Modelling in Infectious Diseases - will Physicians trust the Results?

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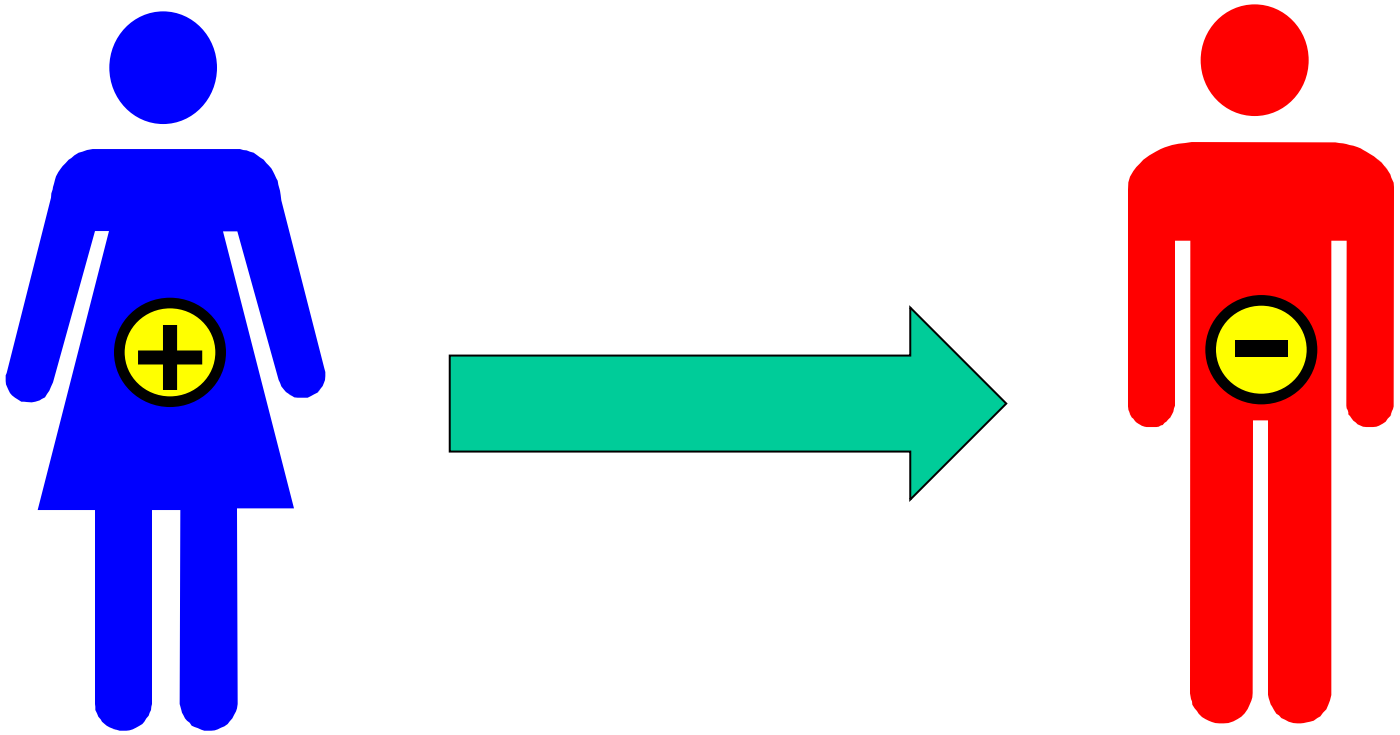
August 30th, 2012 – St.Gallen

Kantonsspital St.Gallen

General concept of an infection



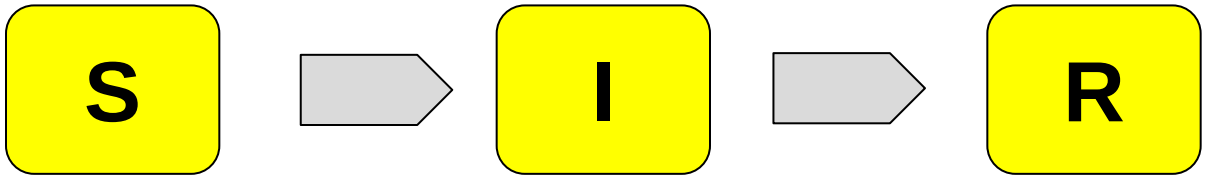
The general concept….

- **Infectious individuals**
  - **Duration of infectivity**
  - **Infectiousness**
- **Susceptible individuals**
  - **Natural protection**
  - **Acquired immunity**
- **The basic reproduction rate R_0**

The clinician‘s view

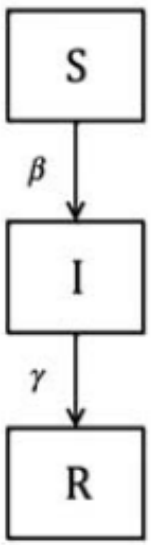
Current state → **Future**

Simple models, clinicians understand



The basic compartemental model

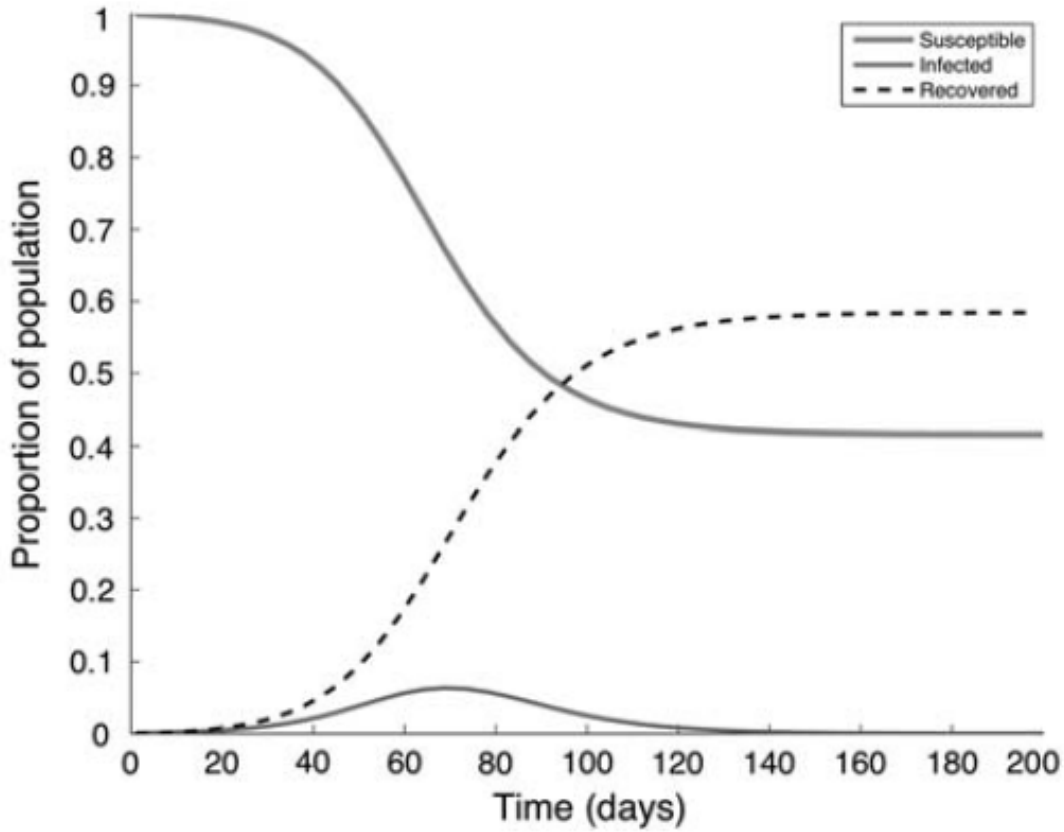
Simple models, clinicians understand



$$\frac{dS}{dt} = -\beta SI$$

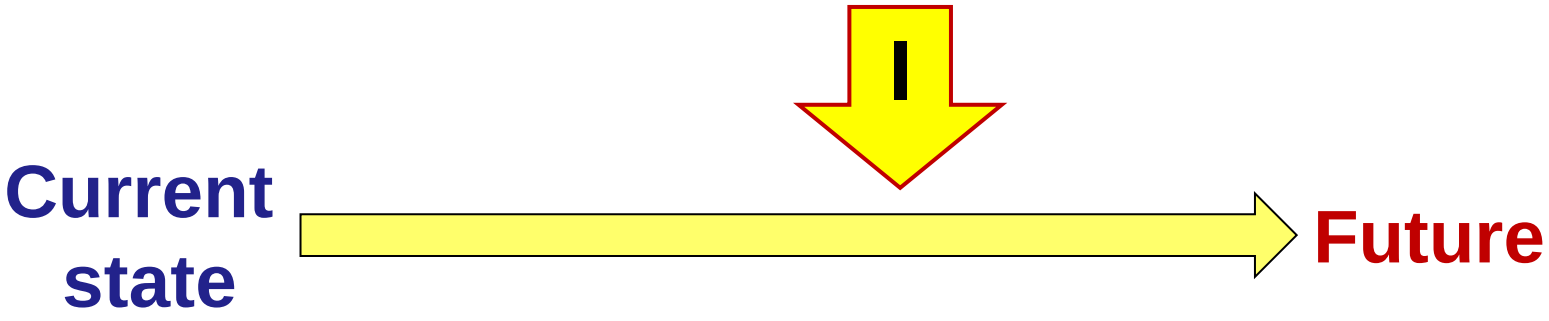
$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

