HIV/STDs and Excretion of HIV in Genital Secretions

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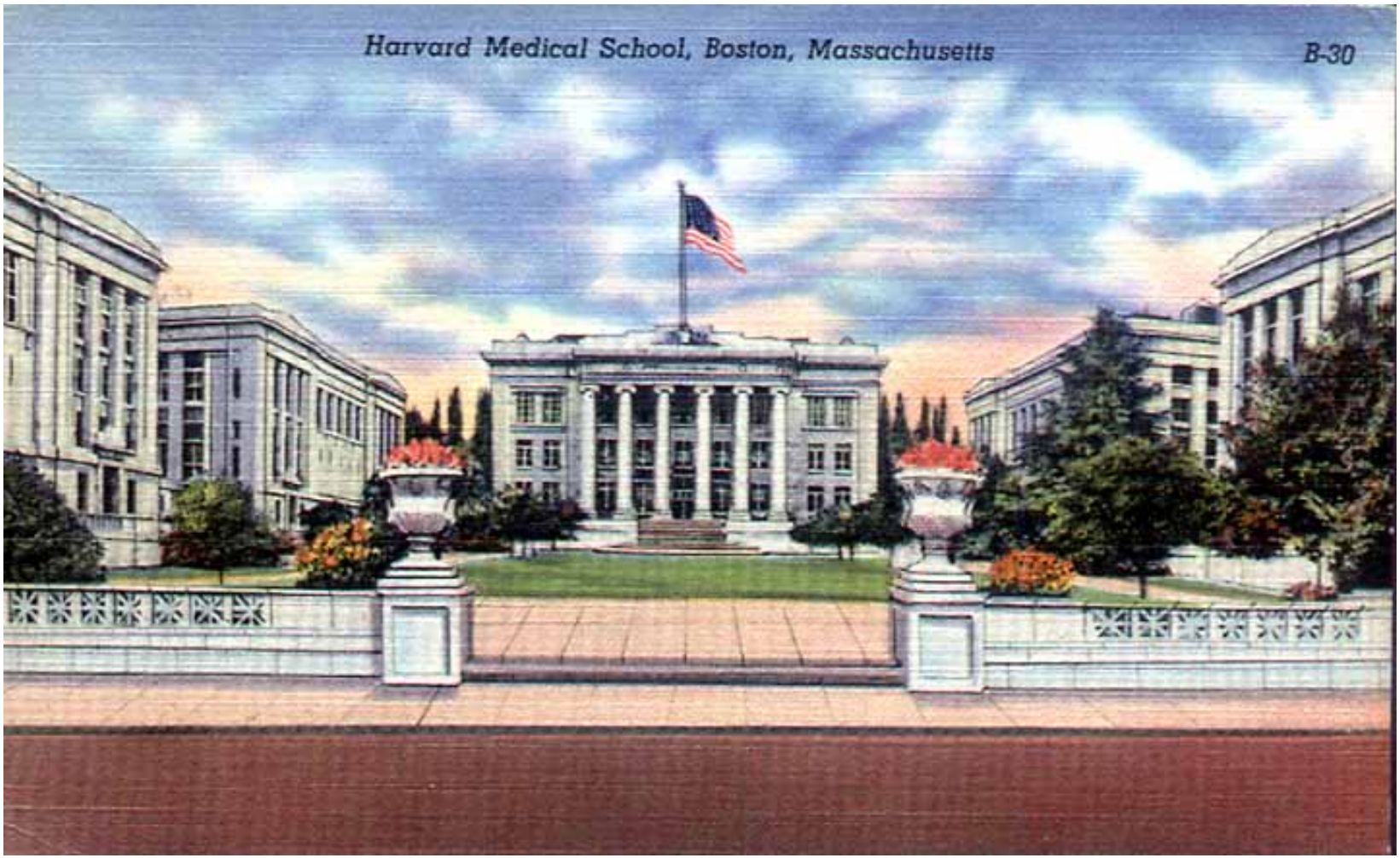
Implications for sexual transmission

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

Where it all began...



ISOLATION OF HTLV-III/LAV FROM CERVICAL SECRETIONS OF WOMEN AT RISK FOR AIDS

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Vogt M, Lancet, 8. March 86

Staff photo by Ted Fitzgerald

RESEARCH TEAM: Doctors Donald Craven, left, Martin Hirsch, center, and Markus Vogt, members of the MGH and Boston City Hospital research team, announce AIDS study results at a press conference.

New study: AIDS virus carried by women

By MICHAEL LASALANDRA

THE DEADLY AIDS virus for the first time has been found in the genital secretions of women, increasing evidence that it can be spread sexually from women to men, researchers said yesterday.

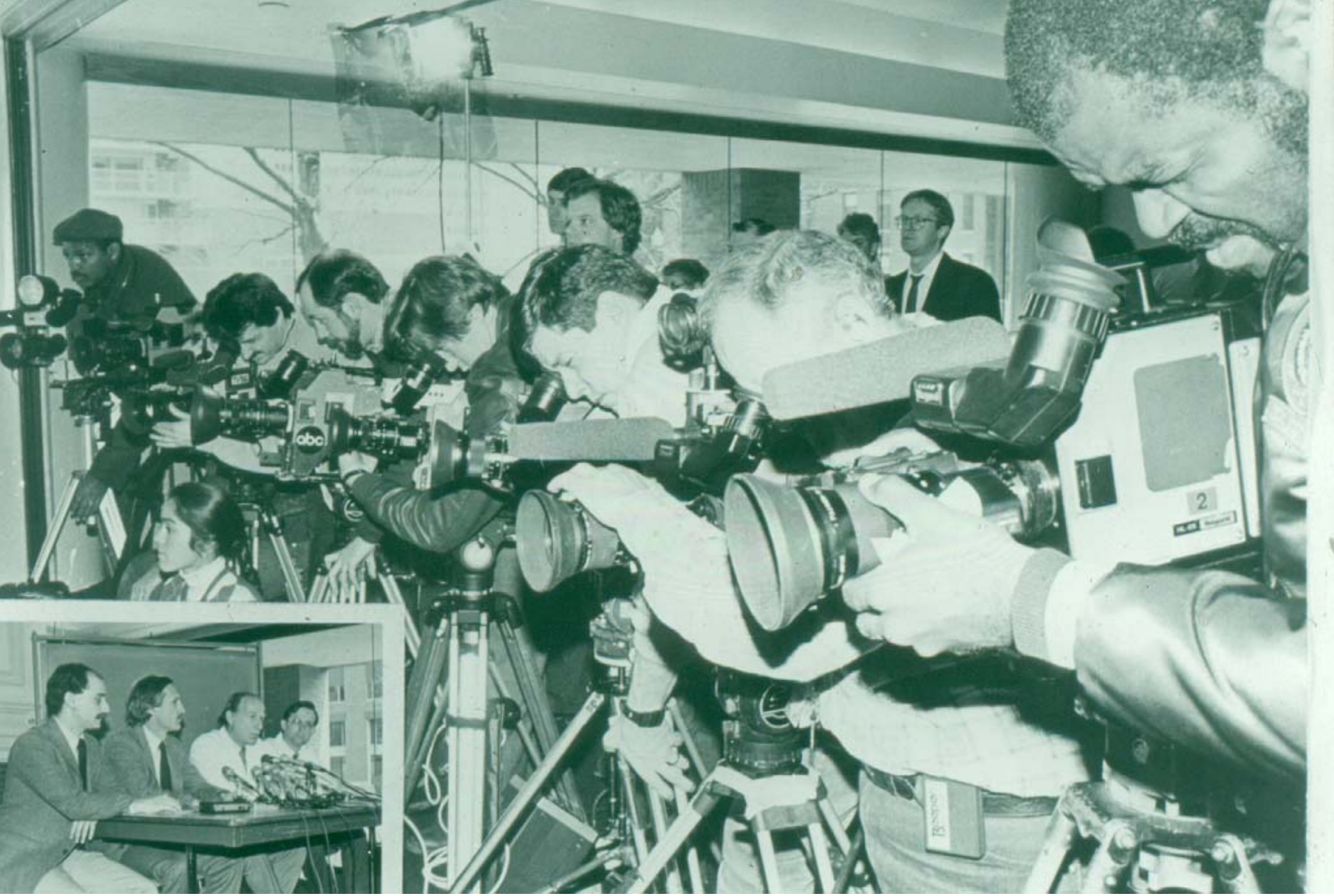
While the study did not prove that women can sexually transmit the virus, it warned that contact with prostitutes or anonymous sexual activity — either

Key find in treatment of disease

WASHINGTON — In a development that may lead toward a treatment for AIDS, researchers reported yesterday they have isolated an enzyme that controls the ability of the AIDS virus to infect people.

The availability of this enzyme in the laboratory means that scientists will be able to test a variety of drugs against it to find the best way to block its activity and thus keep the AIDS virus from infecting normal cells.

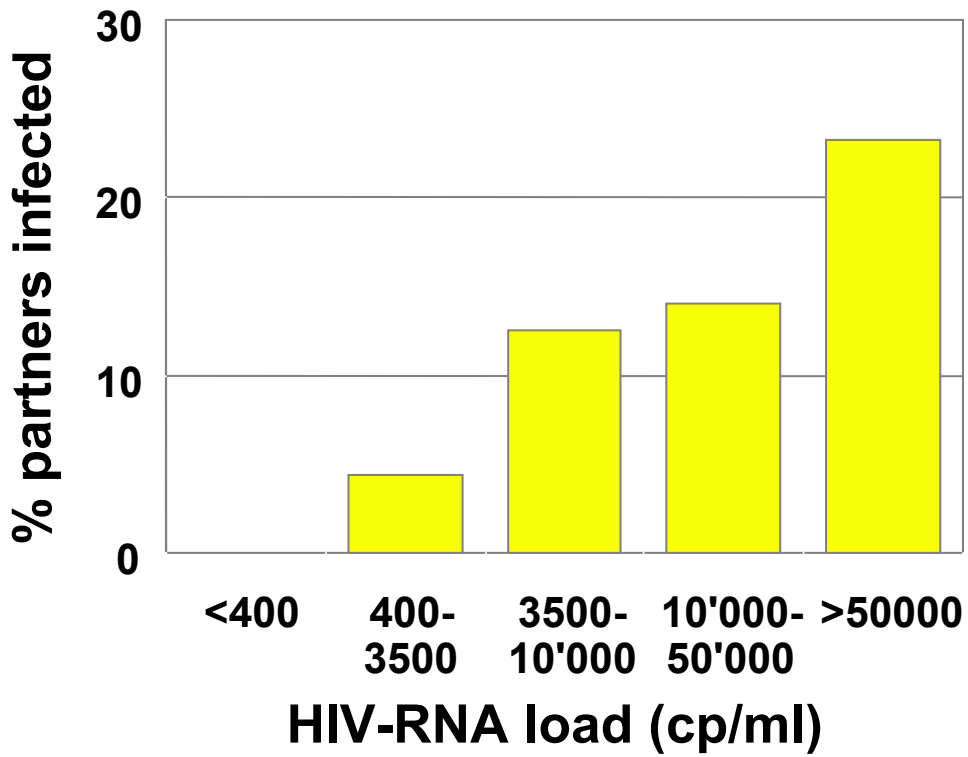
Several drugs are being studied for possible activity against the deadly Acquired Immune Deficiency Syndrome but there is as yet no way to stop the progression of the disease.


