

ART for Prevention of Sexual Transmission of HIV



Myron S. Cohen, MD

**J. Herbert Bate Distinguished Professor
Medicine, Microbiology and Public Health
Director, UNC Institute for Global Health
Associate Vice Chancellor for Global Health**

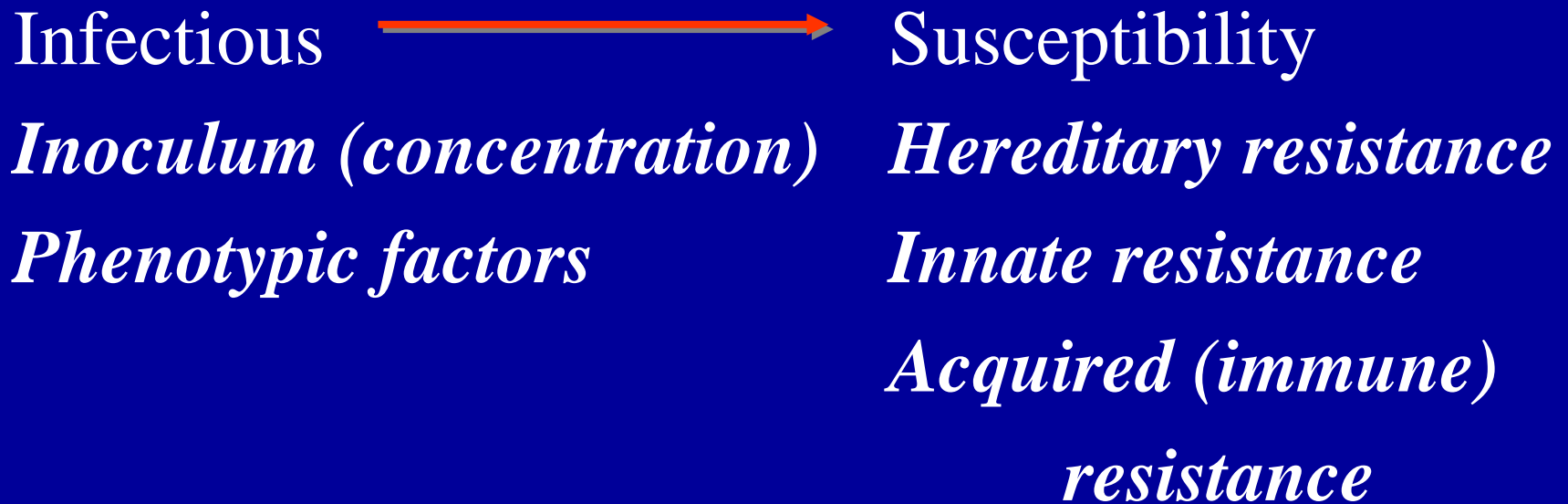
Options for ART

Cohen et al. Annals Int Med 2007

- **Post-exposure prophylaxis (nPEP)**
- **Pre-exposure prophylaxis (PrEP)**
- **Treatment of the infected person (index case)**
- **Protection during conception for a couple?**

...and topical microbicides and ART release devices (tenofovir, TMC 120)

