

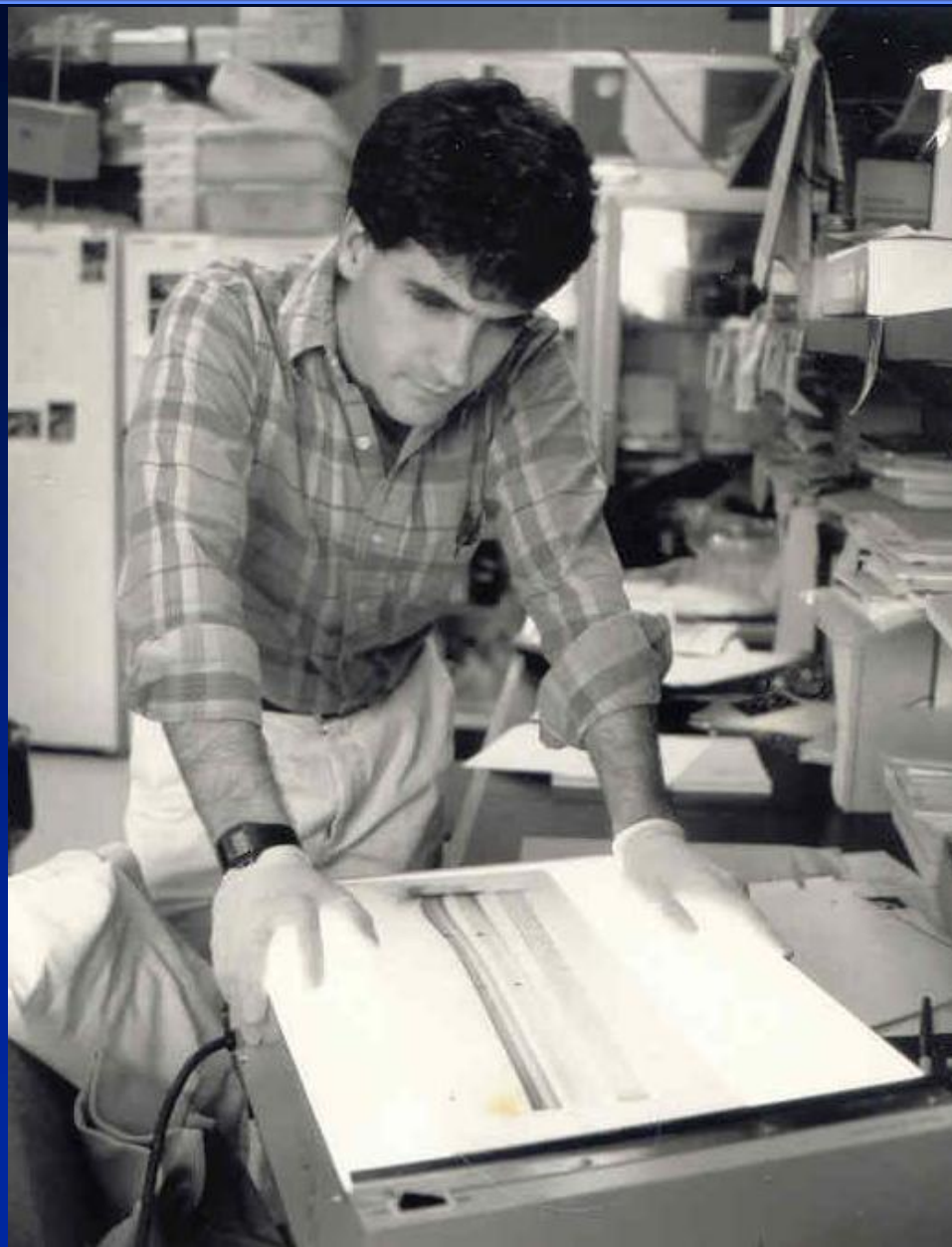
PREVENTION OF HIV-1 Infection

Myron S. Cohen, MD

Institute for Global Health

The University of North Carolina





“Telling A Story”

- A beginning
- A middle
- We ABSOLUTELY don't know the ending

Transmission of HIV-1

Biological Requirements

Infectious



Inoculum (concentration)

Phenotypic factors

Susceptibility

Hereditary resistance

Innate resistance

*Acquired (immune)
resistance*

Probability of HIV Transmission?

~1/1000 episodes for couples??
(Most recently Hughes et. al. JID)

IS 1/1000 AN UNDERESTIMATE??

- "exposed uninfected" partners
- benefits of counseling
- missing amplification factors