abc
2

Schultz et al. BMJ 1999;319:1596-1600

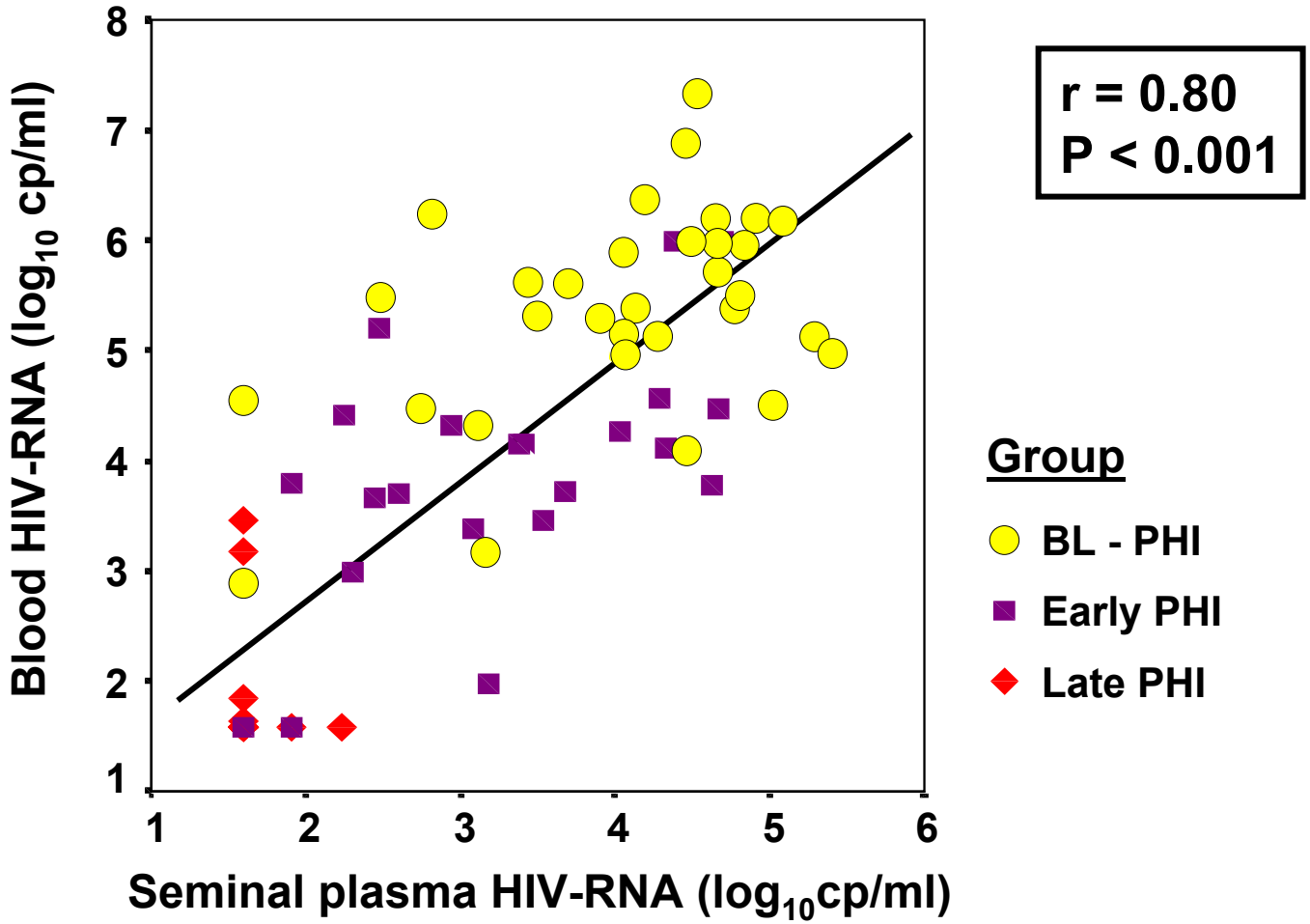
VL and HIV-Transmission-Risk

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



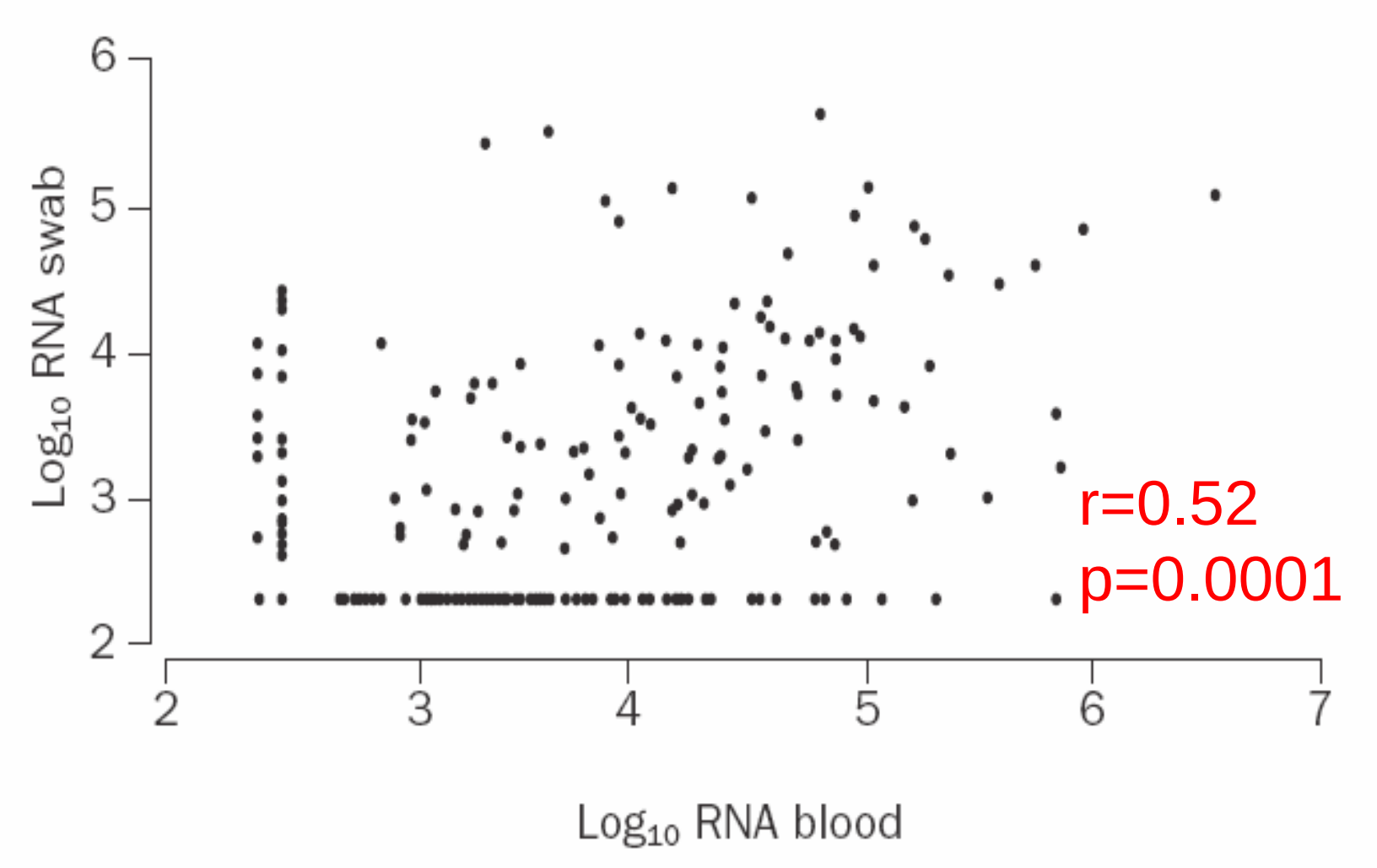
Quinn, NEJM, 2000; 342:921-9.

