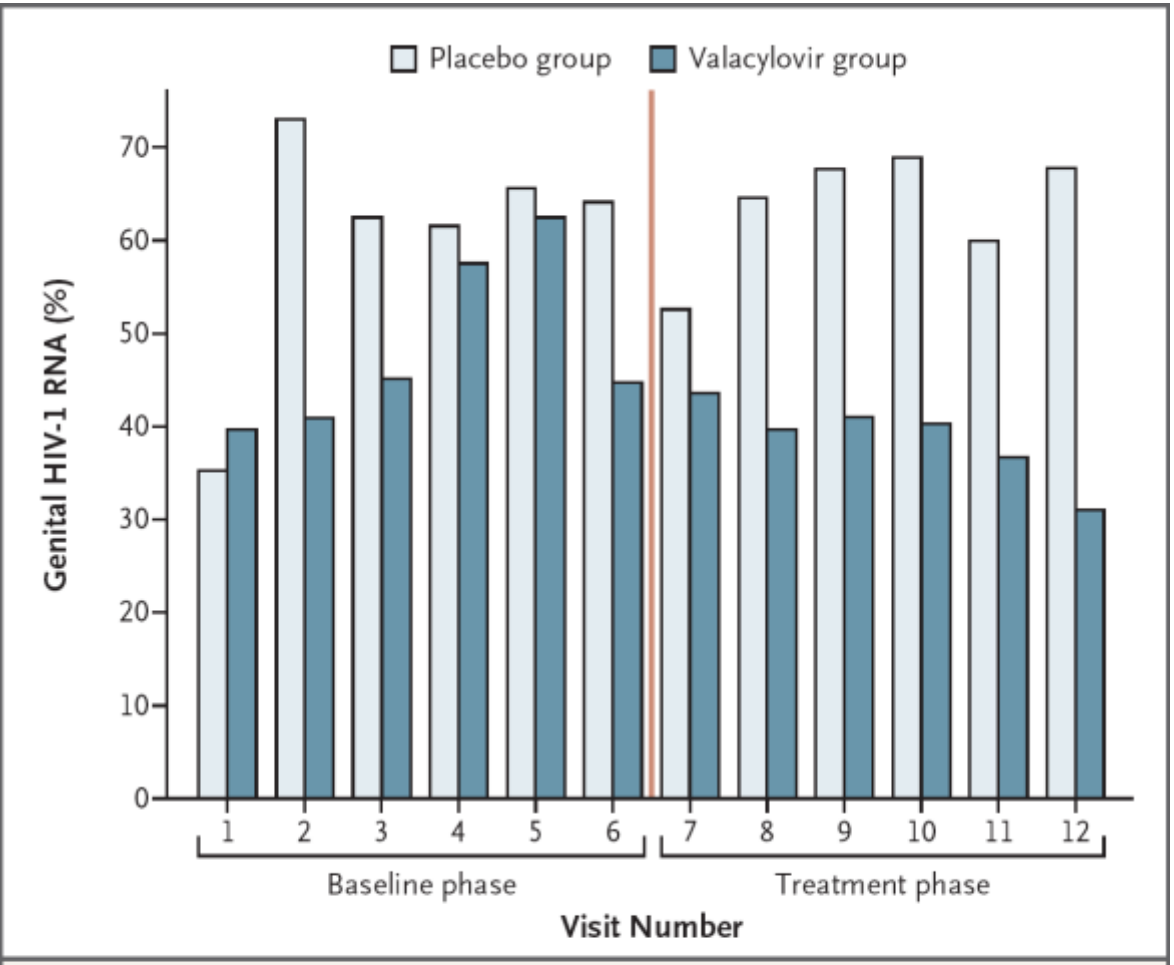
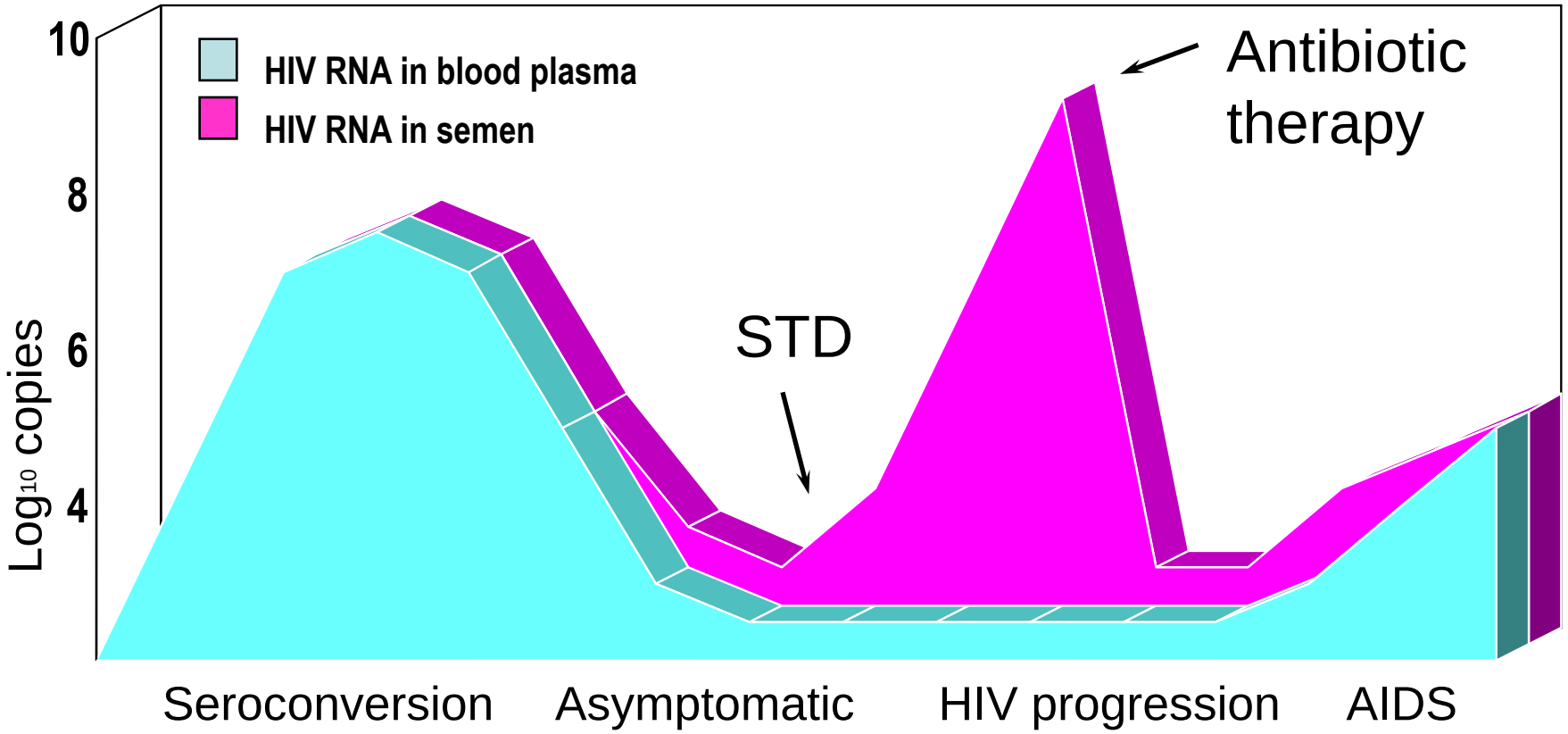