Amplified Transmission of HIV-1

Infectiousness

Blood Viral Load

Genital Tract Viral Load

-Inflammatory STDs

Viral clade

ACUTE INFECTION

Susceptibility

Genital ulcers

Inflammatory STDs

Lack of Circumcision

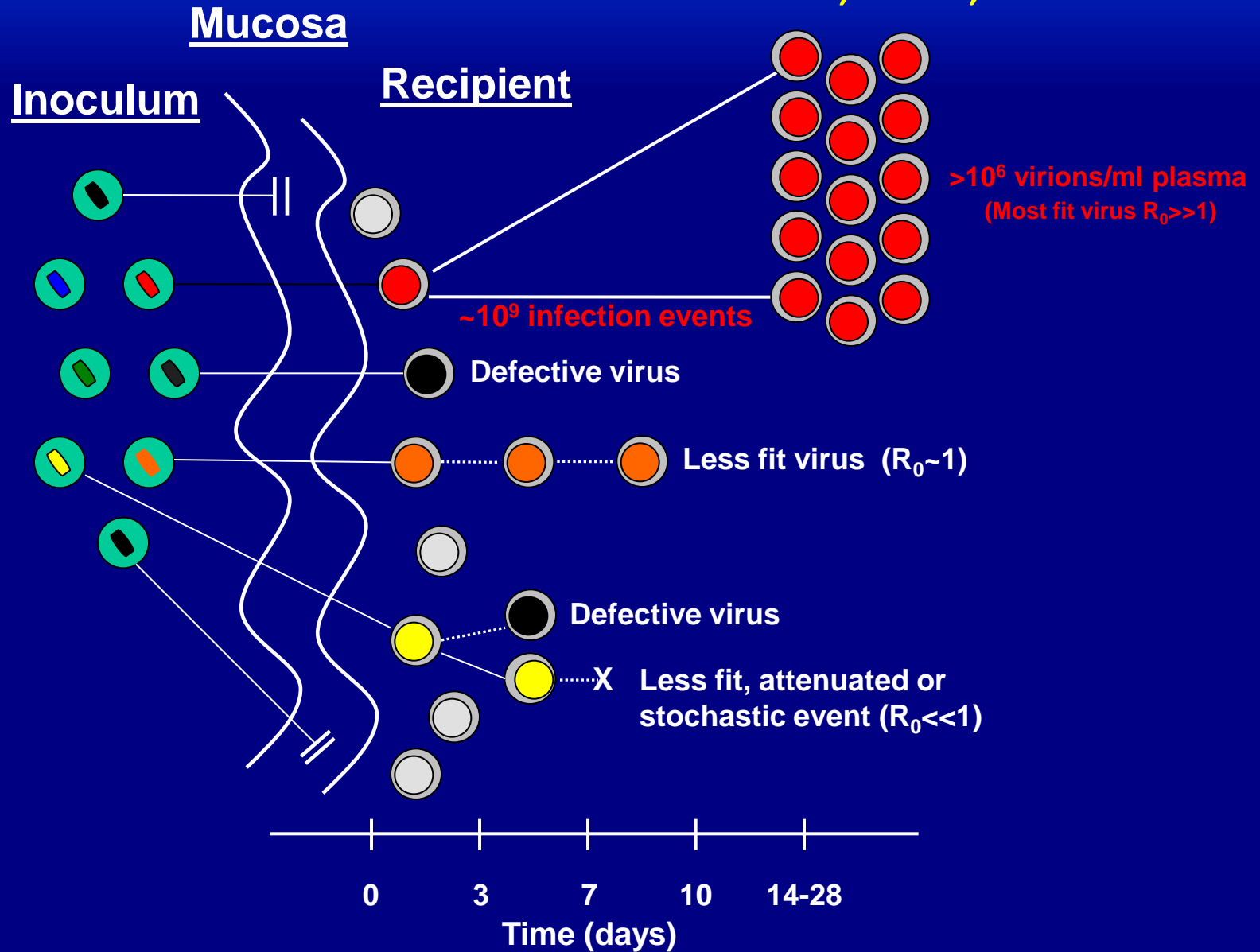
Cervical ectopy

HLA Haplotype

Cytokine profile

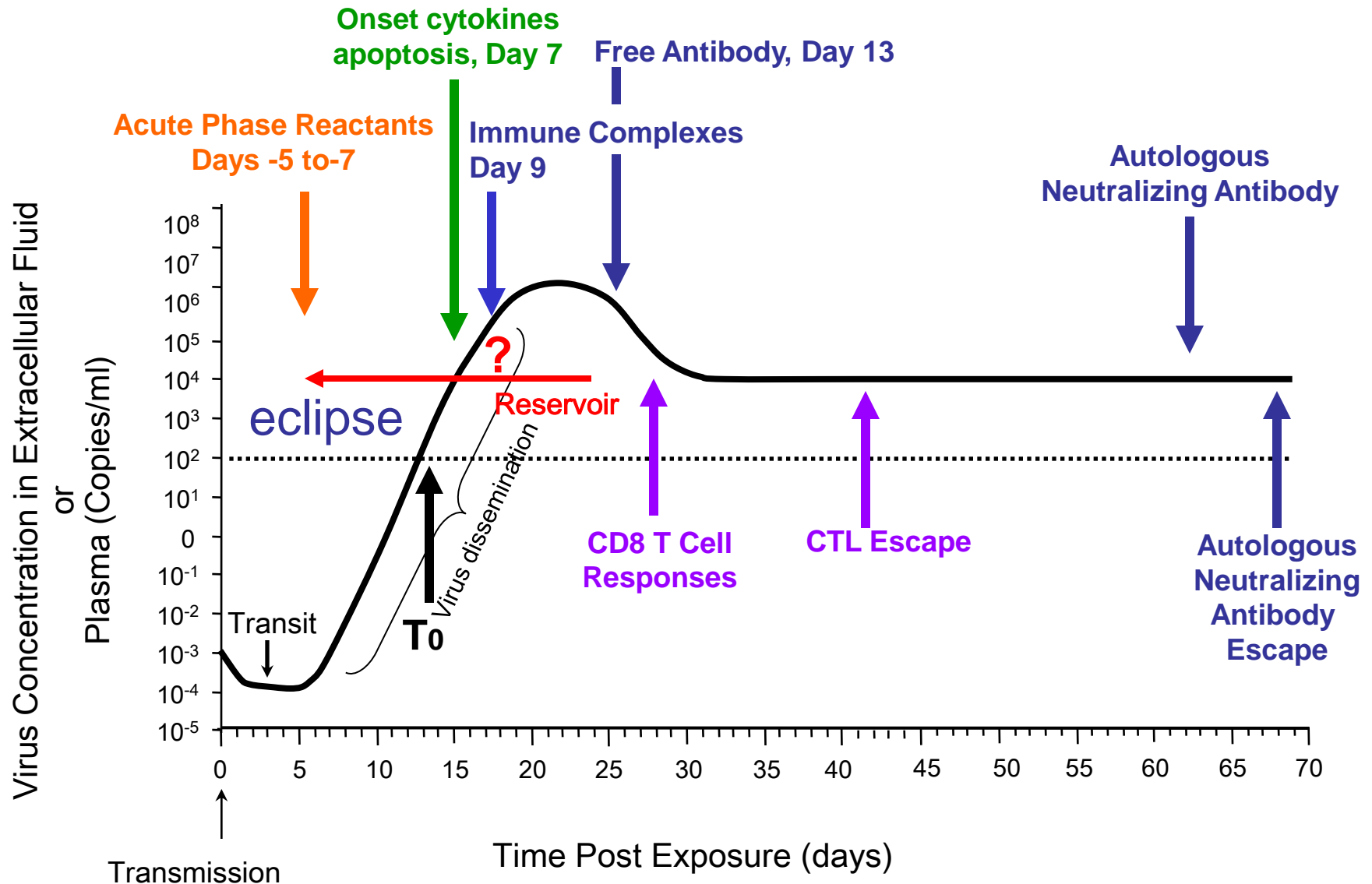
HIV-1 Transmission Model

Cohen et al, NEJM, 2011



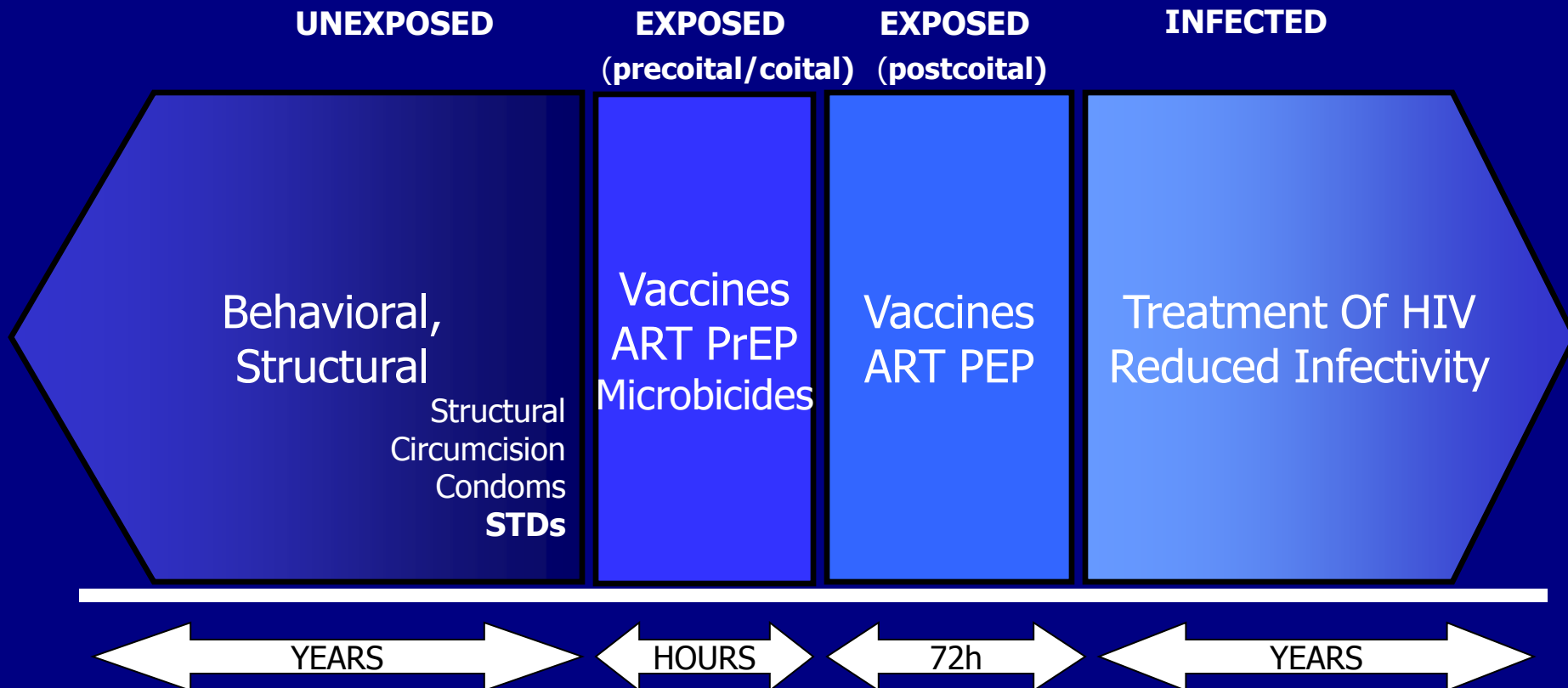
Acute HIV-1 Infection

Cohen et al, NEJM, 2011



Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008



ART to Prevent Sexual Transmission of HIV

- Post-exposure Prophylaxis (PEP)???
- Pre-exposure prophylaxis (PrEP) ????
- Treatment of the infected person ???

CAPRISA 004: Topical Tenofovir for Women



Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women
Quarraisha Abdool Karim, *et al.*
Science 329, 1168 (2010);
DOI: 10.1126/science.1193748

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,^{1,2,*†} Salim S. Abdool Karim,^{1,2,3,*} Janet A. Frohlich,¹ Anneke C. Grobler,¹ Cheryl Baxter,¹ Leila E. Mansoor,¹ Ayesha B. M. Kharsany,¹ Sengeziwe Sibeko,¹ Koleka P. Mlisana,¹ Zaheen Omar,¹ Tanuja N. Gengiah,¹ Silvia Maarschalk,¹ Natasha Arulappan,¹ Mukelisiwe Mlotshwa,¹ Lynn Morris,⁴ Douglas Taylor,⁵ on behalf of the CAPRISA 004 Trial Group†

The PrEP “Conundrum”

Oral TVF-FTC (Truvada Combination)

SUCCESS

- *iPREX : 42% prevention in MSM*
- *TDF2 : 63% protection with high risk*
- *PIP: 73% protection in EU*

FAILURE

- **FEMPREP: Trial in women stopped**
- **VOICE: Tenofovir in women stopped**
- **VOICE: Tenofovir gel stopped (????)**
- **VOICE: TVF-FTC oral ONGOING**

Does PrEP WORK and HOW WELL?

- **Adherence**
- **Tissue levels**

... Truvada PrEP APPROVED

-MSM

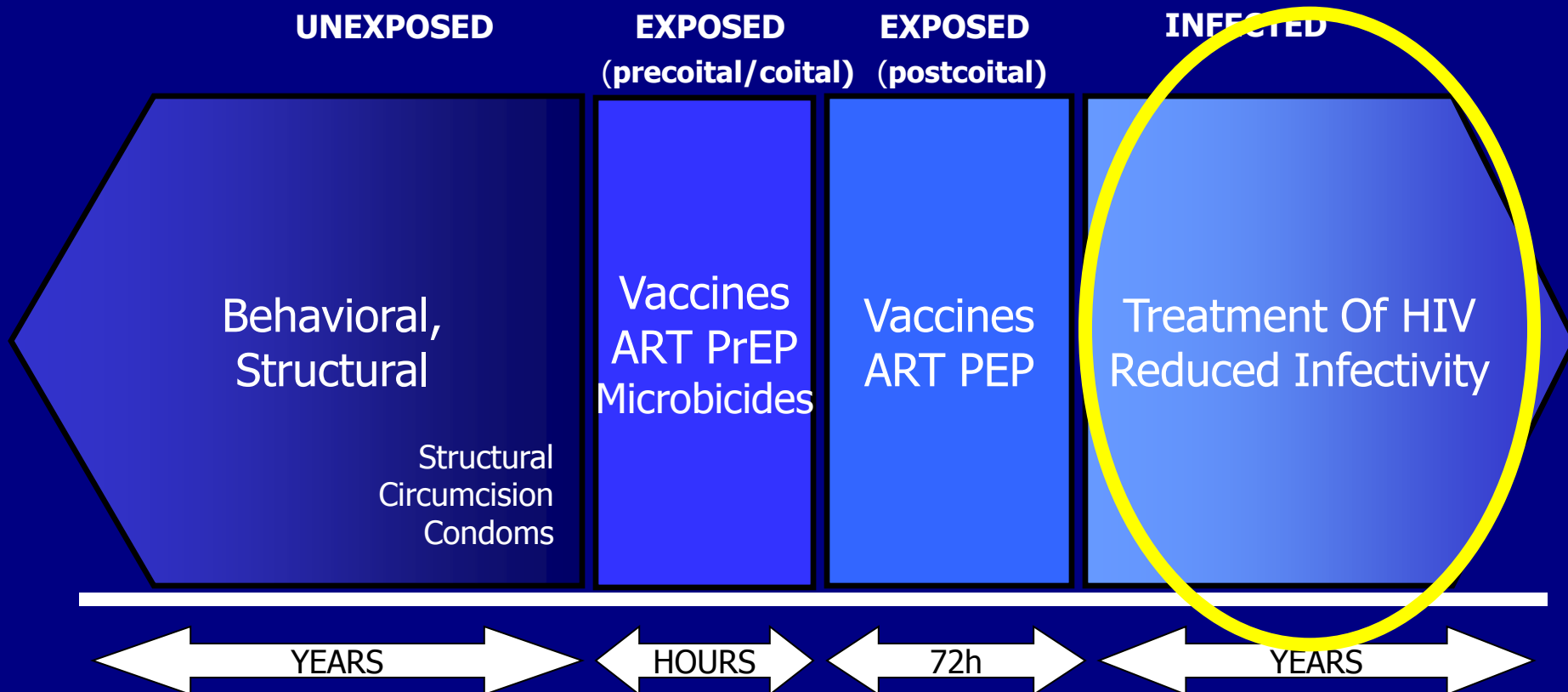
-Couples (??)