HIV-RNA in blood and semen



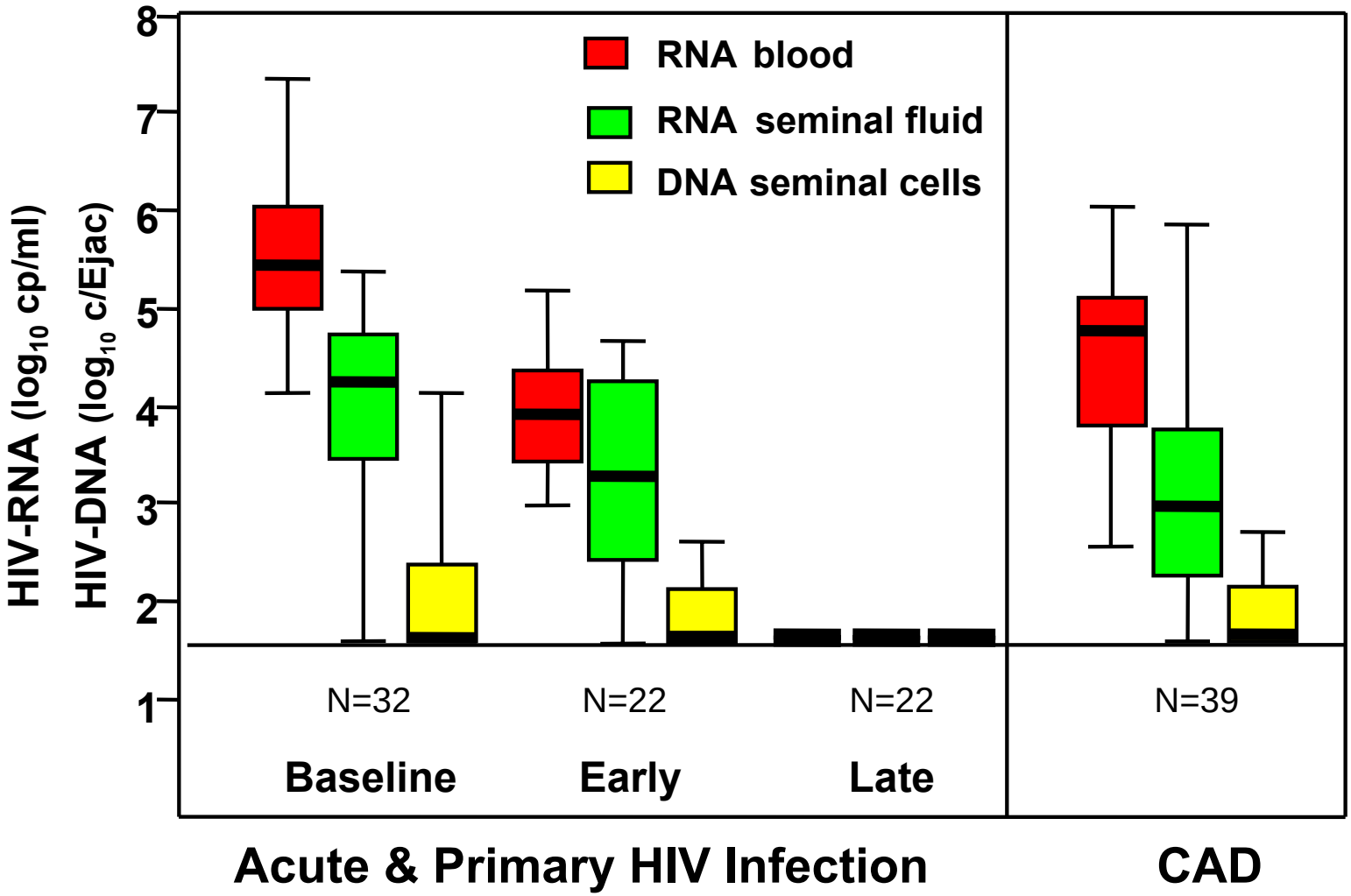
Vernazza, 2000, Quest-Study Group

Genital and blood VL in women



Kovacs et al, Lancet 2001; 358: 1593–601

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



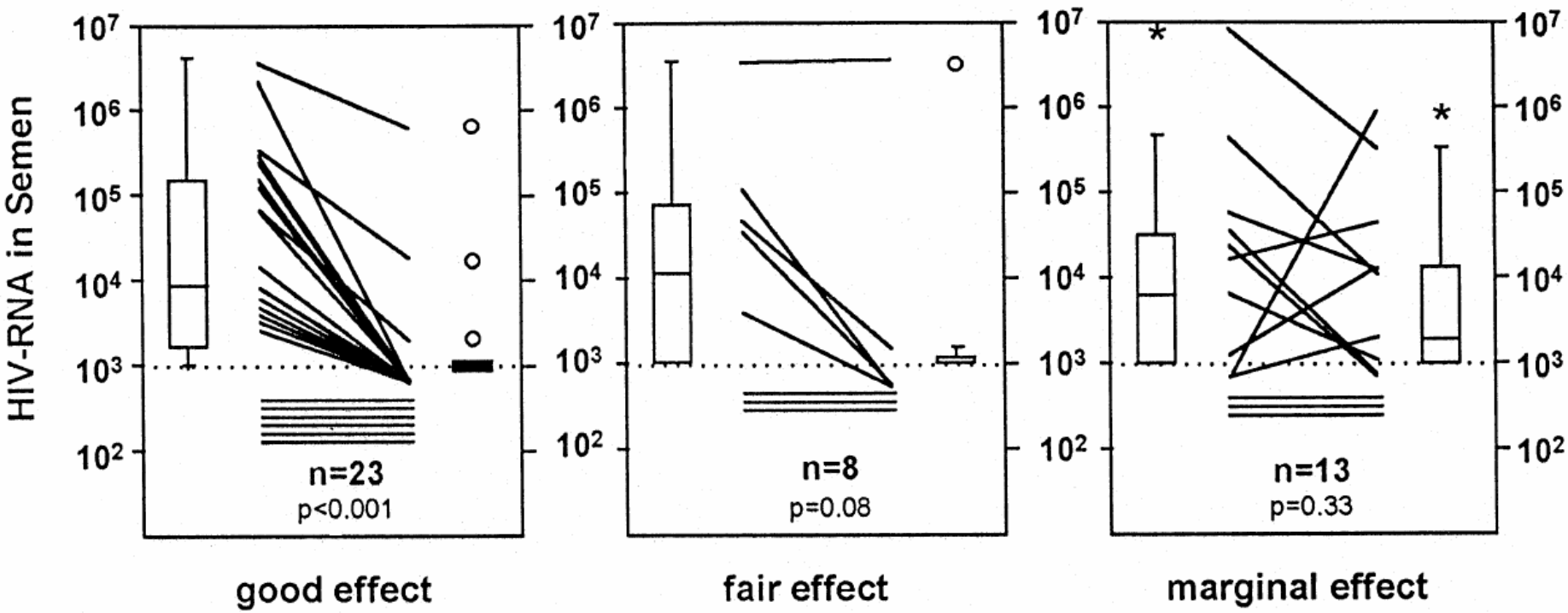
Summary 1

- **HIV in genital tract follows blood VL**

→Q: Is there a genital compartment

→Q: What is the effect of treatment

HIV in semen under HIV therapy

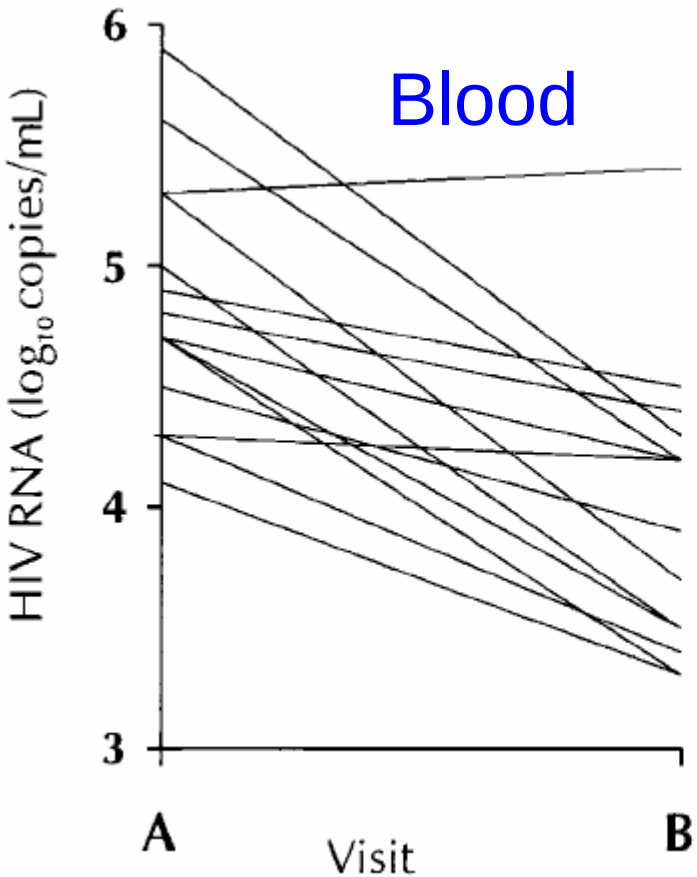


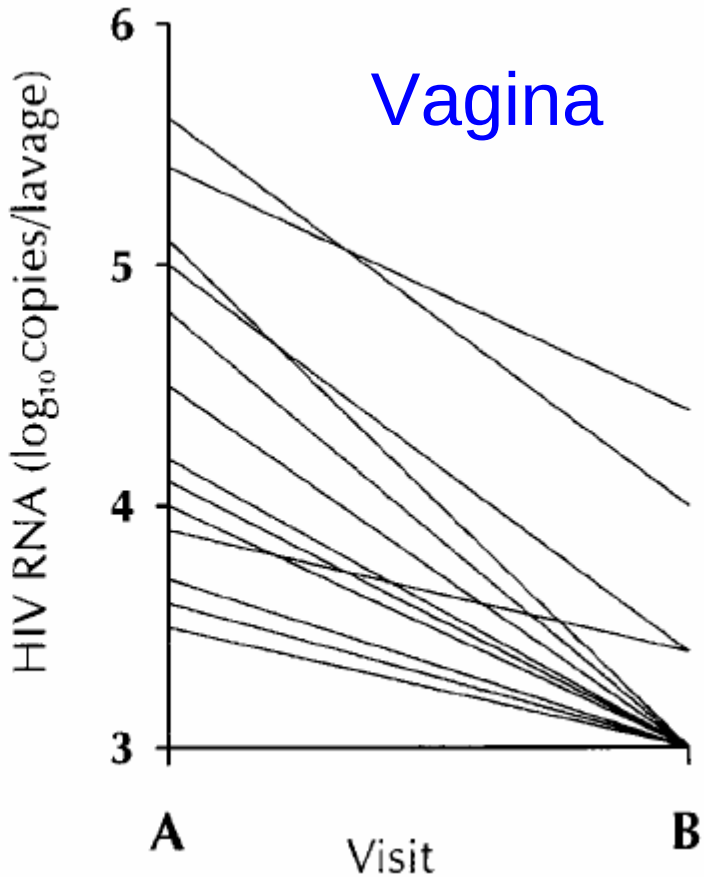
>1 log drop

<0.5 log drop

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

