
Treatment as prevention

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Acknowledgement: Julio Montagner, Helen
Rees, Mike Cohen, HPTN/NIH, Ian Sanne,
Connie Cellum

Is sex now safe?



Why should we worry?

- All HIV spread is from a discordant couple
- Discordant couples > concordant HIV couples

Effect of HAART on HIV Transmission

HAART stops HIV replication



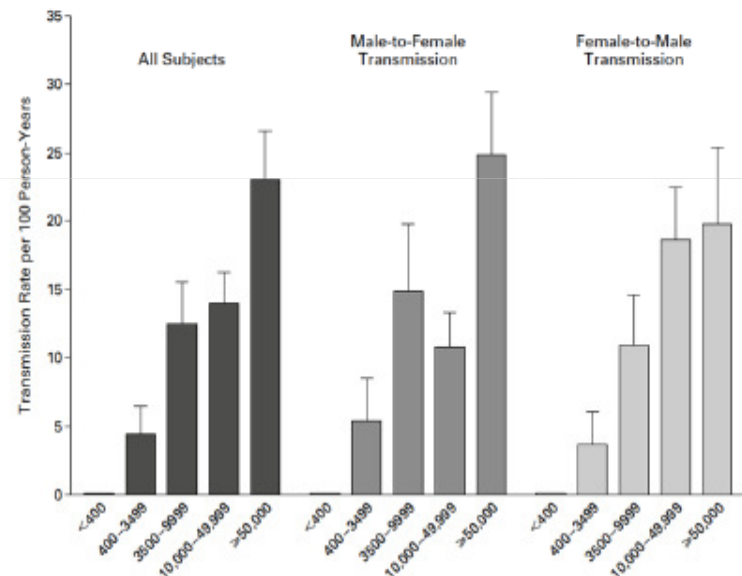
HIV levels fall to undetectable in
blood as well as sexual fluids



Sharp reduction in HIV transmission

HIV-1 levels & HIV-1 infectiousness

- High plasma HIV-1 RNA concentrations are associated with increased HIV-1 transmission risk
- Plasma and genital HIV-1 levels are correlated (coefficient ~0.5-0.6)
 - But, genital HIV-1 more variable than plasma and tight correlation not found in all individuals