-High RISK (???)

INFRASTRUCTURE/LIMITS?

Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008



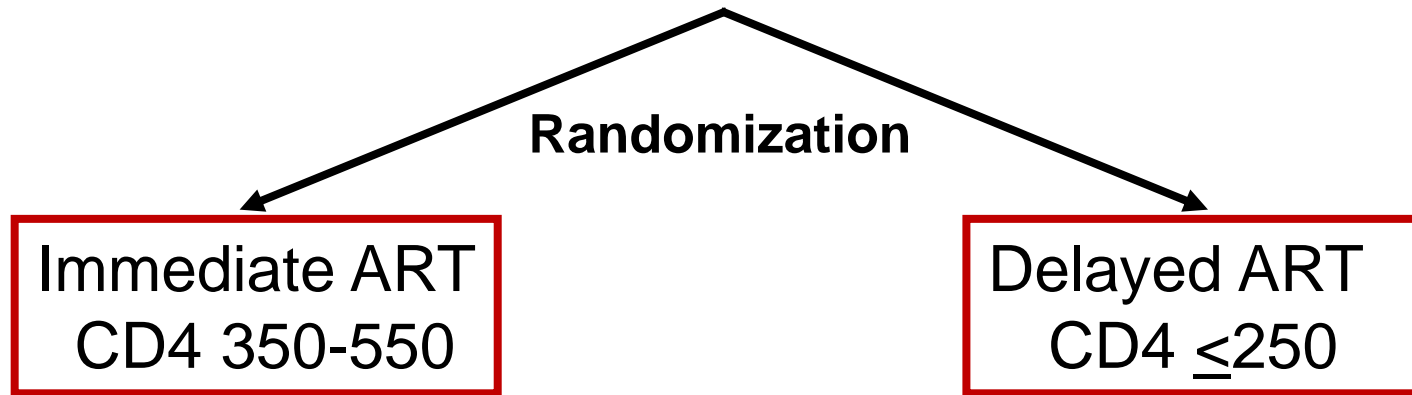
Treatment as Prevention

“The Four Questions”

- 1) Do ART drugs prevent HIV transmission?
- 2) What do we tell infected people?
- 3) Can we reduce population HIV incidence ?
- 4) Barriers to “Treatment as Prevention”?

HPTN 052 Study Design

Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm³



Primary Transmission Endpoint
Virally linked transmission events

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

HPTN 052 Recognition

U.S. Sponsors:

- National Institutes of Health (NIH)
- Division of AIDS (DAIDS), U.S. National Institute of Allergy and Infectious Diseases (NIAID)

HIV Prevention Trials Network (HPTN):

- Network Laboratory, Johns Hopkins University
- ***Statistical Center for HIV/AIDS Research & Prevention (SCHARP) and University of Washington***
- Coordinating and Operations Center, Family Health International (FHI)
- HPTN Leadership

AIDS Clinical Trials Group (ACTG):

- ACTG Leadership and Investigators

Pharmaceutical Companies:

- Abbott Laboratories
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Bristol-Myers Squibb
- Gilead Sciences, Inc.
- GlaxoSmithKline
- Merck & Co., Inc.

Sites (Investigators of Record):

- Porto Alegre, Brazil (Breno Santos)
- Rio de Janeiro, Brazil (Beatriz Grinsztejn)
- Boston, United States (Kenneth Mayer)
- Chennai, India (N. Kumarasamy)
- Pune, India (Sheela Godbole)
- Chiang Mai, Thailand (Suwat Chariyalertsak)
- Gaborone, Botswana (Joseph Makhema)
- Kisumu, Kenya (Lisa Mills)
- Blantyre, Malawi (Johnstone Kumwenda)
- Lilongwe, Malawi (Mina Hosseinipour)
- Johannesburg, South Africa (Ian Sanne)
- Soweto, South Africa (Guy De Bruyn)
- Harare, Zimbabwe (James Hakim)

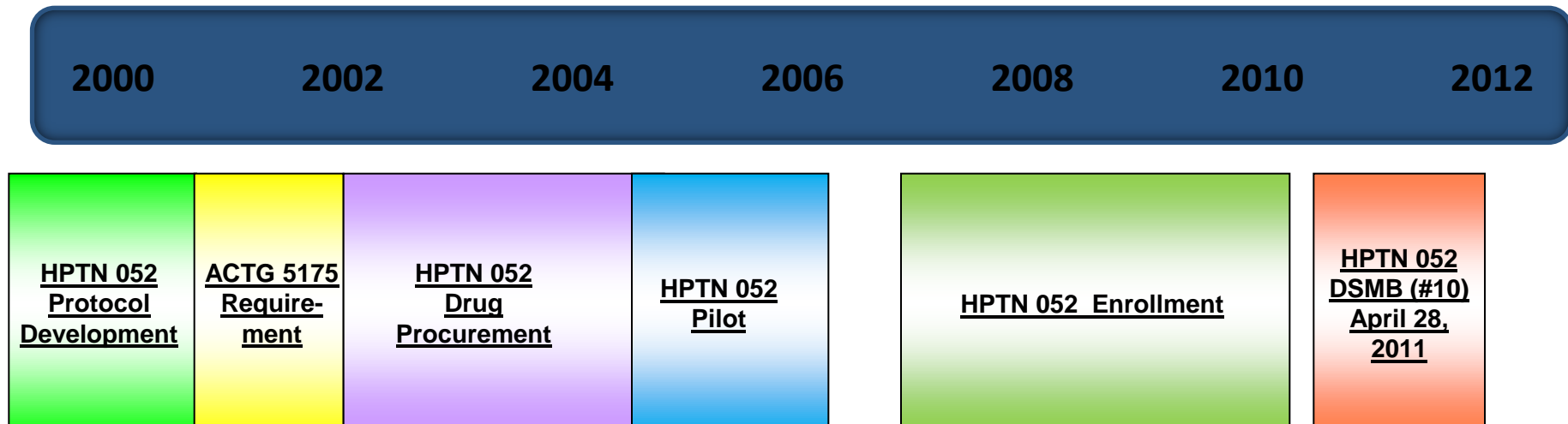
Study Participants



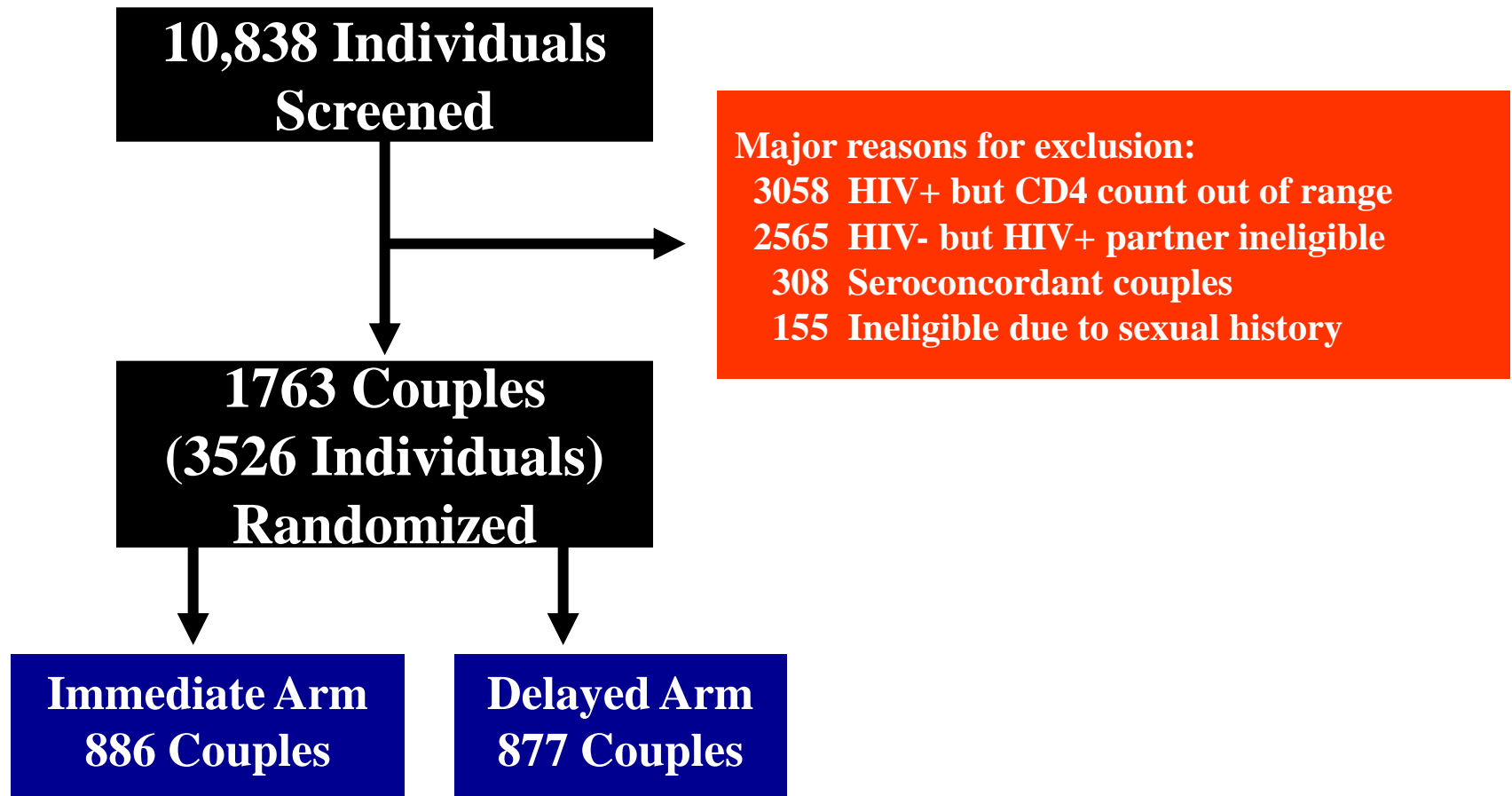
HIV PREVENTION TRIALS NETWORK

HPTN 052 Timeline: The Fast Track?