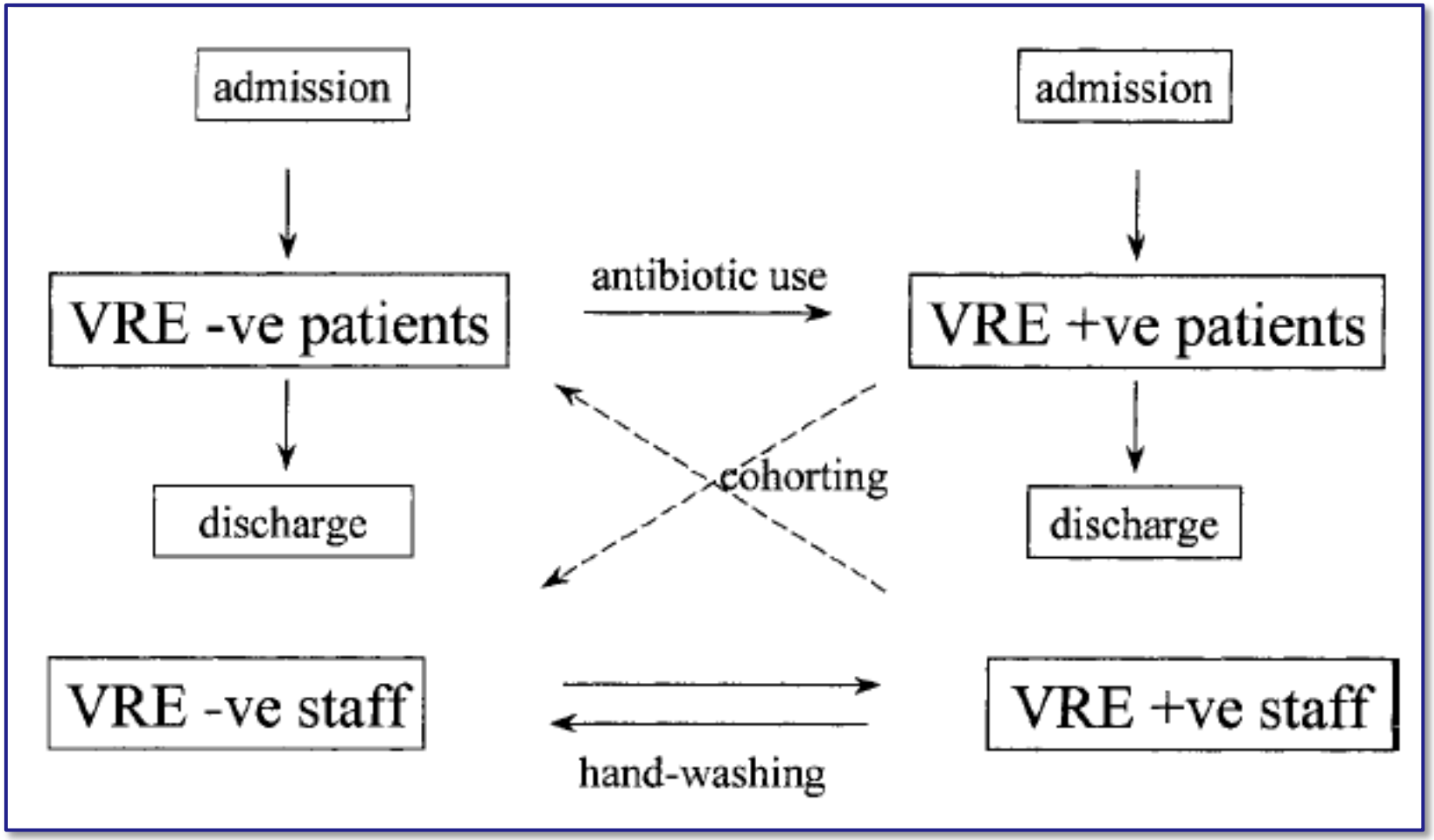


Keeling & Danon, British Medical Bulletin 2009; 92: 33–42

The clinician‘s view

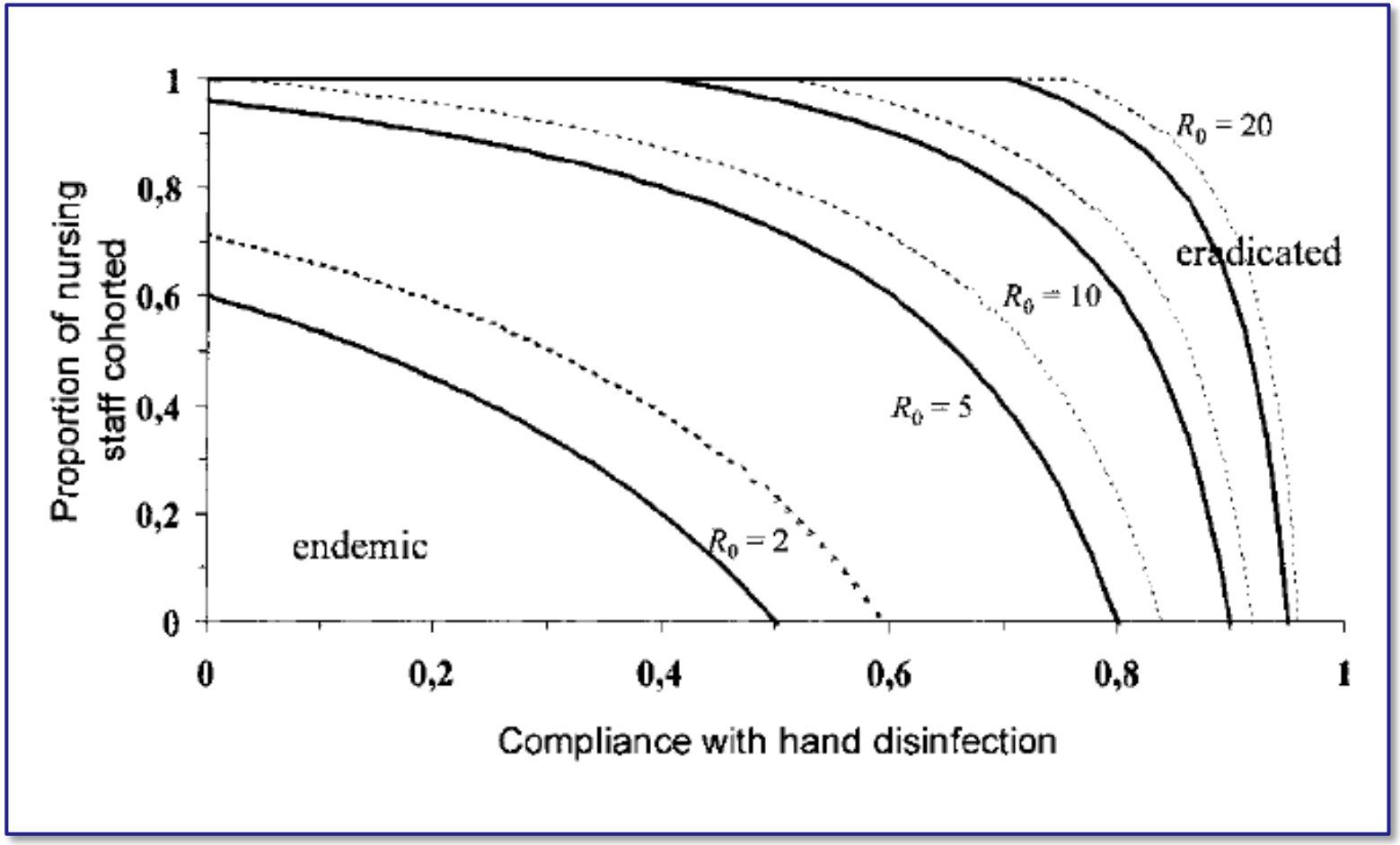


Hand washing and Transmission of Resistant Bacteria



Bonten et al, Clinical Infectious Diseases 2001; 33:1739–46

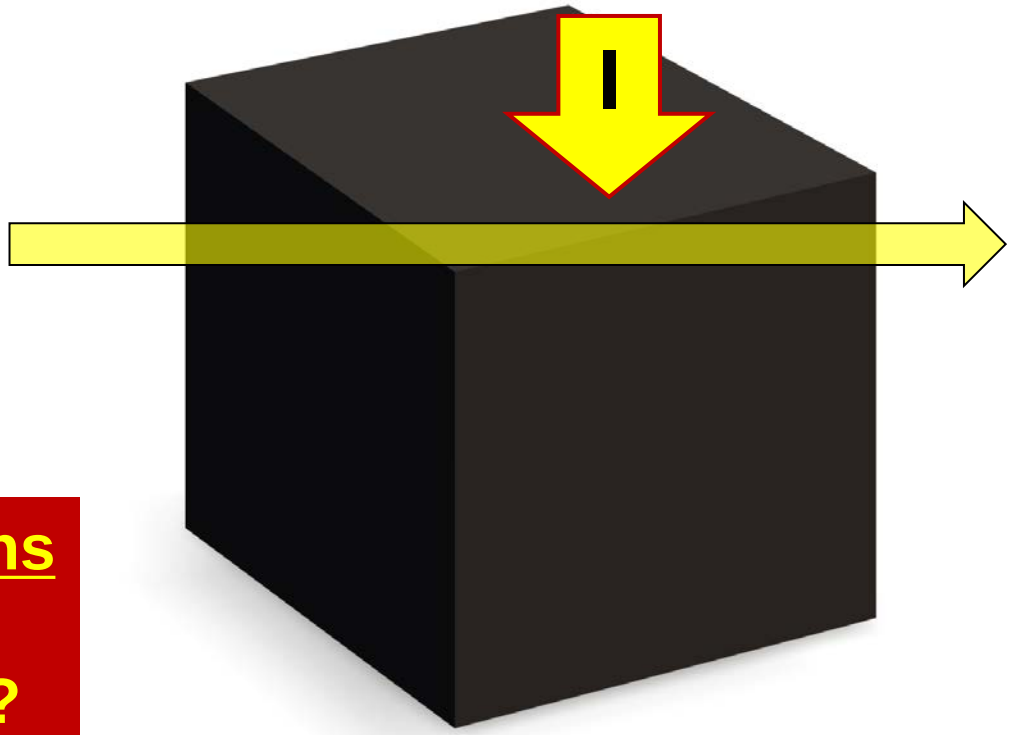
Combination of interventions



Bonten et al, Clinical Infectious Diseases 2001; 33:1739–46

The clinician‘s view

Current state



Future

Assumptions
- valid ?
- evidence ?
- applicable ?

Another black-box – Validation is the key

Google trends: Crowd computing

google.org Grippe-Trends

Sprache: Deutsch

Google.org - Startseite
(Englisch)

Grippe-Trends weltweit verfolgen

Historische Schätzungen

Daten anzeigen für: Schweiz

Grippe-Häufigkeit Schweiz

Grippe-Schätzung

● Google Grippe-Trends - Schätzungen ● Daten zu Schweiz

Schweiz: Daten zu grippeähnlichen Erkrankungen (Influenza-Like Illness, ILI) wurden zur Verfügung gestellt vom European Influenza Surveillance Network des Europäischen Zentrums für die Prävention und Kontrolle von Krankheiten.

Individual based modeling

- Every single individual is considered
