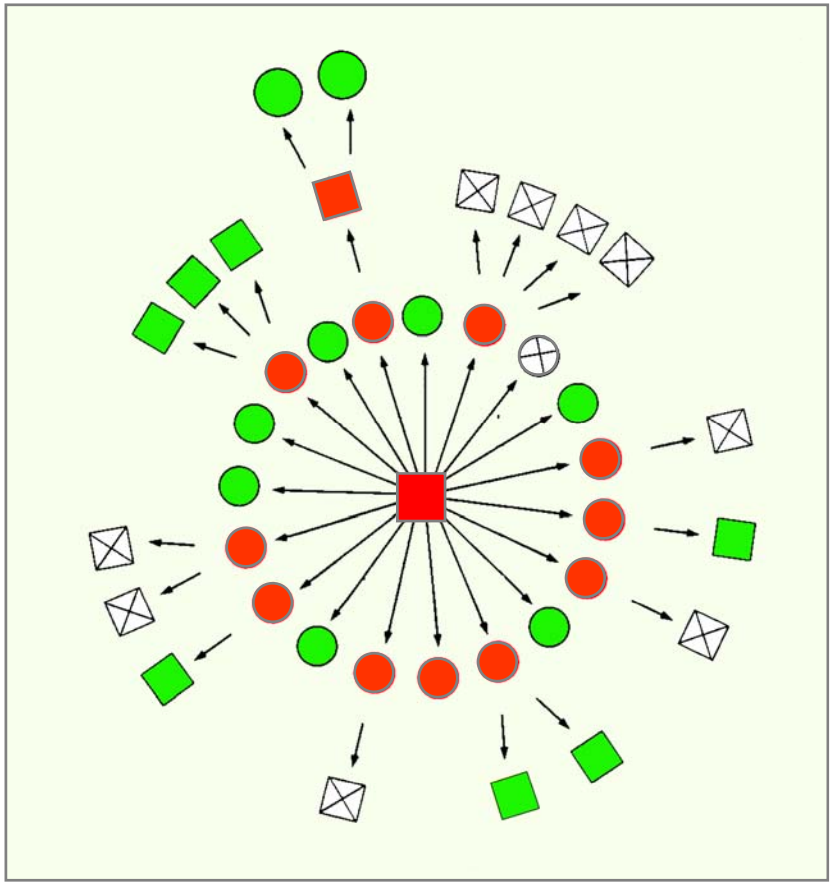
HIV in Semen
-
Is it as infectious as patients may think ?

Pietro L. Vernazza,
KSSG, St. Gallen, Switzerland

Heterosexual Transmission



HIV-pos.

HIV-neg.

Clumeck N, et al, NEJM, 1989;321:1460

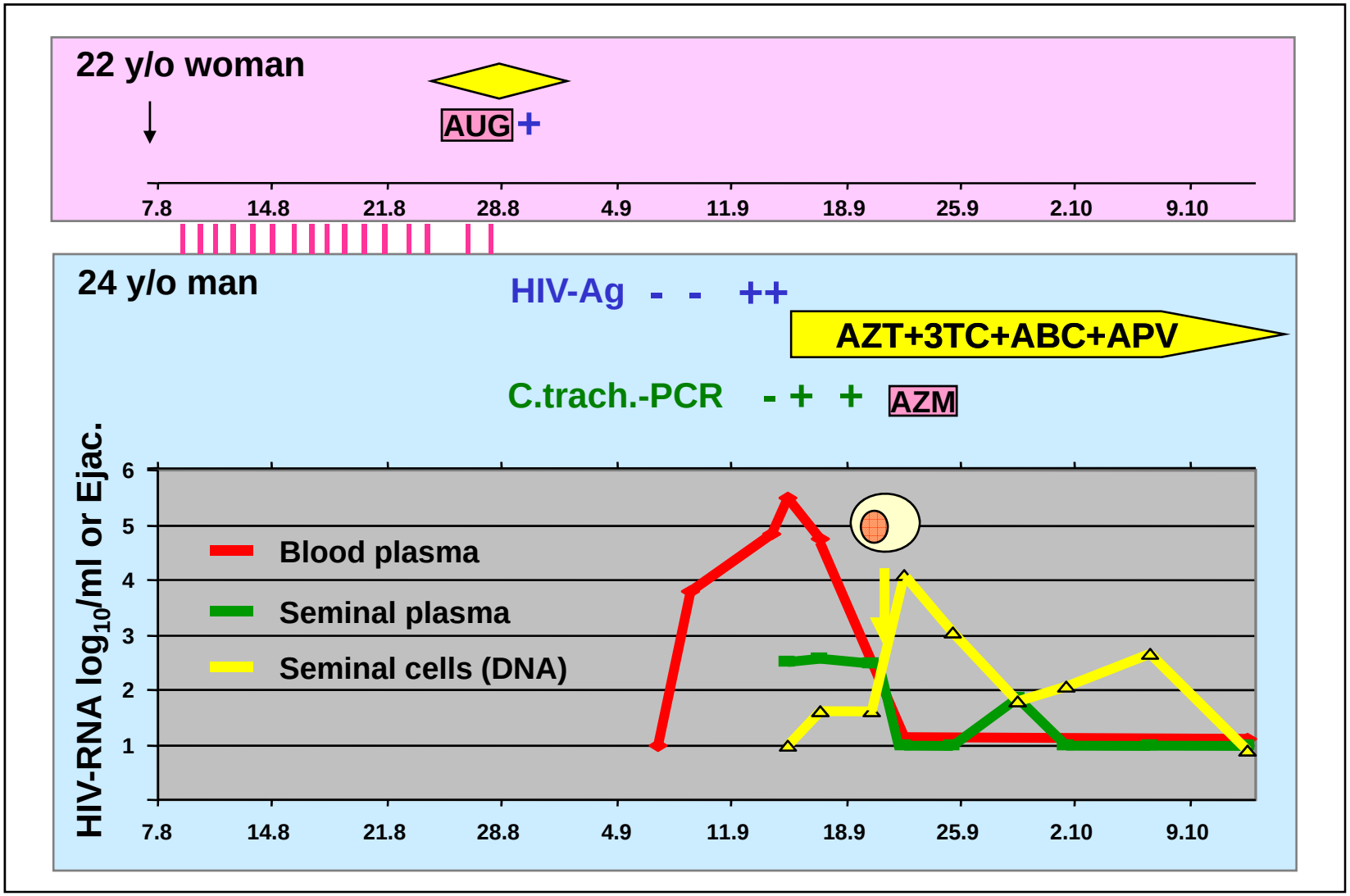
Is it as infectious as patients may think

What do you think ?

- **What is your estimate of transmission risk after one single sexual act**
  - **A) in the absence of treatment**
  - **B) during fully supressive HAART**

100% - 10% - 1% - $1:10^3$ - $1:10^4$ - $1:10^5$ - $1:10^6$

PHI Transmission couple



Transmission risk per sex contact

	Partner studies	Anonymous contact
♀→♂	1- 9% partner pos. <0.3% per contact	3.1% - 8.2%
♂→♀	9-18% partner pos 0.3% per contact	

Padian, JAMA 1987
De Vincenzi, NEJM 1994
Nicolosi, Epidemilogy 1994

Mastro, AIDS 1994
Cameron, Lancet 1989

Risk after single sexual exposure

- 422 customers of Kenyan prostitutes
- 293 HIV-neg, prospectively followed
- 12% s/c rate in 12 wk period
  - Non circumcision: OR 8.2 (3-23)
  - GUD OR 4.7 (1.3-17)
- 73 men: only one single contact
  - 8.2% s/c rate (6/73), 43% of uncircumcised

Cameron et al, 1989, Lancet ii:403-7

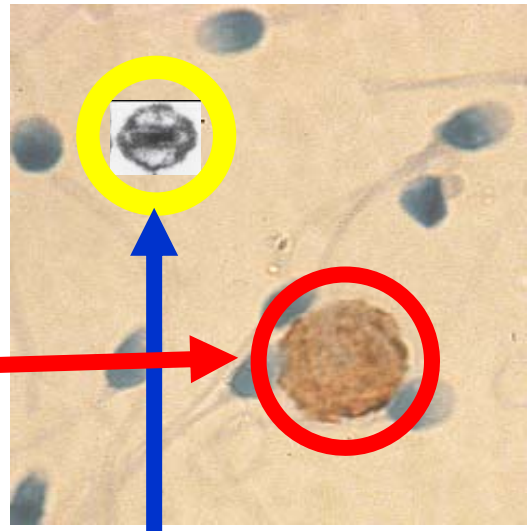
Mastro study, Thailand

- 1115 military conscripts (21y)
  - 6.9% HIV-pos (n=77)
- Sex with female prostitutes
- mathematical modelling:
  - risk after single contact: 3.1% (2.5-4.0)
  - adjusted for random error in self reported frequency of contact: 5.6% (4.1-7.5%)
- Risk signif. higher in men reporting Hx of STD