- ART for prevention of HIV 1993- THE PRESENT

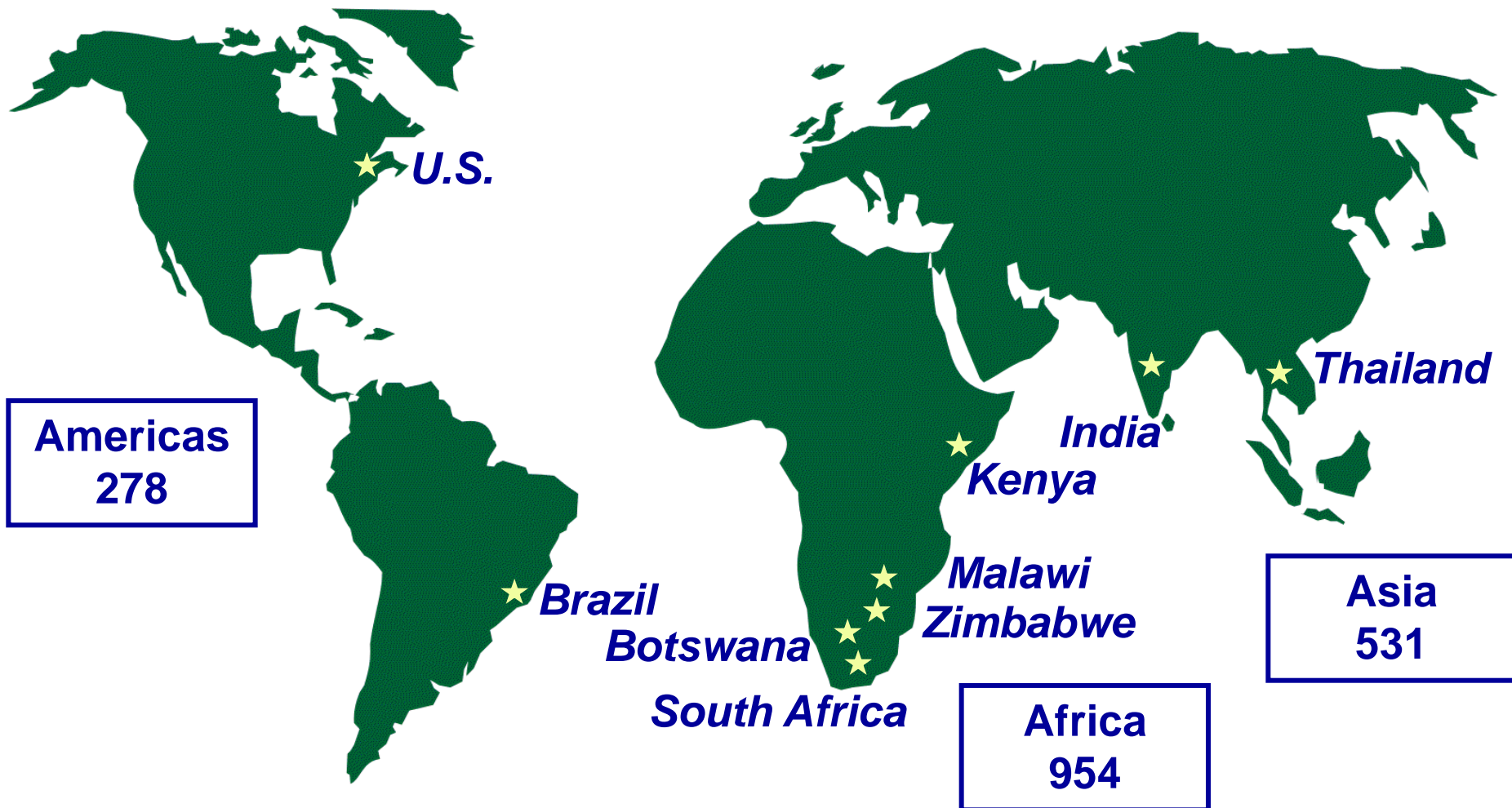


HPTN 052 Enrollment



HPTN 052 Enrollment

(Total Enrollment: 1763 couples)

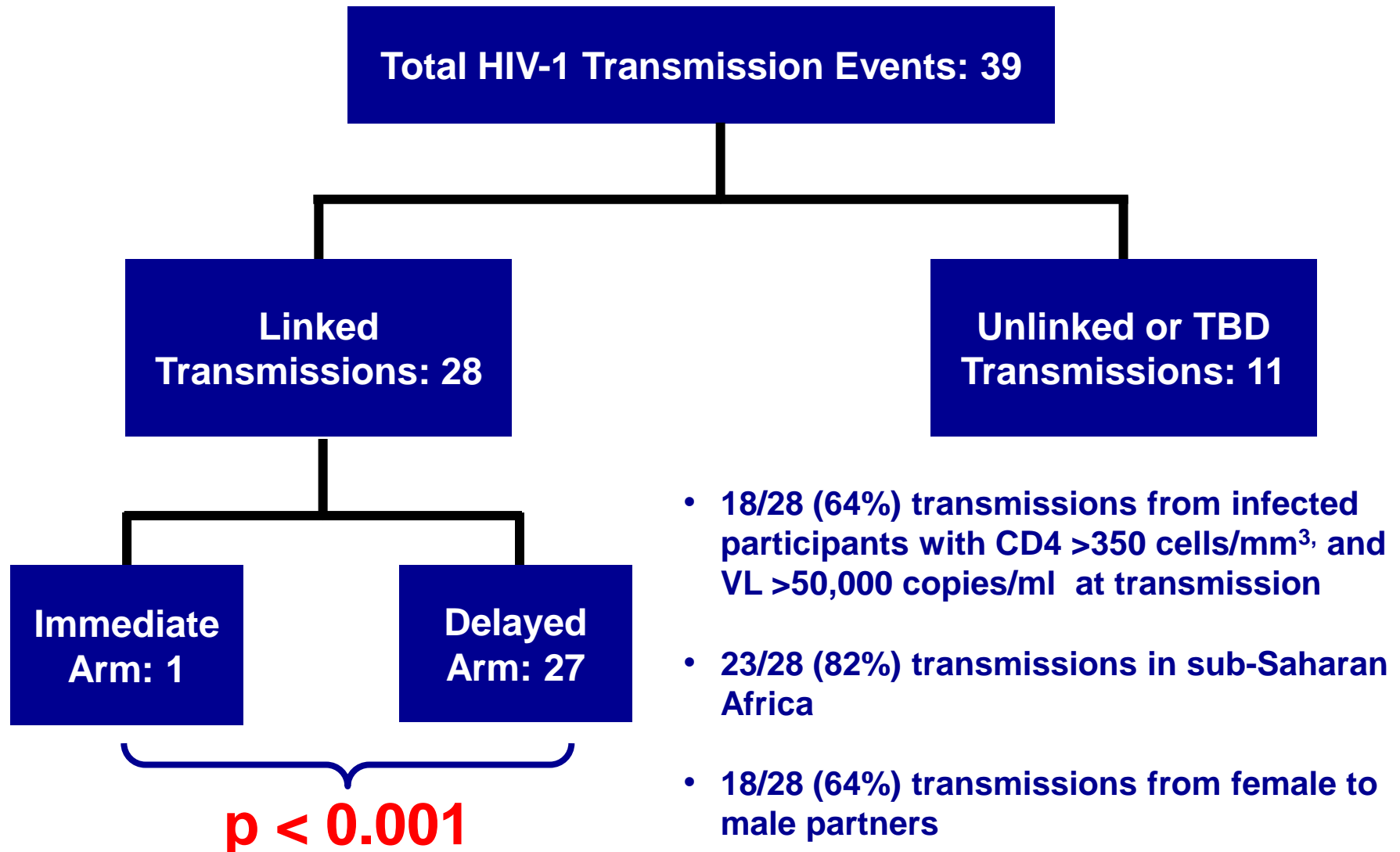


DSMB Recommendation

April 28, 2011 (DSMB 10th Biannual Review)

“The Board recommends that the results of the trial be announced as soon as possible”