- More variables can be included:
  - Age distribution
  - Stochasticity (events happen at random)
  - Risk Structure (e.g. number of partners)
  - Infectious distributions (Change over time)
  - Spatial structure (local vs. global spread)

Keeling & Danon, British Medical Bulletin 2009; 92: 33–42

Application of the concept on Sexually Transmitted Diseases

Nature. 1991 Mar 28;350(6316):356-9.

Potential of community-wide chemotherapy or immunotherapy to control the spread of HIV-1.

Anderson RM, Gupta S, May RM.

Biology Department, Imperial College, University of London, UK.

Basic reproductive rate R_o

$$R_o = \beta \cdot c \cdot D$$

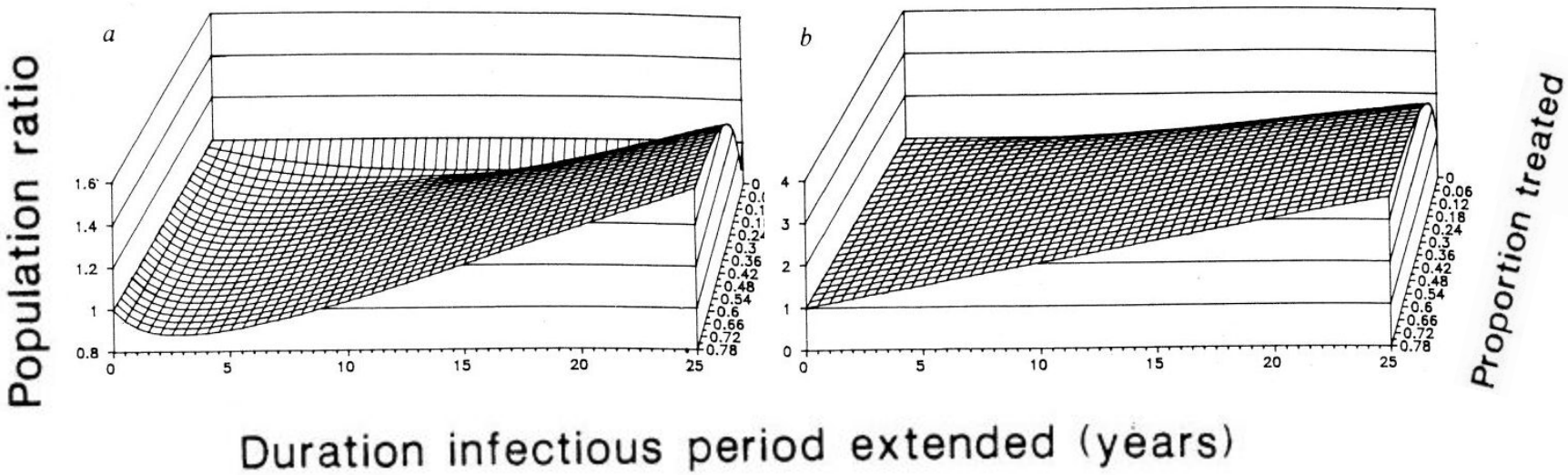
β : Infectiousness / txm per partnership

c : Number of partnerships / unit of time

D : Duration of infectious period

HIV Treatment will further spread the epidemic

β▪c = 0.16 /yr **β▪c = 1 /yr**



$$R_o = \beta \cdot c \cdot D$$

Anderson & Gupta, Nature, 28.3.1991 350:356-9

The One Million Dollar Question

CAN HIV INFECTIVITY BE MEASURED / INFLUENCED

Sensitive method for the detection of infectious HIV in semen of seropositive individuals