Mastro et al, 1994, Lancet 343:204-7

Sexual Transmission of HIV

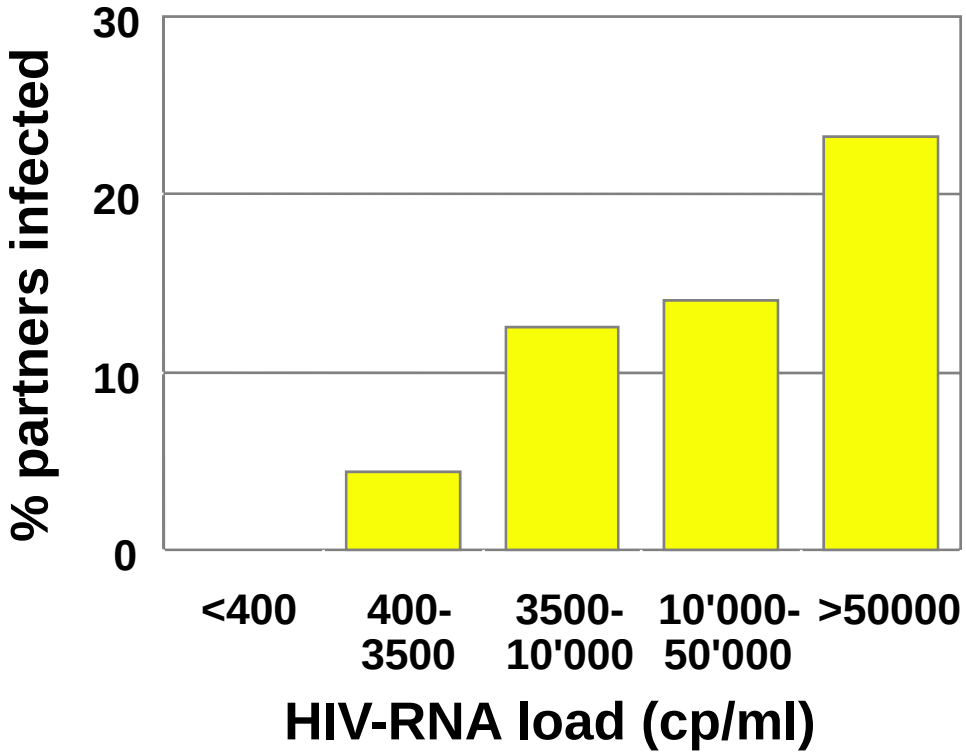
- **Risk of transmission enhanced with:**
  - **Low CD4 counts**
  - **Symptomatic disease**
  - **High blood viral load**
  - **Genital inflammation**
  - **PHI**



r = 0.5-0.6

VL and HIV-Transmission-Risk

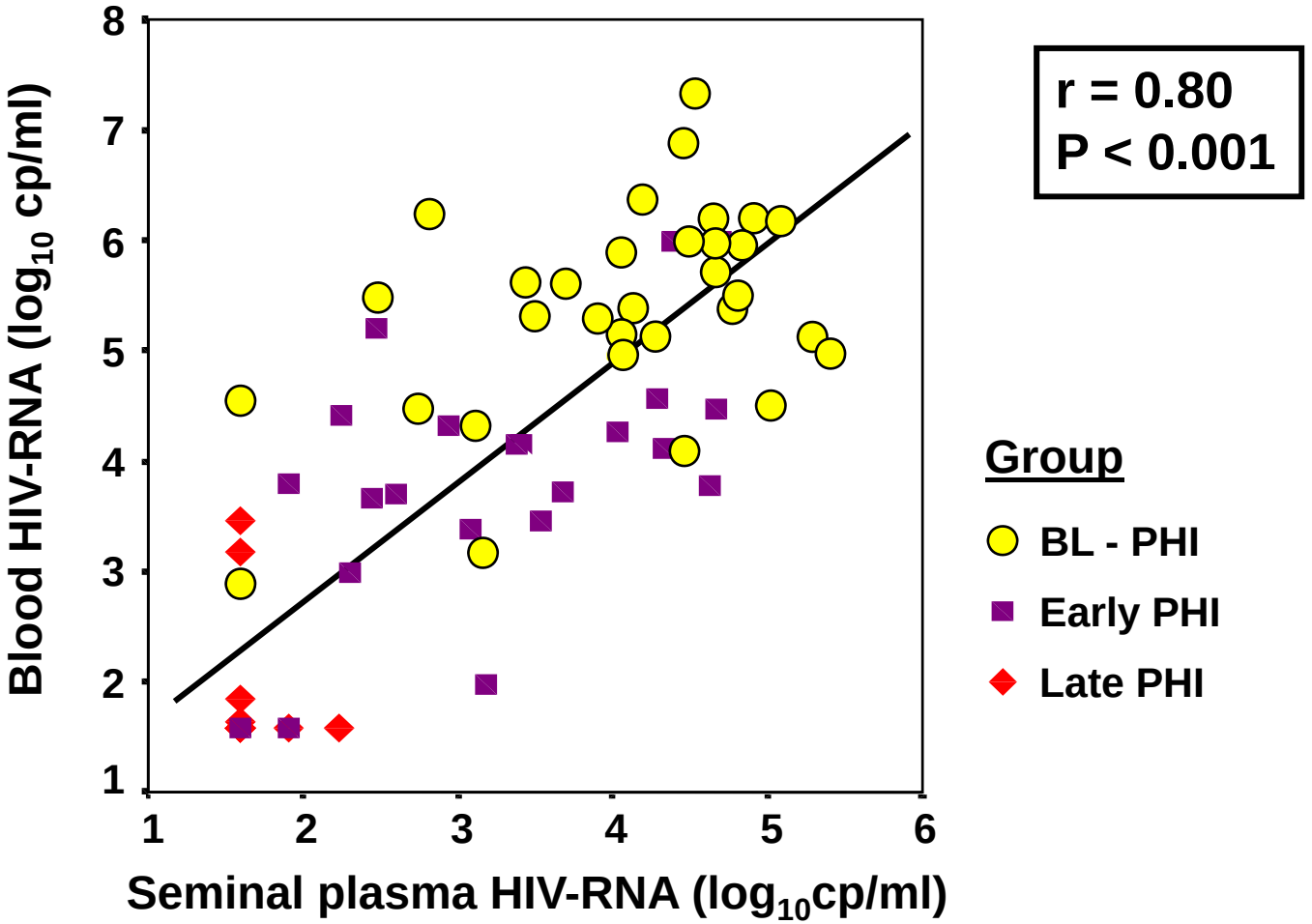
- Rakai (Uganda)
- 453 HIV-disc. couples
- 11.6 % TR / year



Quinn, NEJM, 2000; 342:921-9.