HPTN 052: HIV-1 Transmission



96%

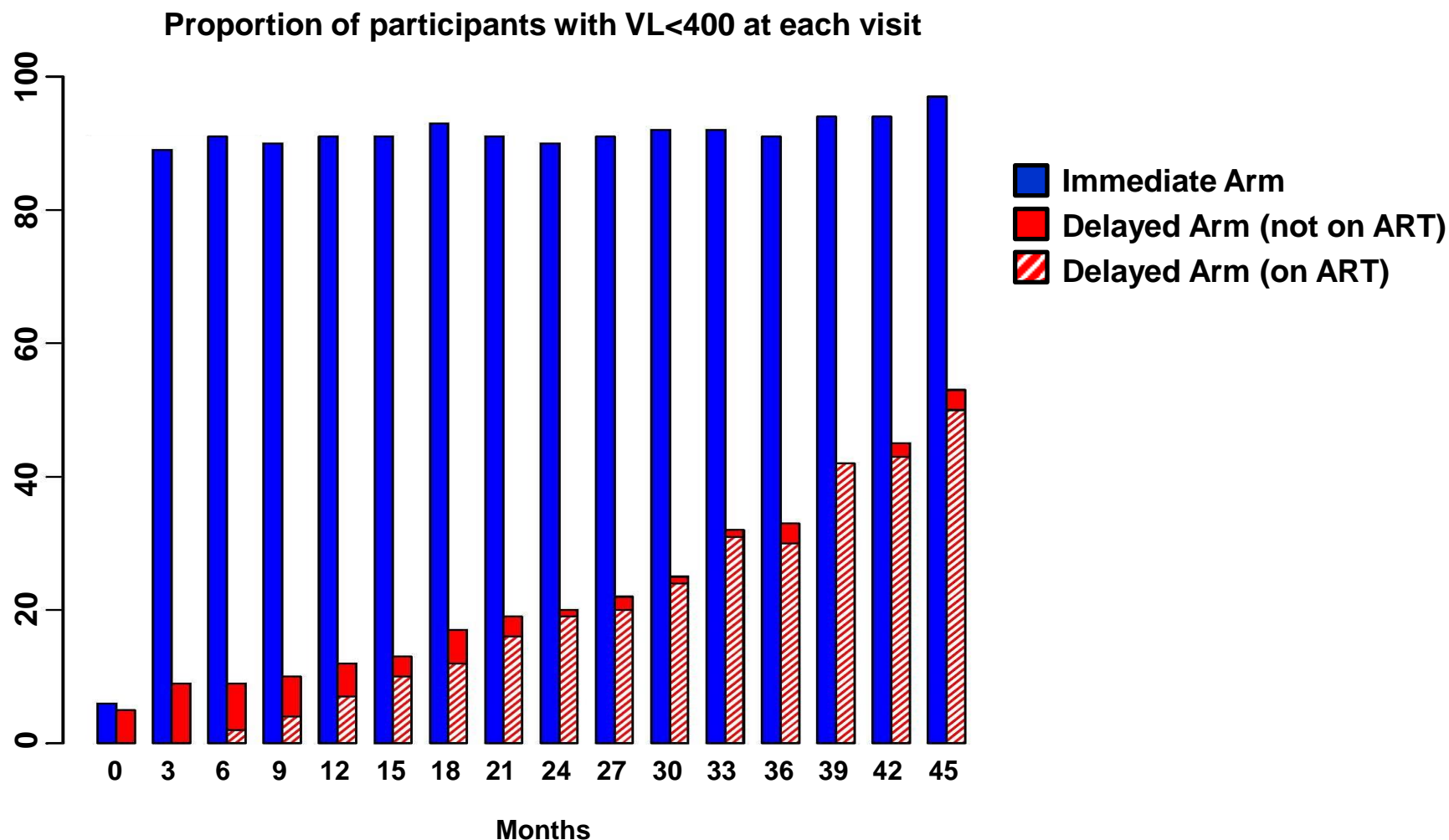
Results of the HPTN052 trial announced on 12 May 2011 show that if an HIV-positive person adheres to an effective antiretroviral therapy regimen, the risk of transmitting the virus to their uninfected sexual partner can be reduced by 96%

**UNAIDS 2011 *AIDS at 30*
*SMARTER , FASTER , BETTER CAMPAIGN***

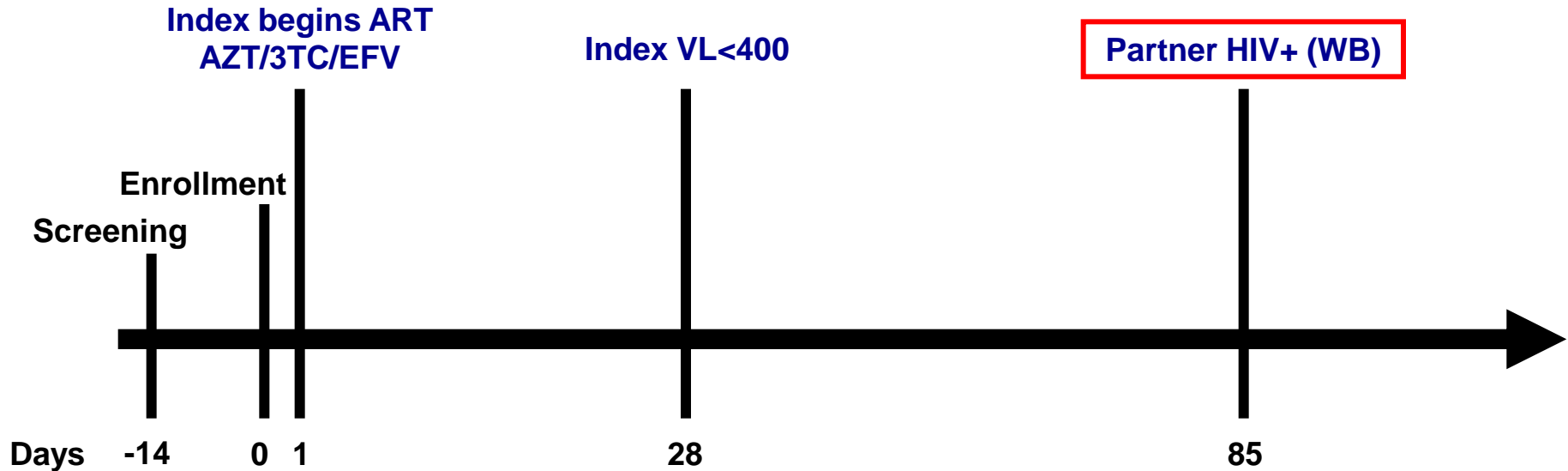
“Treatment for prevention is a game changer”.

**Michel Sidibe
Executive
Director of
UNAIDS**

HPTN 052: ADHERENCE MATTERS



One Transmission Event on ART



Partner VL < 400
Index VL = 87,202

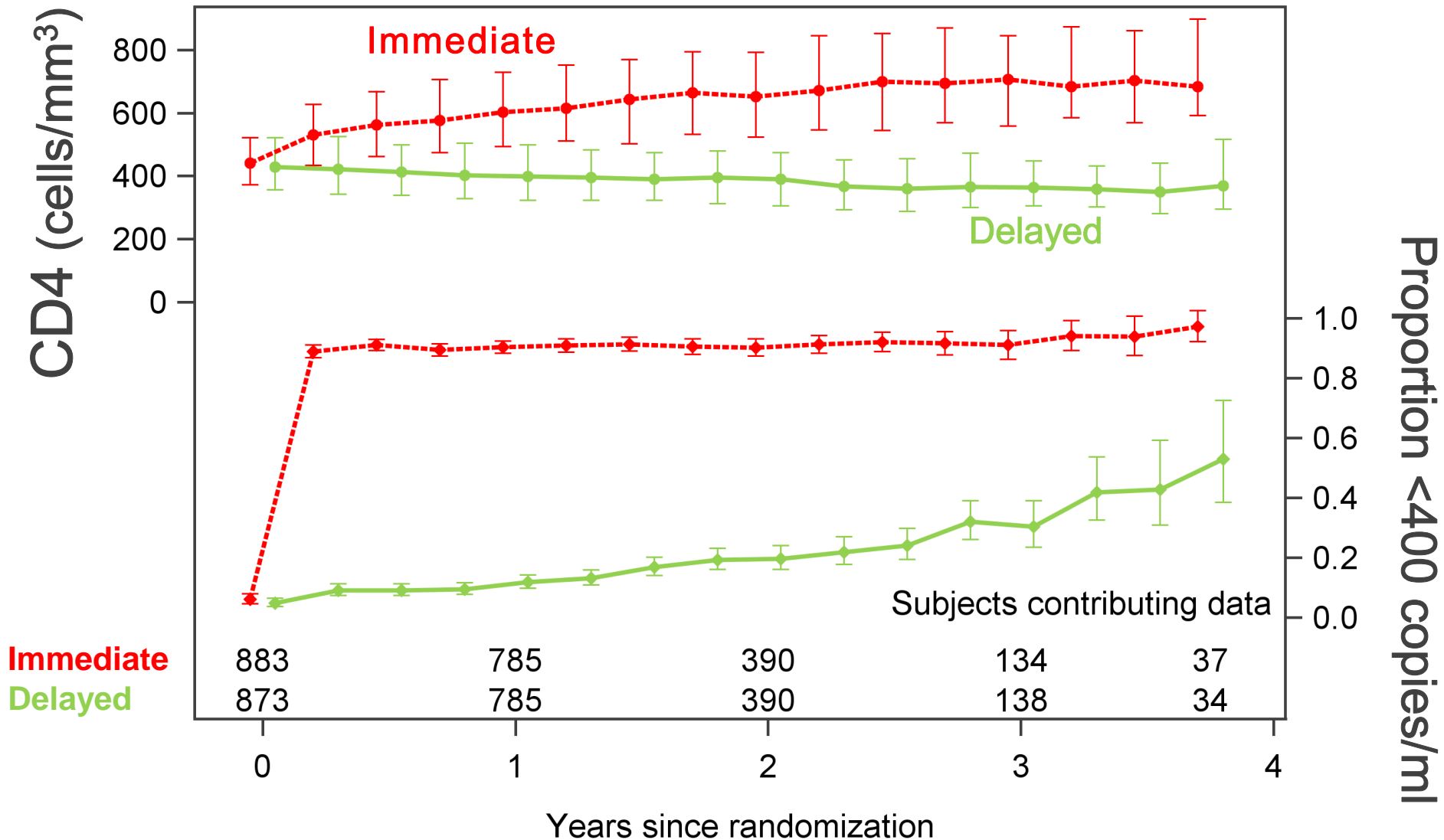
Single Genome Analysis: 1-2 viruses transmitted

Analysis of Transmission: >50 days earlier (84 – 190 days)

HPTN 052 Clinical Results

- **105 morbidity and mortality events ($p < .01$)**
 - 65 in delayed arm
 - 40 in immediate arm
- **20 cases of extrapulmonary TB ($p = 0.0013$)**
 - 17 in delayed arm
 - 3 in immediate arm
- **23 deaths (NS)**
 - 13 in delayed arm
 - 10 in immediate arm

HIV-1 RNA and CD4 Over Time (ITT)