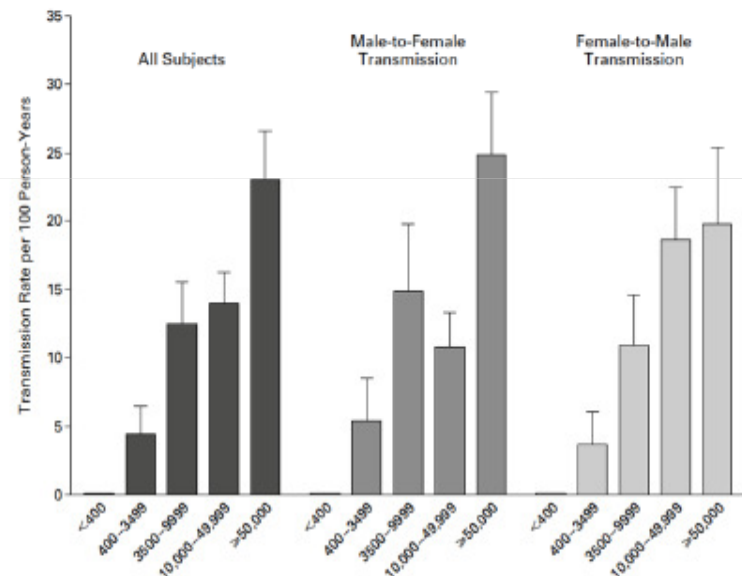


Quinn et al NEJM 2000

Thanks Connie Cellum

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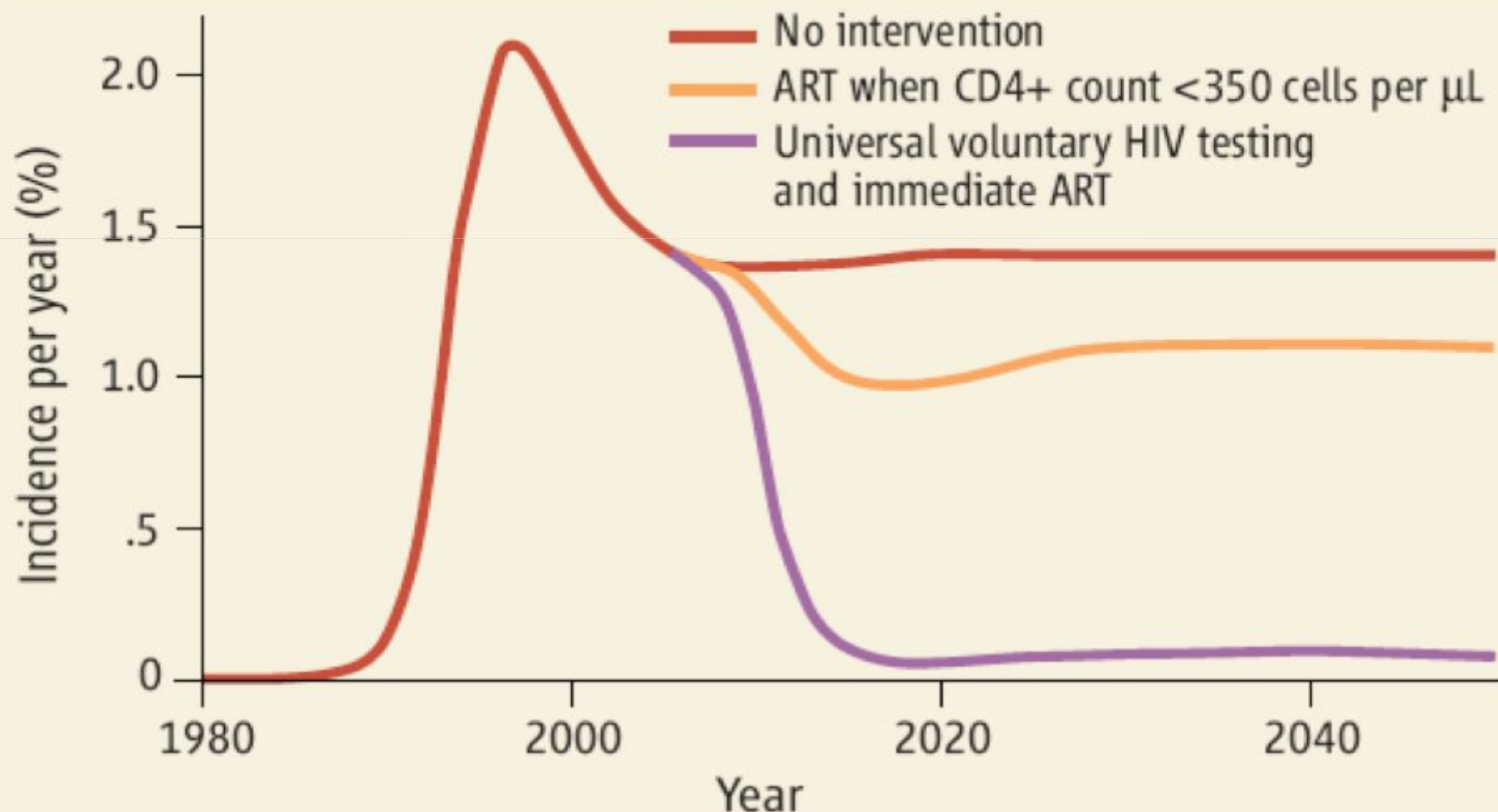


Quinn et al NEJM 2000

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Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

R Granich, C Gilks, C Dye, K De Cock, B Williams. The Lancet Nov 26th 2008



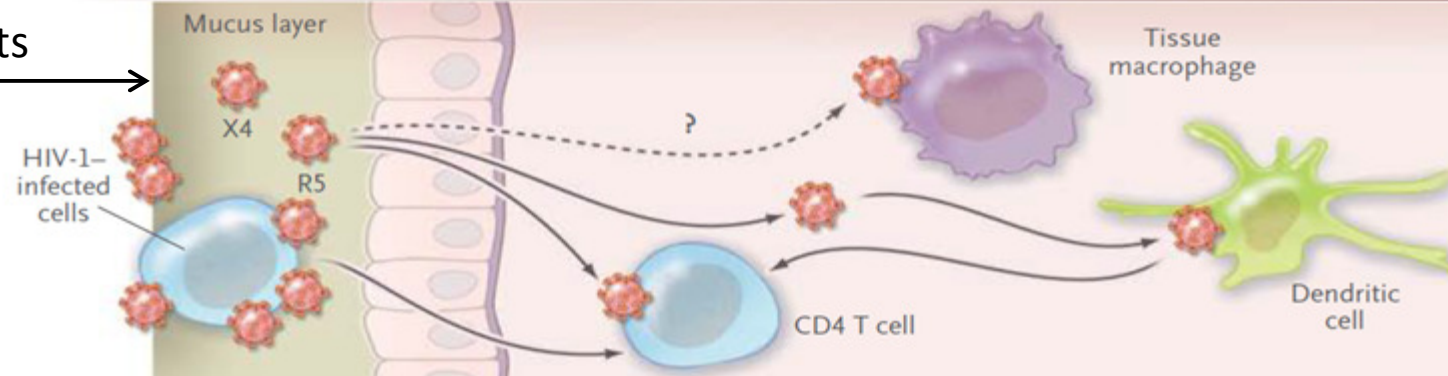
So how does transmission work?