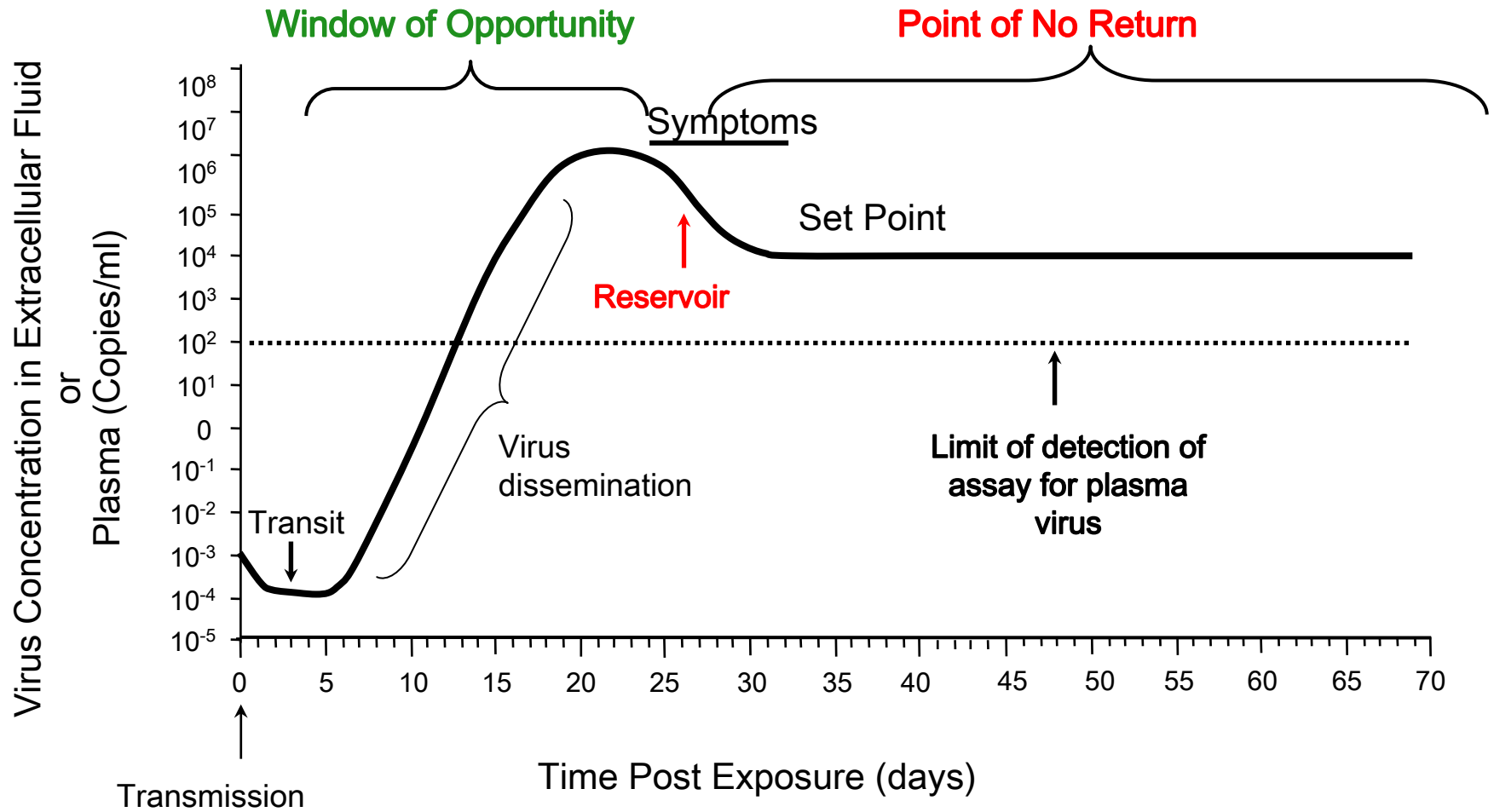
Transmission of HIV Biological Requirements



...from Cohen and Galvin

Nature Microbiology Reviews 2:33-42, 2004

Acute HIV-1 Infection



ART for Prevention

- Does it work?
- Is it safe for the individual and the “community”?
- Does it inspire “sexual disinhibition”?

Lessons from Macaques I

...leading to PEP guidelines

nPEP: The Animal Data

reviewed in "Current Clinical Topics in Infectious Disease, 2002"

- Daily subQ injection of Tenofovir (TDF) prevented infection in all macaques given 48 hrs before, 4 hrs after, or 24 hrs after inoculation. (Tsai, Science, 1995)