HPTN 052: SWITCH TO ART

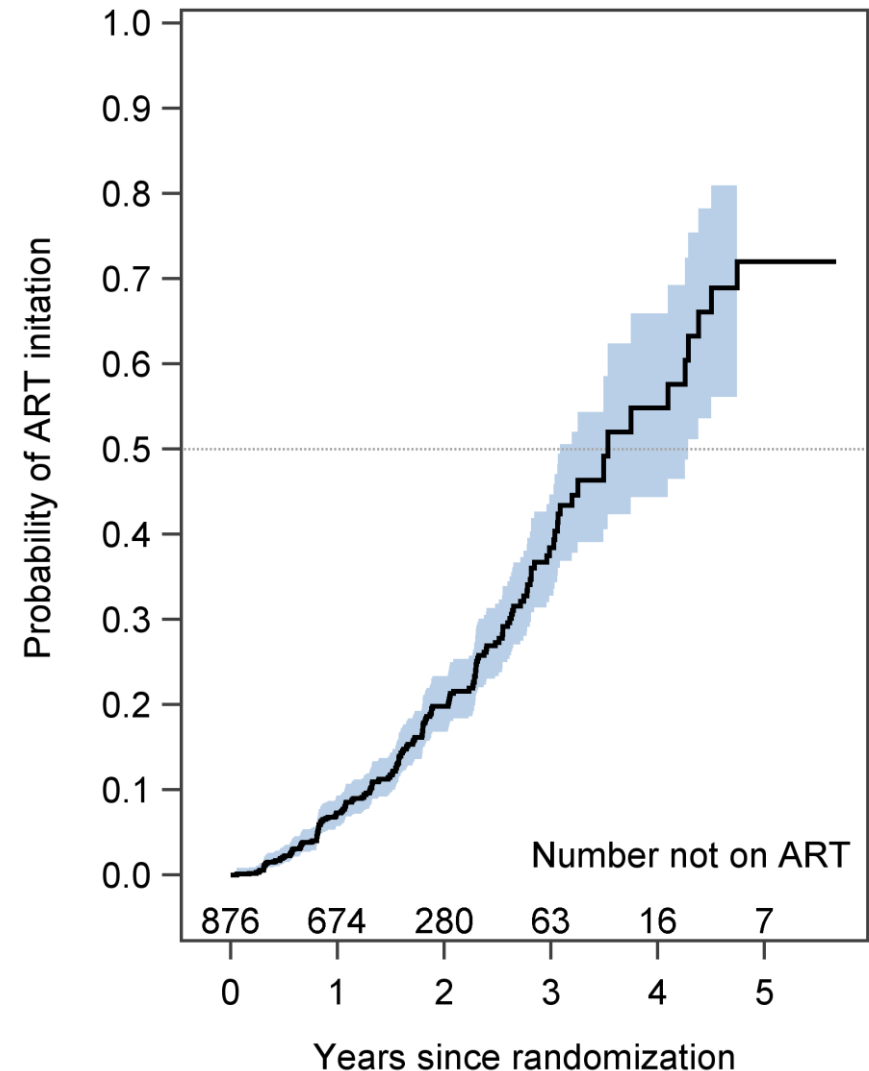
21% initiated therapy

- Mostly (75%) triggered by a decline in CD4 count

Median time to initiation was 3.5 years

Median CD4 at initiation was 225 cells/mm³

- Q1–Q3: 199 – 247



THE HPTN 052 TRANSITION... BEFORE AND AFTER APRIL 28

HPTN 052: An Ethical Odyssey

Cohen et al. ClinTrials (in press)



HPTN 052 and The New York Times

Early H.I.V. Therapy Sharply Curbs Transmission

By DONALD G. McNEIL Jr.
Published: May 12, 2011

Dr. Fauci and Dr. Myron Cohen, an AIDS specialist at North Carolina at Chapel Hill and the study's lead researcher, collected data since the study began in 2005. The results were reviewed by an independent safety review panel.

On T EDITORIAL
from

When Treatment Is Also Prevention

Published: May 22, 2011

The discovery of a near-perfect way to halt sexual transmission of the AIDS virus has the potential to change the way that doctors and nations cope with the epidemic. It also addresses some of the most troubling issues of cost and access.

EDITORIAL

No Time to Let Up on the Fight

Published: June 5, 2011

Of the estimated 34 million people infected with the virus could be treated. A study found that if an infected person was treated with drugs immediately, the risk of transmission to an uninfected partner was cut by 96 percent. The upfront cost to everyone would be huge, but in the long run it could well save money by greatly reducing the number of people who become infected and need treatment.

Drugs Stop AIDS. Take Your Medicine.

THERE is now, for the first time, hard clinical evidence of an effect that [AIDS](#) doctors have suspected for years: If you are H.I.V.-positive, being on antiretroviral drugs will probably save not only your life, but also the lives of your sexual partners.

By DONALD G. McNEIL Jr.
Published: May 21, 2011

This month, a randomized clinical trial — the gold standard in medical research — showed that people on antiretroviral drugs passed the virus to their partners by 96 percent.

EDITORIAL

Still Fighting Against AIDS

Published: November 27, 2011

...on to others. New research has shown that treating infected people with antiretroviral drugs will pass on the virus by 96 percent.

New Cases of AIDS Hit Plateau

By DONALD G. McNEIL Jr.
Published: November 21, 2011

Dr. Bernhard Schwartländer, the agency's chief of strategy, said AIDS had seen a "game-changing year in science," noting especially [a study](#) showing that people on drugs lowered by 96 percent their chances of passing on the infection. And he highlighted areas where progress had been made.

The Economist



HPTN 052

Bruce Alberts, Editor of Science explains the choice of this work

“The results have galvanized efforts to end the world’s AIDS epidemic in a way that would been inconceivable even a year ago”



HPTN 052: What's Happened Next

- ⚡ All HIV infected subjects offered ART**
- ⚡ Continued follow-up in HPTN 052**

- 1682 index cases /1763 (96% retention)**
- 1502 discordant couples (85% retention)**
- 1561/1682 index cases are NOW on ART**

DURABILITY OF PREVENTION?

DELAYED ART & CLINICAL OUTCOMES?

HPTN 052 and IAS 2012

- **Mayer et al: Sexual Behavior**
- **Grinjszstein et al: WHEN TO START (A1 Evidence)**
- **Walensky et al: ART in India and Africa (CE or CS?)**

PEPFAR, WHO AND HPTN 052

www.pepfar.gov/documents/organization

www.who.int/hiv/pub/guidelines/9789241

- ART for heterosexual discordant couples
- Treat HIV before CD4 count falls below 350
- Does ART prevent HIV transmission in...
 - MSM couples?
 - IDU transmission?

TnT: Aspiration Meets Reality

Smith et al. PLOS MED (in press)

ECOLOGICAL STUDIES

OBSERVATIONAL STUDIES

ACUTE INFECTION

“THE CASCADE”

British Columbia and ART?

Lancet, Montaner, 2010: “NEW DIAGNOSIS”

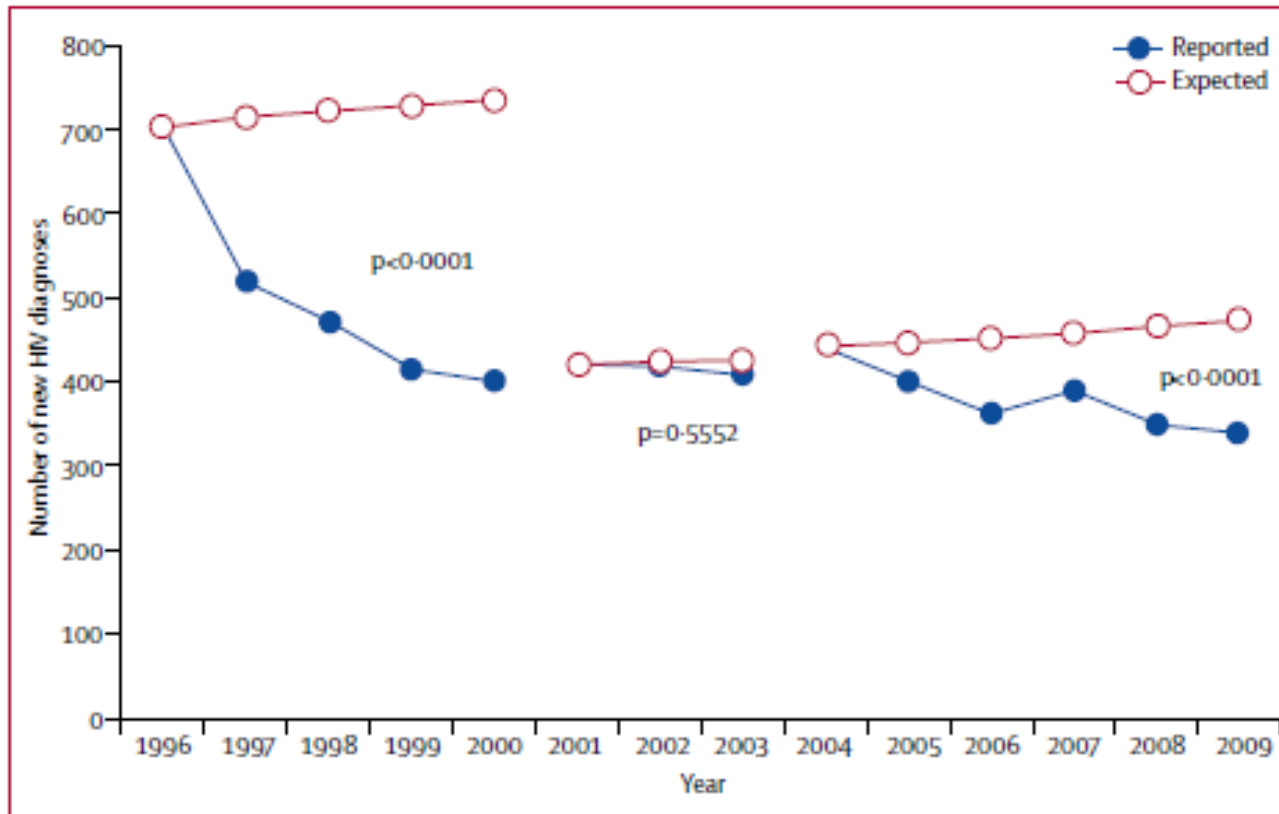
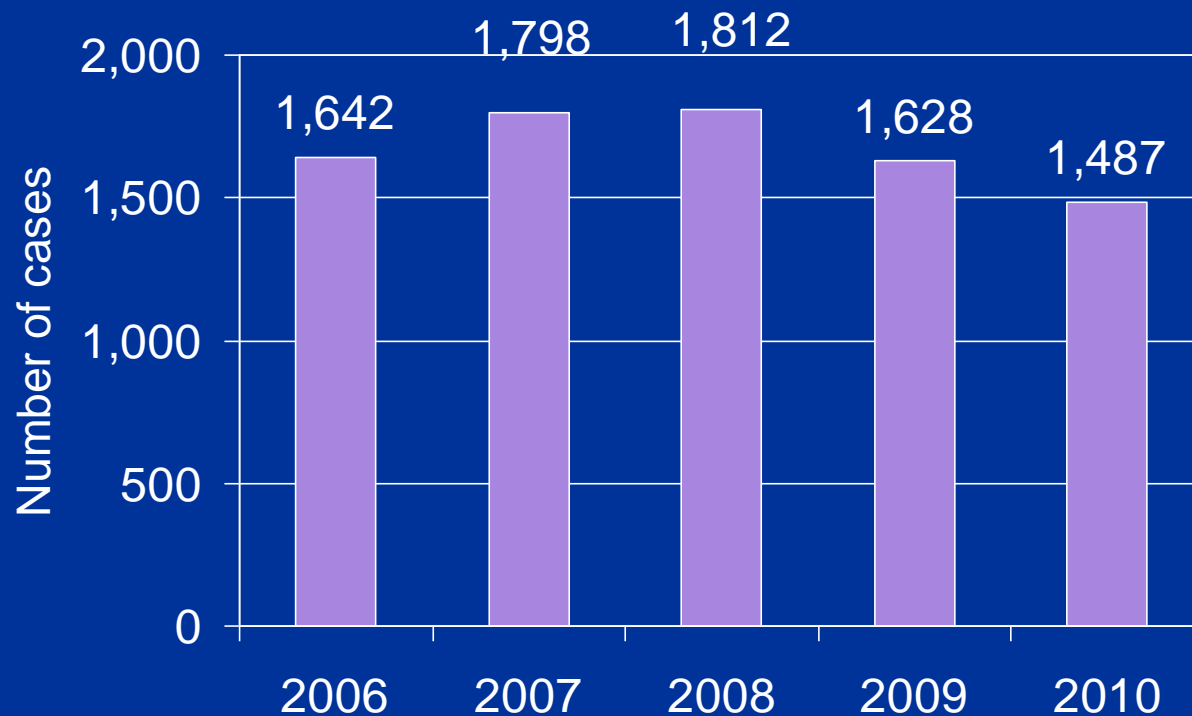