A HIV-1 translocation through female epithelium

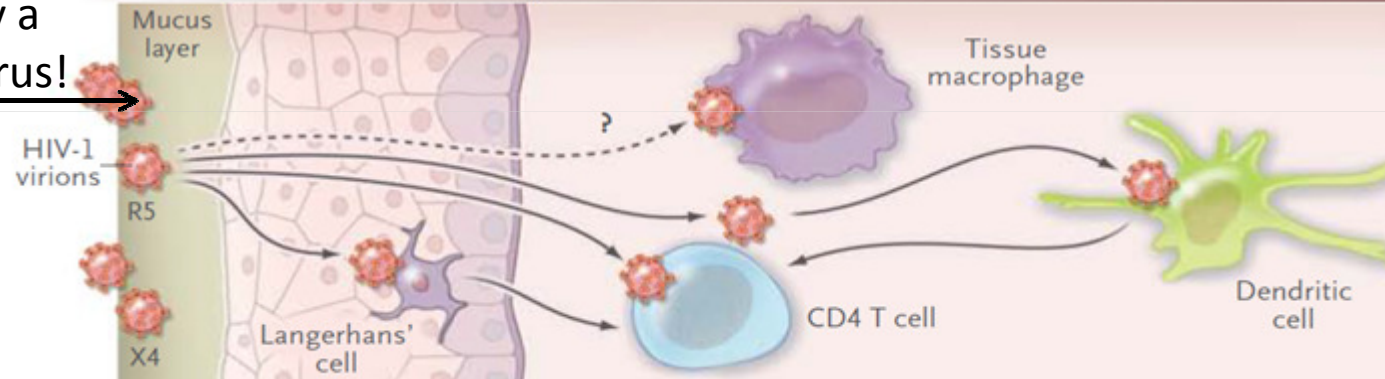
Columnar epithelium in rectum and endocervix

Multiple targets



Stratified squamous epithelium in vagina and ectocervix

Usually a single virus!