- TDF blocked IV SIV/SHIV IF given within 24 hrs for 28 days (Black, AJM, 1997)
- TDF NOT as effective if started 48-72 hrs post-exposure or used for 3 or 10 days, rather than 28 days (Tsai, JV, 1998)
- TDF blocked vaginal challenge IF given within 36 hrs for 28 days; $\frac{3}{4}$ macaques protected IF TDF started within 72 hrs (Otten, JV, 2000)

nPEP US Guidelines

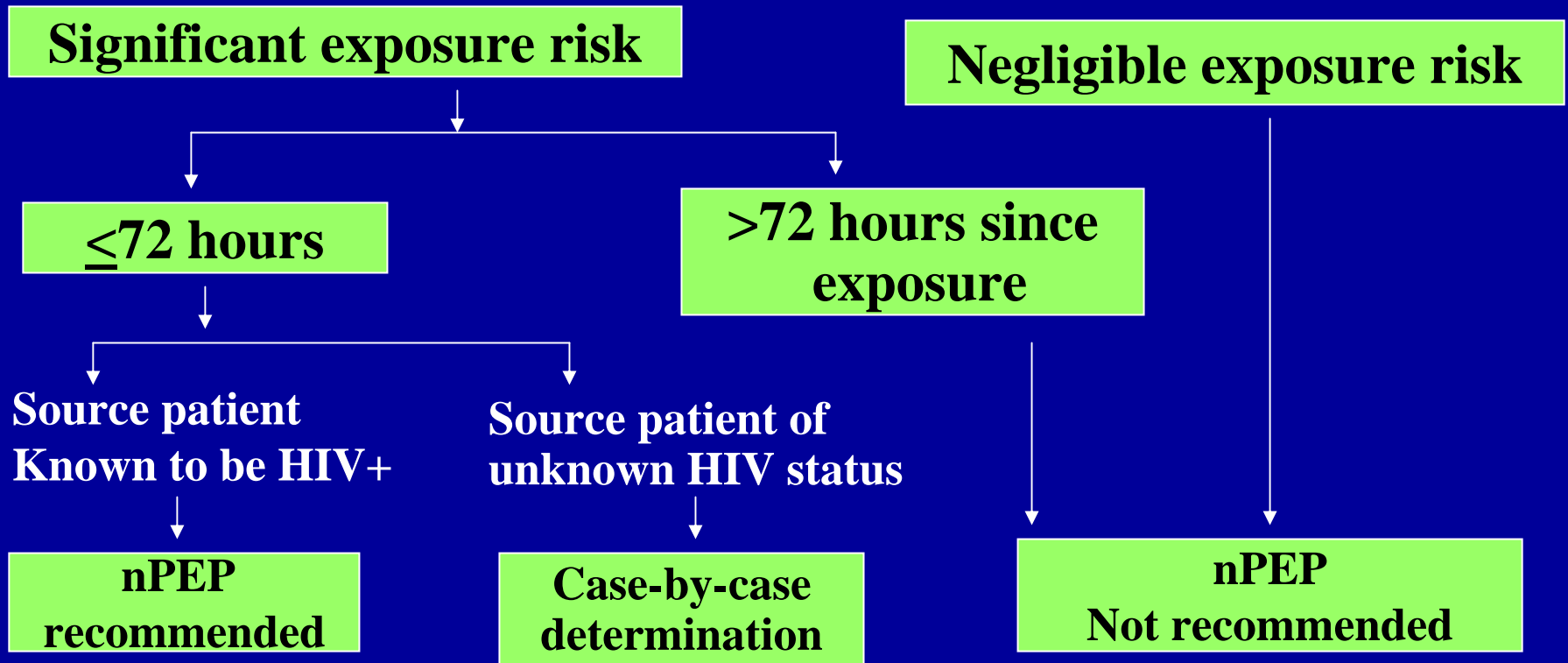
- **A clinical trial to PROVE that nPEP works cannot be developed (and it sometimes fails!!)**
- **CDC Guidelines generated based on consensus**