Figure 2. Proportion of Women with Genital HIV-1 RNA According to Visit, Trial Phase, and Study Group.

The red line indicates the point of randomization.

Nagot N, et al NEJM 2007; 356:790

Hypothetical model of impact of STD on HIV genital shedding in men



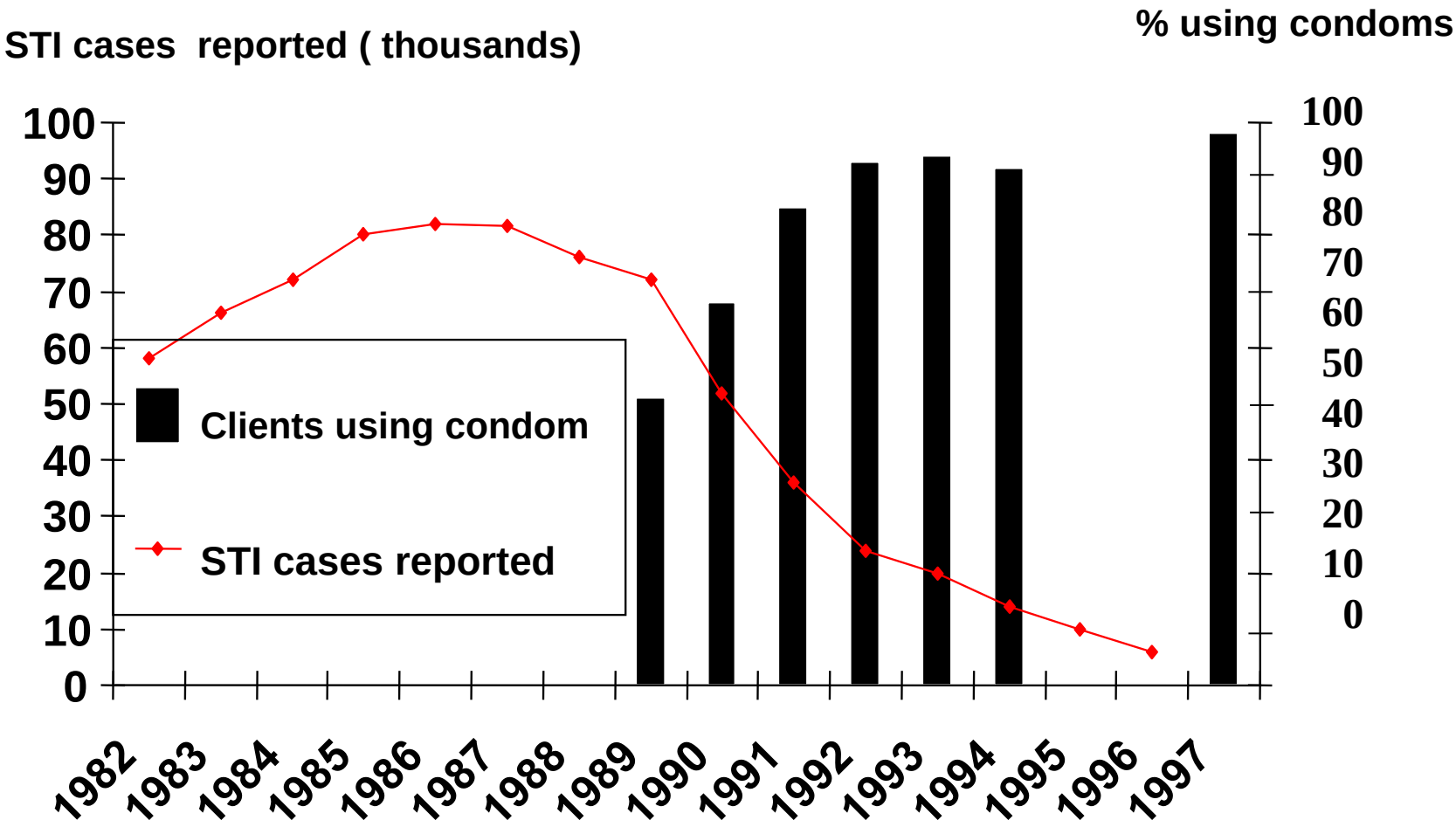
From ISSTDR, Seville 1997; M. Cohen, plenary presentation