C Timing of HIV-1 infection events

Virus or virus-infected cells crossing mucosal barrier

Local propagation of infection on CD4 T cells

Systemic dissemination

2-6 hours

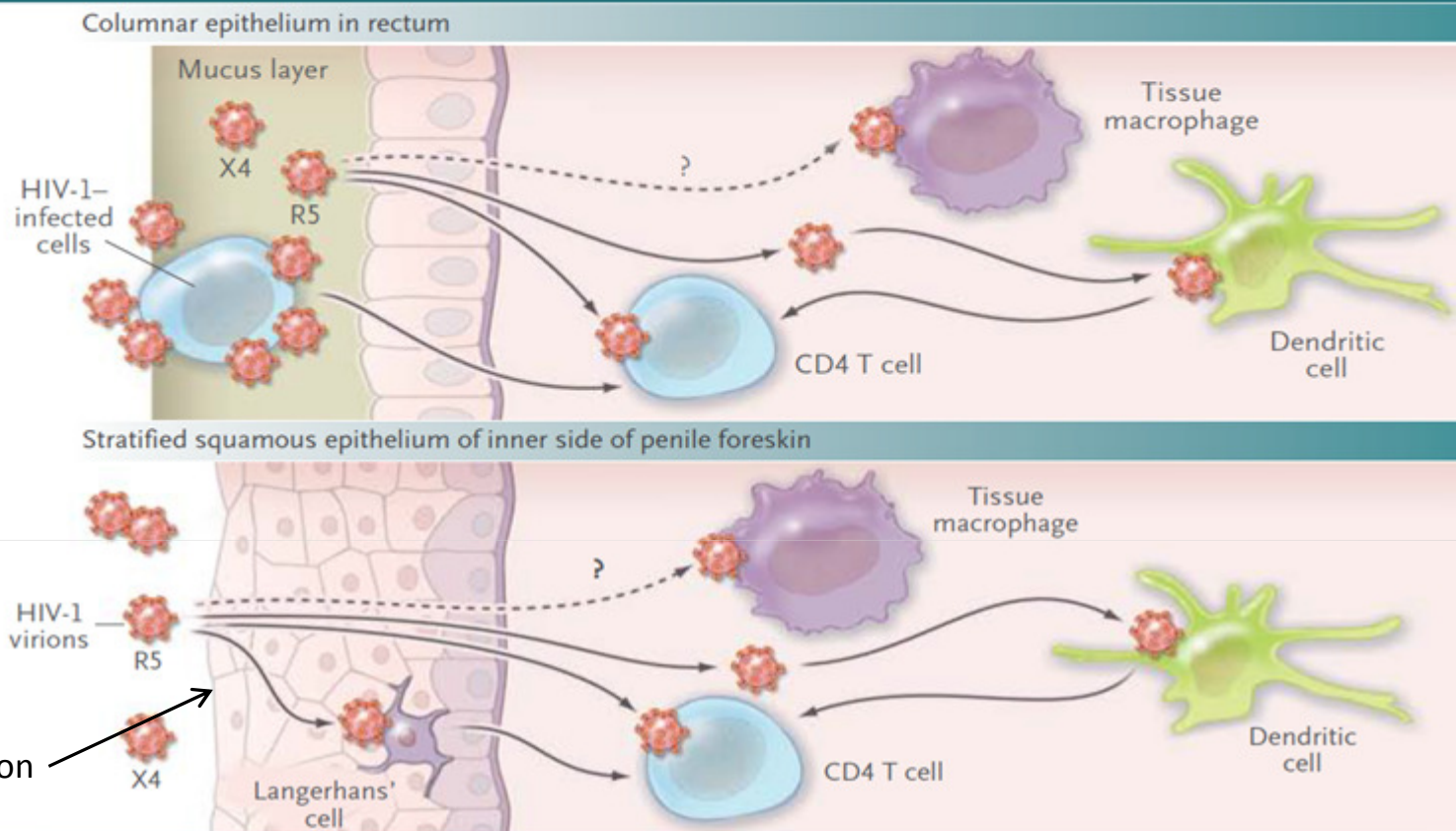
3-6 days

6-25 days

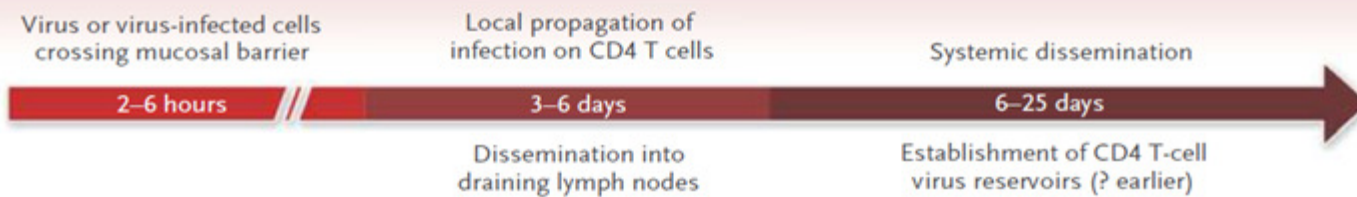
Dissemination into draining lymph nodes

Establishment of CD4 T-cell virus reservoirs (? earlier)

B HIV-1 translocation through male epithelium



C Timing of HIV-1 infection events



How does this help us?

Routes of Exposure and HIV.

INFECTION ROUTE

RISK OF INFECTION

Sexual Transmission

- a. Female-to-male transmission.....1 in 700 to 1 in 3,000
- b. Male-to-female transmission.....1 in 200 to 1 in 2,000
- c. Male-to-male transmission.....1 in 10 to 1 in 1,600
- d. Fellatio??..... .0 %

It is hard to get HIV!

Parenteral transmission

- a. Transfusion of infected blood.....95 in 100
- b. Needle sharing.....1 in 150
- c. Needle stick.....1 in 200
- d. Needle stick /AZT PEP.....1 in 10,000

Transmission from mother to infant

- a. Without AZT treatment.....1 in 4
- b. With AZT treatment.....Less than 1 in 10

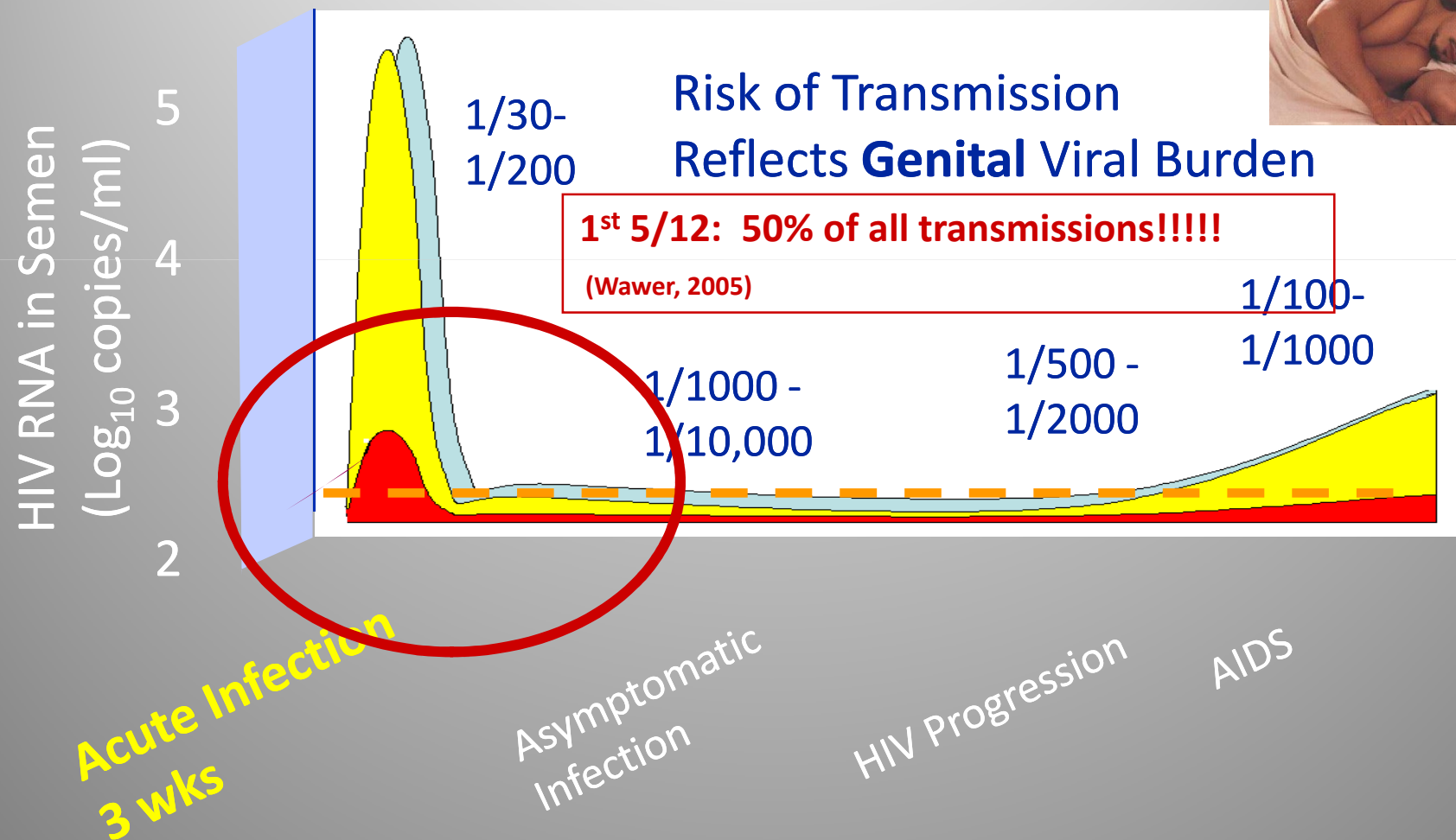
Adapted from Royce, Sena, Cates and Cohen, NEJM 336:1072-1078, 1997