MMWR Jan 21, 2005 Vol 54: 1-20

“Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States”

US ALGORITHM FOR nPEP USAGE

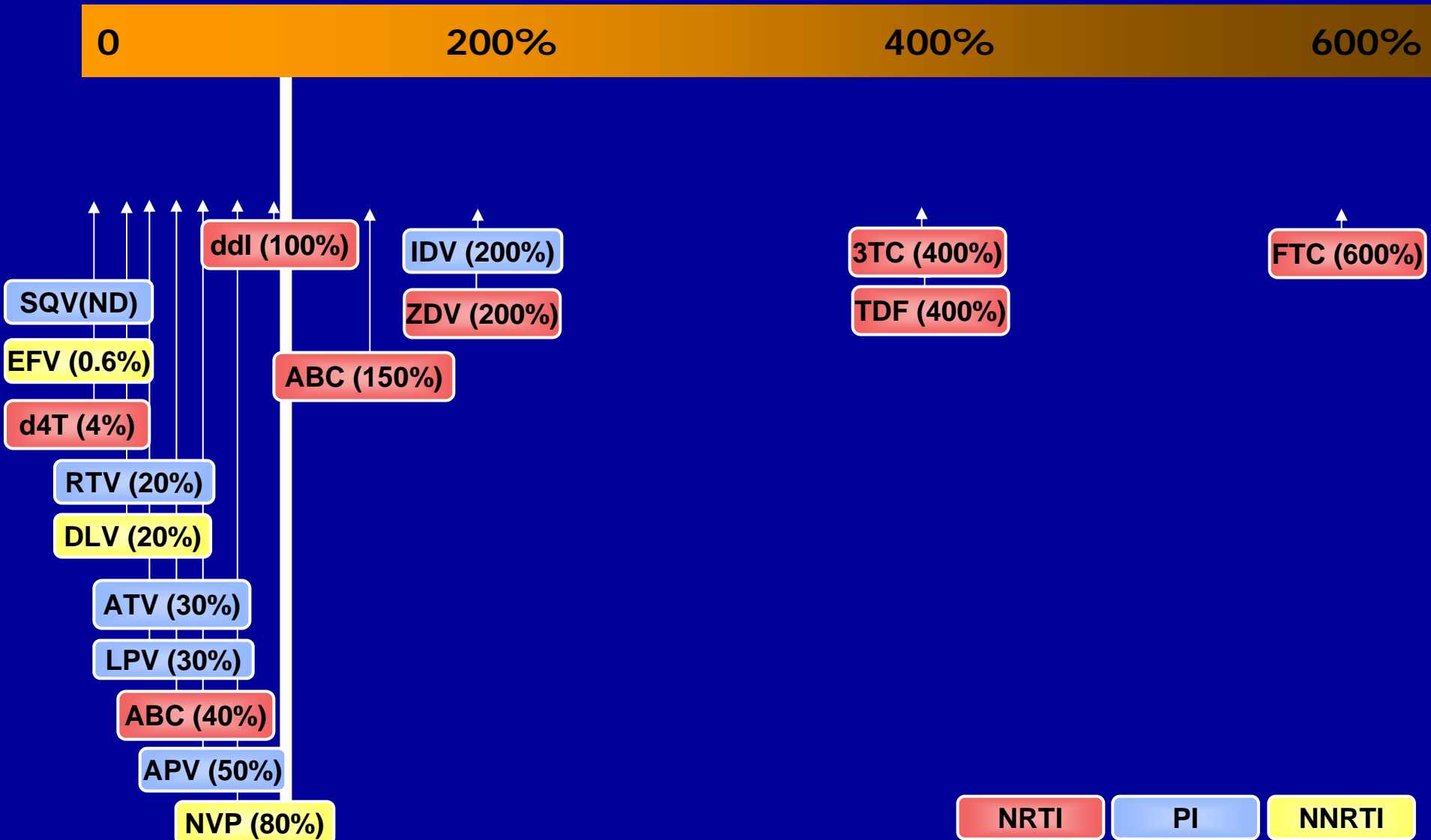
MMWR Jan 21, 2005 Vol 54: 1-20



Female Genital Tract Exposure

(% blood plasma)

Dumond et al. AIDS 2007



Lessons from Macaques II

...leading to “PrEP” Trials

Tenofovir (TDF) as a single agent?

-long half-life

-well-tolerated

-a modest barrier to resistance (k65r)

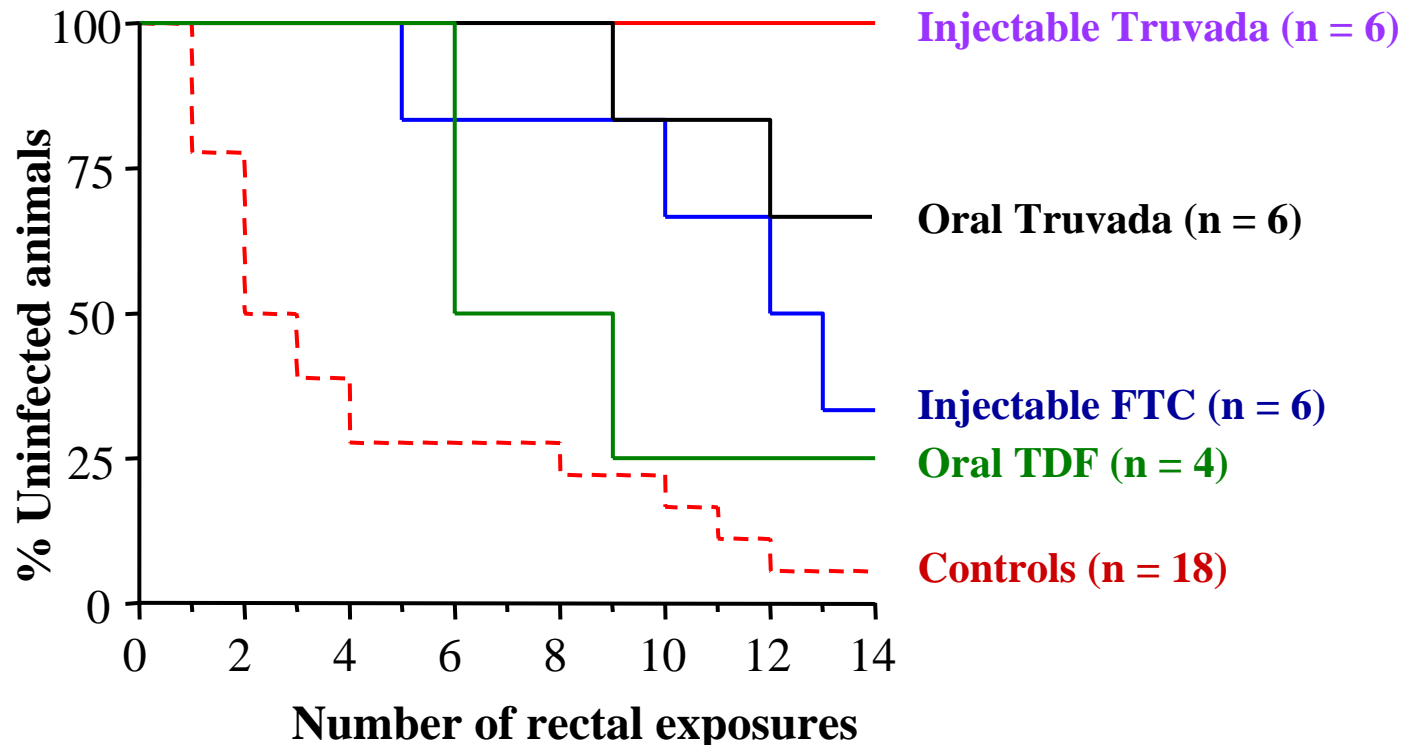
Truvada (Tenofovir PLUS FTC) as combo-PrEP?