Figure 2: Reported and expected number of new HIV diagnoses per year in British Columbia, Canada, during the three phases of the study, 1996–2009

p values refer to the total reported number of HIV diagnoses compared with the total expected number of HIV diagnoses at the end of each study phase.

New HIV Diagnosis in North Carolina 2006-10

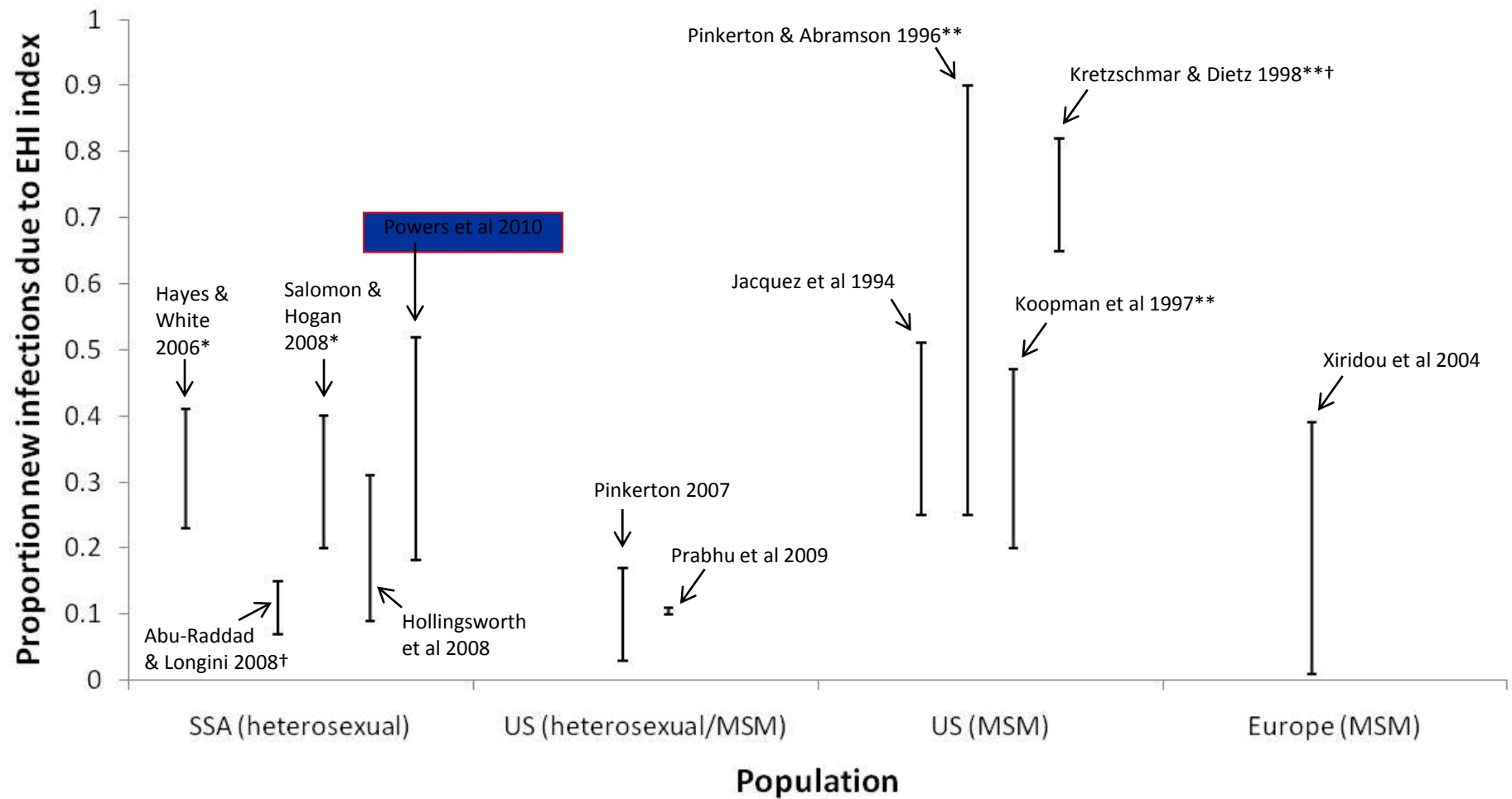
WHAT DOES THIS MEAN?



Source: 2010 HIV/STD Surveillance Report; www.epi.state.nc.us/epi/hiv/surveillance.html

Effect of Acute and Early HIV Infection on Spread

Cohen et al, NEJM, 2011, PLOS MED in press

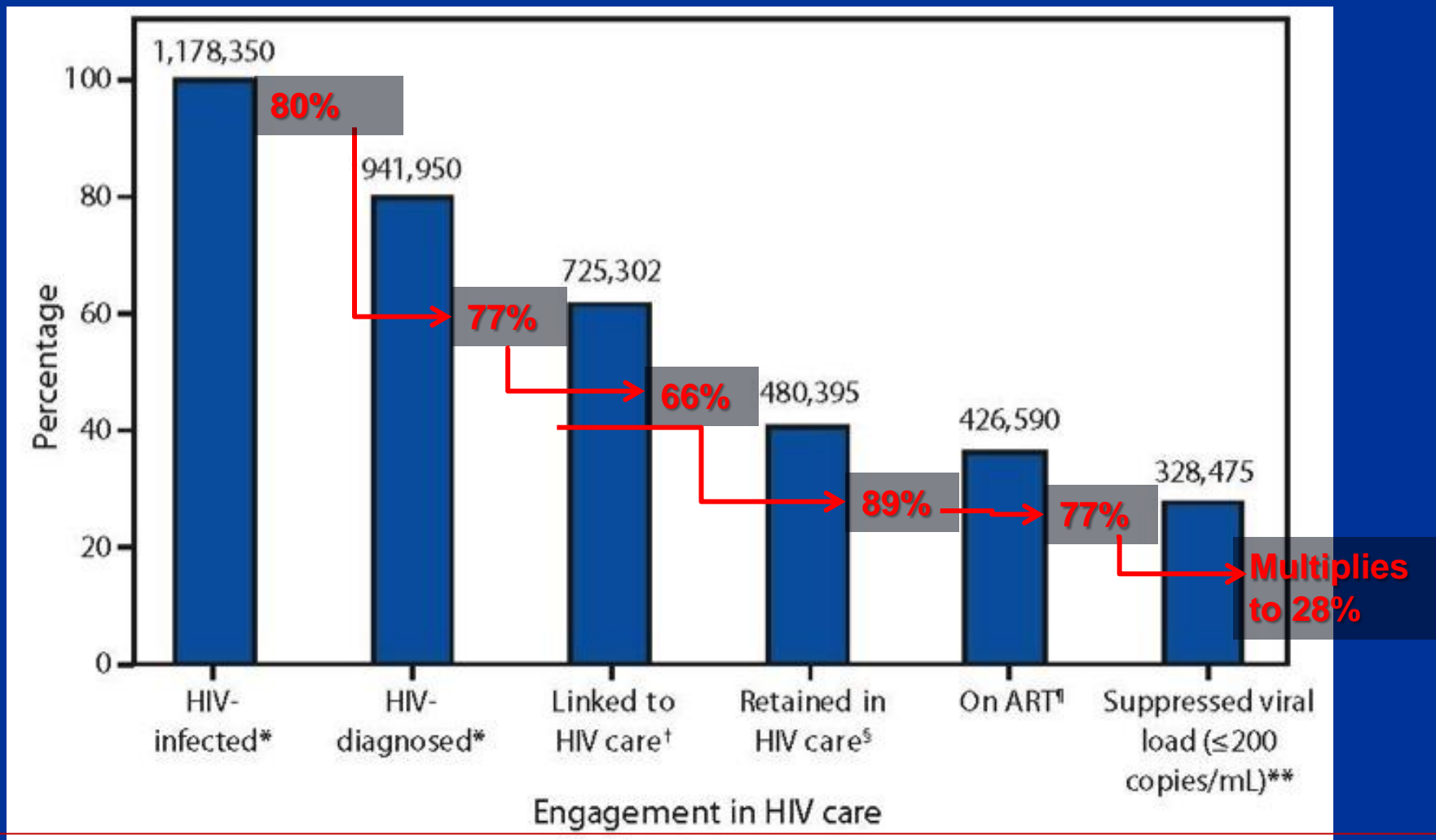


* Range of estimates reflects the proportion of all transmissions *during an individual's entire infectious period* that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI *at the population level* will depend on the epidemic phase and the distribution of sexual contact patterns in the population.