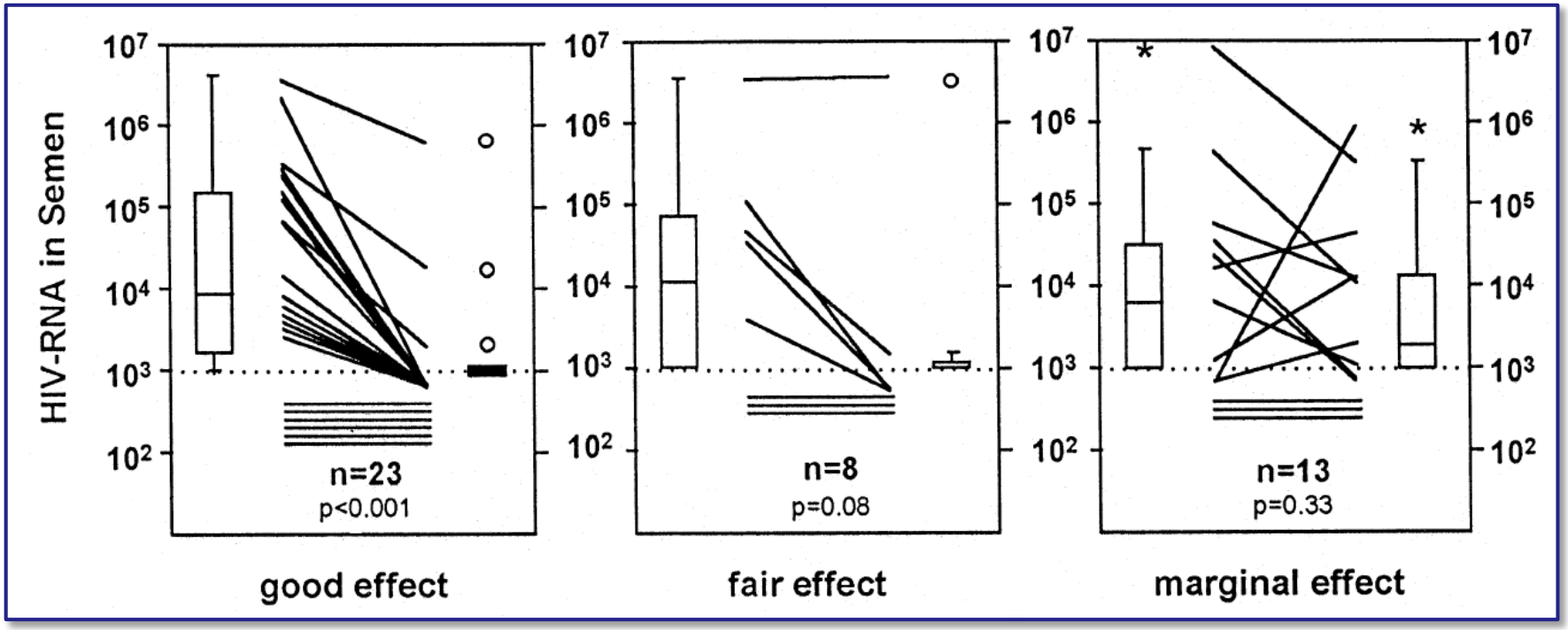
Pietro L. Vernazza[a,*], Joseph J. Eron[a], Susan A. Fiscus[b]

[a]*Department of Medicine, University of North Carolina, Chapel Hill, USA*
[b]*Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, USA*

Accepted 10 July 1995

Journal of Virological Methods 56 (1996) 33–40

HIV in semen under HIV therapy



>1 log drop

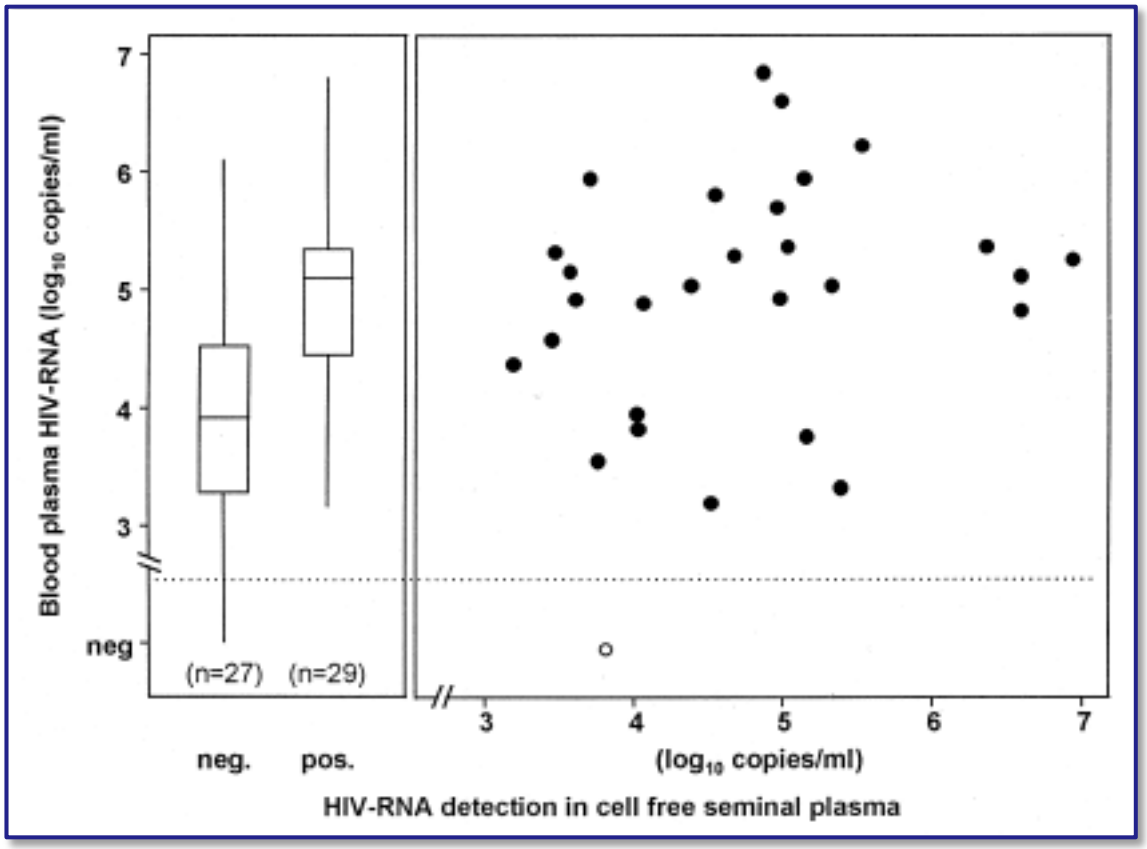
<0.5 log drop

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

Quantification of HIV in semen: correlation with antiviral treatment and immune status

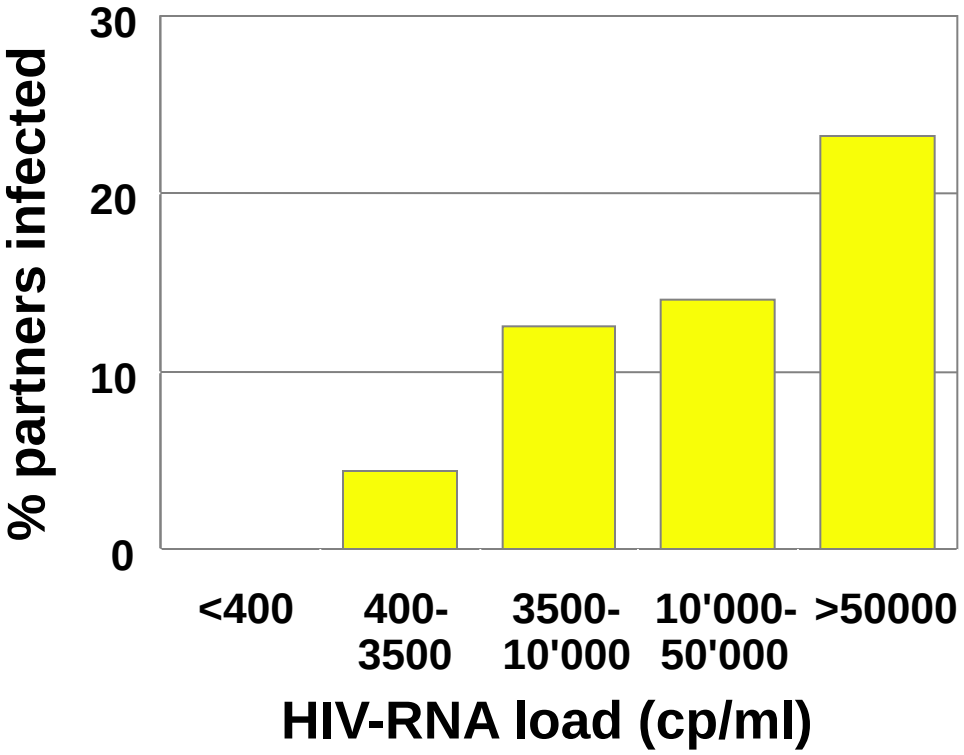
Pietro L. Vernazza*[§], Bruce L. Gilliam[†], John Dyer[†], Susan A. Fiscus[‡], Joseph J. Eron[‡], Andreas C. Frank[§] and Myron S. Cohen[†]