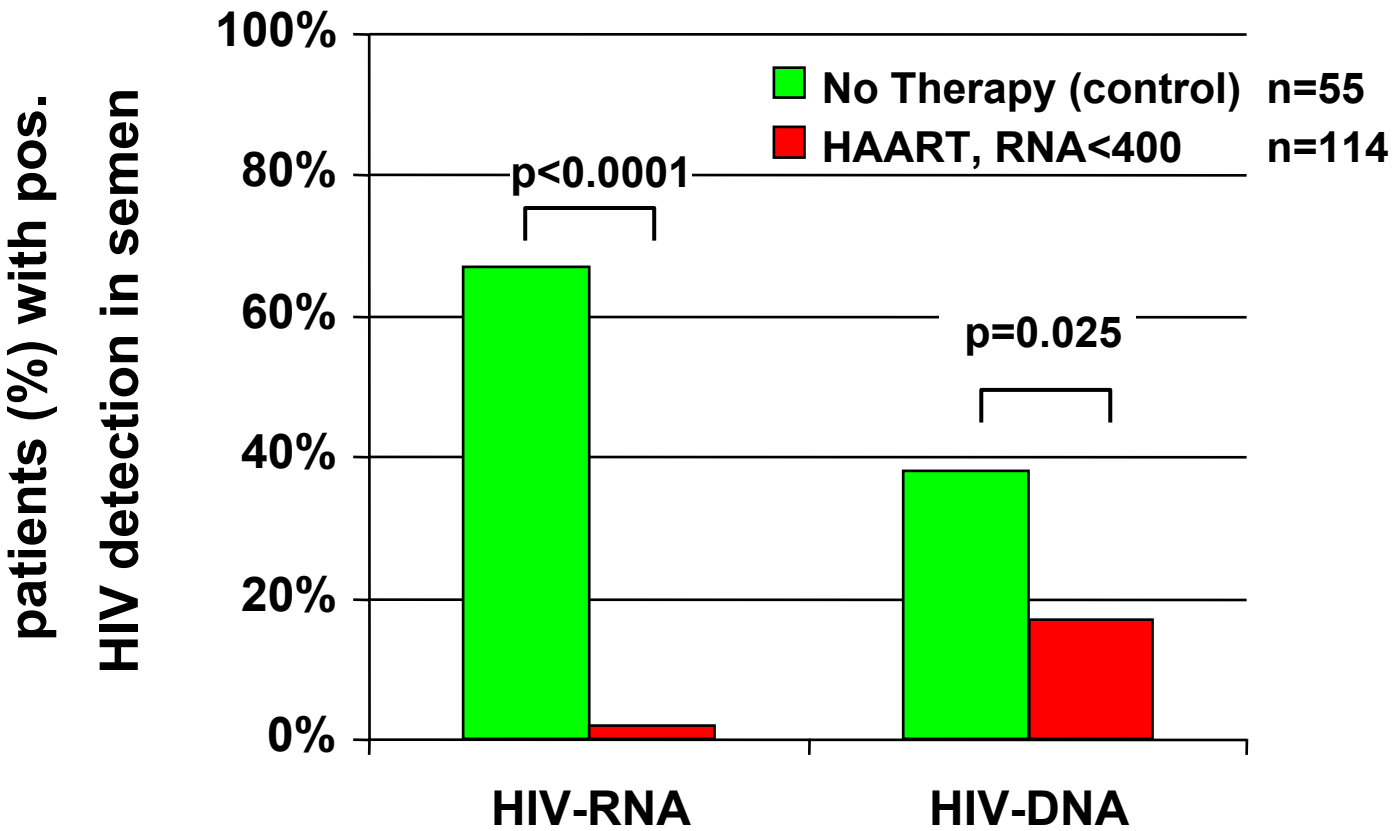
Vaginal HIV under HIV therapy





Hart C. et al, JID, 1999;179:871-82

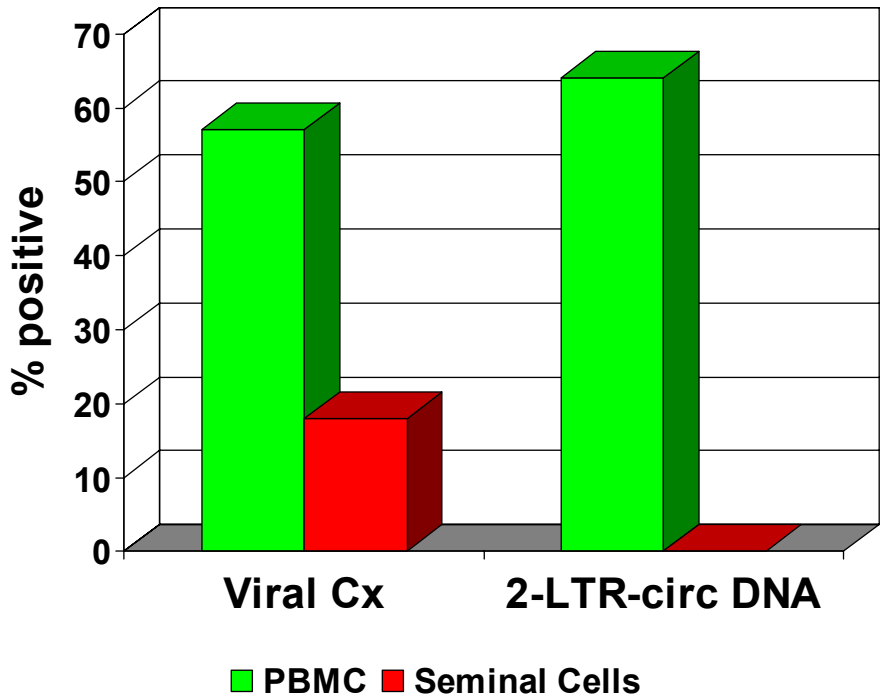
HIV in Semen during HAART



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

HAART: Latent HIV in seminal cells

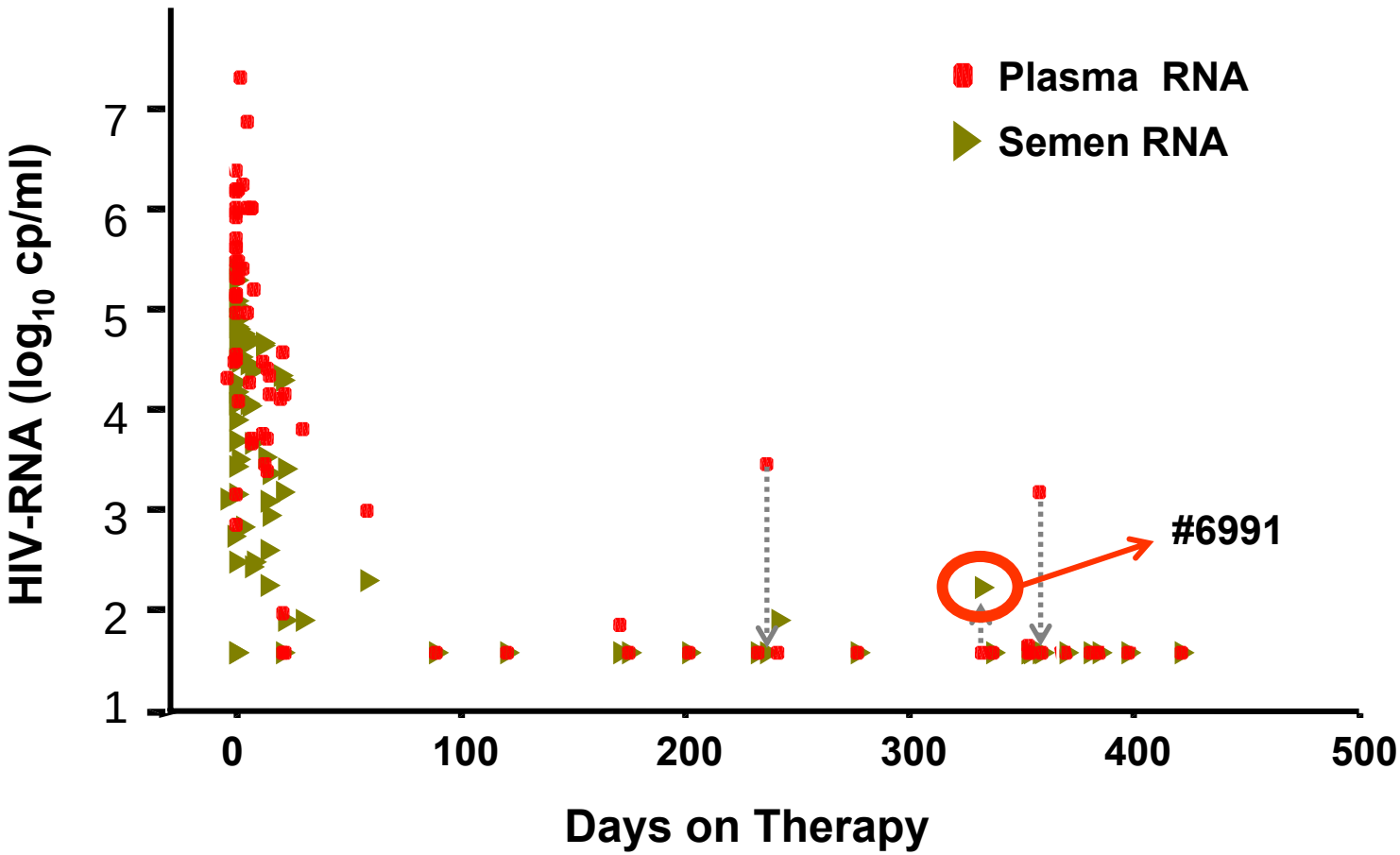
- 28 men
- Supressive HAART
- PBMC and SC
  - Viral growth
  - 2-LTR-circular DNA



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

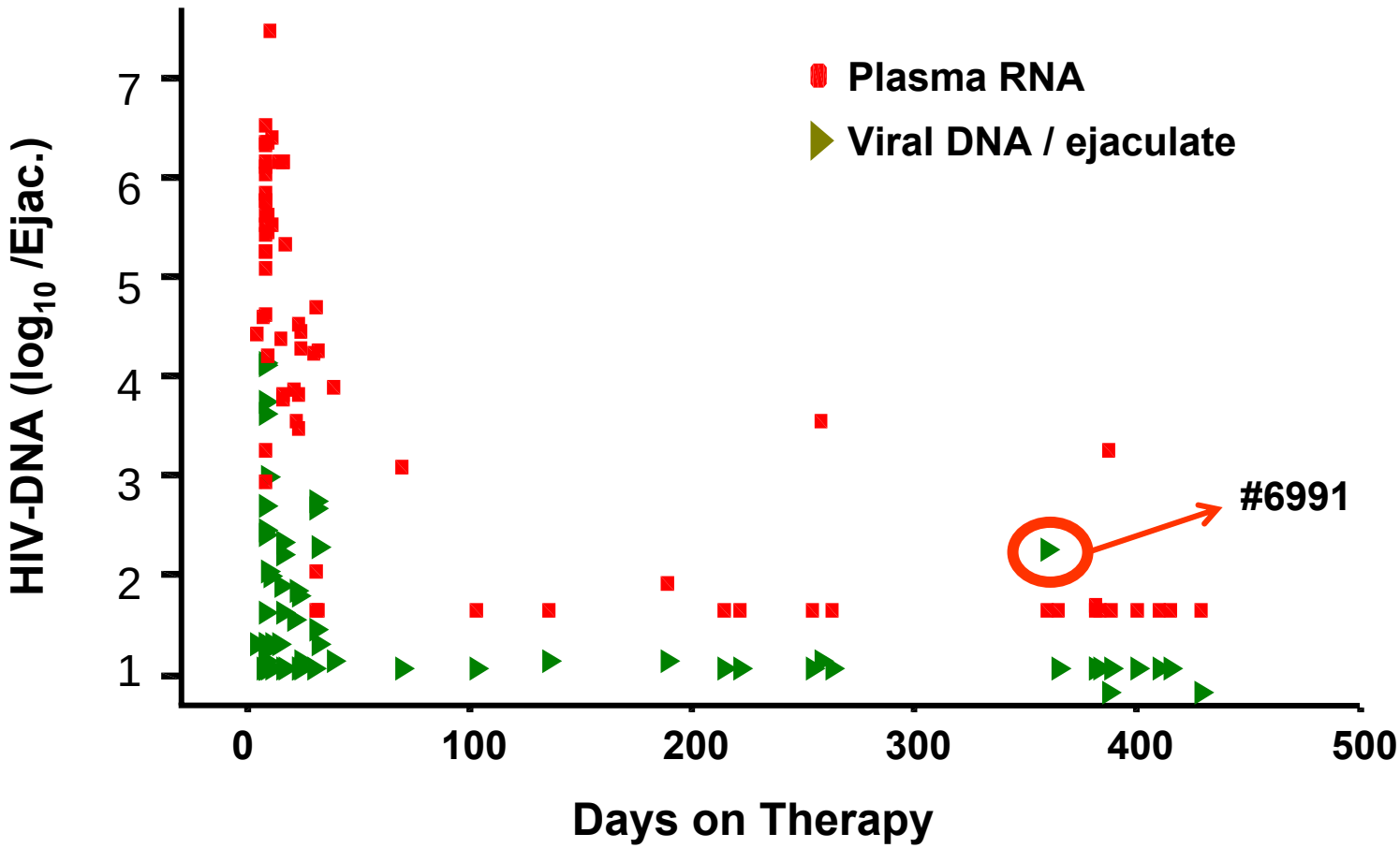
QUEST:

HIV-RNA in semen during tx

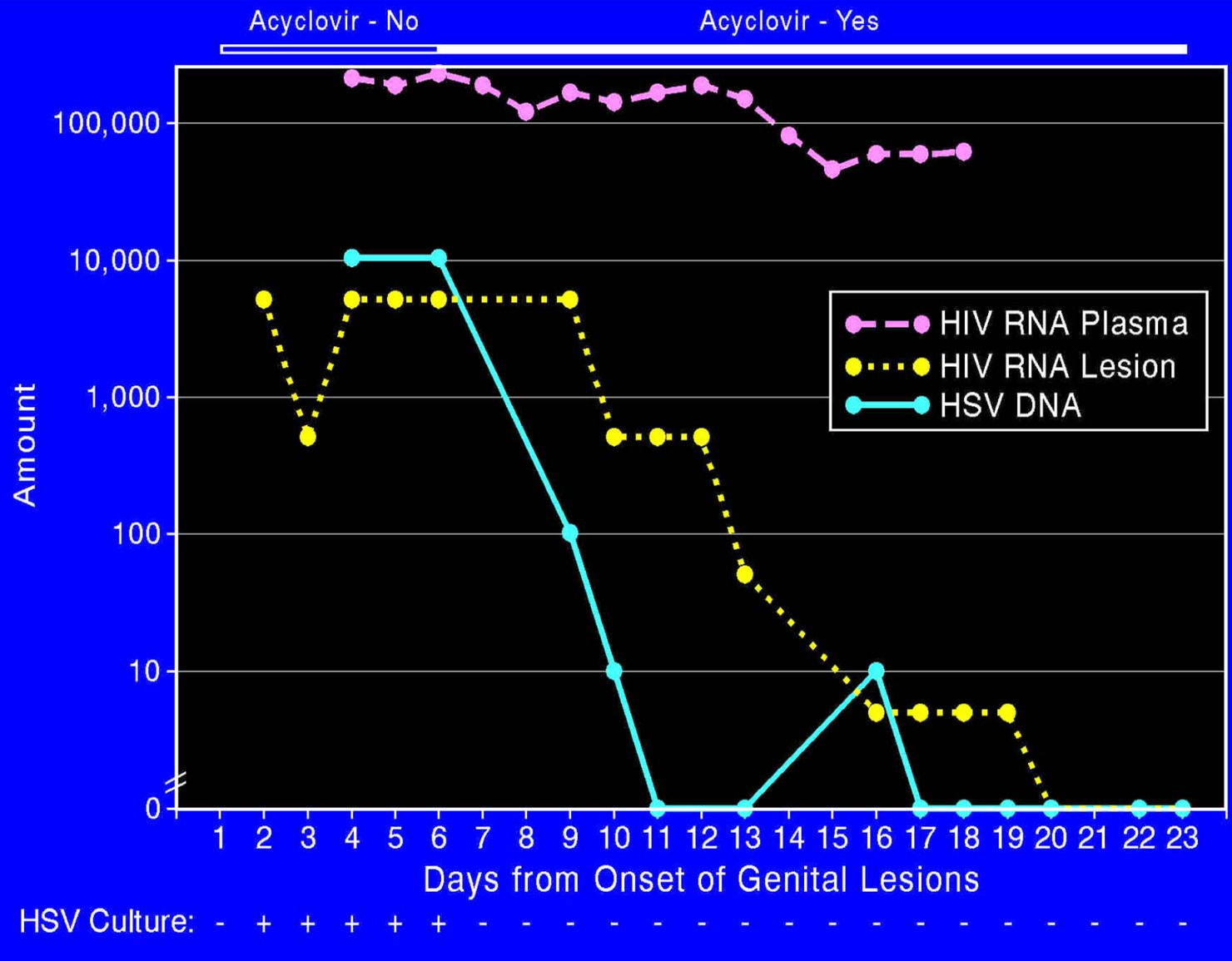


QUEST:

HIV-DNA in semen during tx



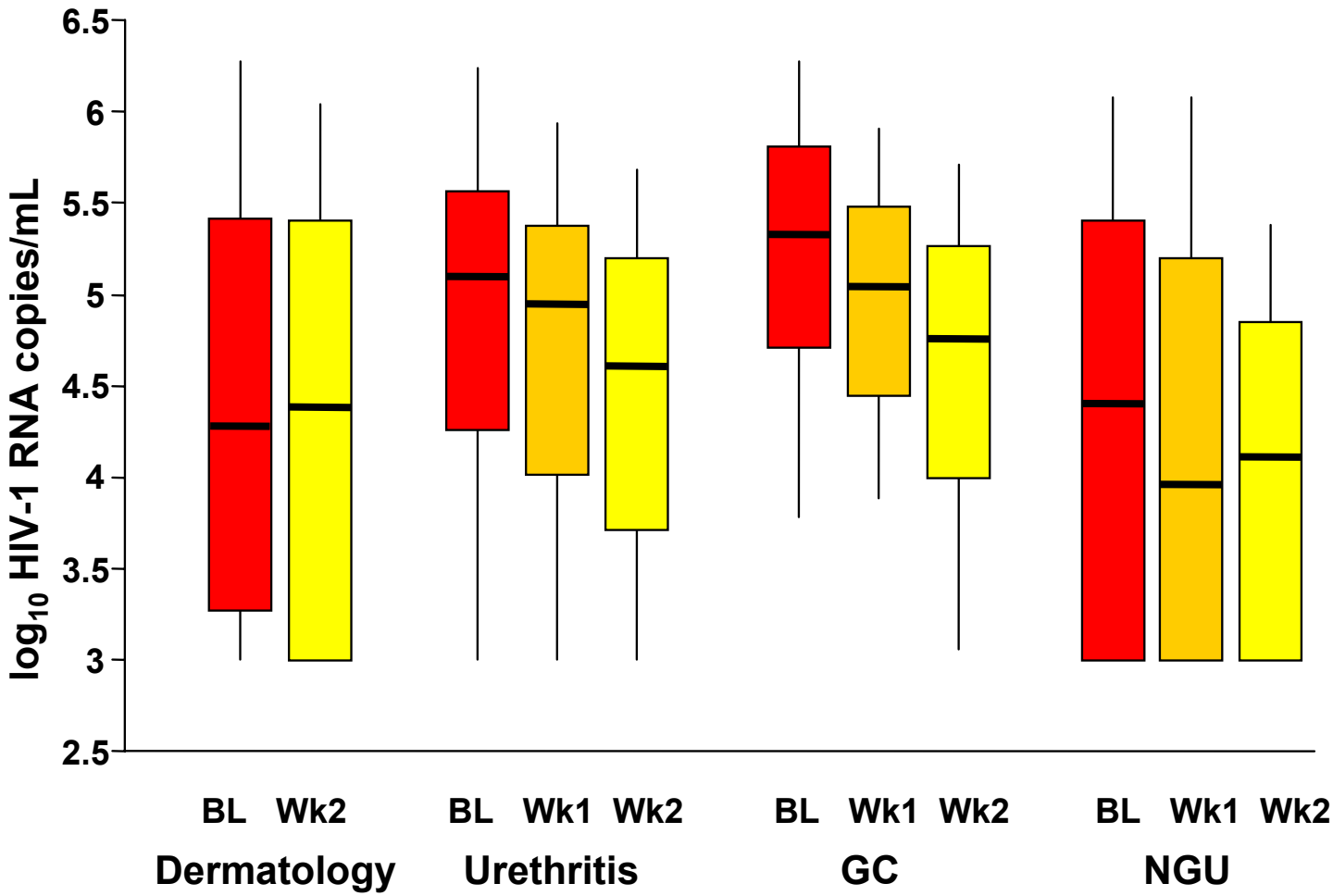
HIV RNA Detected in a Genital HSV Lesion During Rx with Acyclovir



LC-2946 7/24/1997

Courtesy slide: L. Corey

Malawi urethritis project: HIV-RNA in semen



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

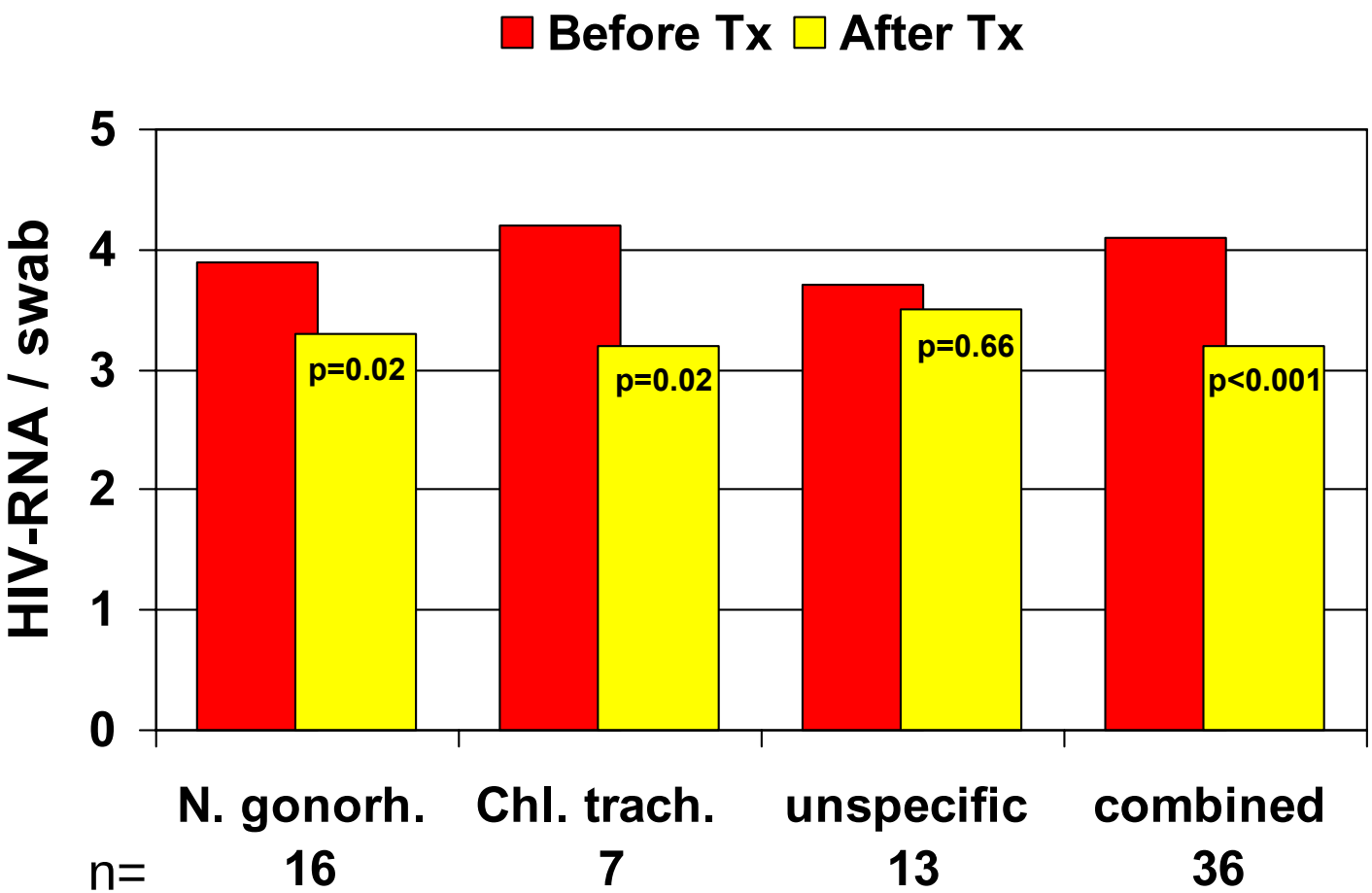
Local inflammation and genital shedding of HIV: Men

Table 3. Significant ($P \leq 0.05$) biological correlates of HIV shedding in the male genital tract in studies published between 1996 and 2002.

Correlate	Endpoint	Study population	Study type	References
Asymptomatic urethritis	RNA	UK	Cross-sectional	[154]
Symptomatic urethritis	RNA	Malawi	Longitudinal	[148]; (reviewed in [120])
	Genetic diversity	Malawi	Longitudinal	[152,153]
Genital ulcer disease	RNA	Malawi	Cross-sectional	[149]
Trichomonas vaginalis	RNA	Malawi	Cross-sectional	[151]
Seminal polymorphonuclear cell count	Culturable virus	US	Observa-tional	[147]
Cytomegalovirus	RNA Culturable virus	US	Observa-tional	[147]