HIV 'natural history'



Sexual Transmission of HIV

(Cohen et al. Lancet 351: 1998)



What is the biggest news of the year?

- HPTN 052

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples



HIV-infected, sexually active
serodiscordant
couples; CD4+ cell count
of the infected partner:
350-550 cells/mm³

(N = 1763 couples)



Immediate ART
Initiate ART at CD4+ cell count 350-550 cells/mm³
(n = 886 couples)

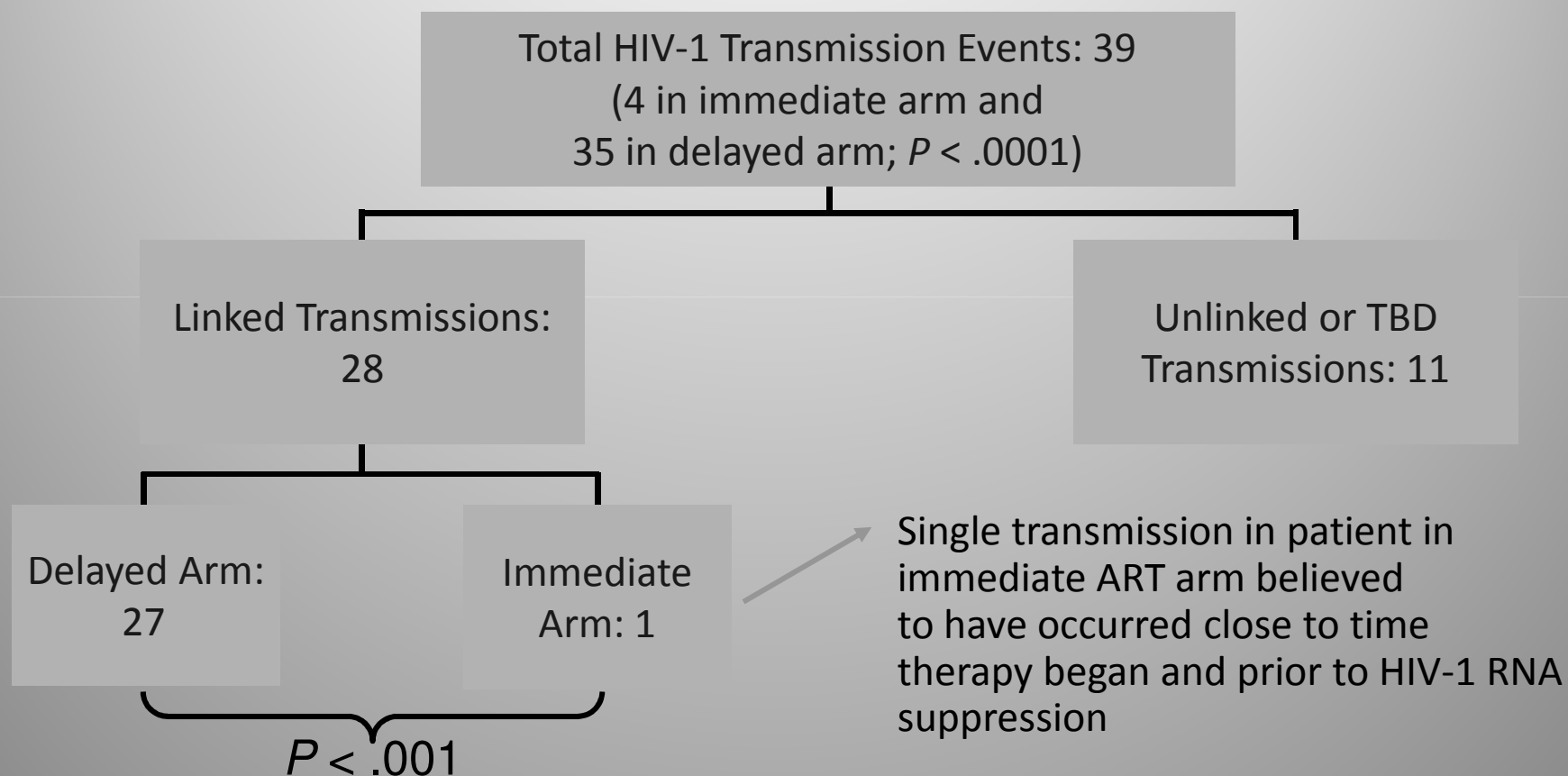
Delayed ART
Initiate ART at CD4+ cell count ≤ 250 cells/mm³*
(n = 877 couples)

*Based on 2 consecutive values ≤ 250 cells/mm³.