AIDS 1997, 11:987–993



VL and HIV-Transmission-Risk

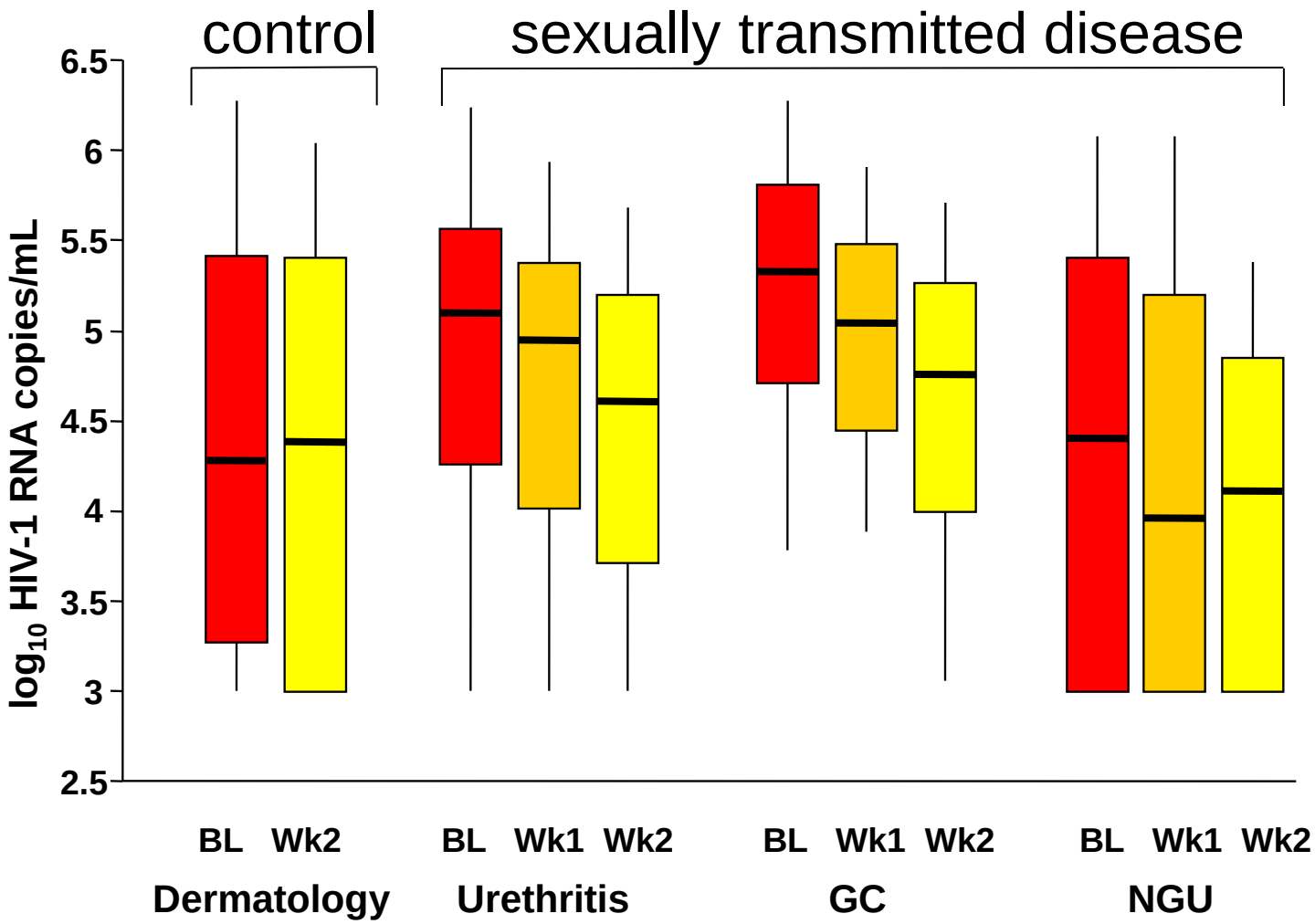
- Rakai (Uganda)
- 453 HIV-disc. couples
- 11.6 % TR / year



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

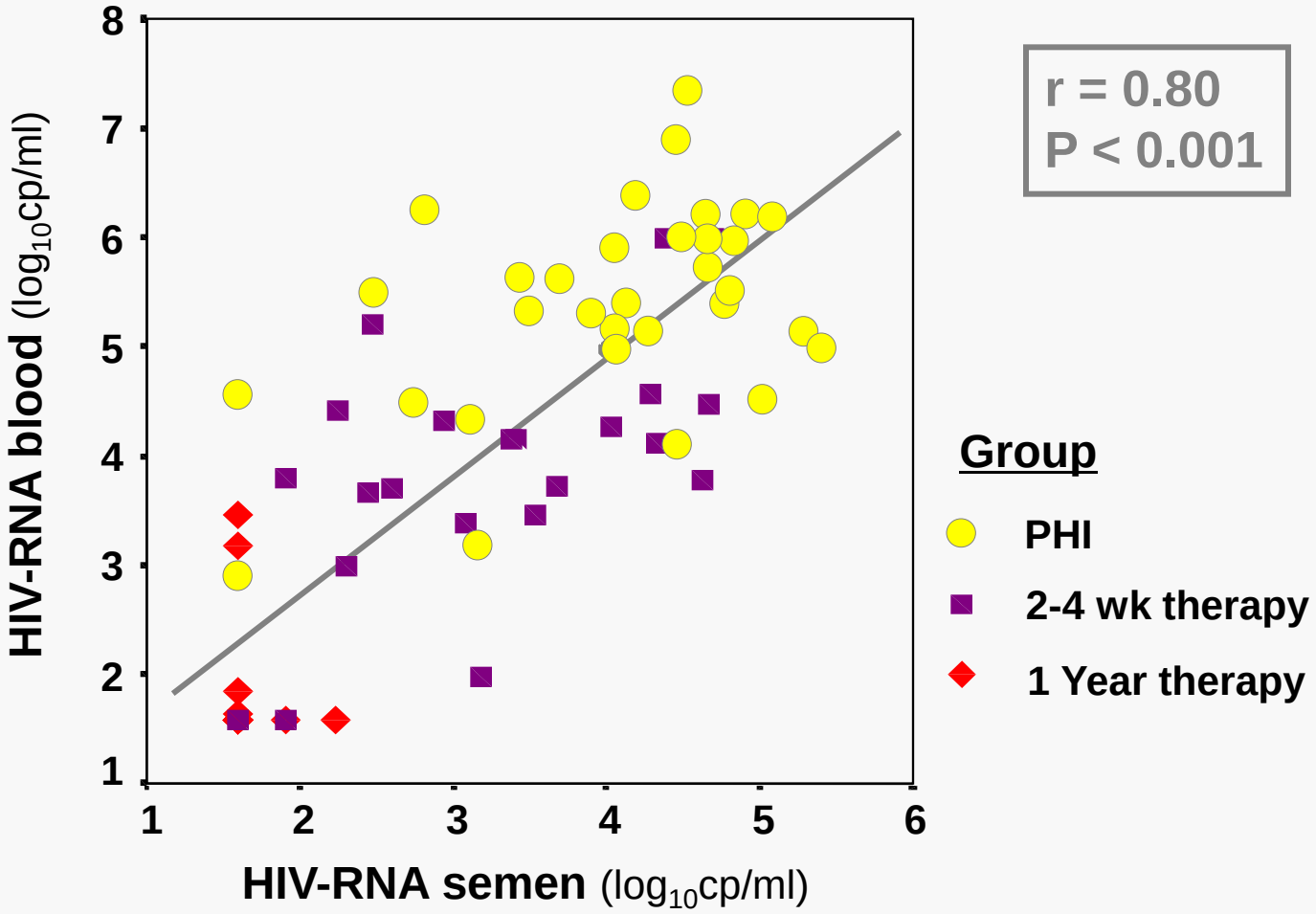
Malawi urethritis project:

HIV-RNA in semen



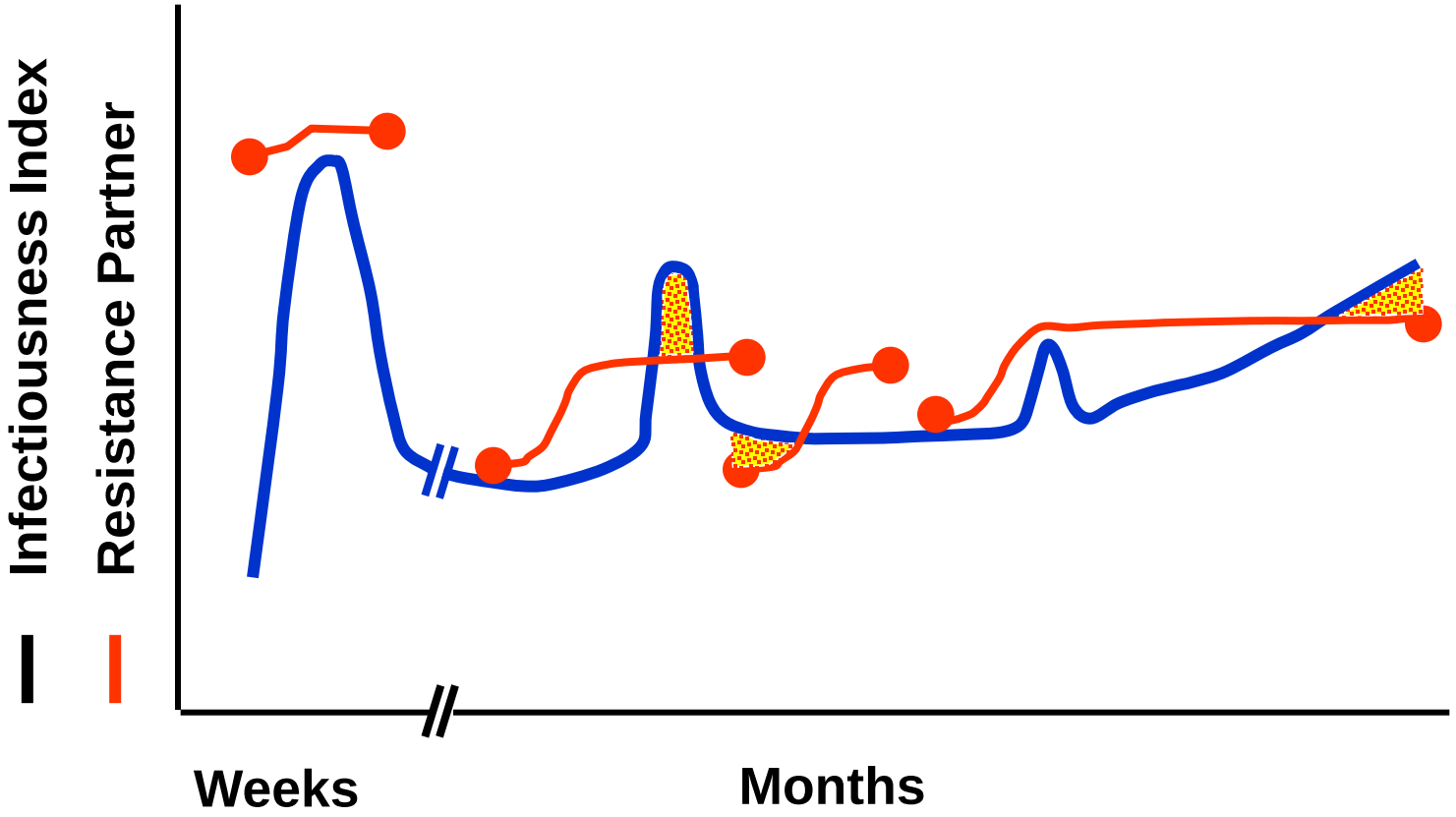
Cohen et al, Lancet 1997; 349:1868-73

HIV- Primary Infection



Vernazza et al., CROI, 2000; Abst 564

Infectiousness & Susceptibility



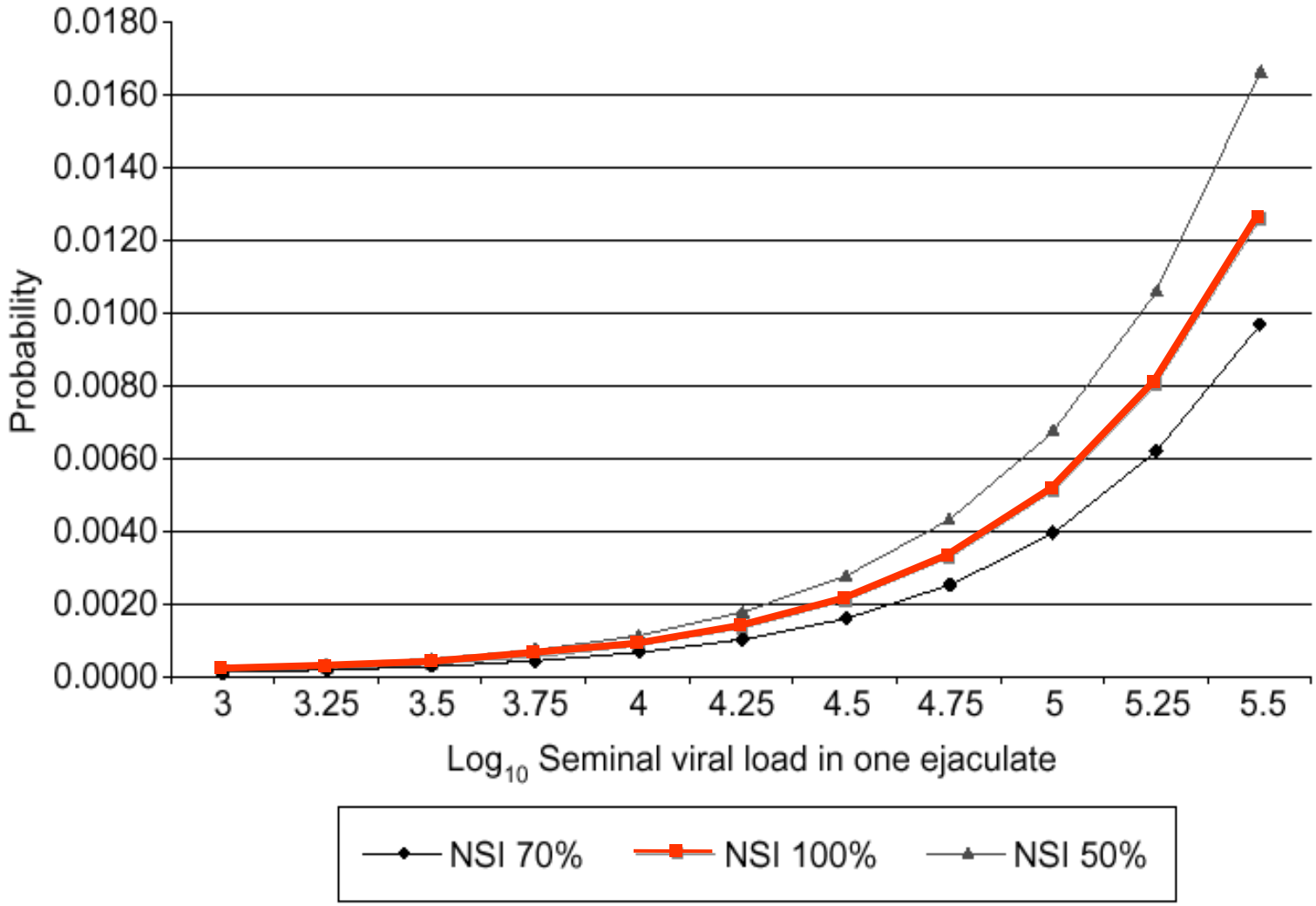
HIV in Semen and Risk of Tx

Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model

Hrishikesh Chakraborty, Pranab K. Sen[a], Ronald W. Helms[a], Pietro L. Vernazza[b], Susan A. Fiscus[c], Joseph J. Eron[d], Bruce K. Patterson[e], Robert W. Coombs[f], John N. Krieger[g] and Myron S. Cohen[d]