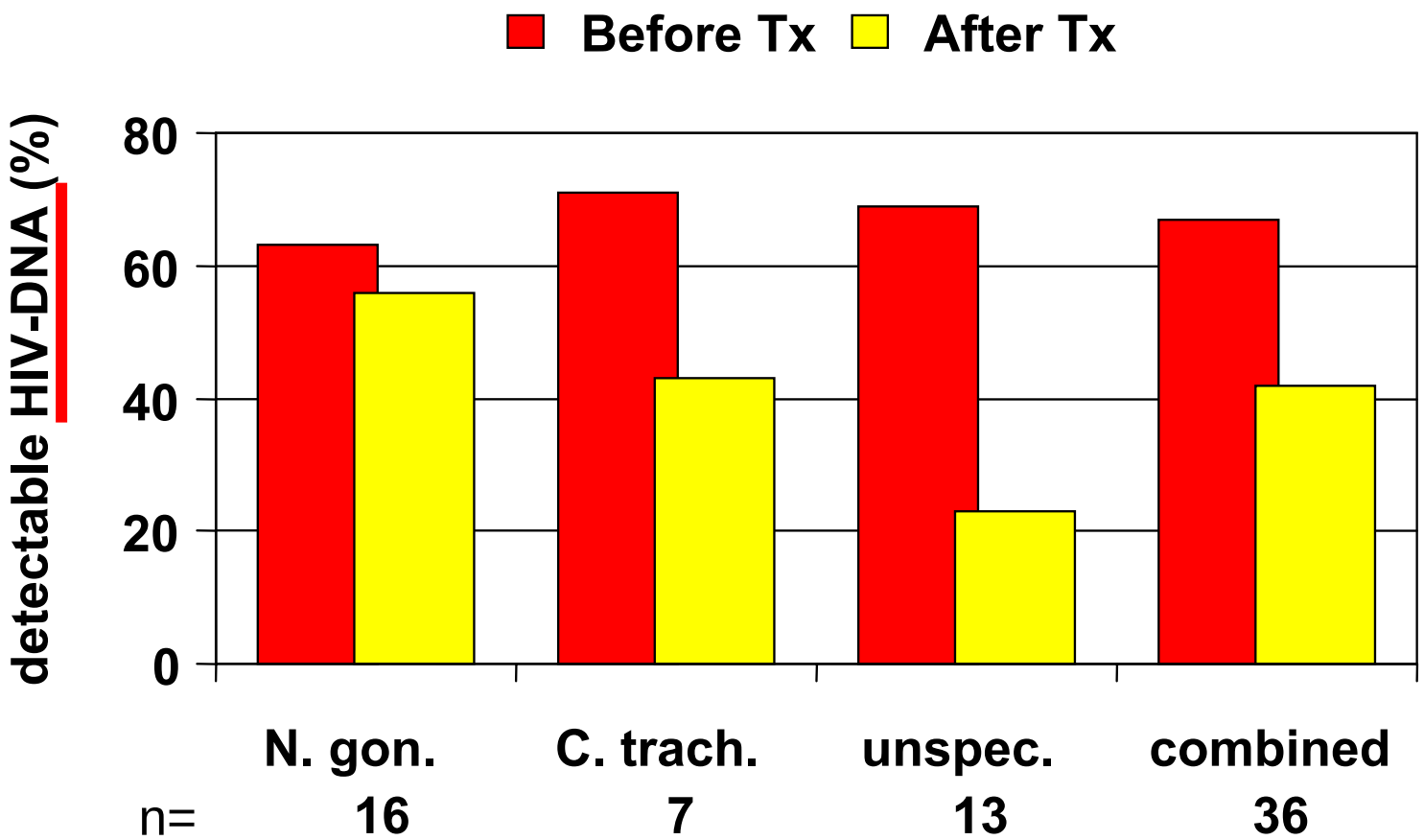
Coombs et al, AIDS, 2003;17:455 -80

Tx of Cervicitis and Shedding of HIV



McClelland et al, AIDS 2001; 15:105-110

Tx of Cervicitis and Shedding of HIV



McClelland et al, AIDS 2001; 15:105-110

Local inflammation and genital shedding of HIV: Women

Table 2. Significant ($P \leq 0.05$) microbiological correlates of HIV-1 shedding in the female genital tract in studies published between 1996 and 2002[a].

Correlate	Endpoint	Study population	Study type	References
Bacterial vaginosis	RNA	US	Cross-sectional	[287]
Herpes simplex virus-2	RNA	Central Africa	Cross-sectional	[118]
Human papillomavirus	Cell-free and cell-associated RNA, not DNA	Italy	Cross-sectional	[176]
Chlamydia trachomatis	Detectable RNA	Côte d'Ivoire	Cross-sectional	[128]
	Swab DNA and RNA	Kenya	Treatment	[129]
	Swab RNA and DNA	Kenya	Treatment	[130]
	Multiple	Africa	Meta-analysis	[119]
Neisseria gonorrhoeae	Detectable RNA	Côte d'Ivoire	Cross-sectional	[128]
	DNA swab	Kenya	Cross-sectional	[127]
	Swab DNA and RNA	Kenya	Treatment	[129]
	Multiple	Multiple	Meta-analysis	[120]
Candida vulvovaginitis	DNA	Kenya	Cross-sectional	[127]
	Swab RNA and DNA	Kenya	Treatment	[130]
Non-specified ulcers and/or inflammation	Cell-free and cell-associated CVL RNA	US	Treatment	[22]
	CVL RNA	US	Treatment	[137]
	Vaginal biopsy DNA and RNA	Thailand	Cross-sectional	[160]
Vaginal discharge	DNA	Kenya		[126]

[a]Many of the analyses assess the contribution of multiple or any co-factor to genital HIV shedding. CVL, cervicovaginal lavage.

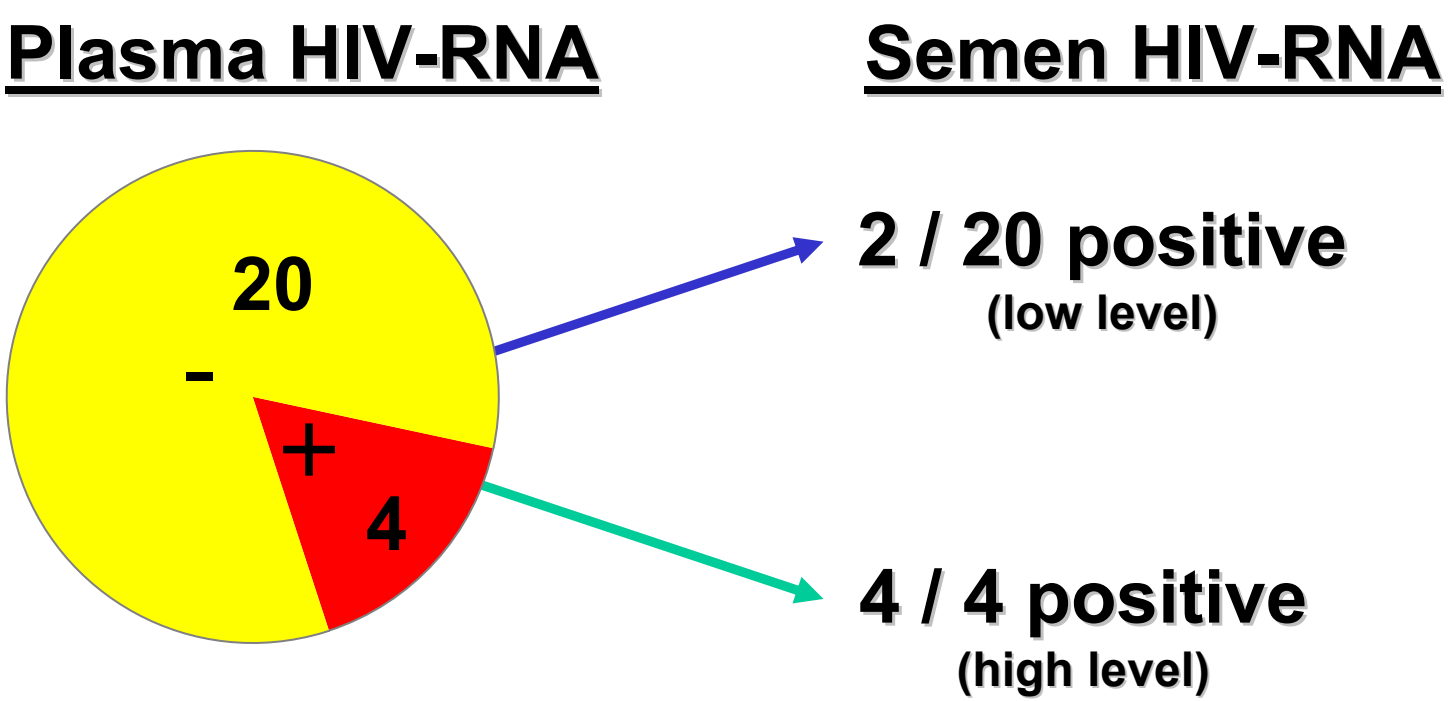
Coombs et al, AIDS, 2003;17:455 -80

Effect of HSV on genital HIV

- 200 women, HSV-2 and HIV seropos.
  - 71 with detectable cervical HSV-2
- ↑ cervical HSV-level (per $\log_{10}$) assoc. w.
  - ↑ HIV-RNA 1.35-fold (1.0-1.81)
  - ↑ HIV-DNA 1.36-fold (1.05-1.75)

McClelland et al, AIDS 2002; 2425-30

Urethritis during HAART (n=24)