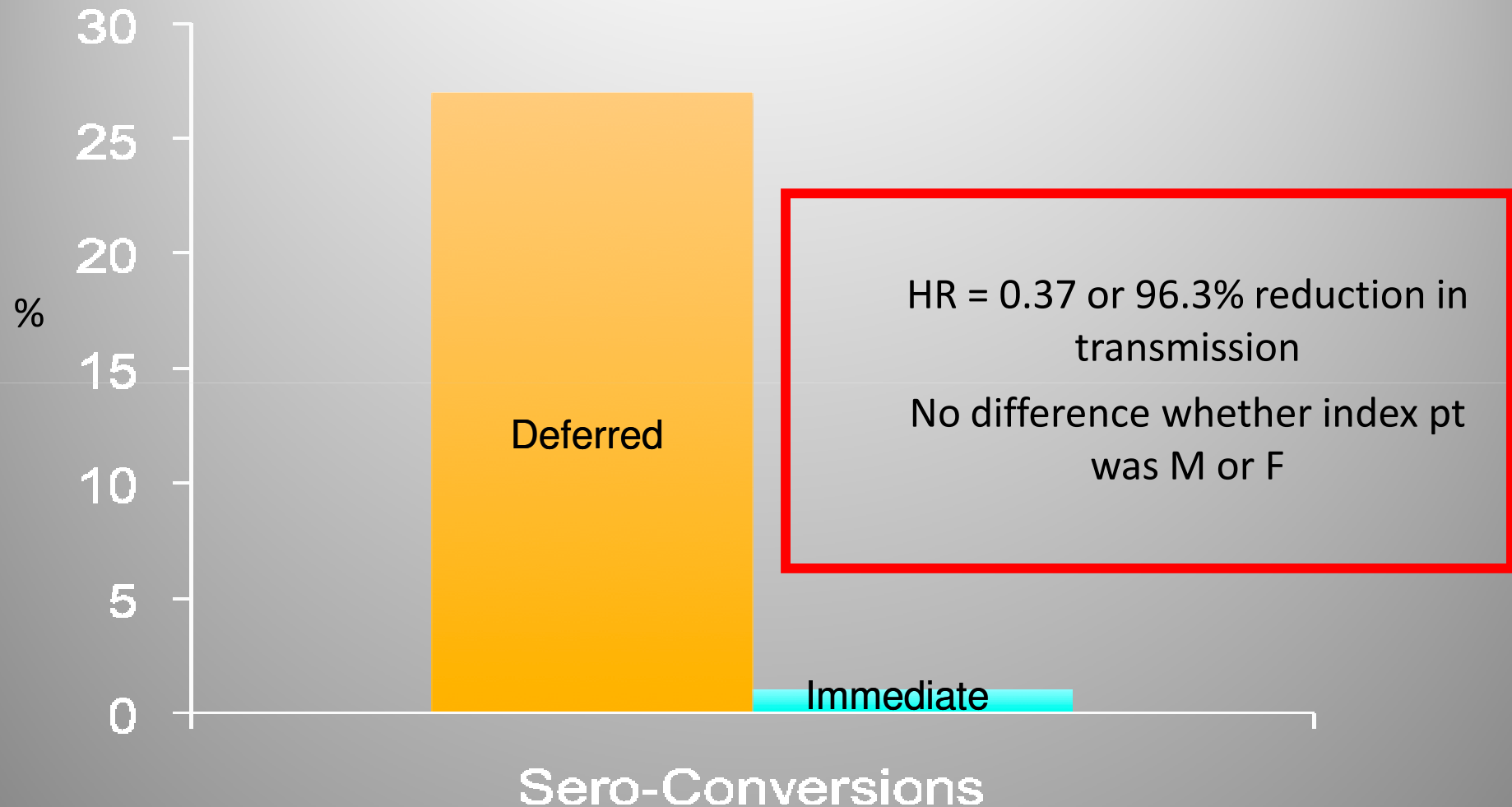
- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

Dr. TB recommended release of results as soon as possible following April 28, 2011 review; follow-up continues but all HIV-infected partners offered ART after release of results