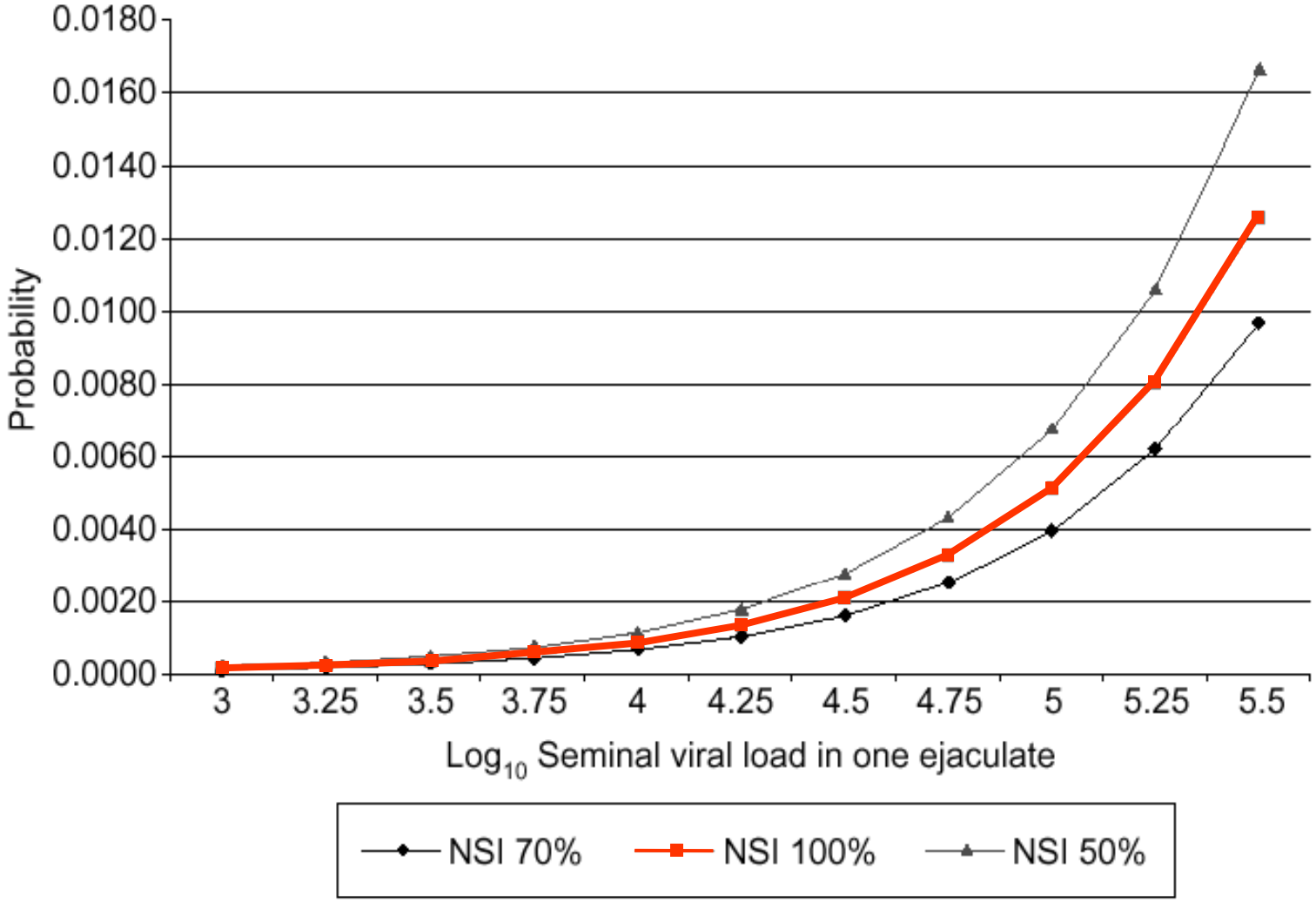
HIV-Primary Infection

HIV-RNA in blood and semen



Vernazza, 2000, Quest-Study Group

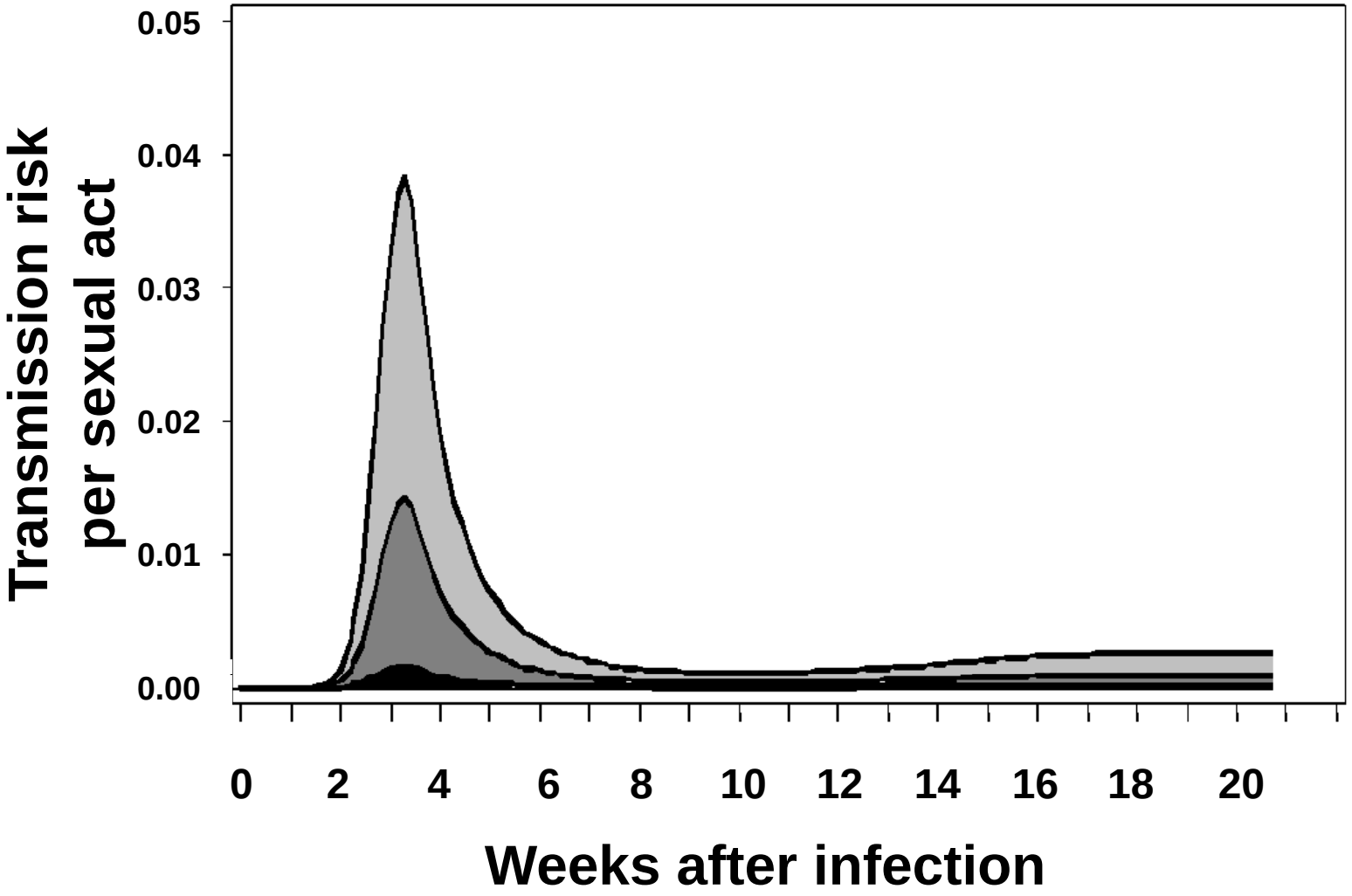
HIV in semen & risk per coital act



Chakraborty et al. AIDS 2001,15: 621-7

Primary HIV Infection

Marked increase of transmission risk



Pilcher et al JID 2004; 189:1785–92

High Rates of Forward Transmission Events after Acute/Early HIV-1 Infection

Bluma G. Brenner,[1] Michel Roger,[2] Jean-Pierre Routy,[3] Daniela Moisi,[1] Michel Ntemgwa,[1] Claudine Matte,[2] Jean-Guy Baril,[4] Réjean Thomas,[5] Danielle Rouleau,[2] Julie Bruneau,[6] Roger Leblanc,[7] Mario Legault,[8] Cecile Tremblay,[9] Hugues Charest,[10] Mark A. Wainberg,[1] and the Quebec Primary HIV Infection Study Group[a]

Results. Viruses from 49.4% (293/593) of PHIs cosegregated into 75 transmission chains with 2–17 transmissions/cluster. Half of the clusters included 2.7 ± 0.8 (mean ± SD) transmissions, whereas the remainder had 8.8 ± 3.5 transmissions. Maximum periods for onward transmission in clusters were 15.2 ± 9.5 months. Coclustering of untreated and treated CIs with PHIs were infrequent (6.2% and 4.8%, respectively). The ages, viremia, and risk factors were similar for clustered and nonclustered transmission events. Low prevalence of drug resistance in PHI supported amplified transmissions at early stages.

Conclusions. Early infection accounts for approximately half of onward transmissions in this urban North American study. Therapy at early stages of disease may prevent onward HIV transmission.

Early infection accounts for approximately half of onward transmissions

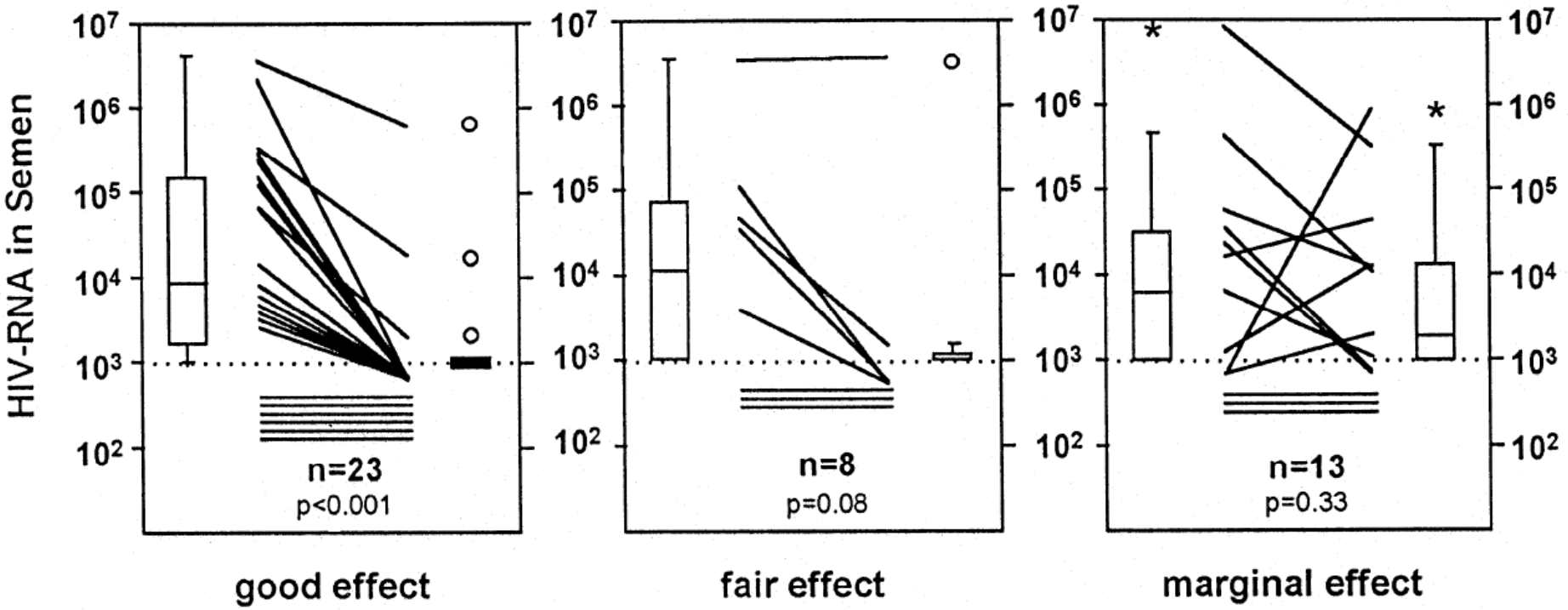
Brenner et al, JID 2007; 195:951–9

Summary 1

- **HIV in genital tract follows blood VL**
- **Transmission risk high during PHI**