-long half-life

-well-tolerated

-a considerable barrier to resistance

Chemoprophylaxis in Macaques



Garcia-Lerma et al PLoS Medicine in press

Cohen and Kashuba PLoS Medicine in press (editorial)

HIV PrEP Safety Trial Completed

Peterson et al PLoS Clin Trials 2007

- Limited toxicity, good reported adherence
- 8 on-product seroconversions observed:
2 TDF/6 placebo (p = 0.24)
- A blood specimen obtained from one of the two participants on TDF showed no evidence of resistance

Oral “PrEP”-Ongoing Trials

Sponsor	Product/Population	N	Sites (Expected Results)
CDC	Tenofovir Male & Female IDUs	2000	Thailand (2008)
CDC	Tenofovir MSM	400	USA (2009)
CDC	Truvada Heterosexual men & women	1200	Botswana (2010)
NIH	Truvada MSM	3000	S.America, US, South Africa, Thailand (2011)

Oral “PreP” – Planned Trials

Sponsor	Product/Population	N	Sites
Gates	Tenofovir/Truvada Discordant couples	2000 men, 2000 women	Eastern Africa
NIH/ MTN	Tenofovir/Truvada Women	2400	Southern/Eastern Africa
USAID	Truvada High-risk women	3900	Southern/Eastern Africa

ART Chemoprophylaxis

Human trials with TDF focused on “very high risk” subjects hindered or stopped because of....

i) “Ethical” Considerations (Cambodia, Cameroon)

Grant et. al. Science, September 30, 2005

Page-Shafer et. al. Lancet, September 2005

ii) Resistance (Malawi)

Tenofovir (k65r) resistance with monotherapy feared, perhaps especially with clade C HIV infection

iii) Public health relevance?

Cohen, New York Times Sunday Magazine, Jan. 2006

ART to Prevent Sexual Transmission of HIV: COUPLES REALLY MATTER!!!!

1. Biological plausibility

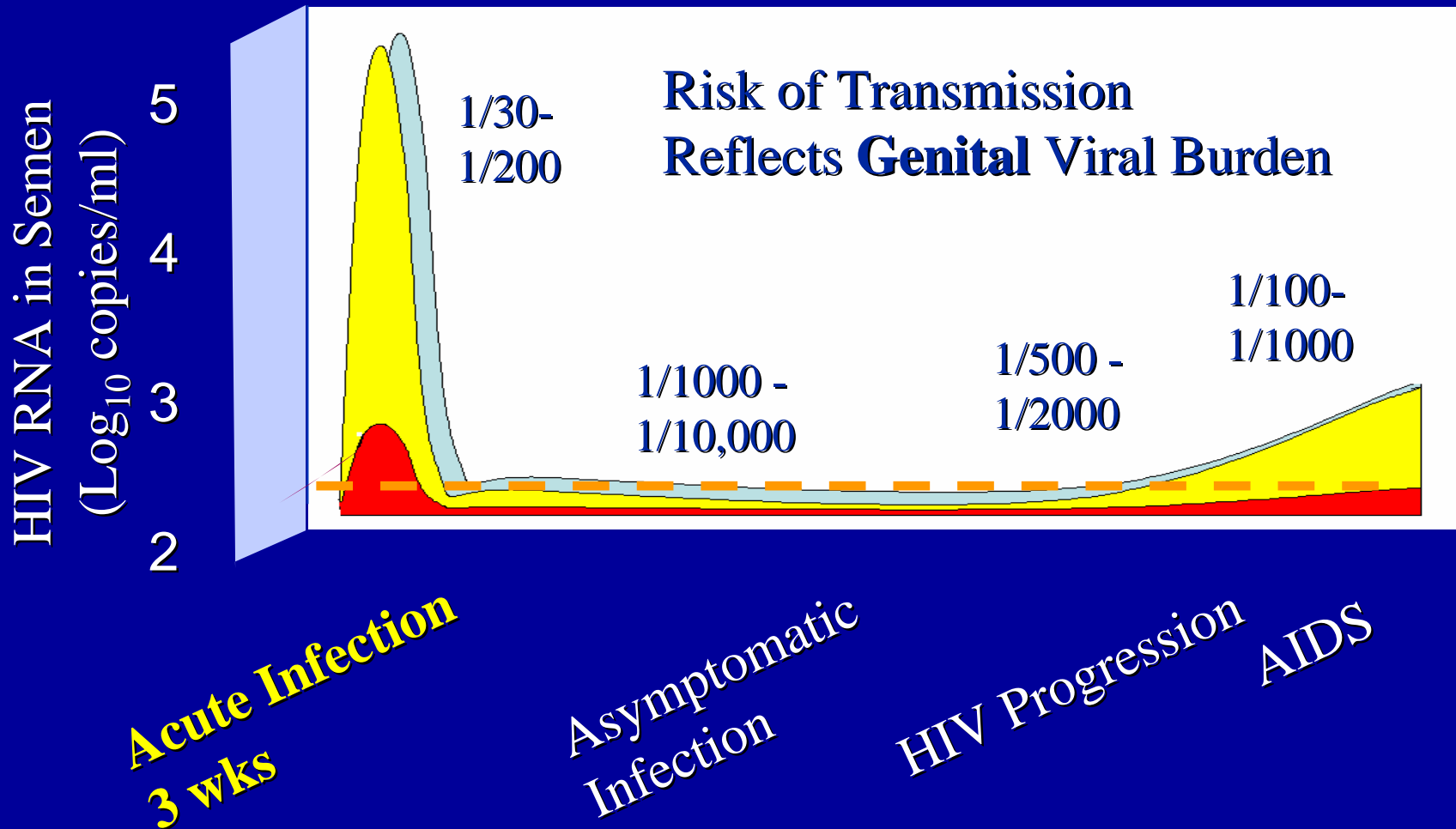
-HIV SUPPRESSION in the blood and the genital tract are readily achieved