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

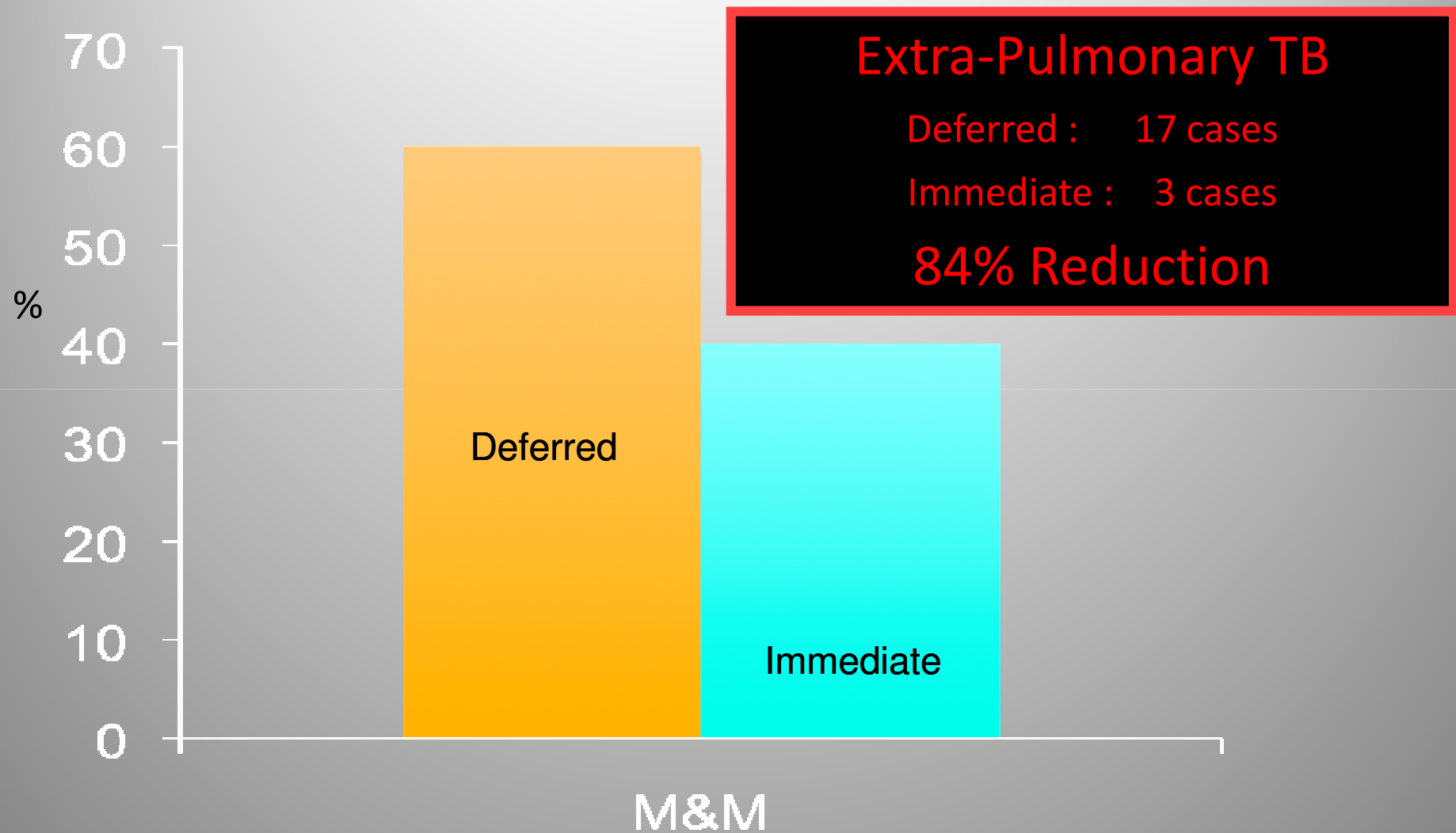


HPTN 052 (www.hptn.org)



M Cohen et al, NIH Press Conference May 12th 2011.
To be presented at IAS-Rome, July 2011

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Most Prevalent Secondary Events

Number of subjects experiencing ≥ 1 event		
	Delayed (N=317)	Immediate (N=298)
Upper respiratory tract infection	87	72
Moderate unexplained weight loss*	61	76
Popular puritic eruption	52	33
Herpes zoster	53	17
Smear positive malaria	49	49
Oral Candidiasis, persistent	47	22
Unexplained severe weight loss	21	37
Dyslipidemia	7	23
Peripheral neuropathy	14	15
Seborrhoeic dermatitis	18	7
Hypertension	8	12
Oral ulcerations	9	10

HPTN 052 Enrollment

(Total Enrollment: 1763 couples)



Clinical trial evidence for preventing sexual HIV transmission – 14 July 2011

Study

Effect size (CI)

Treatment for prevention

(Africa, Asia, America's)

PrEP for discordant couples

(Partners PrEP)

PrEP for heterosexuals

(Botswana TDF2)

Medical male circumcision

(Orange Farm, Rakai, Kisumu)

PrEP for MSMs

(America's, Thailand, South Africa)

STD treatment

(Mwanza)

Microbicide

(CAPRISA 004 tenofovir gel)

HIV Vaccine

(Thai RV144)

96% (73; 99)

73% (49; 85)

63% (21; 48)

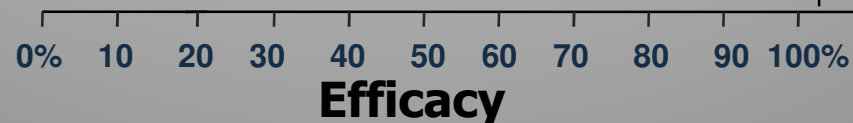
54% (38; 66)

44% (15; 63)

42% (21; 58)

39% (6; 60)

31% (1; 51)



What's not to like????

- Sex is inherently risky – ‘safe sex’ is nonsense



But the vast majority of us think its very, very worth it.

Does ART prevent HIV transmission among MSM?