What are the implications of the interactions ?

Interventions to control other STIs will reduce the incidence of HIV in the intervention population

Country experiences

Clients Using Condoms and STI Cases Reported - Thailand



Source: Sentinel Serosurveillance, Division of Epidemiology, Ministry of Public Health.

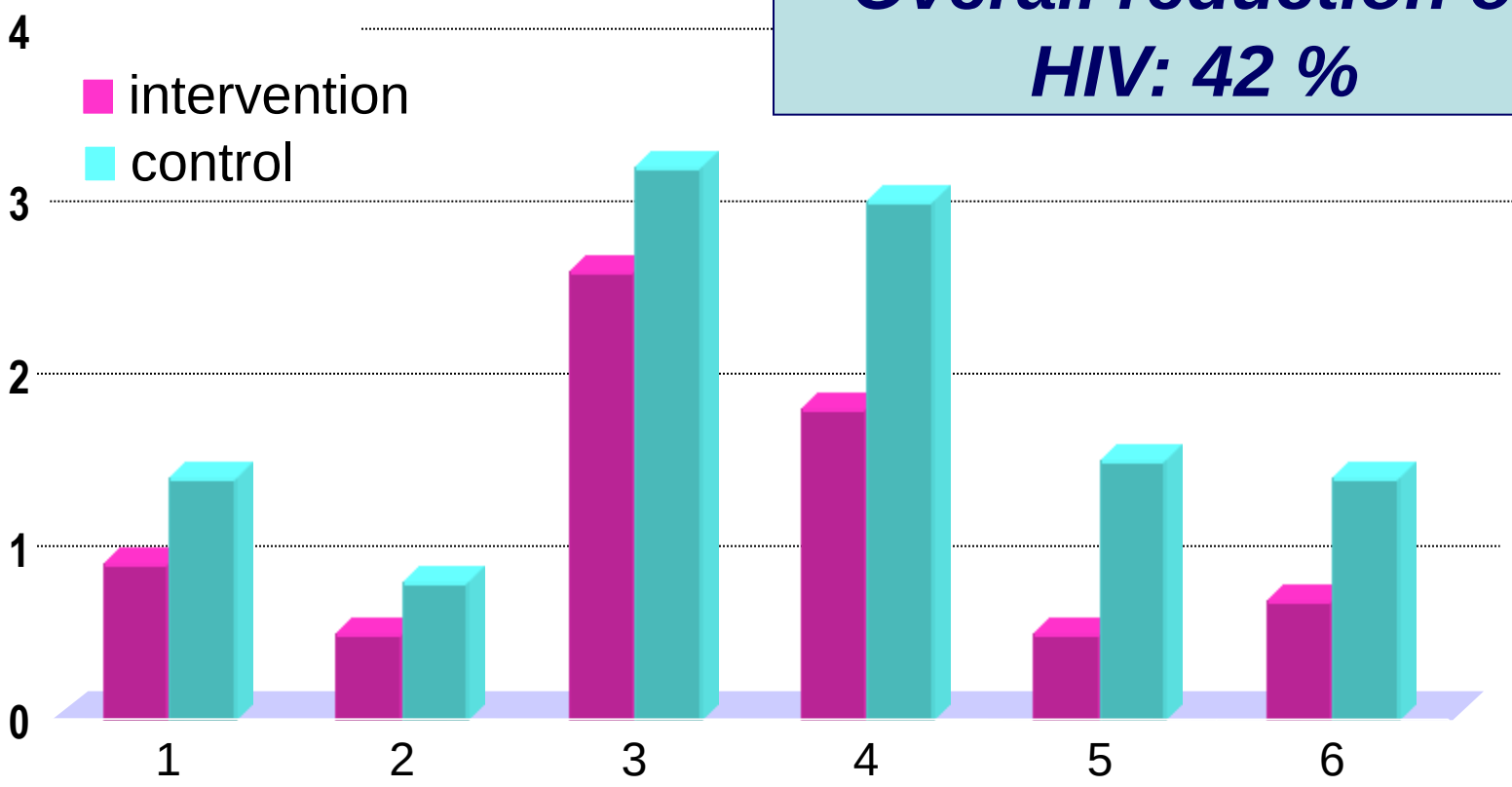
STI Programs

- STI control has been shown to be feasible in a wide range of countries at different levels of development
- Several countries documented large reductions in common STIs in Cambodia, Senegal, China, Kenya, Sri Lanka and Thailand
- In some countries this probably has influenced declines in HIV incidence and prevalence