2. Expectations from “the literature”

3. **HPTN052: A Clinical Trial**

Sexual Transmission of HIV

(Cohen and Pilcher, *JID* May 2005)



ART Prevents HIV Transmission?

Retrospective Analysis

Musicco *et al.* Archives Int Med 154: 1971; 1994

Castilla *et al.* JAIDS 40, 96, 2005

Observational Studies

Kayitenkore *et al.* IAS, 2006

Bunnell *et al.* AIDS 20: 85-92, 2006

Ecological Analysis

***Katz et al.* Am J. Public Health 92: 388, 2002 (-)**

***Porco et al.* AIDS 18:81, 2004 (+)**

***Fang et al.* JID, September 2004 (++)**

***Montaner et al.* Lancet, August 2006 (??)**

The impact of ART on HIV transmission among HIV serodiscordant couples: Kayitenkore et al (IAS,2006)

- ✦ **ART offered in Kigali, Rwanda since 2003**
- ✦ **1034 serodiscordant couples followed**
- ✦ **248 “index cases” receiving ART (CD4<200)**
- ✦ **In spite of counseling, 42 seroconversions**
- ✦ **Only 2/42 seroconversions with partner on ART**
- ✦ **ART leads to 80% reduction in HIV?? (OR=0.19 (95% CI 0.05-0.80))**

Bunnell et al. AIDS 20: 85-92, 2006

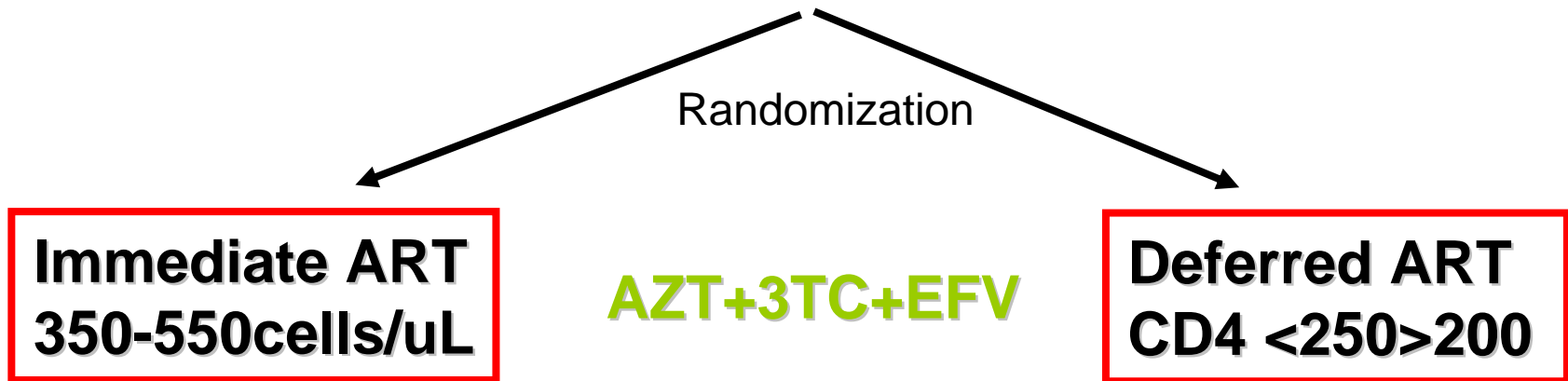
- ✦ ART offered May, 2004 in Uganda
- ✦ 454 subjects and co-habiting partners available for 24 month follow-up
- ✦ Baseline viral load (122,500 copies) “suppressed”
- ✦ Increased sex, but reduced risky behavior
- ✦ HIV Seroconversions reduced from 45.7/1000 py to 1/1000 py
- ✦ *Only one seroconversion in 2 years*

ART Prevents HIV Transmission????