Kathryn E. Muessig^a, M. Kumi Smith^b, Kimberly A. Powers^{a,b},
Ying-Ru Lo^c, David N. Burns^d, Andrew E. Grulich^e,
Andrew N. Phillips^f and Myron S. Cohen^{a,b,g}

transmitted infections (STIs). Additional studies are needed on the impact of ART on HIV sexual risk behaviors and transmission among MSM outside of developed countries in North America, western Europe, and Australia.

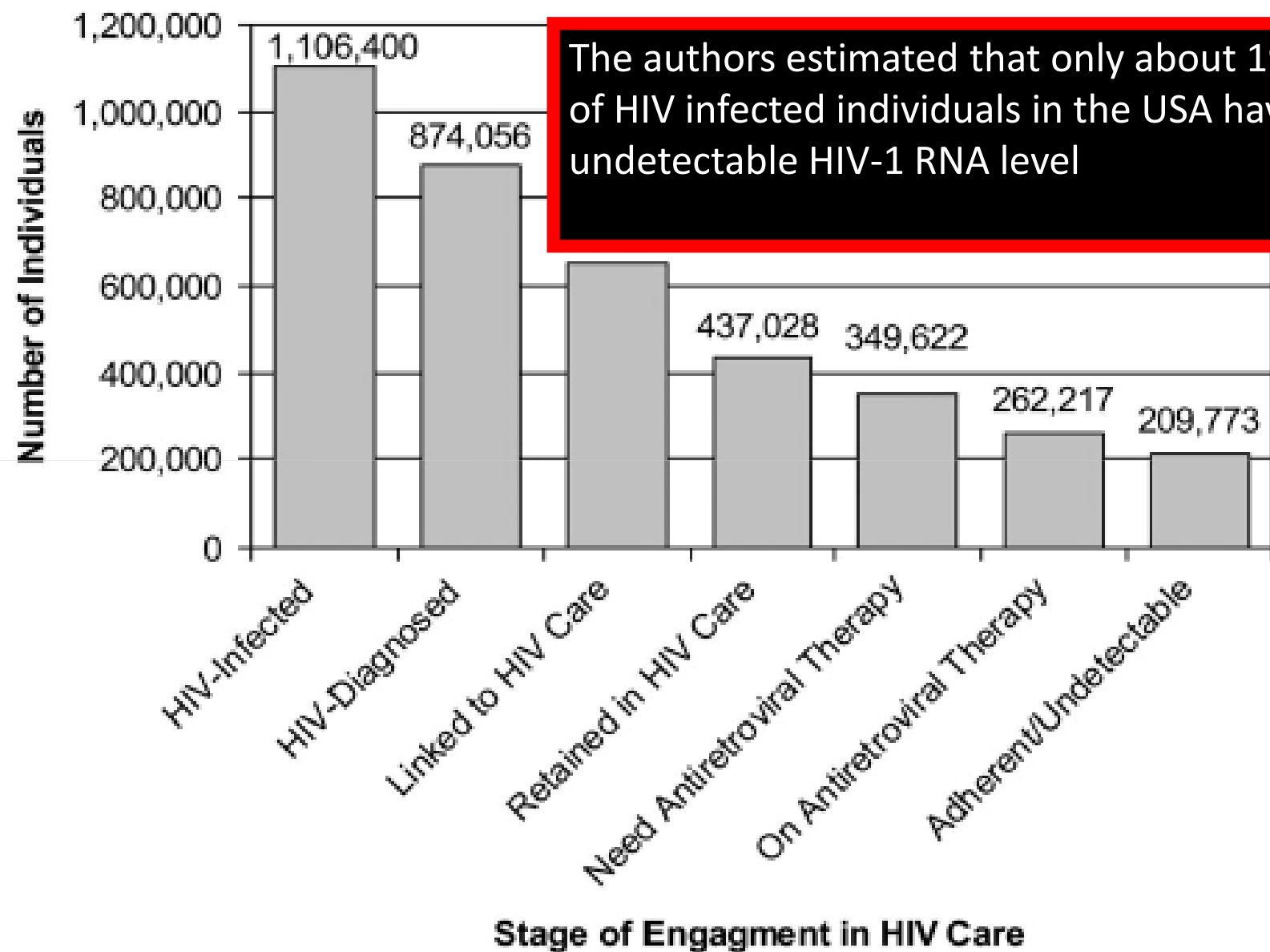
Conclusion: The benefits of treatment as prevention for MSM are highly plausible, but not certain. In the face of these unknowns, treatment guidelines for earlier ART initiation should be considered within a combination prevention strategy that includes earlier diagnosis, expanded STI treatment, and structural and behavioral interventions.

052 was a clinical trial

- Will we get adherence like this?
- If it's not your partner?
- Disinhibition?
- Transmission events disproportionately came from Africa (!!!)



Spectrum of Engagement in HIV Care - USA



Several questions

- Will people take it for their own health?
- Will it have a population impact? (noting the transmission dynamic in acute seroconversion)
- Will it actually work? Randomised studies

Treatment as prevention

- Incredibly exciting BUT
- Will require huge investment in health systems
- For discordant couples – yes (but how?)
- For general roll-out? We need more data