AIDS 2001,15: 621-7

HIV in semen & risk per coital act

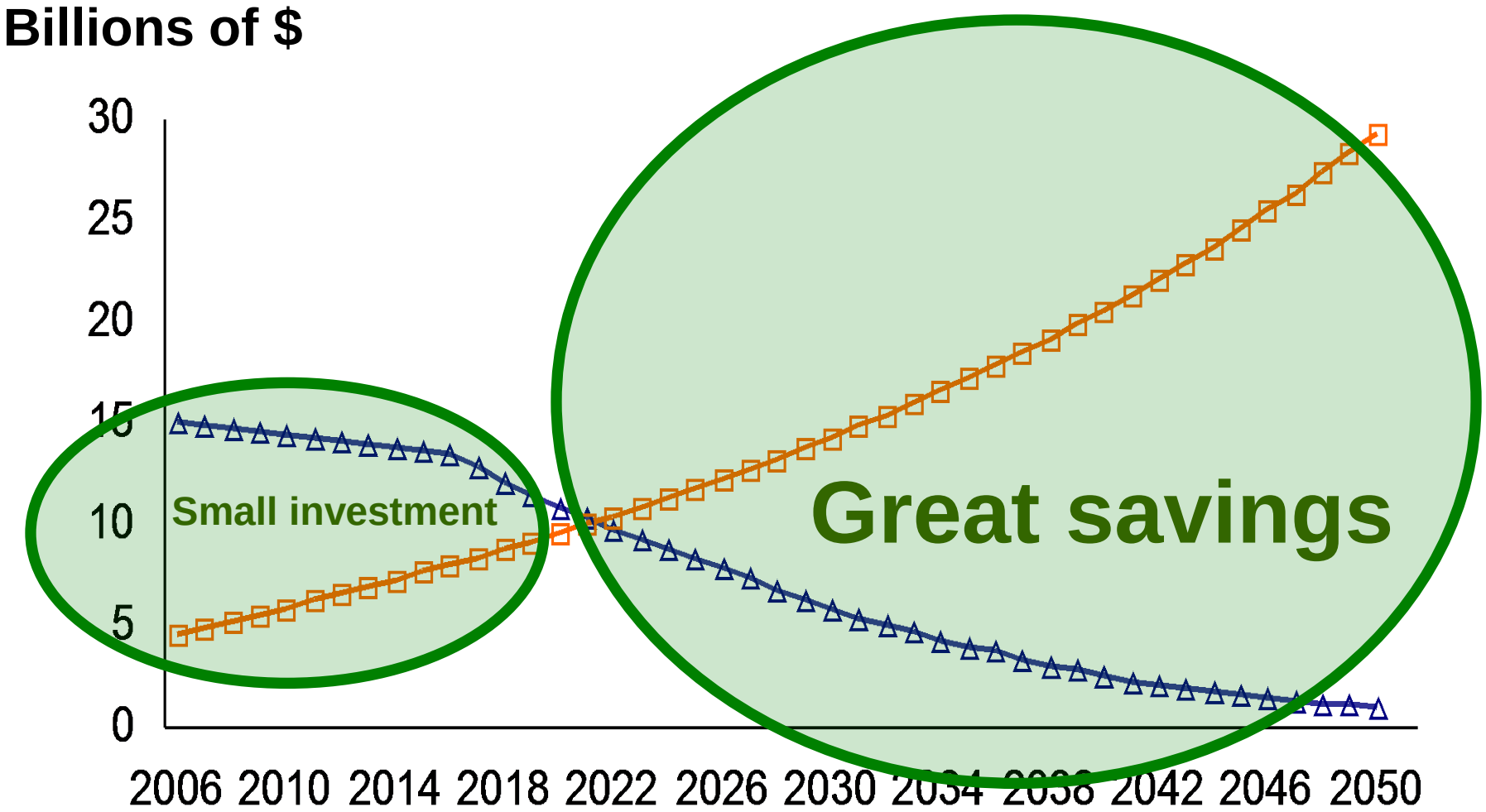


Chakraborty et al. AIDS 2001,15: 621-7

Projections for British Columbia

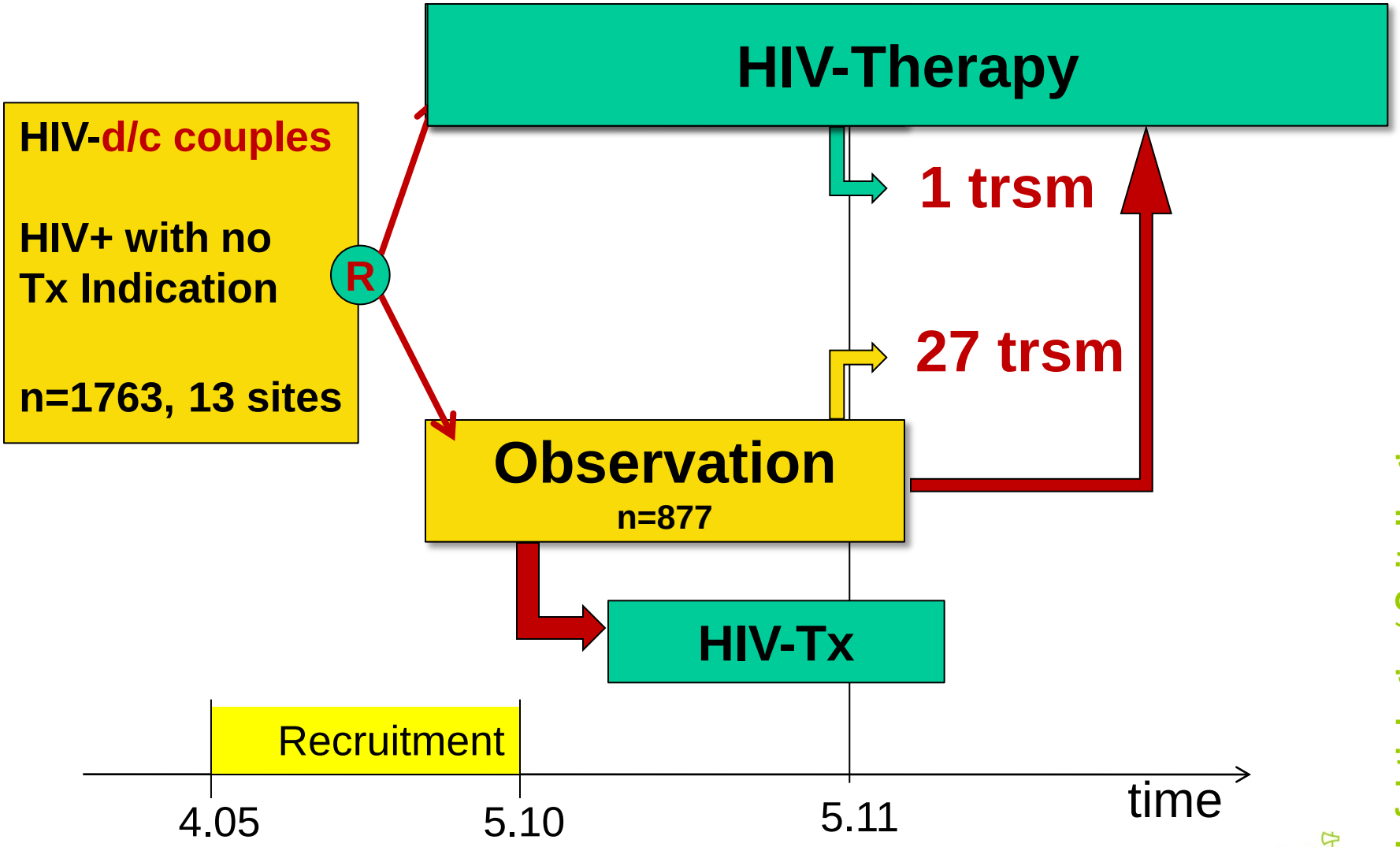
Hogg et al. Unpublished, 2006

Cost of Treatment next 40 yrs



Hogg / Montaner, WAC Toronto 2006

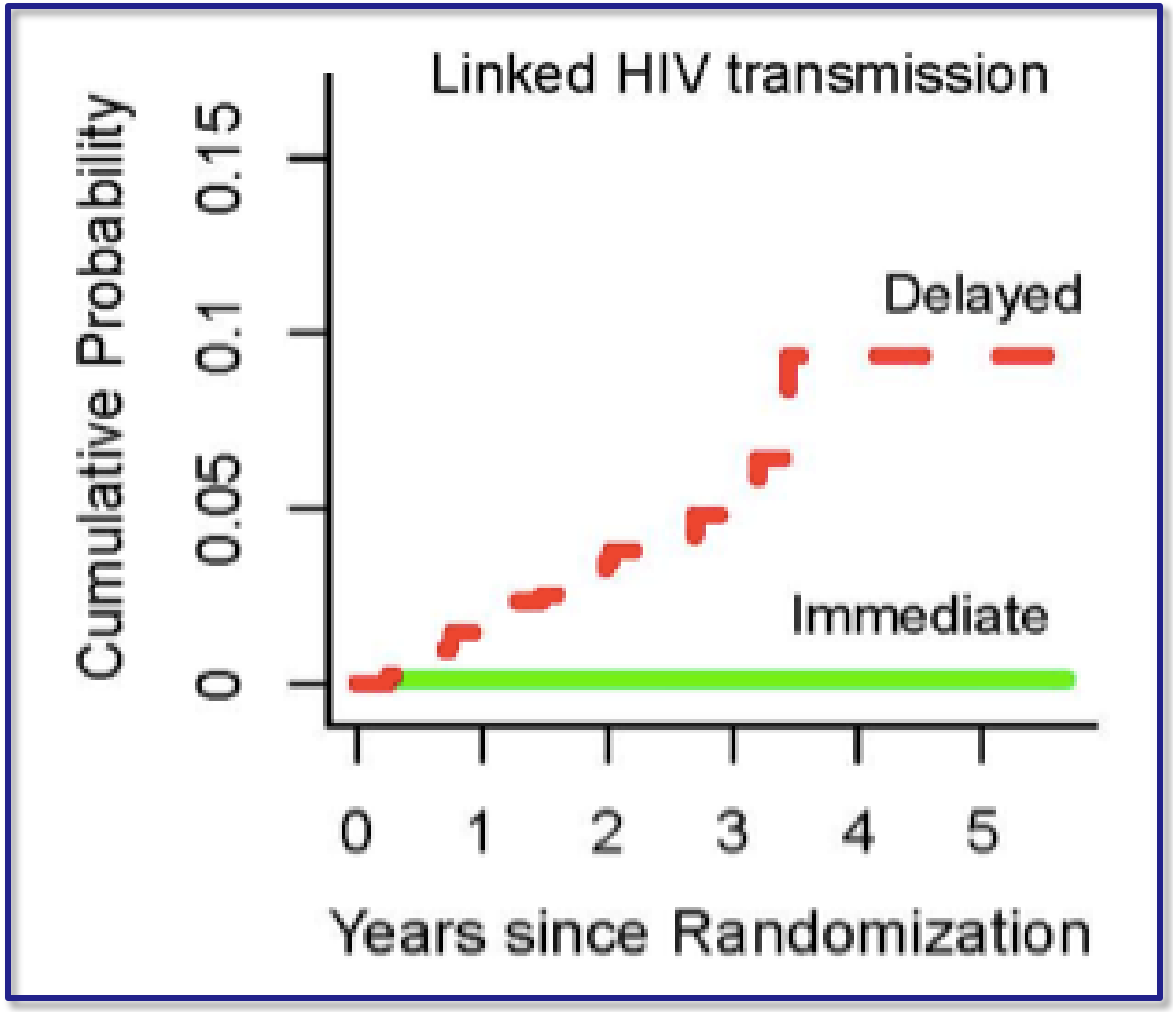
HPTN 052: Study design and results



Cohen et al, NEJM 2011

Results of HPTN 052 on linked transmission among couples

HIV treatment prevents transmission



Cohen et al, NEJM, July 2011

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

Summary:

The interdisciplinary Approach

- Epidemiologists
- Mathematicians
- Clinicians

$$\frac{d}{dt}\langle I\rangle = \beta\,\langle SI\rangle - \gamma\langle I\rangle + \tilde{\beta}\,\langle RI\rangle, \tag{1}$$

$$\frac{d}{dt}\langle R\rangle = \gamma\langle I\rangle - \alpha\langle R\rangle - \tilde{\beta}\,\langle RI\rangle, \tag{2}$$

$$\frac{d}{dt}\langle SI\rangle = \alpha\langle RI\rangle - (\gamma+\beta)\,\langle SI\rangle + \beta(Q-1)\,\langle SI\rangle - \beta\frac{Q-1}{Q}\frac{(2\langle SI\rangle + \langle