- ✦ **Observational studies cannot control for which couples choose therapy, drop-out rates**
- ✦ **Observational studies cannot control for behavior changes**
- ✦ **Observational and retrospective studies focus on ART for subjects who require therapy because of low CD4 count...not all couples**
- ✦ **Observational studies do not follow couples long enough to demonstrate sustained prevention benefit**

HPTN 052/CHAVI007/ACTG5245

HIV-infected subjects with CD4 350 to 550cells/ μ L



Endpoints: i) Transmission Events
ii) Death, TB, WHO Stage Events
iii) ART Toxicity

HPTN052:

Sites/Sample Size

Study Population: 8 sites

Malawi (2 sites), India (2 sites), Thailand,
Zimbabwe, Brazil (2 sites), South Africa

Sample size: n=1750 serodiscordant couples

Power: 90% power to detect 35% reduction in
sexual transmission of HIV

HPTN 052 Baseline HIV RNA

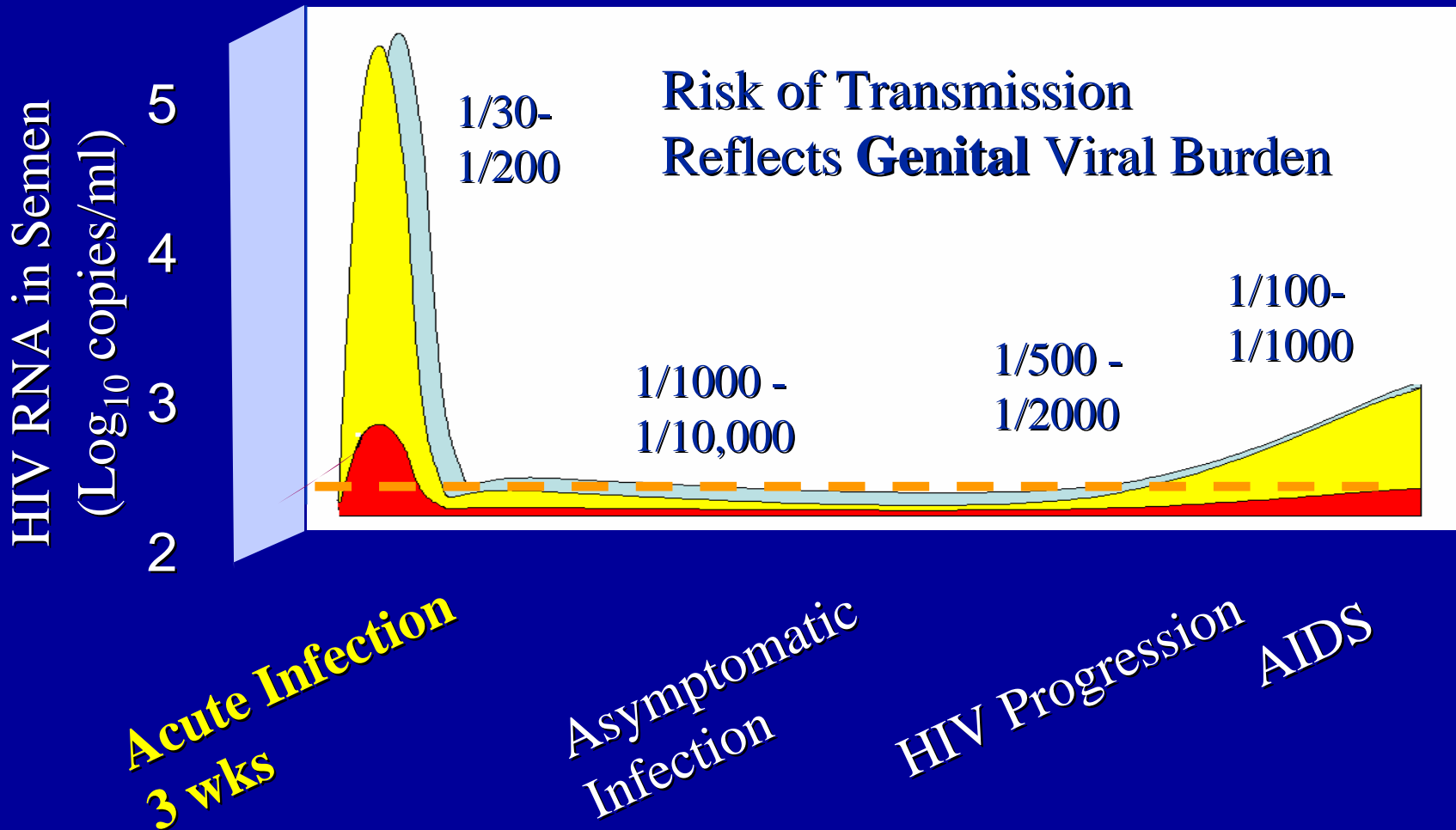
Site	HIV RNA at Enrollment (log 10 scale)	
	Mean	SD
Porto Alegre, Brazil	-	-
Rio de Janeiro, Brazil	4.4	0.5
Chennai, India	4.8	0.5
Pune, India	4.3	0.6
Blantyre, Malawi	5.3	0.3
Lilongwe, Malawi	4.6	0.7
Chiang Mai, Thailand	4.5	0.6
Boston, US	4.5	-
Harare, Zimbabwe	4.7	0.0
Total	4.6	0.6

Limitations of ART for Prevention

- **Cost and Acquisition of ART?**
- **ART Resistance?**
- **Public Health Impact?**
 - ...Can we treat enough people?*
 - ...Which infected subjects are most contagious?*
 - ...Breakthrough viremia observed with STDs*