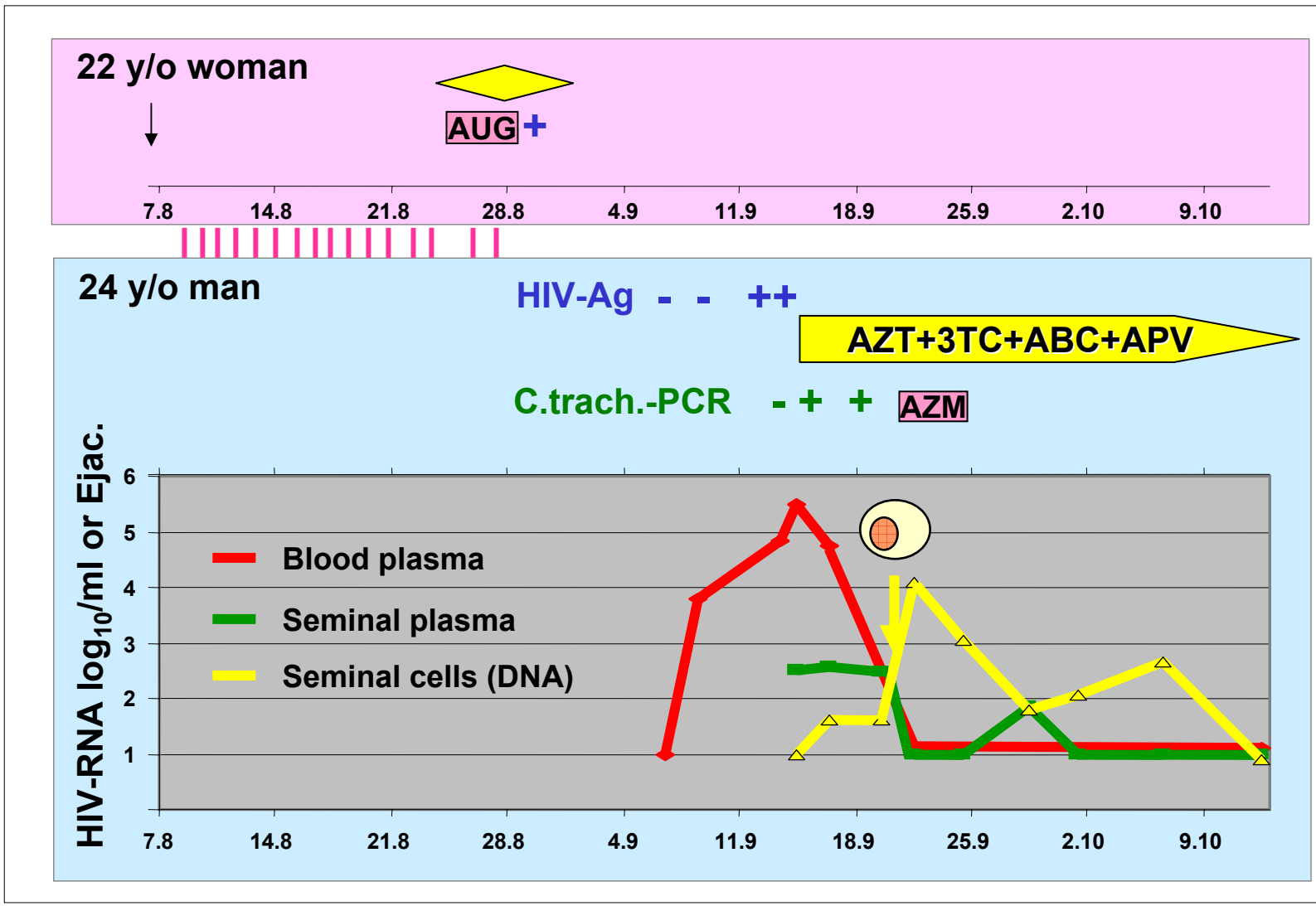
Sadiq et al, AIDS 2002;16:219-25

Summary 2

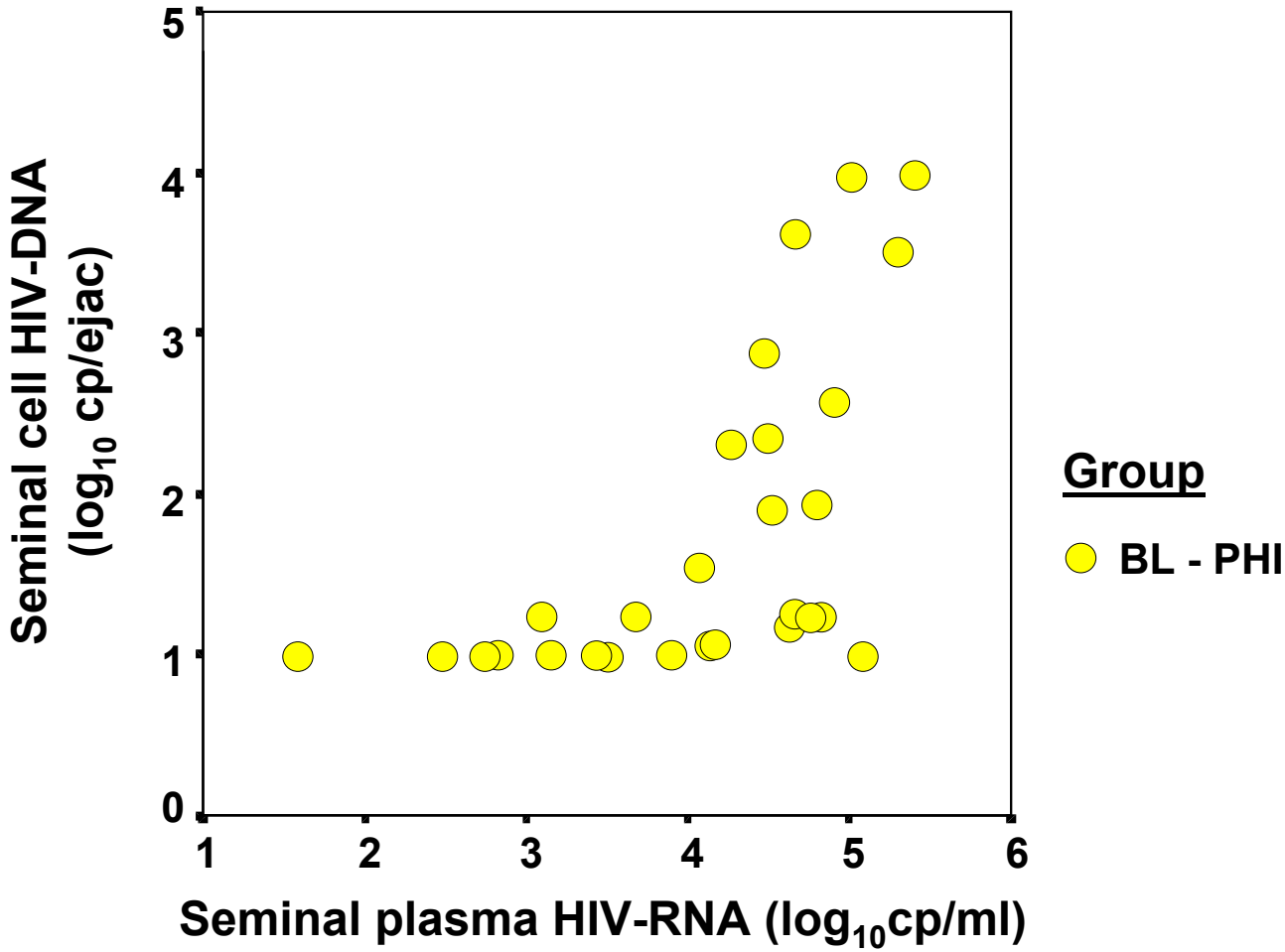
- HIV in genital tract follows blood VL
- **Compartmentalized HIV-shedding possible with local inflammation**

→Q: Contribution of cells vs. free HIV in STDs?

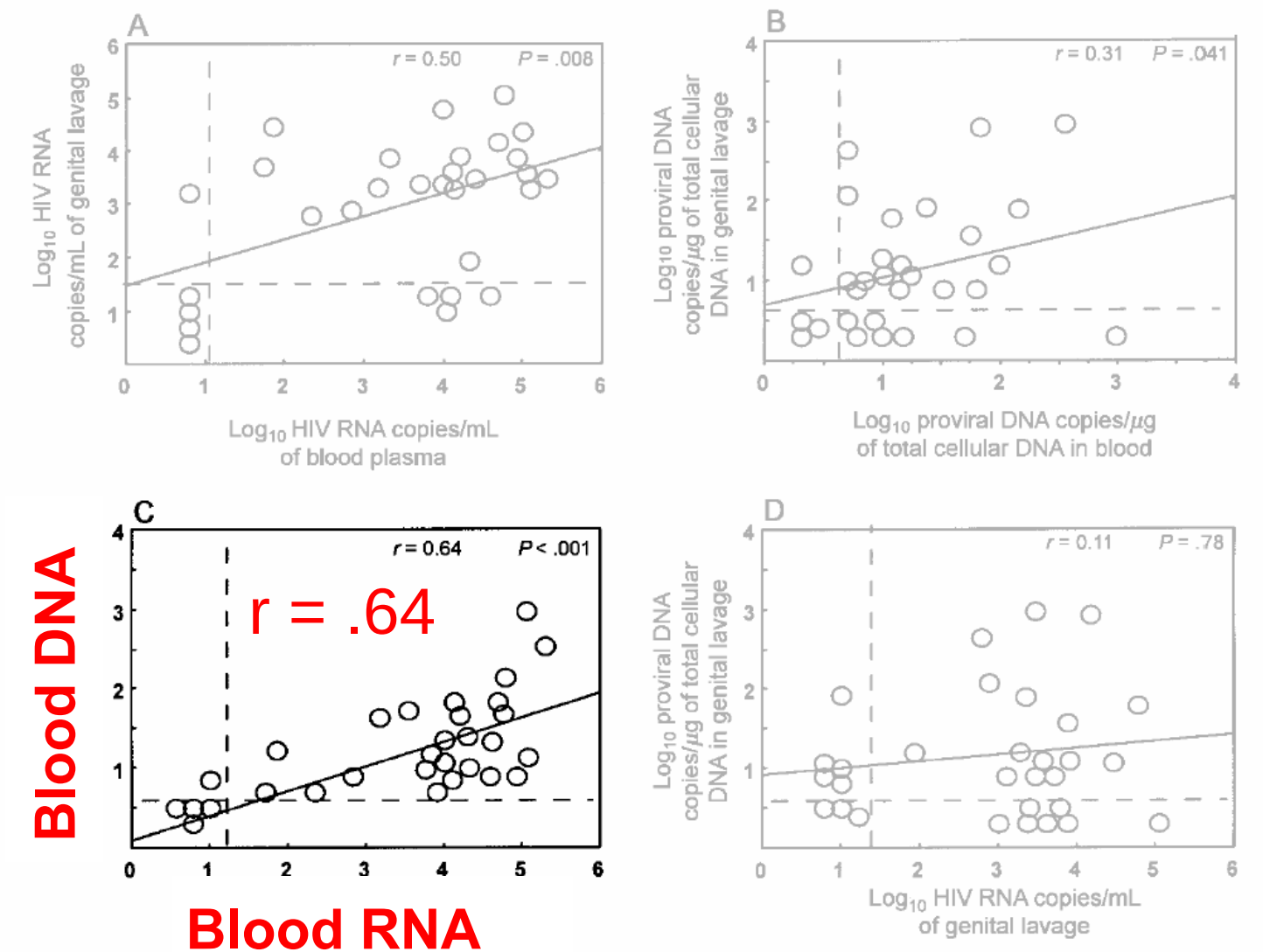
PHI Transmission couple



HIV-DNA and RNA in semen during PHI (QUEST-Study)