Results of randomised controlled trials

Syndromic management of bacterial STI to reduce HIV acquisition and transmission: the Mwanza study

HIV incidence:



Overall reduction of HIV: 42 %

Grosskurth *et al., Lancet,* 1995

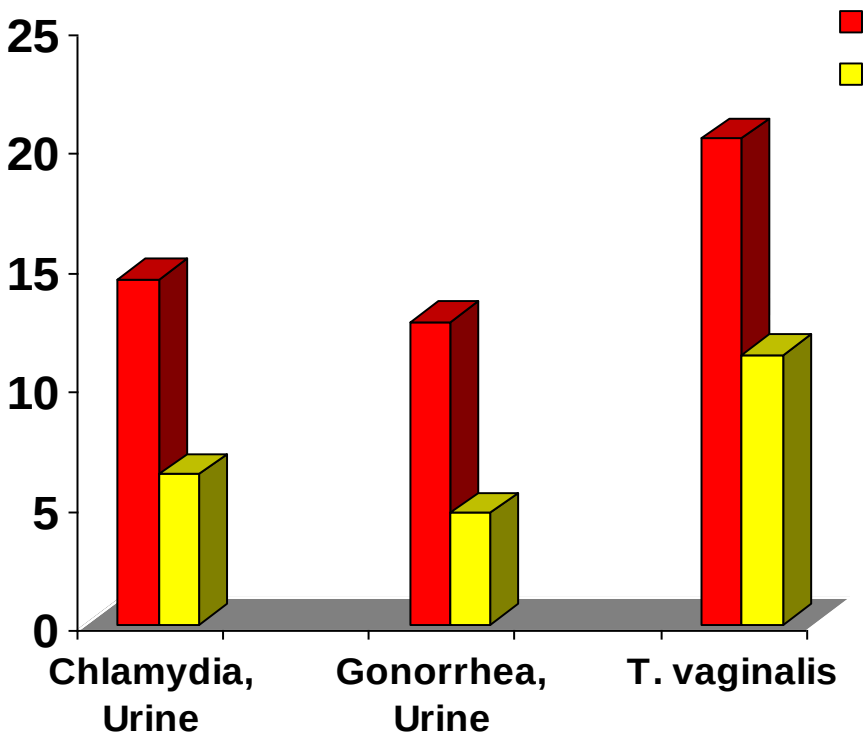
Syndromic management of bacterial STI to reduce HIV acquisition and transmission: the other RCTs

- 5 of 6 randomised community trials, all in Africa, did not have any effect on HIV incidence

1. *Waver MJ, Lancet 1999; 353: 525 – 35*
2. *Kamali A, Lancet 2003; 361: 645 – 52*
3. *Gregson S, PLoS Med 2007; 4: e102*
4. *Kaul R, JAMA 2004; 291: 2555 – 62*
5. *Gray RH, Am J Obstet Gynecol 2001; 185: 1209 - 17*

Periodic Presumptive Treatment of FSW for STI/HIV Prevention.

Impact of Placebo (N=236) vs. Azithromycin 1 gm monthly (N=230) on STI incidence per 100 person-years in Nairobi FSW



p<0.001 for each pathogen

No impact on syphilis (new RPR ≥ 1:8), GUD, or HIV seroconversion.

Kaul R, et al. JAMA 2004; 291: 2639

RCTs for HIV prevention by HSV-2 suppressive therapy in high risk populations

- 821 femal workers at recreational facilities in Tanzania
- HIV incidence of 4.27 / 100 prs / year (follow-up ~ 18 months) - Rate ratio for the acyclovir group 1.08 95% C.I. 0.64 – 1.83)

Watson-Jones D, N Engl J Med 2008; 358: 1560 - 71

- Women in Africa and MSM in US and Peru (n= 3172)
- HIV incidence of 3.60 / 100 prs / year – Rate ratio for the acyclovir group 1.16 95% C.I. 0.83 – 1.62)

Celum C, Lancet 2008; 371: 2109 - 719

Summary of the evidence

- Randomised control trials consistently failed to demonstrate that control of STI in the HIV negative population can reduce the rate of HIV acquisition