SR\rangle)\cdot\langle SI\rangle}{N-\langle I\rangle-\langle R\rangle} + \tilde{\beta}\frac{Q-1}{Q}\frac{\langle SR\rangle\,\langle RI\rangle}{\langle R\rangle}, \tag{3}$$

$$\frac{d}{dt}\langle RI\rangle = \gamma\,(Q\langle I\rangle - \langle SI\rangle) - (\alpha + 2\tilde{\beta})\,\langle RI\rangle + \beta\frac{Q-1}{Q}\frac{\langle SR\rangle\,\langle SI\rangle}{N-\langle I\rangle-\langle R\rangle} + \tilde{\beta}\frac{Q-1}{Q}\frac{(Q\langle R\rangle - \langle SR\rangle - 2\langle RI\rangle)\cdot\langle RI\rangle}{\langle R\rangle}, \tag{4}$$

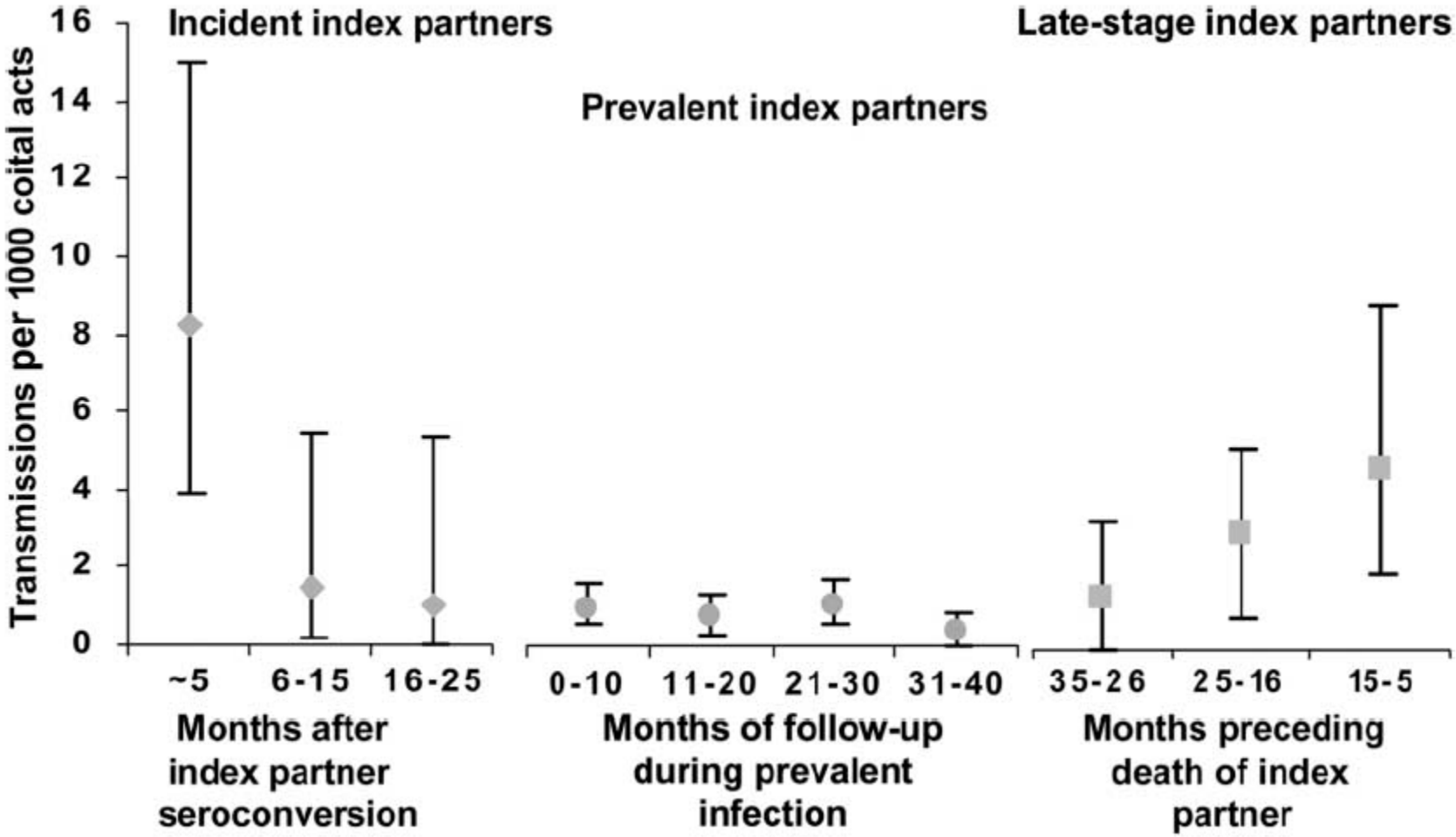
$$\frac{d}{dt}\langle SR\rangle = \gamma\langle SI\rangle + \alpha\,(Q\langle R\rangle - 2\langle SR\rangle - \langle RI\rangle) - \beta\frac{Q-1}{Q}\frac{\langle SR\rangle\,\langle SI\rangle}{N-\langle I\rangle-\langle R\rangle} - \tilde{\beta}\frac{Q-1}{Q}\frac{\langle RI\rangle\,\langle SR\rangle}{\langle R\rangle}. \tag{5}$$

$$R_0 = \beta \cdot c \cdot D$$

Assumptions
- valid ?
- evidence ?
- applicable ?
- ....

Risk per coital act in couples

- 235 monogamous, discordant couples, Uganda



Waver et al. JID 2005,191: 1403-9