→ Q: What is the effect of treatment

HIV in semen under HIV therapy

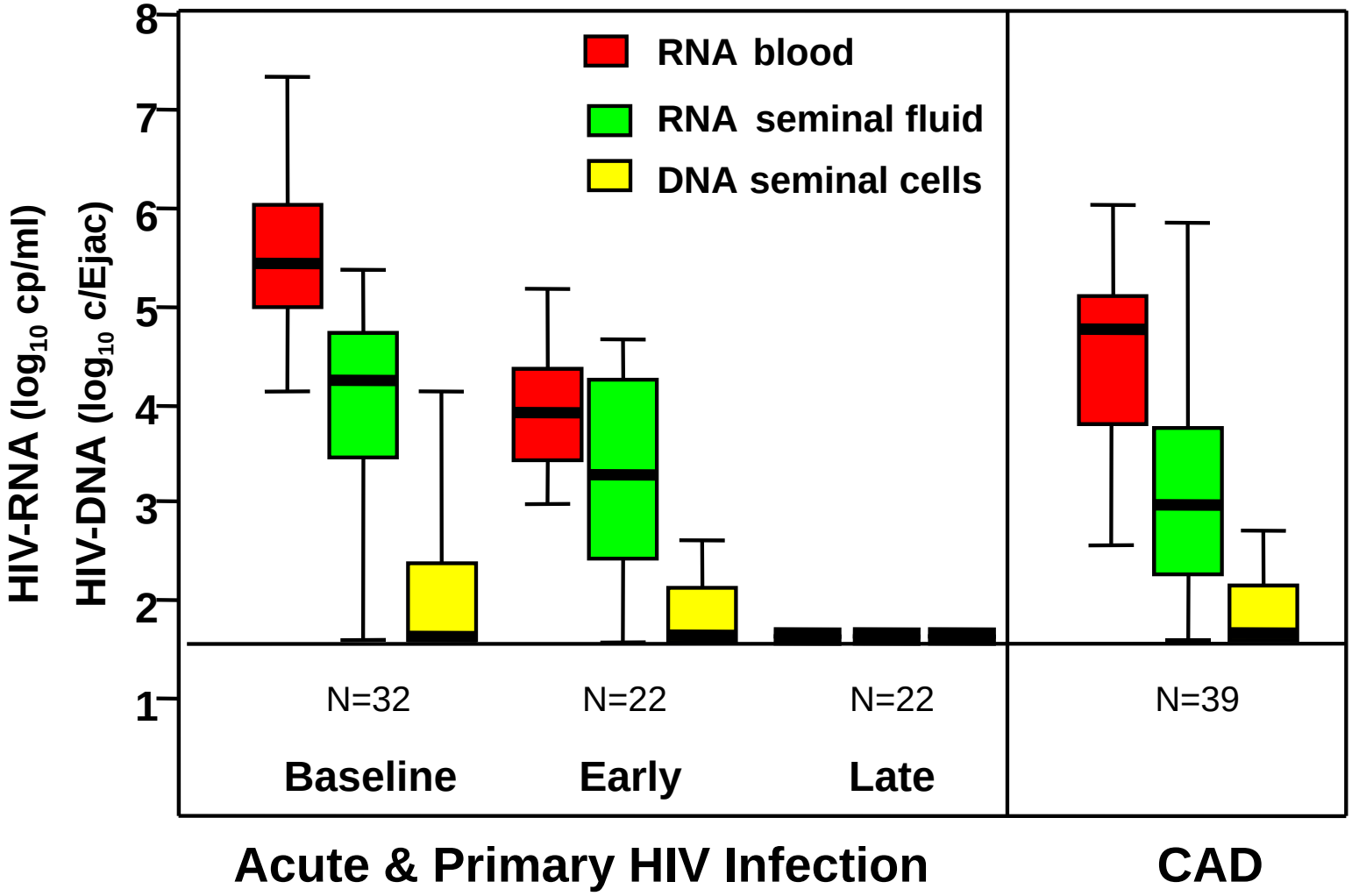


>1 log drop

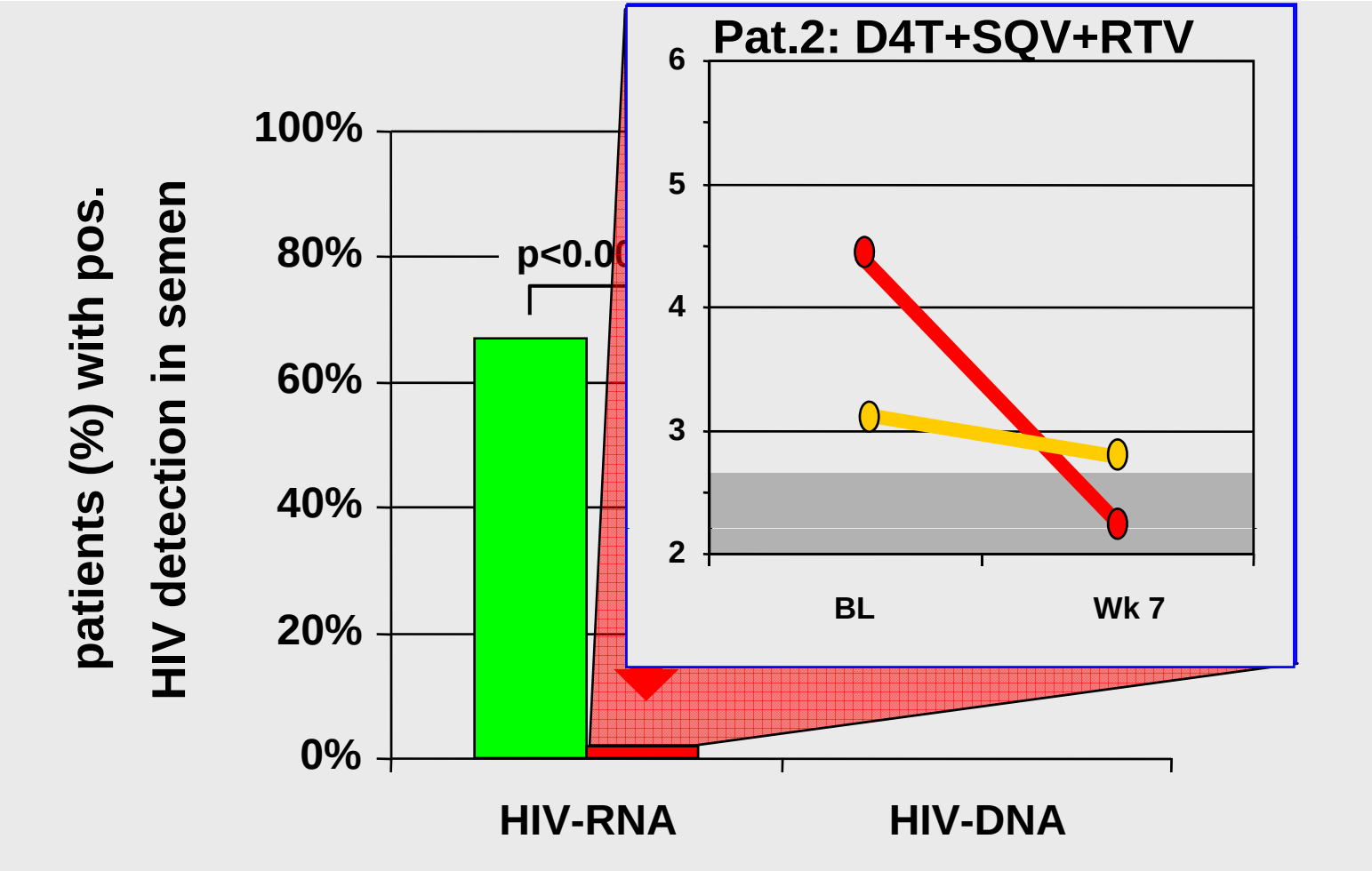
<0.5 log drop

Vernazza P. et al, AIDS, 1997;11:1249–1254

Viral load in blood vs. semen during the course of treatment in PHI

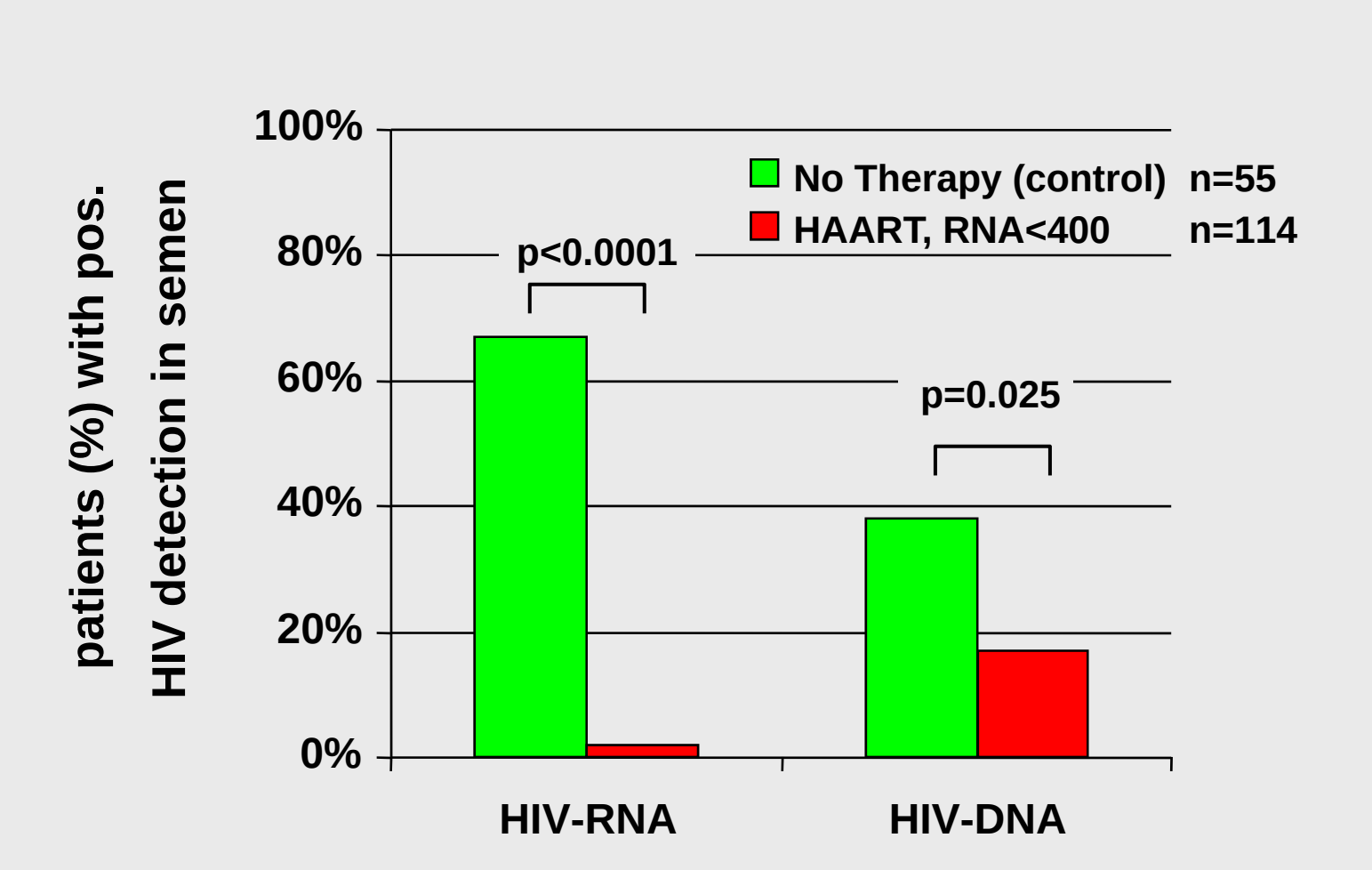


HIV in Semen during HAART



Vernazza et al., AIDS, 2000; 14:117-21

HIV in Semen during HAART



Vernazza et al., AIDS, 2000; 14:117-21

Genetic Characterization of Human Immunodeficiency Virus Type 1 in Blood and Genital Secretions: Evidence for Viral Compartmentalization and Selection during Sexual Transmission

TUOFU ZHU,[1] NING WANG,[1] ANDREW CARR,[2] DANIEL S. NAM,[1] ROBERT MOOR-JANKOWSKI,[1] DAVID A. COOPER,[2] AND DAVID D. HO[1]*

To explore the mechanism of sexual transmission of human immunodeficiency virus type 1 (HIV-1), we compared HIV-1 gp120 sequences in longitudinal samples from five acute seroconvertors with those from their corresponding sexual partners (transmitters). We used a quantitative homoduplex tracking assay to compare the overall genetic composition of HIV-1 quasispecies in each transmission pair and to track the transmitted viruses during the acute and asymptomatic stages of HIV-1 infection. In the chronically infected transmitters, HIV-1 variants in genital secretions differed from those in blood and variants in cells differed from those in cell-free plasma, indicating remarkable sequence heterogeneity in these subjects as well as compartmentalization of the virus in different bodily sites. Conversely, two of five seroconvertors had only a few related variants and three of five harbored only one viral population, indicating that in these subjects the transmitted viruses were typically homogeneous. **Transmitted viruses were evident in the donor's seminal plasma (one of five cases) and even more so in their seminal cells (three of five cases), suggesting that both cell-associated and cell-free viruses can be transmitted.