The way forward for STI control as an HIV prevention tool

1. Target the population at risk for STI (to reduce acquisition of HIV)

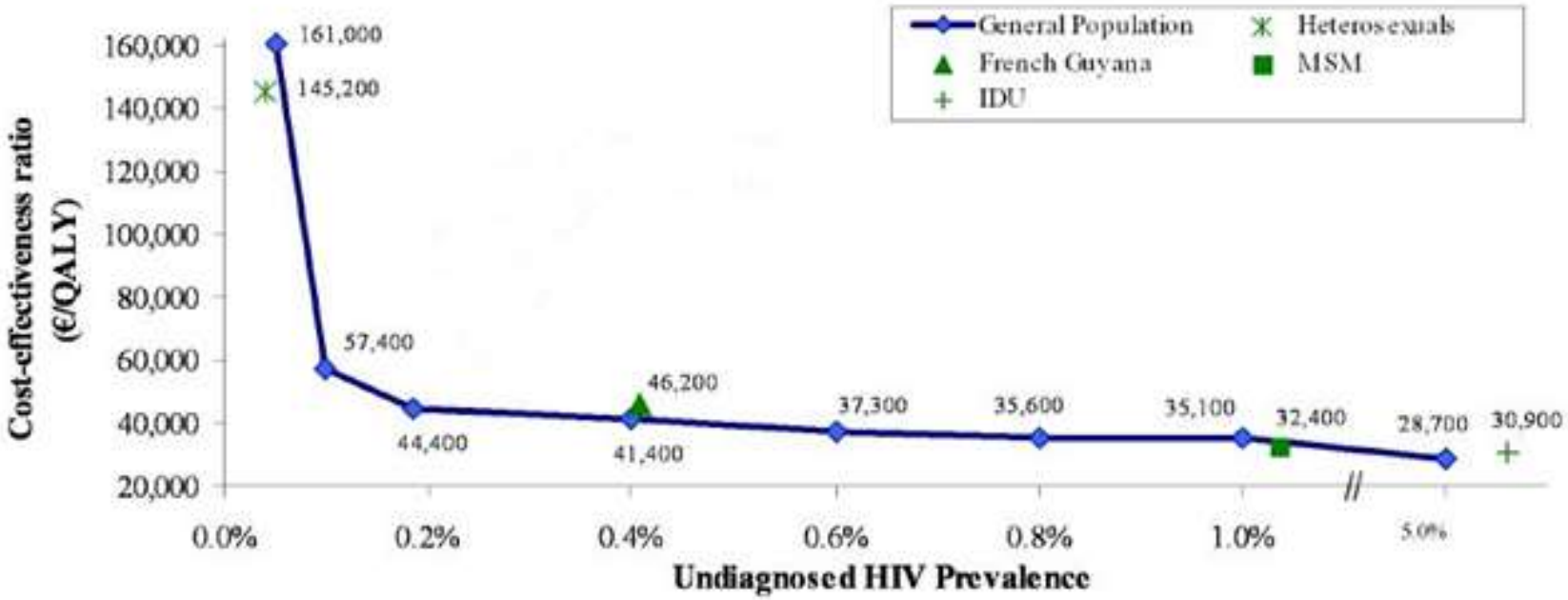
2. Target the population with HIV infection (to reduce transmission of HIV)

Population at risk for STI (at STI clinics)

- HIV testing (to early detect HIV infection)
- HIV counselling (to reduce HIV risk)
- Diagnosis and treatment of STI (to reduce HIV risk)

Is it cost-effective to test for HIV STI affected persons ?

Studies from the US and France suggest that HIV testing remains cost-effective as long as the undiagnosed HIV prevalence is above 0.1%



Yazdanpanah Y, et al. PLoS One. 2010; 5:e13132

HIV infected population (at HIV clinic)

- Promote safe sex behaviors
- ART to reduce transmission of HIV via the sexual route
- Regular STI screening and treatment to reduce genital viral load

Actively prevent STI infection and further transmission of STI and HIV

- A sexual history including questions for high-risk behaviour should be taken at each appointment and status of sexual partners discussed
- Consider reminding HIV-infected women to use latex condoms during every act of sexual intercourse
- Information regarding post-exposure prophylaxis should be proactively provided in a HIV serodiscordant couple
- HBV vaccination should be offered to all susceptible women

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

ABSTRACT

BACKGROUND

Antiretroviral therapy that reduces viral replication could limit the transmission of human immunodeficiency virus type 1 (HIV-1) in serodiscordant couples.

METHODS

In nine countries, we enrolled 1763 couples in which one partner was HIV-1–positive and the other was HIV-1–negative; 54% of the subjects were from Africa, and 50% of infected partners were men. HIV-1–infected subjects with CD4 counts between 350 and 550 cells per cubic millimeter were randomly assigned in a 1:1 ratio to receive antiretroviral therapy either immediately (early therapy) or after a decline in the CD4 count or the onset of HIV-1–related symptoms (delayed therapy). The primary prevention end point was linked HIV-1 transmission in HIV-1–negative partners. The primary clinical end point was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a World Health Organization stage 4 event, or death.

RESULTS

As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; P<0.001). Subjects receiving early therapy had fewer treatment end points (hazard ratio, 0.59; 95% CI, 0.40 to 0.88; P=0.01).

CONCLUSIONS

The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy. (Funded by the National Institute of Allergy and Infectious Diseases and others; HPTN 052 ClinicalTrials.gov number, NCT00074581.)