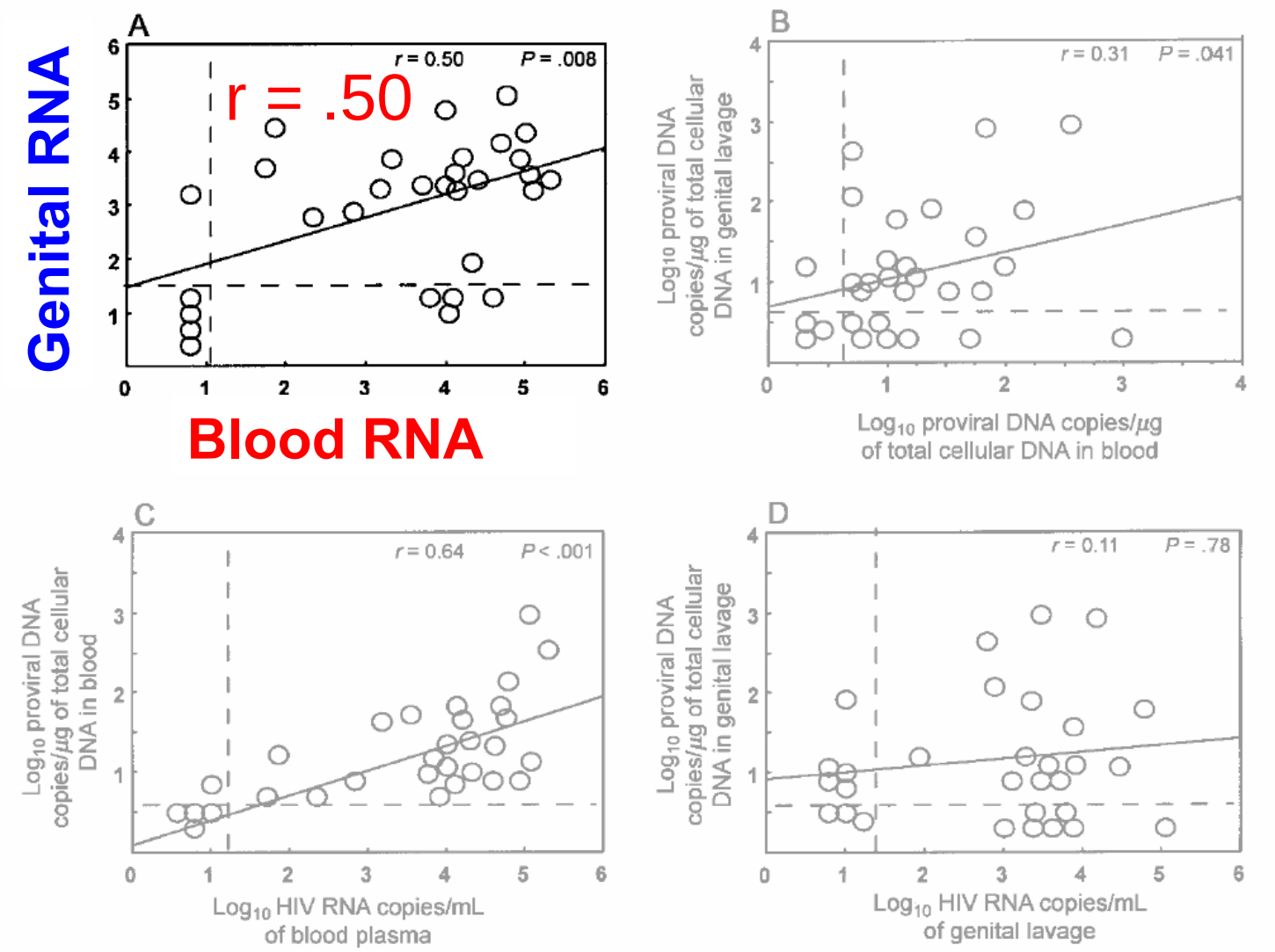


Viral load in female genital tract



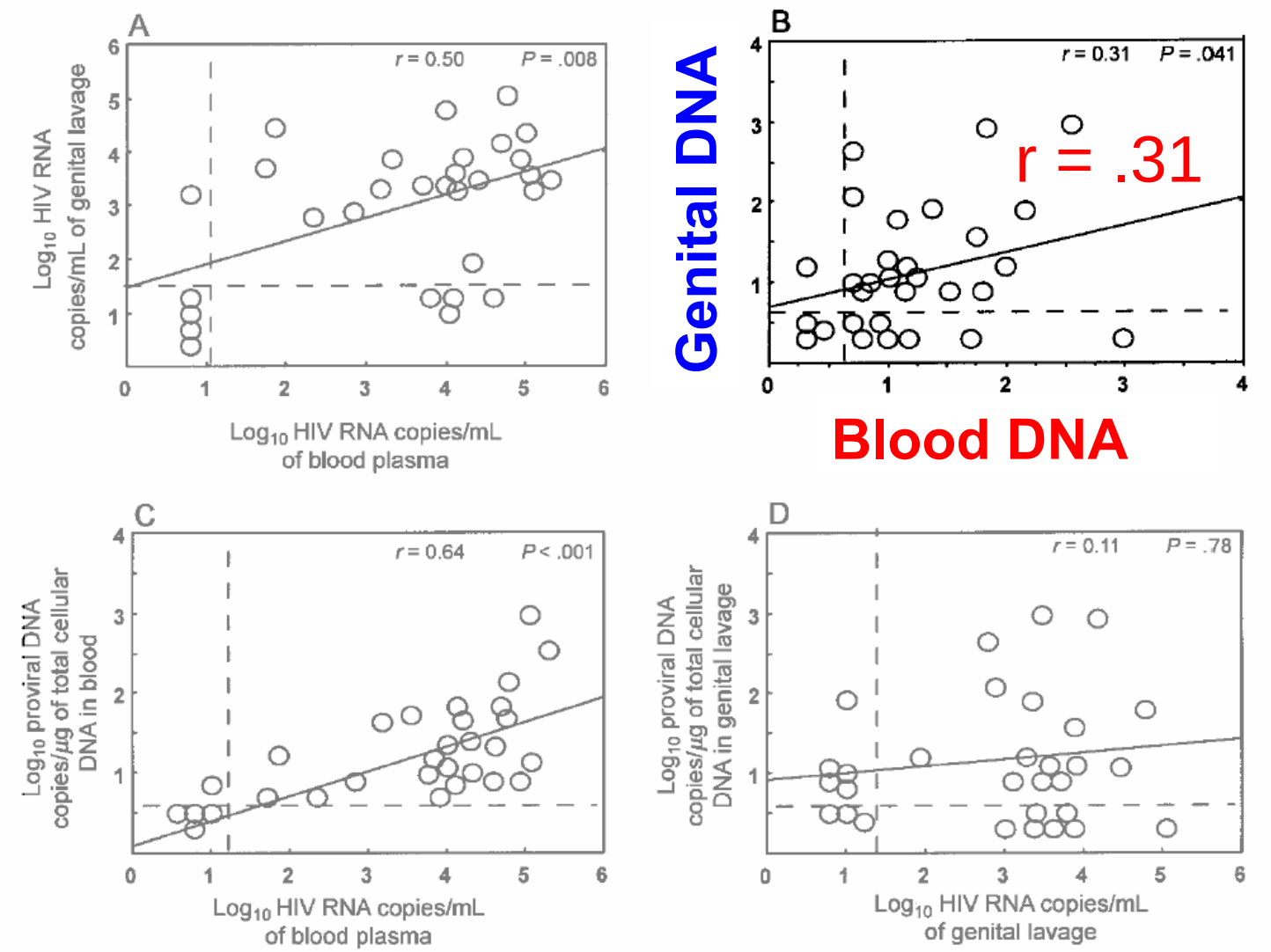
Andreoletti, JID, 2003;189:549-54

Viral load in female genital tract



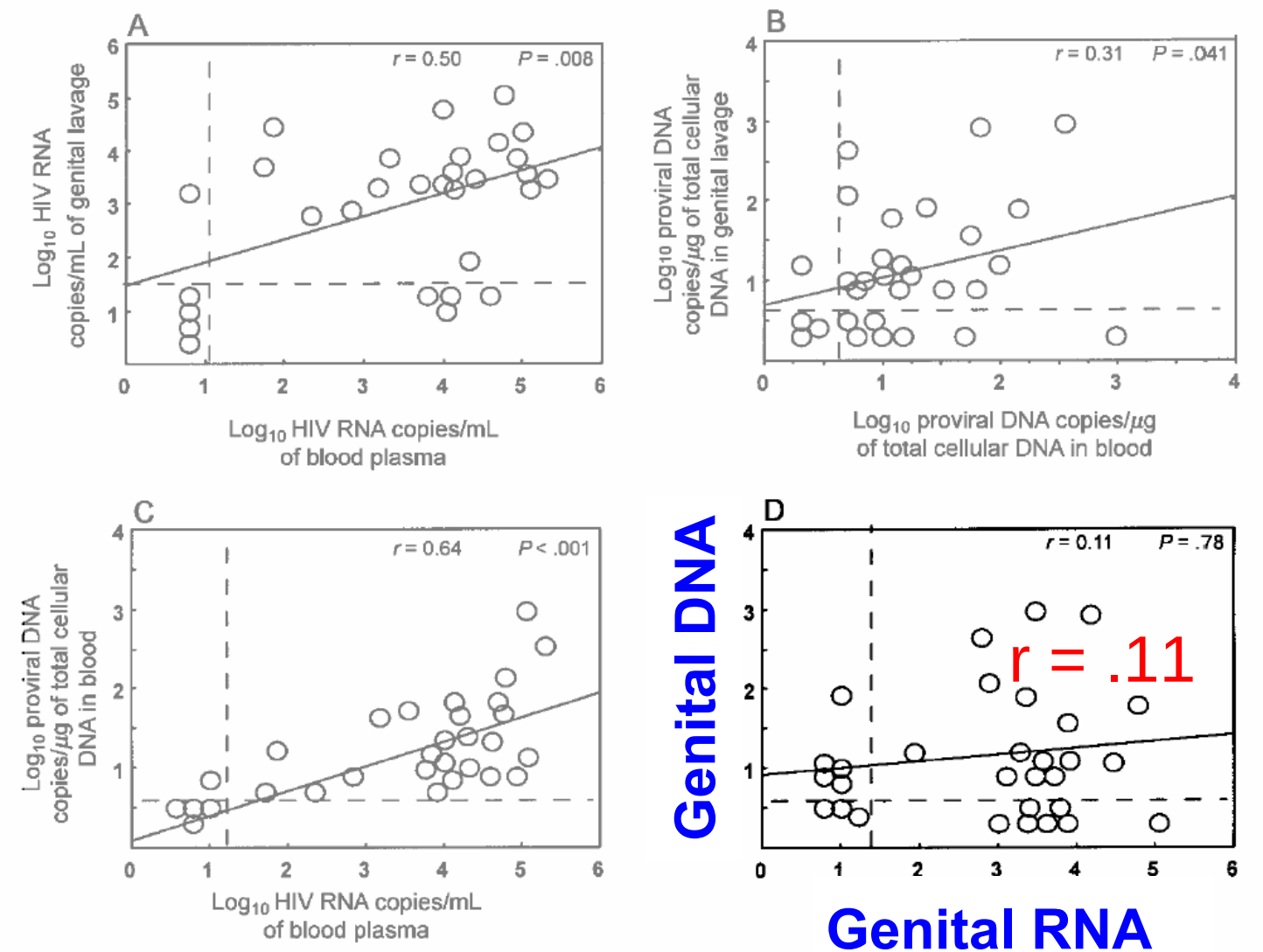
Andreoletti, JID, 2003;189:549-54

Viral load in female genital tract



Andreoletti, JID, 2003;189:549-54

Viral load in female genital tract



Andreoletti, JID, 2003;189:549-54

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

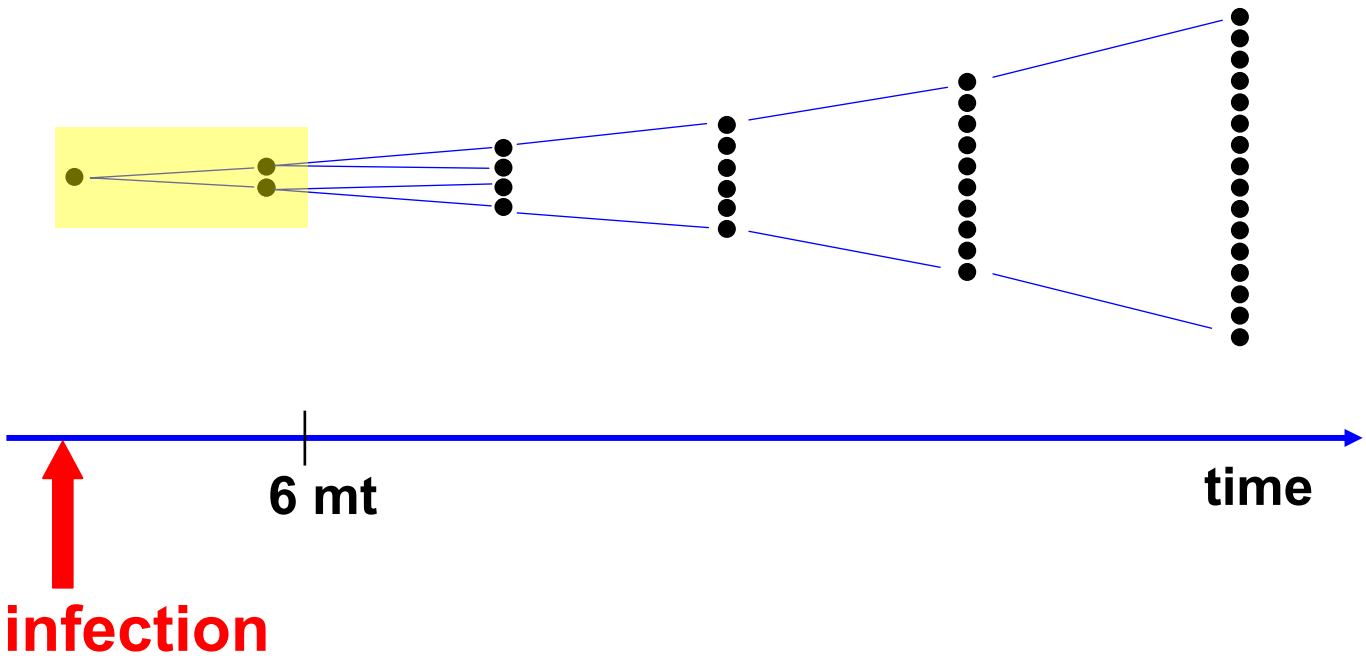
Gender differences in HIV-1 diversity at time of infection

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

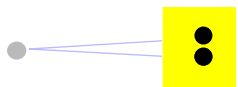
Long et al, Nat Med, 2000; 6:71-5

HIV diversity develops over time



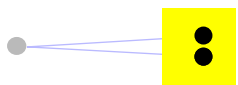
HIV diversity in early infection

- **Men: 1 pattern**

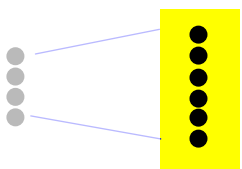


→ <5% diversity: homogenous pattern

- **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

Summary 3

- HIV in genital tract follows blood VL
- Compartementalised HIV-shedding possible with local inflammation
- **Cell-associated HIV-DNA needs more attention**
- **STD-associated transmission might be more cell-associated**