** Transmission probabilities were drawn from the population category shown, but the reported estimates result from a range of hypothetical sexual behavior parameters that do not necessarily reflect a specific population.

† The range of estimates shown was extracted from the endemic-phase portion of graphs showing the proportion of new infections due to EHI over calendar time.

HIV Rx “Cascade”: Aspiration Meets Reality



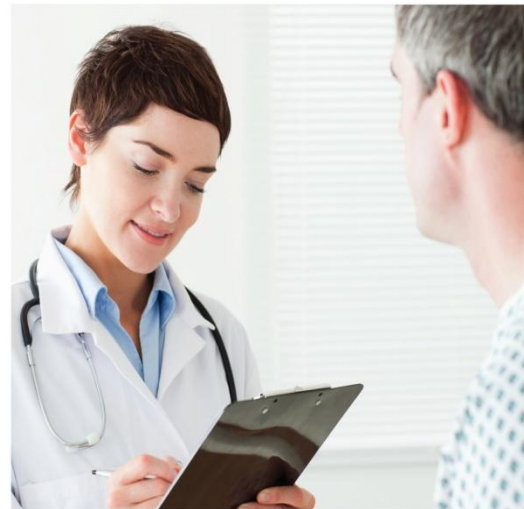
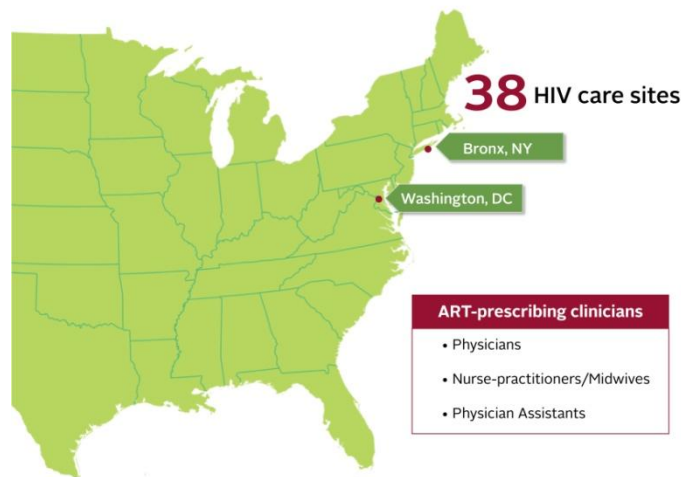
850,000 HIV+ Americans (72%) lack viral control

Refs: *MMWR* 2011; see also Gardner *CID* 2011; Burns *CID* 2010

HPTN 065 (TLC-Plus) Provider Survey

Study Population and Participants

- ART-prescribing providers at 38 participating HPTN 065 care sites in Bronx, NY and Washington, DC
- Internet-based survey (anonymous)



STUDY PARTICIPANTS

165

ART-PRESCRIBING
CLINICIANS

59%

FEMALES

66%

WHITE

77%

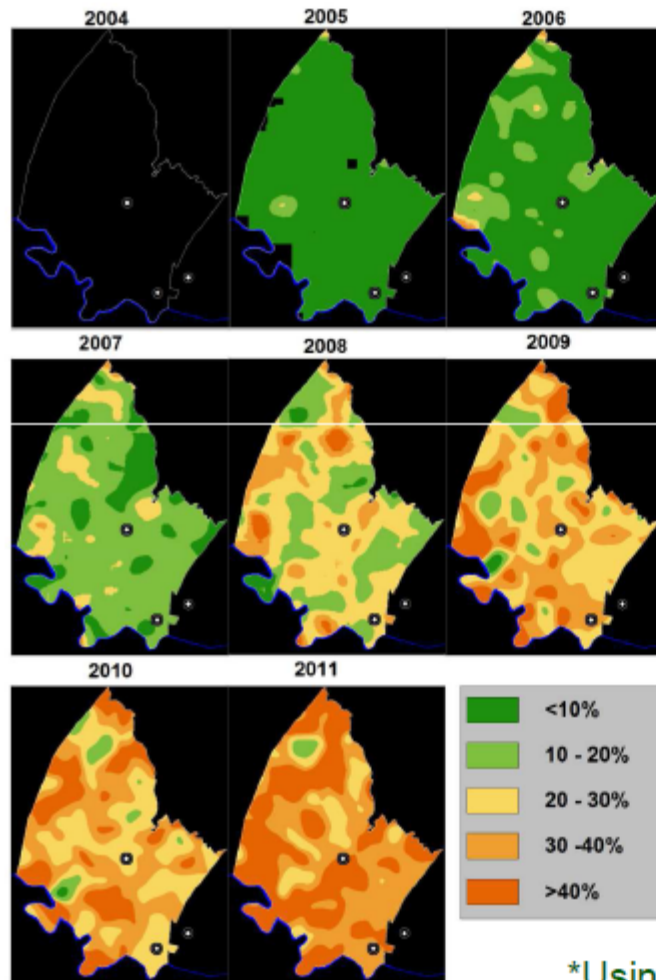
HIV Specialists

46.1 Years

(SD + 10.2)
Mean Age

Glimmers of Hope

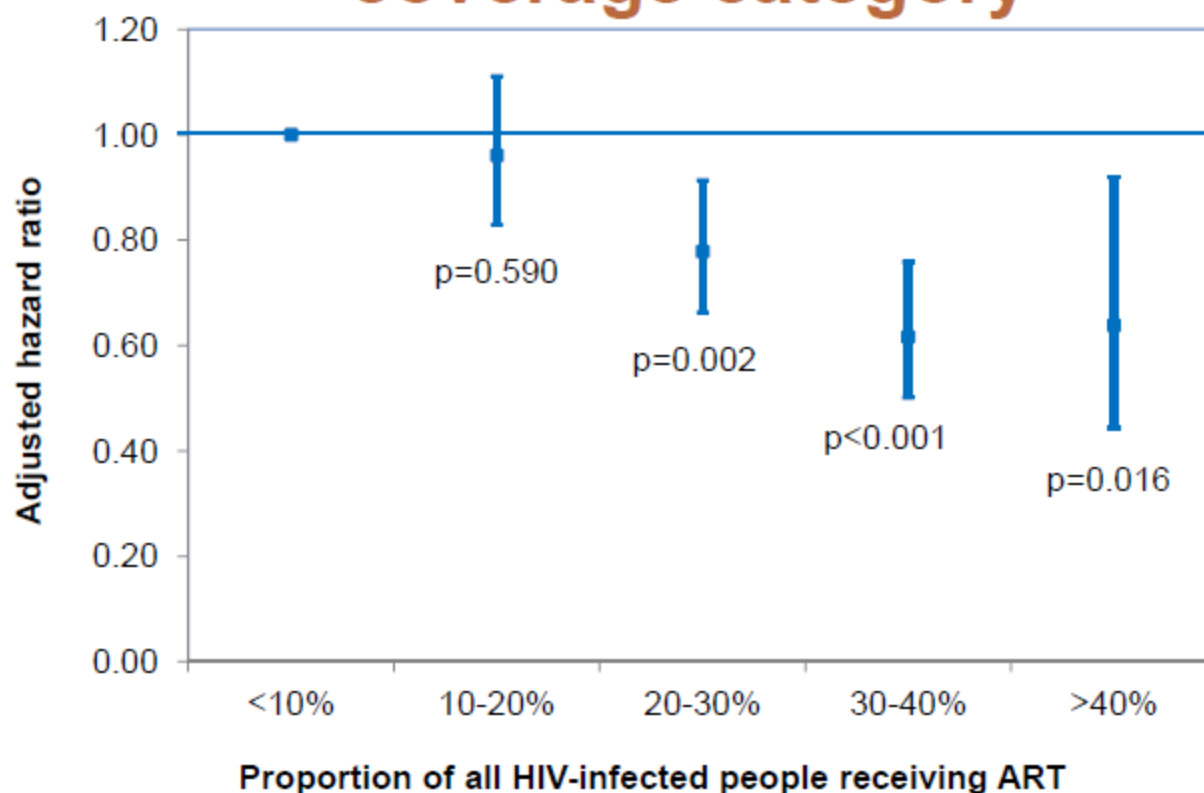
ART coverage 2004-2011



- **ART coverage** = proportion of the total HIV-infected population receiving ART
- **Patients on treatment:** Individual, geo-located DOH programme adult patients actively on treatment in June (2004-2011)
- **HIV-infected:** Individual, geo-located, HIV positive adults identified through population-based HIV surveillance data (2004-2011)

*Using a standard Gaussian kernel of radius 3km

Adjusted HIV acquisition hazard by ART coverage category



Adjusted for age, sex, community-level HIV prevalence, urban vs. rural locale, marital status, >1 partner in last 12 months, and household wealth index



Treatment as Prevention

*The “Test and Treat” Movement (Granich *et al* Current Opinion in HIV)*

More than 50 studies described!!

- US HPTN 065 Linkage in NYC, DC, (*El-Sadr*)
- ANRS PILOT in South Africa (*Newell*)
- THE PEPFAR Combination Prevention Trials:
 - CDC- BOTSWANA (*Essex*)
 - NIH HPTN 071 -South Africa, Zambia (*Hayes*)
 - USAID JHU-Tanzania (*Celentano*)

HPTN 071 Intervention Package

Community HIV Care Providers (CHiPs team):

- Counselling, condom provision, syndromic STI Rx
- Referral of pregnant women for ANC/PMTCT services
- Universal voluntary HIV testing house-to-house
- **HIV-uninfected men offered circumcision**
- **HIV-infected persons**
 - Arm A: **Immediate ART** (analogous to HPTN 052)
 - Arm B: **“Enhanced” Standard of Care** (CD4<350)
 - Arm C: **Standard of Care** (CD4<350)

Clinton speech November 8, 2011



HIV Prevention 2012