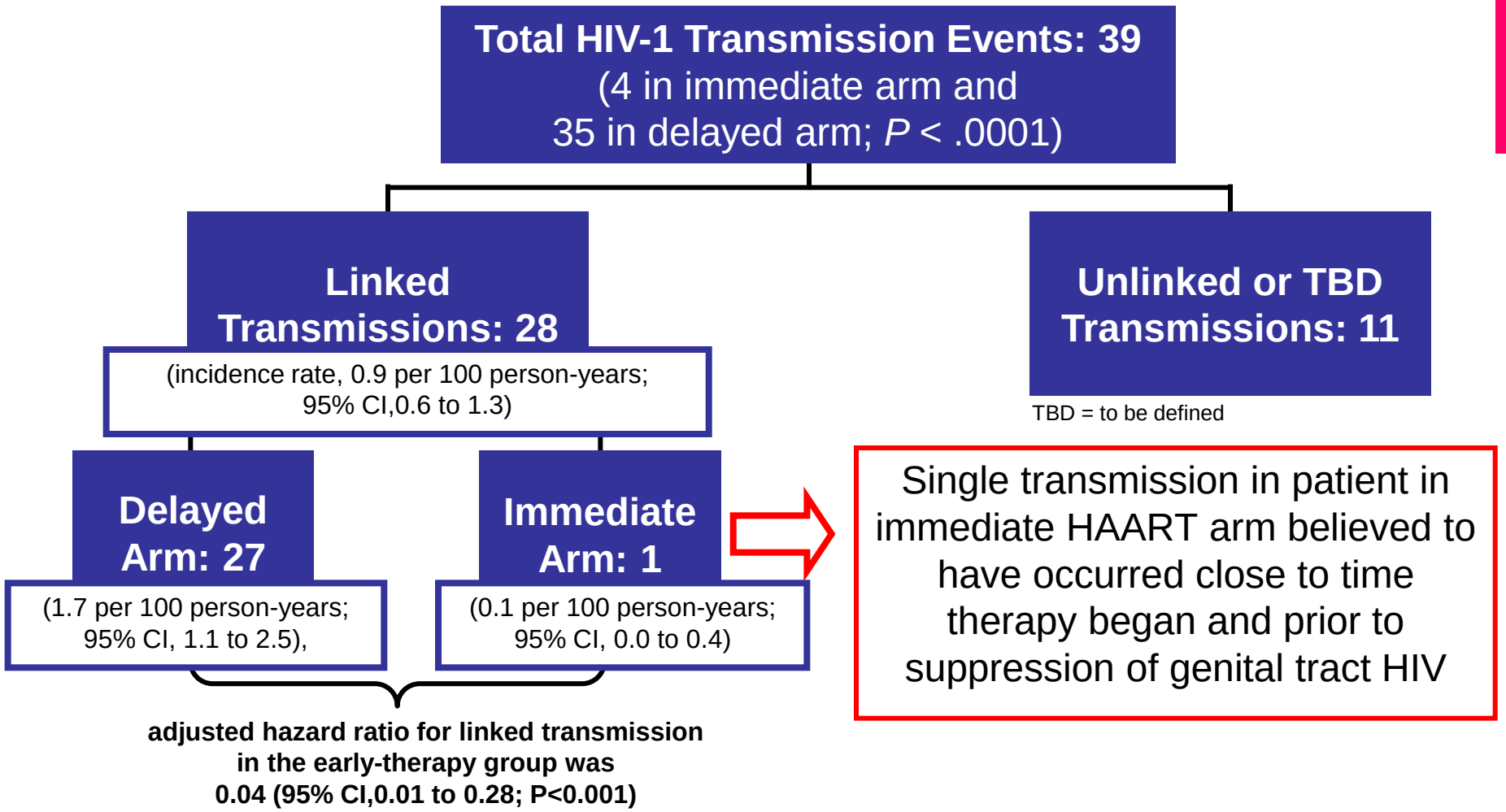
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Cohen at the University of North Carolina at Chapel Hill, Institute for Global Health and Infectious Diseases, Suite 2115, Bioinformatics Bldg., 130 Mason Farm Rd., CB 7030, Chapel Hill, NC 27599, or at mscohen@med.unc.edu.

*Other members of the HIV Prevention Trials Network (HPTN) 052 Study Team are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1105243) was published on July 18, 2011, at NEJM.org.

N Engl J Med 2011;365:493-505.

Viremia e ART



Results from the HPTN 052 trial demonstrated antiretroviral therapy (ART) to be a powerful tool for both treatment and prevention, reducing the likelihood of HIV transmission by 96% in Serodiscordant Couples

Cohen MS, et al. N Engl J Med. 2011;365: 493-505..

Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie sexuelle

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Commission fédérale pour les problèmes liés au sida (CFS), Commission d'experts clinique et thérapie VIH et sida de l'Office fédéral de la santé publique (OFSP)

a Prof. Dr méd., président de la Commission fédérale pour les problèmes liés au sida (CFS) et responsable de la Division des maladies infectieuses et de l'hygiène hospitalière de l'Hôpital cantonal de St-Gall

b Prof. Dr méd., membre de la Commission d'experts clinique et thérapie VIH et sida de l'OFSP et responsable de l'unité VIH-SIDA des Hôpitaux Universitaires de Genève

Après avoir pris connaissance des faits scientifiques, à la demande de la Commission d'experts clinique et thérapie VIH et sida (CCT) de l'Office fédéral de la santé publique (OFSP) et après avoir longuement délibéré, la Commission fédérale pour les problèmes liés au sida (CFS) arrive à la conclusion suivante:

Une personne séropositive ne souffrant d'aucune autre MST et suivant un traitement antirétroviral (TAR) avec une virémie entièrement supprimée (condition désignée par «TAR efficace» ci-après) ne transmet pas le VIH par voie sexuelle, c'est-à-dire qu'elle ne transmet pas le virus par le biais de *contacts sexuels*.