** In every pair studied, the transmitted variant(s) represents only a minor population in the semen of the corresponding transmitter, thereby providing evidence that HIV-1 selection indeed occurs during sexual transmission.

Zhu et al, 1996, JVirol

Cell-free vs. Cell-associated trm

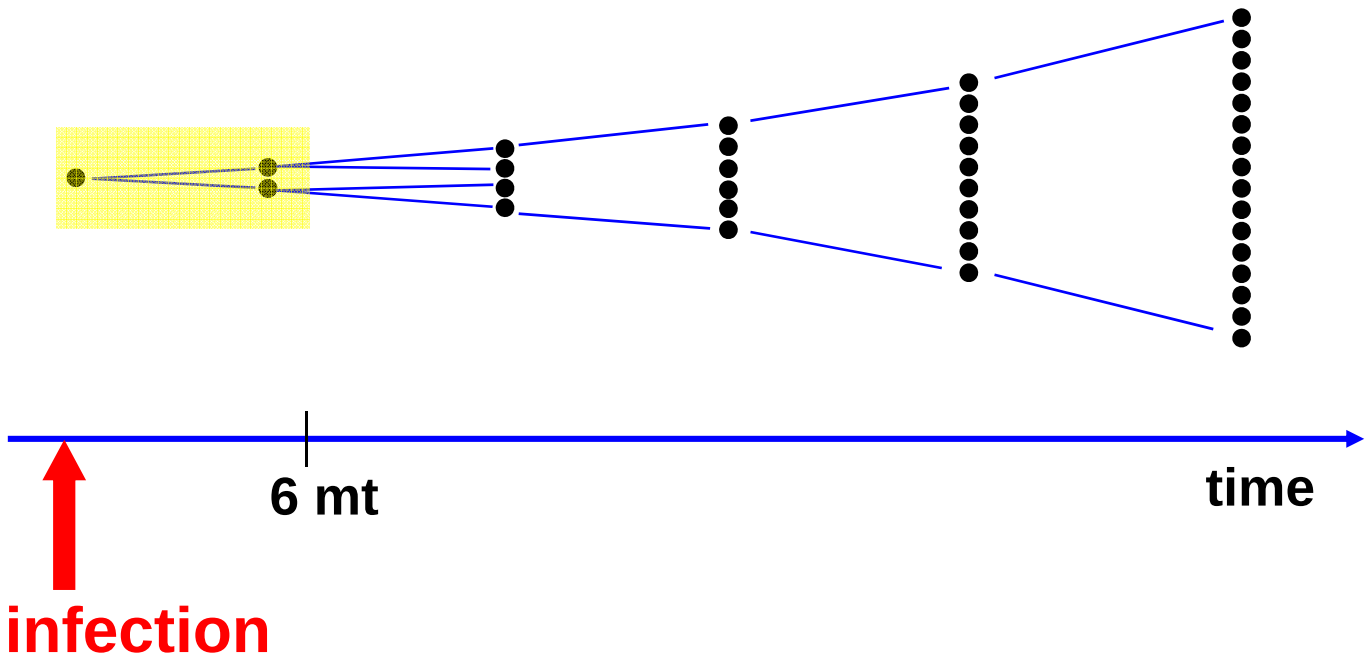
Gender differences in HIV-1 diversity at time of infection

E. Michelle Long[1,2,3], Harold L. Martin, Jr.[4], Joan K. Kreiss[4], Stephanie M.J. Rainwater[1,3], Ludo Lavreys[4], Denis J. Jackson[4,5], Joel Rakwar[5], Kishorchandra Mandaliya[6] & Julie Overbaugh[1,3]

[1]Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
[2]Molecular and Cellular Biology Program, [3]Departments of Microbiology,
[4]Medicine and Epidemiology, University of Washington, Seattle, Washington. USA
[5]Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya
[6]Coast Provincial General Hospital, Mombasa, Kenya.
Correspondence should be addressed to J.O.; email: joverbau@fhcrc.org

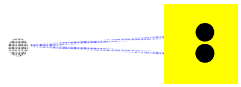
Long et al, Nat Med, 2000; 6:71-5

HIV diversity develops over time



HIV diversity in early infection

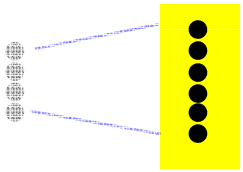
- **Men: 1 pattern**



→ <5% diversity: homogenous pattern

- **Women: 2 patterns**

→ homogenous pattern



→ heterogenous pattern

Potential hypotheses

- **Infected by different partners**
  - **Similar # sex acts / wk**
  - **Similar fraction with single partner**
  - **Phylogenetic clustering**
- **Differences in immune response**
  - **5/6 w already heterogenous before s/c**
- **→ Difference in transmitted virus**

Hypothesis

- **Sex. Trsm of HIV = rare event → 1 hit**
- **One single hit could be**
  - **Free virus**
  - **HIV-infected cell**
- **Multiple strains → Cell-associated**