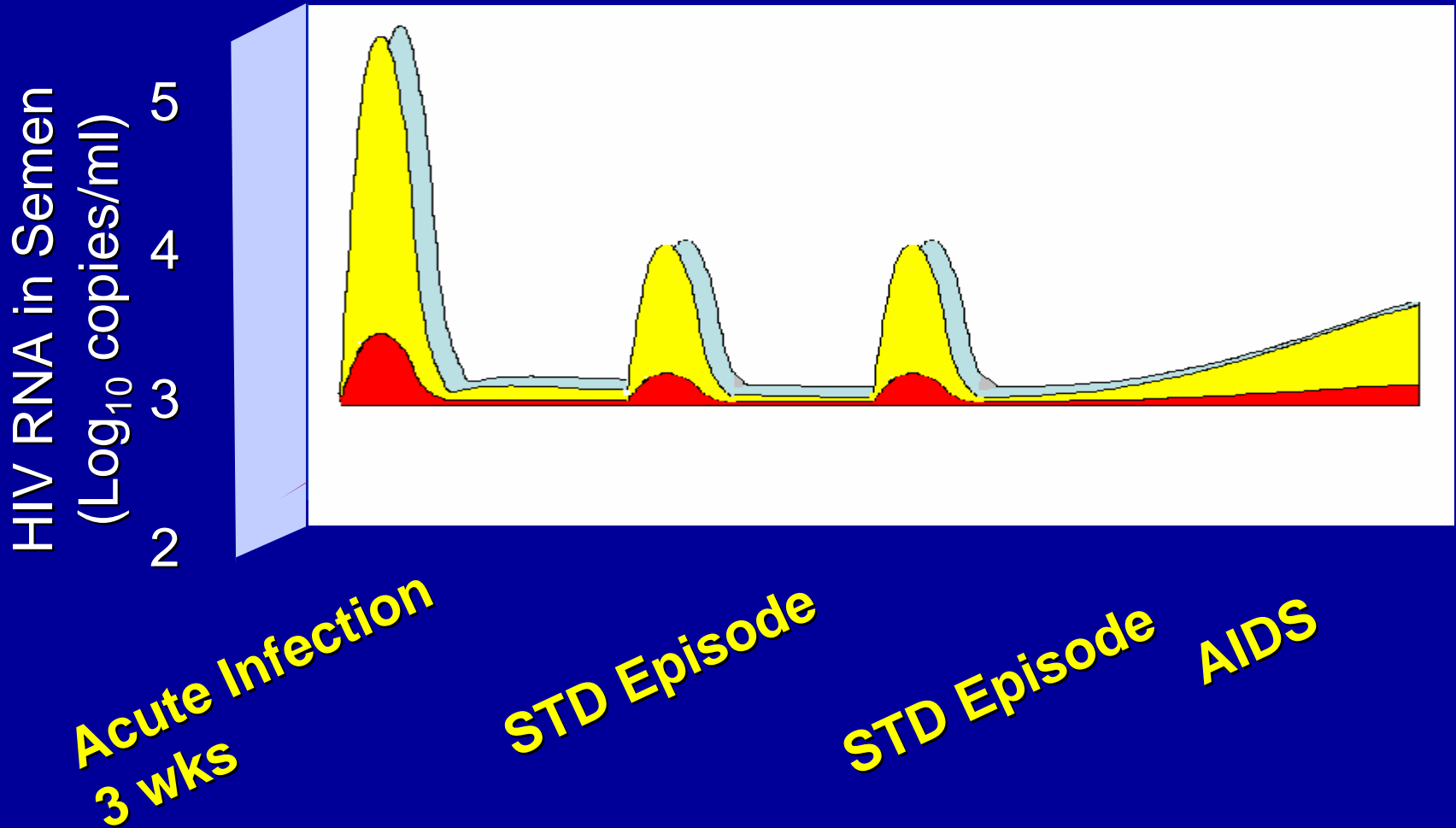
Sexual Transmission of HIV

(Cohen and Pilcher, *JID* May 2005)



Acute HIV and STD episodes

Cohen and Pilcher, JID, 2005



ART and Conception

Vernazza et al. IAS Sydney 2007

- 21 discordant couples trying to conceive
 - Male partners suppressed with ART
 - Female partners offered TDF 36 and 12 hours BEFORE unprotected intercourse
 - 15/21 pregnancies within 10 “cycles; 50% impregnated in 3 cycles
 - No HIV seroconversions (BUT???)
- ...REAL WORLD GUIDELINES???

ART for Prevention: Conclusions

- nPEP will be used **BUT** we will not be able to “prove” its benefits
- “PrEP” trials **WILL** determine the benefit(s) of the approach...but we will **NEED** to test real PrEP
- ART suppression **WILL** serve as part of our HIV prevention strategy and...

**WE HAVE NO OPTION BUT TO STUDY
THE EFFECTS OF ART ON
TRANSMISSION**