Cette affirmation reste valable à condition que:

- la personne séropositive applique le traitement antirétroviral à la lettre et soit suivie par un médecin traitant;

prouvent pas qu'un TAR efficace *empêche* toute infection au VIH (en effet, il n'est pas possible de prouver la non-survenance d'un événement certes improbable, mais théoriquement envisageable). Reste que du point de vue de la CFS et des organisations concernées, les informations disponibles à ce jour sont suffisantes pour justifier ce message. La situation est comparable à celle de 1986, lorsqu'il a été communiqué publiquement que le VIH ne se transmet pas par un baiser avec la langue. Si cette constatation n'a jamais pu être prouvée, plus de vingt années d'expérience du VIH ont néanmoins permis d'étayer sa forte plausibilité. Cependant, les faits et critères scientifiques soutenant l'affirmation selon laquelle les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par la voie sexuelle sont nettement plus favorables qu'en 1986. En conséquence, la CFS et les organisations

compartimentalizzazione

Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men

Joseph A. Politch[a], Kenneth H. Mayer[b,d], Seth L. Welles[c], William X. O'Brien[b], Chong Xu[a], Frederick P. Bowman[a] and Deborah J. Anderson[a]

Objective: Although HAART can suppress genital shedding and sexual transmission of HIV, men who have sex with men (MSM) have experienced a resurgent HIV epidemic in the HAART era. Many HIV-infected MSM continue to engage in unsafe sex, and sexually transmitted infections (STIs) or other factors may promote genital HIV shedding and transmission in this population despite HAART. In this study, we determined the prevalence of seminal HIV shedding in HIV-infected MSM on stable HAART, and its relationship with a number of clinical, behavioral and biological variables.

evaluated paired blood and semen samples from 101 HIV-infected men on stable ART, nearly all of whom reported sex with men.

Clinical and behavioral data were obtained from medical records and questionnaires. Herpes simplex virus 2 (HSV-2) serostatus, seminal HSV-2 DNA, and markers of genital inflammation were measured using standard laboratory methods.

Results: Overall, HIV-1 was detected in 18 of 101 (18%) blood and 30 of 101 (30%) semen samples. Of 83 men with undetectable HIV in blood plasma, 25% had HIV in semen with copy numbers ranging from 80 to 2560. Multivariate analysis identified STI/urethritis ($P = 0.003$), tumor necrosis factor α ($P = 0.0003$), and unprotected insertive anal sex with an HIV-infected partner ($P = 0.007$) as independent predictors of seminal HIV detection.

Conclusion: STIs and genital inflammation can partially override the suppressive effect of HAART on seminal HIV shedding in sexually active HIV-infected MSM. Low seminal HIV titers could potentially pose a transmission risk in MSM, who are highly susceptible to HIV infection.

AIDS 2012, **26**:1535–1543

Overall, 21 (25%) of the 83 men with undetectable HIV in blood simultaneously had detectable virus in semen