HIV-diversity, STDs and DNA

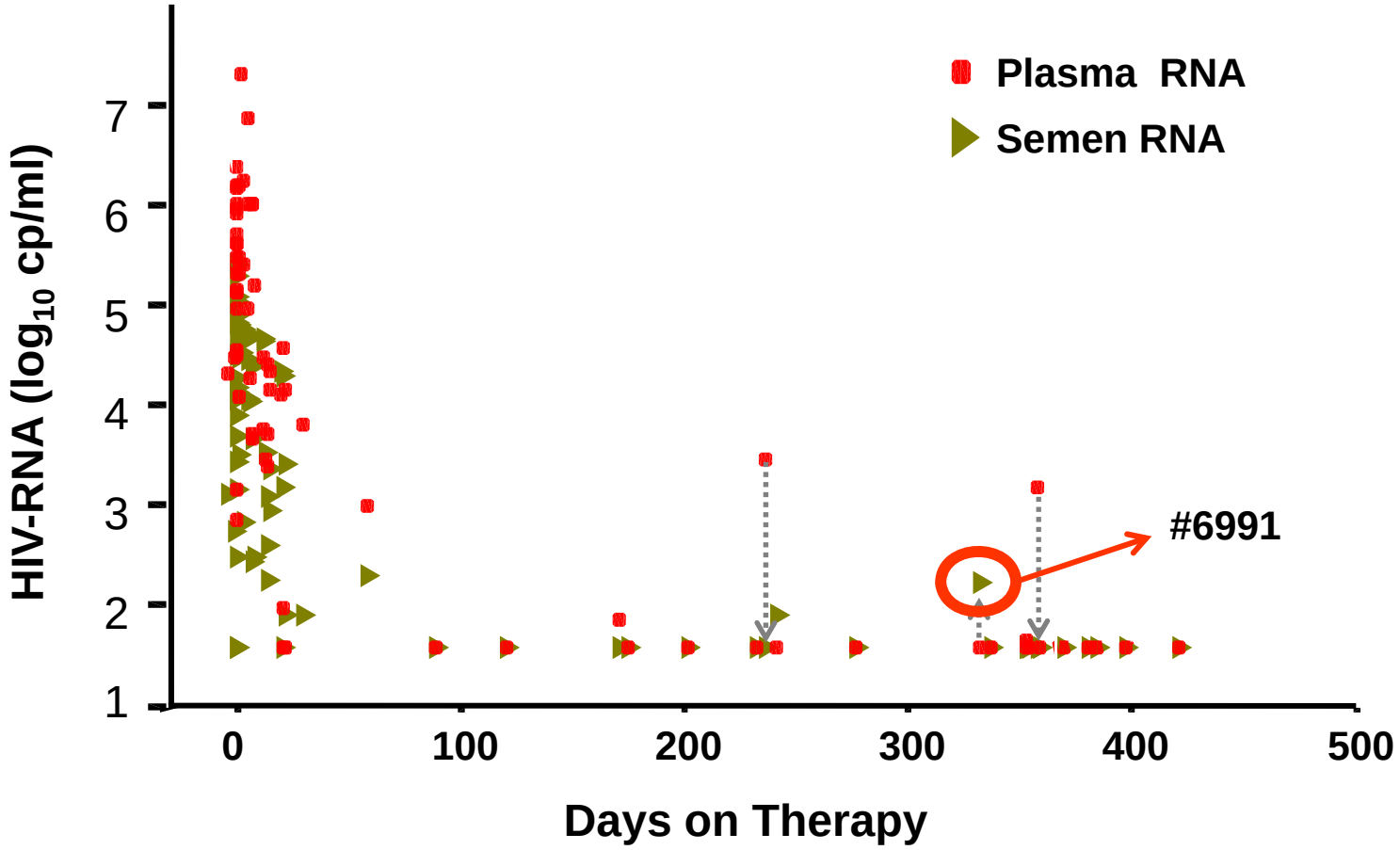
Table 2. Association between HIV-1 genetic complexity and factors present at the time of infection.

	Heterogeneous proportion (%)	Homogeneous proportion (%)	OR (95% CI)[a]	*P*
Bacterial vaginosis	41/88 (47)	27/65 (41)	1.2 (0.6–2.6)	0.5
Candida vaginitis	27/88 (31)	13/67 (19)	1.8 (0.8–4.2)	0.1
Chlamydia[b]	2/74 (3)	1/57 (2)	1.6 (0.1–93.4)	1.0
Gonorrhea	6/89 (7)	9/67 (13)	0.5 (0.1–1.6)	0.2
Genital ulcer disease	4/89 (4)	4/67 (6)	0.7 (0.1–4.2)	0.7
Trichomoniasis	12/88 (14)	10/67 (15)	0.9 (0.3–2.4)	0.8
Vaginal discharge	30/89 (34)	13/67 (19)	2.1 (0.9–4.8)	0.05
Cervicitis	23/88 (30)	7/66 (11)	3.0 (1.1–8.3)	0.02
Cervical mucopus	9/89 (10)	3/67 (4)	2.4 (0.6–14.3)	0.2
Vulvitis[c]	7/74 (9)	3/53 (6)	1.7 (0.4–10.9)	0.5
Any genital infection[d]	52/57 (91)	29/42 (69)	4.7 (1.4–18.1)	0.005
Oral contraceptives	21/51 (41)	11/49 (22)	2.4 (0.9–6.4)	0.04
Depo-medroxyprogesterone[e]	35/65 (54)	15/53 (28)	3.0 (1.3–6.9)	0.005
Any hormonal contraception[e]	56/86 (65)	26/64 (40)	2.7 (1.3–5.6)	0.003

Sagar, AIDS, 2004;18:615-9

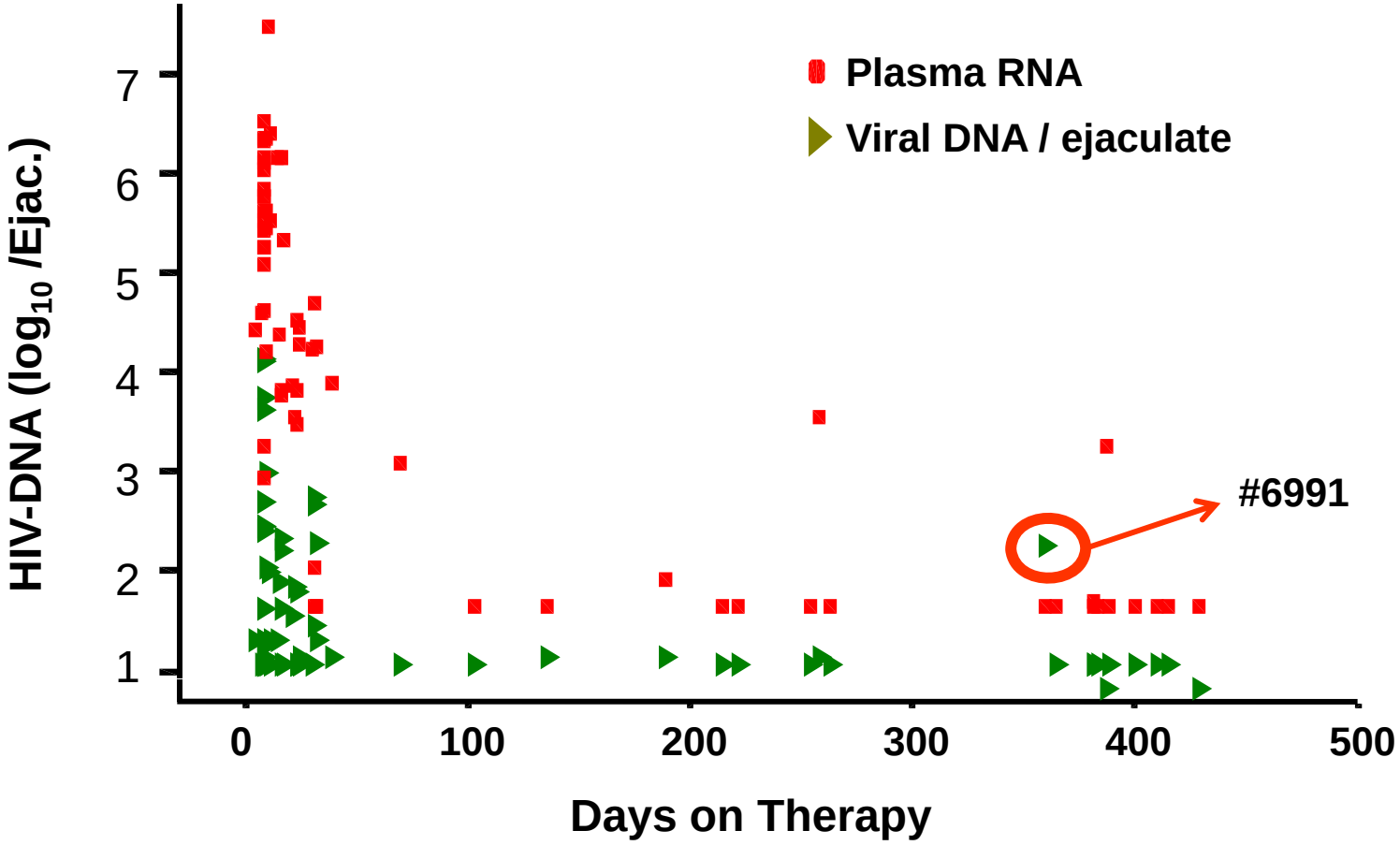
QUEST:

HIV-RNA in semen during tx

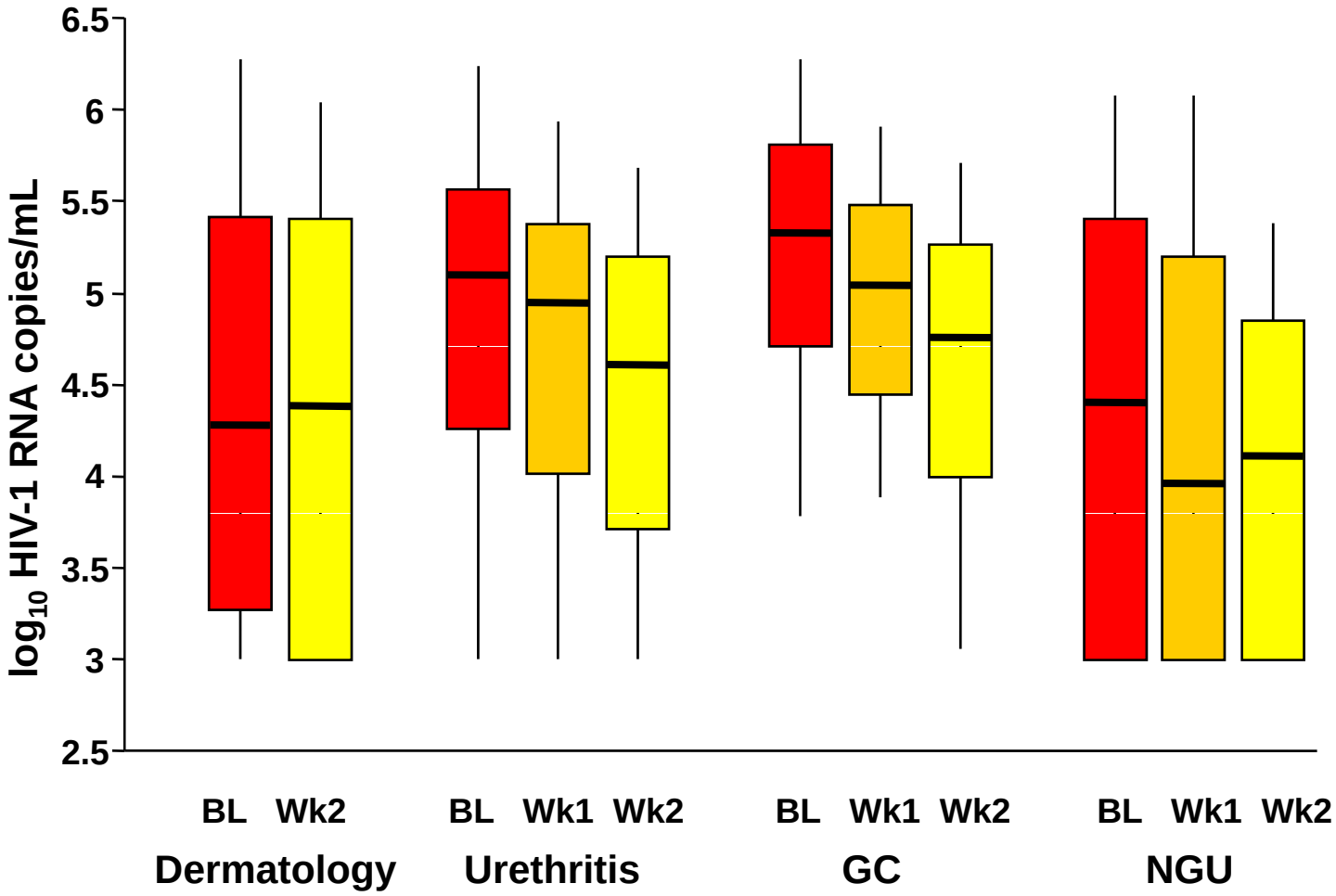


QUEST:

HIV-DNA in semen during tx

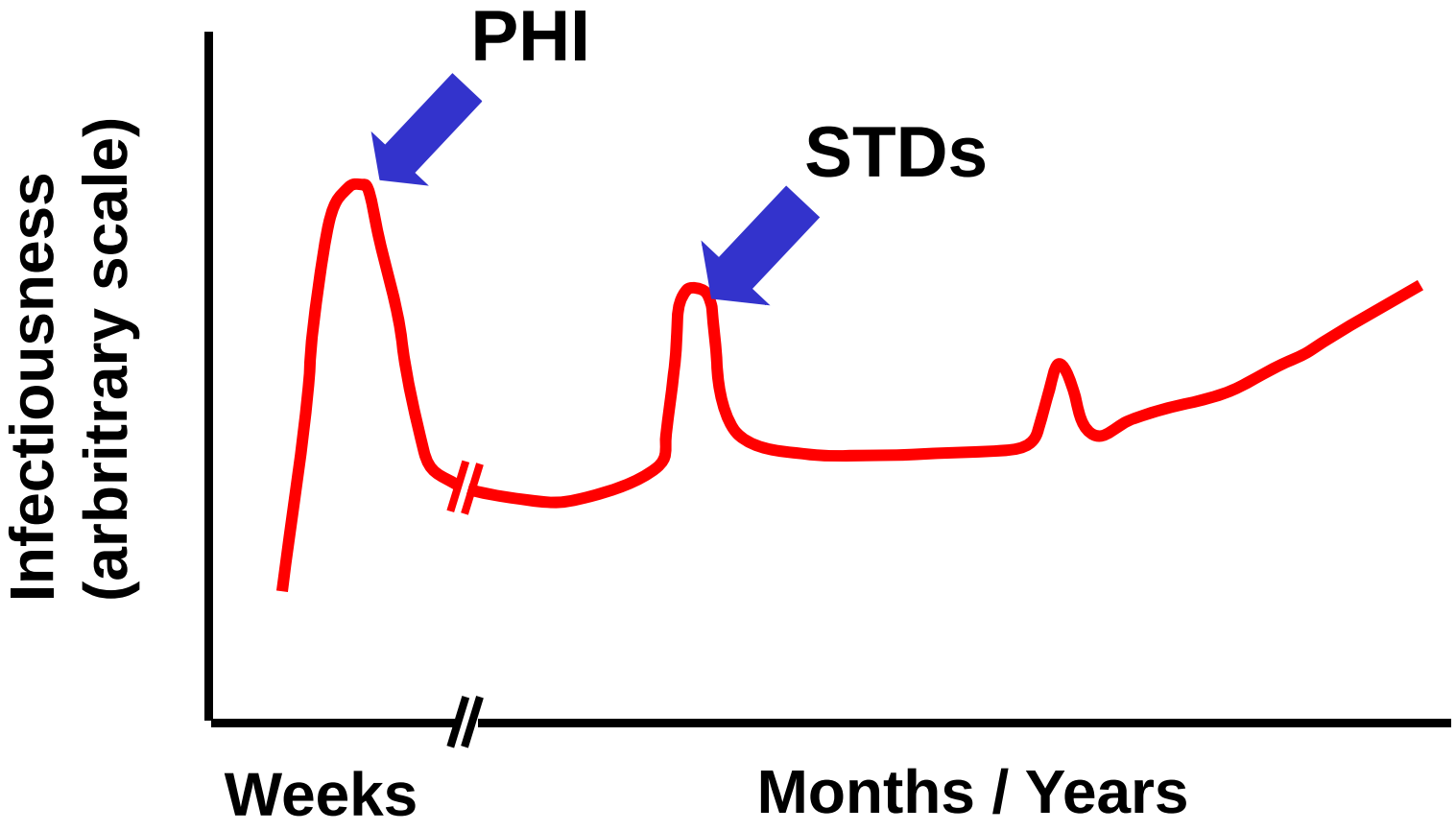


Malawi urethritis project: HIV-RNA in semen

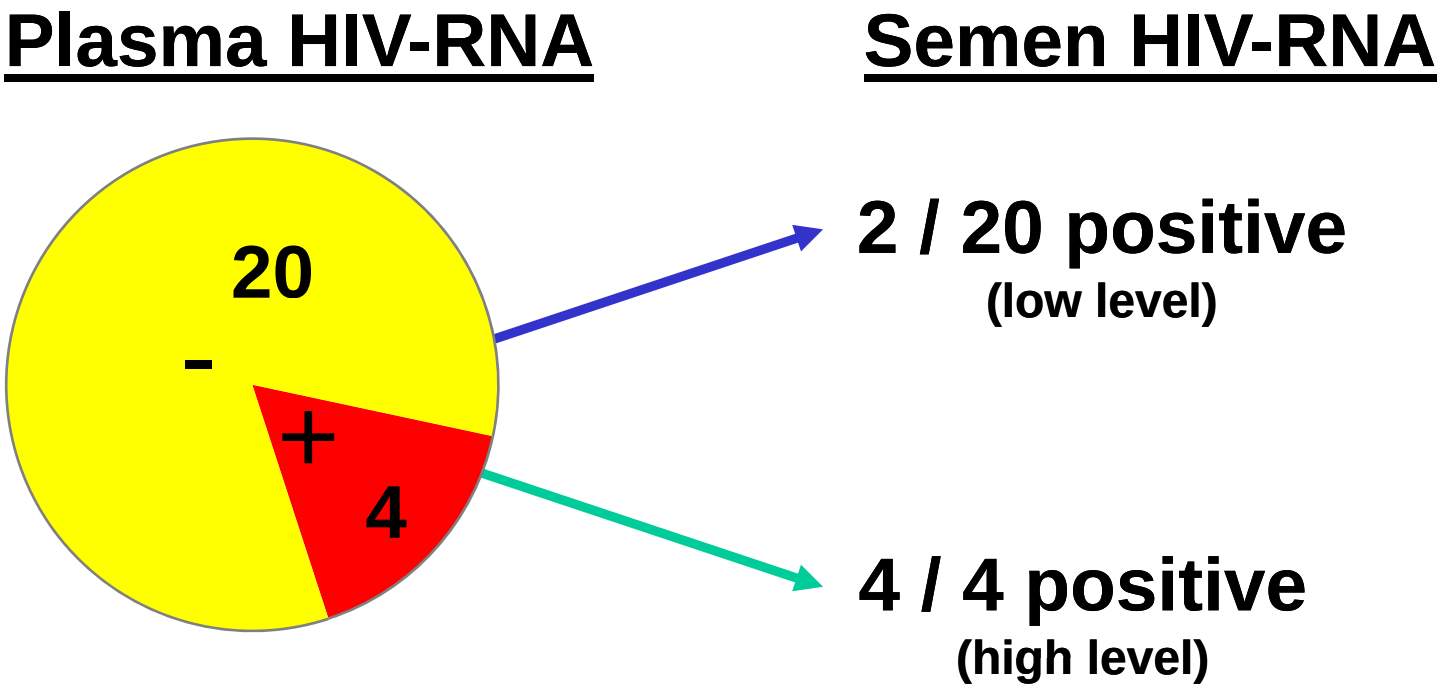


Cohen et al, Lancet 1997; 349:1868-73

HIV-Infectiousness over time



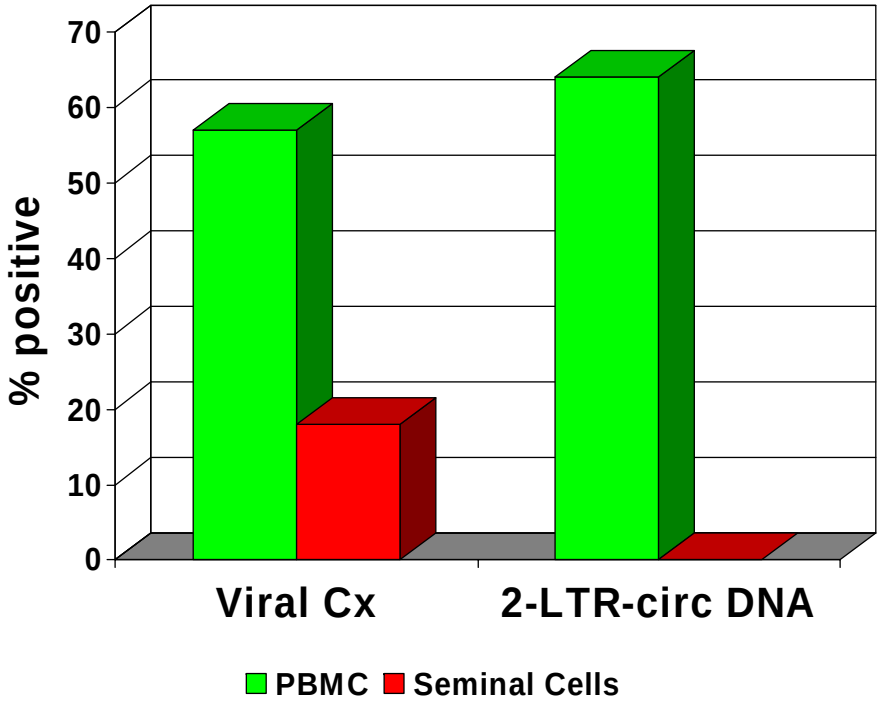
Urethritis during HAART (n=24)



Sadiq et al, AIDS 2002;16:219-25

HAART: Latent HIV in seminal cells

- 28 men
- Supressive HAART
- PBMC and SC
  - Viral growth
  - 2-LTR-circular DNA



Nunnari G. et al, AIDS, 2002; 16:39-45

Decline in infectivity* w. HAART

- **HIV incidence in SF-MSM during 1994-1999**

Time period at risk for infection	No. of Subjects	Infectivity*	Mean no. of unprotected RAI partners	Crude incidence rate/year
4/94 – 9/95	534	0.12	0.6	1.36%
9/95 – 11/96	481		0.75	1.29%
11/96 – 9/97	445	0.048	0.8	0.78%
9/97 – 3/99	320		1.3	1.02%

- 60%

* per-partnership probability of trx from HIV+ partner

Porco et al, AIDS 2004, 18:81–88

Literature Review

Case reports of trsm under HAART

Artificial Insemination in HIV-discordant couples(KSSG)

- **Experiences until 24.6.04**

- **Couples counselled 72**
- **Inseminations started 43** (60%)
- **Total Inseminations 145**
  - **Insem/couple: Median 3 (1-16)**
- **Pregnancies 17**
  - 12% of all Cycles
  - 40% of all couples

HIV und Kinderwunsch

HIV-discordant couples and parenthood: how are we dealing with the risk of transmission?

Parenthood is a strong, biologically motivated, instinctive desire. In the past, individuals infected with HIV struggled with the dilemma of a limited life expectancy and the strong wish to reproduce themselves. The risk of viral transmission to uninfected partners and offspring posed an additional barrier to conception. Many couples have practised unprotected intercourse to conceive, despite the risk of HIV transmission. The introduction of antiretroviral therapy with dramatically improved life expectancy has resulted in a resurgence of interest in parenting by HIV-affected couples.

couples worldwide practising unprotected sex for the purpose of conception could number in the millions.

The counseling provided to HIV-discordant couples seeking assisted reproduction at these centres includes a discussion of strategies aimed at maximizing protection from HIV transmission (such as adoption, intrauterine insemination or in-vitro fertilization and intracytoplasmic sperm injection with processed semen), but also includes important information on other risk-reduction measures that draw on recent ad
scientific understanding

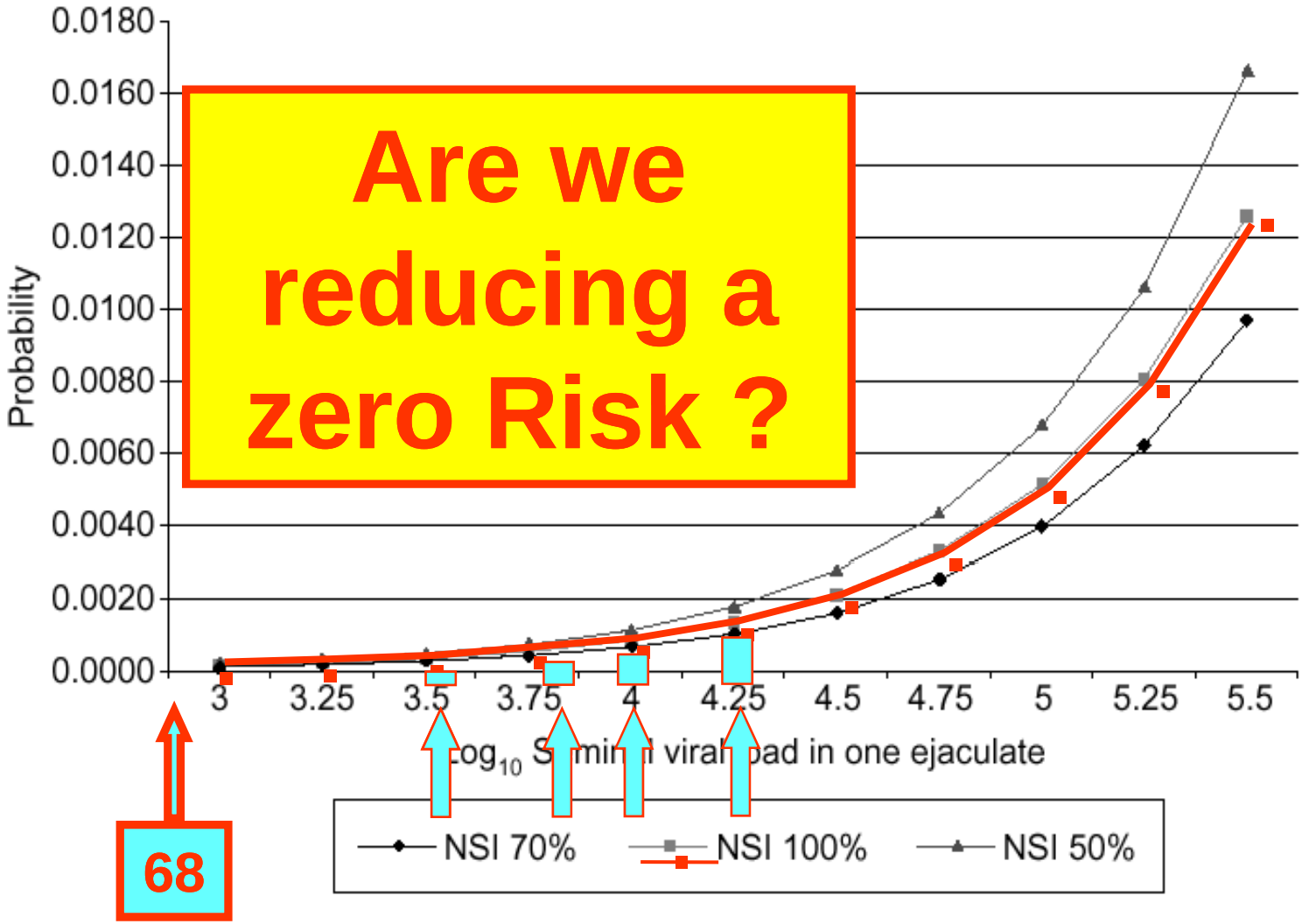
- **Retrospective analysis Semprini:**
  - **500 couples contacted after counselling**
  - **Half of couples had conceived natrually**
  - **1 woman was HIV-infected**

➔ **Is our intervention missing it‘s target?**

Vernazza et al, AIDS 28.2.06, S. 635-6

HIV-discordant couples in Insemination Program

HIV-RNA in semen



Chakraborty et al. AIDS 2001,15: 621-7

HAART und Transmissionsrisiko

- **Biologische Daten: Risiko reduziert**
- **HAART: Ø Transmission dokumentiert**
- **Epid. Studien**
- **Fallserien**

  z.B. Barroso, JAIDS 2006→

TABLE 1. Reproductive Outcome in 62 HIV-Discordant Couples in Which the HIV-Infected Partner Was Receiving Effective HAART

76 natural conceptions
52 couples with 1 pregnancy
6 couples with 2 consecutive pregnancies
4 couples with 3 consecutive pregnancies
1 twin pregnancy
9 fetal deaths
7 (23%) in 30 pregnancies among HIV-positive women
2 (4.7%) in 42 pregnancies among HIV-negative women
(OR = 6.1, 95% CI: 1.02 to 46.68; $P = 0.02$)
68 newborns
HIV transmission
Sexual: 0 cases in 76 pregnancies
Maternofetal: 1 case in 23 pregnancies among HIV-positive women

License to Love

Counselling of HIV-d/c couples

1. Information of both partner about transmission risks
2. Rule out asymptomatic STDs
3. Maintain fully suppressive HAART
4. Timing of unprotected intercourse (LH-urine test)
5. HIV-Pre-Exposure Prophylaxis (TDF)

License to Love

Pregnancy-rates in first 21 couples