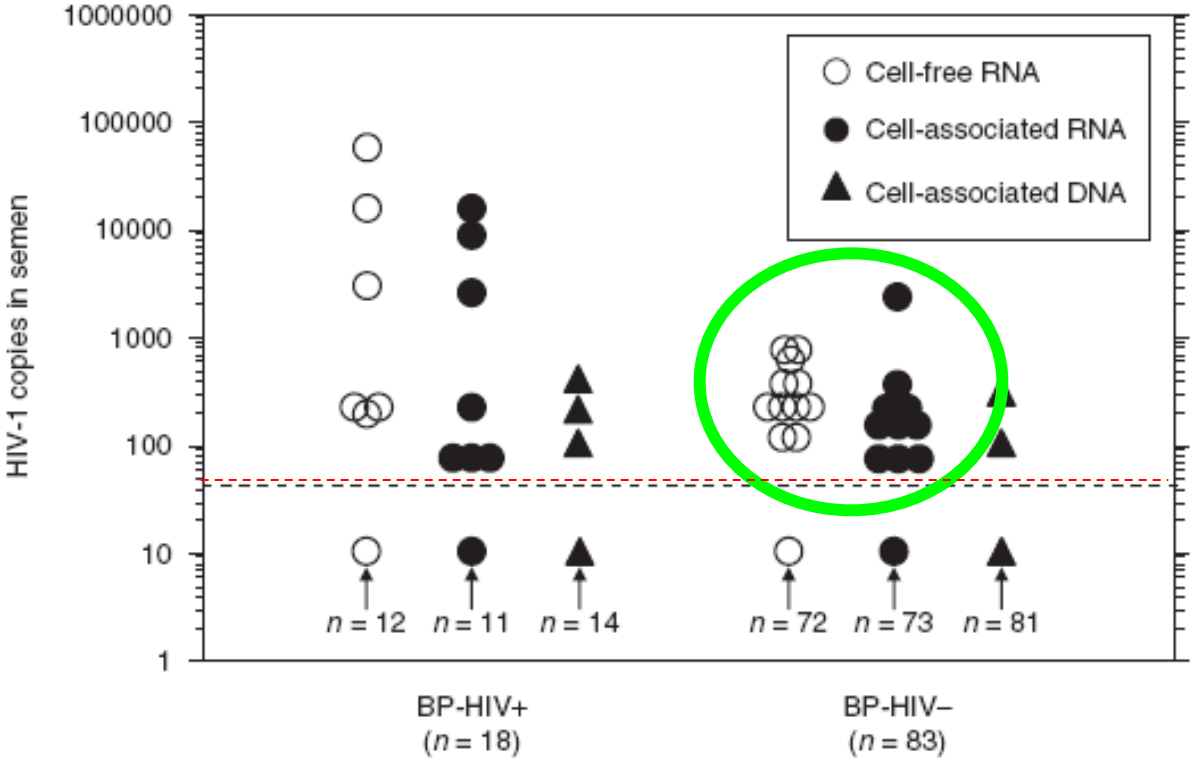

Fig. 1. Cell-free and cell-associated HIV RNA and DNA in semen of men with detectable (BP-HIV$^+$) and undetectable (BP-HIV$^-$) HIV in blood plasma. Cell-free HIV is expressed as HIV-1 copies per millilitre seminal plasma. Cell-associated HIV RNA and DNA are numbers of copies per sample. The dotted line indicates the lower limit of HIV detection, and values under this line represent samples with 'undetectable' HIV. BP-HIV$^+$ men had significantly higher concentrations of cell-free HIV RNA (mean + SE = 4438 ± 3388 vs. 51 ± 17, $P < 0.03$), cell-associated HIV RNA (1604 ± 1006 vs. 50 ± 31, $P < 0.005$) and cell-associated HIV DNA (41 ± 26 vs. 5 ± 4, $P < 0.009$).

Politch et al, AIDS 2012, 26:1535-1543

compartimentalizzazione

Table 2. Univariate analysis of variables associated with HIV in semen of men with undetectable HIV in blood plasma ($n = 83$).

Risk factor	HIV in semen[a] Positive ($n = 21$)	Negative ($n = 62$)	P^b
Duration of ART			
>1 year ($n = 66$)	17/21 (81%)	49/62 (79%)	0.74
Duration of current HAART regimen			
>3 months ($n = 83$)	21/21 (100%)	62/62 (100%)	>0.99
>6 months ($n = 62$)	17/21 (81%)	45/62 (73%)	0.57
>12 months ($n = 39$)	9/21 (43%)	30/62 (48%)	0.80
Peripheral CD4 cell count (cells/μl)			
≤200 ($n = 7$)	2/21 (10%)	5/62 (8%)	0.99
>200 ($n = 76$)	19/21 (91%)	57/62 (92%)	
STI risk group			
Low risk group ($n = 21$)	1/21 (5%)	20/62 (32%)	0.02
High risk group[c] ($n = 62$)	20/21 (95%)	42/62 (68%)	
High risk sexual behavior			
UIAS[d] ($n = 36$)	14/21 (67%)	22/62 (36%)	0.02
UIAS-HIV[e] ($n = 28$)	13/203 (65%)	15/62 (24%)	0.002
STI status			
Current STI/urethritis ($n = 8$)	6/21 (29%)	2/62 (3%)	0.003
HSV-1 seropositive ($n = 57$)	14/21 (67%)	43/62 (69%)	0.79
HSV-2 seropositive ($n = 53$)	11/21 (52%)	42/62 (68%)	0.29
Genital inflammation			
Leukocytospermia			
Yes ($n = 20$)	12/21 (57%)	8/62 (13%)	0.0001
No ($n = 63$)	9/21 (43%)	54/62 (87%)	
PMN (#/ml × 10^6)	1.12 (ND-12)[f]	0.04 (ND–6.8)	0.003
TNF-α (pg/ml)	8 (2–77)	6 (ND-78)	<0.0001
IL-6 (pg/ml)	105 (11–2773)	23 (3–1400)	<0.0001
IL-8 (pg/ml)	1152 (134–41 482)	546 (42–4270)	0.005
Lysozyme (ng/ml)	157 (59–242)	180 (50–413)	0.21
SLPI (ng/ml)	10.5 (5–279)	5.8 (4–107)	0.009

Men with STIs or urethritis were 29 times as likely as men without these conditions to have detectable HIV in semen despite undetectable virus in blood.
Unprotected insertive anal intercourse and
the presence of genital inflammation were also significantly associated with increased likelihood of a discordant blood/semen result.

Politch et al, AIDS 2012, 26:1535-1543

Screen STI through history taking and clinical examination

- Persons should be queried concerning symptoms of STIs at each visit

- Clinical examination at first visit and at least annually should include
  - Visual inspection of perineum/genitalia and anus
  - Speculum examination of cervix

Screen STI through lab investigations at first visit

- All individuals
  - Syphilis (VDRL, TPHA); *T.vaginalis* (vaginal swab); *C.trachomatis* (cervical and urethral samples for antigen detection or NAATs); *N.gonorrhoeae* (cervical and urethral culture or NAATs); HPV-associated dysplasia (cervical Pap smear); hepatitis B (HBsAg, HBsAb, HBcAb) and C (HCV-Ab)
- Individuals reporting receptive anal sex
  - *C.trachomatis* (anal samples for antigen detection or NAATs); *N.gonorrhoeae* (anal culture); HPV-associated dysplasia (anal Pap smear)
- Individuals reporting receptive oral sex
  - *N.gonorrhoeae* (pharyngeal culture or NAATs)

Screen for STI at regular intervals

- Syphilis, *C.trachomatis*, *N.gonorrhoeae, T.vaginalis*
  - Annually and more frequently if symptomatic or after unprotected sexual intercourse
- HPV-associated dysplasia (Pap smear)
  - Every six months during the first year
  - Annually if initial Pap tests are normal
  - Every 6 months or less if: previous history of an abnormal Pap test, after treatment for cervical dysplasia, symptomatic HIV infection, HPV infection