HIV Treatment as Prevention

Myron S. Cohen, MD

HIV Prevention Trials Network

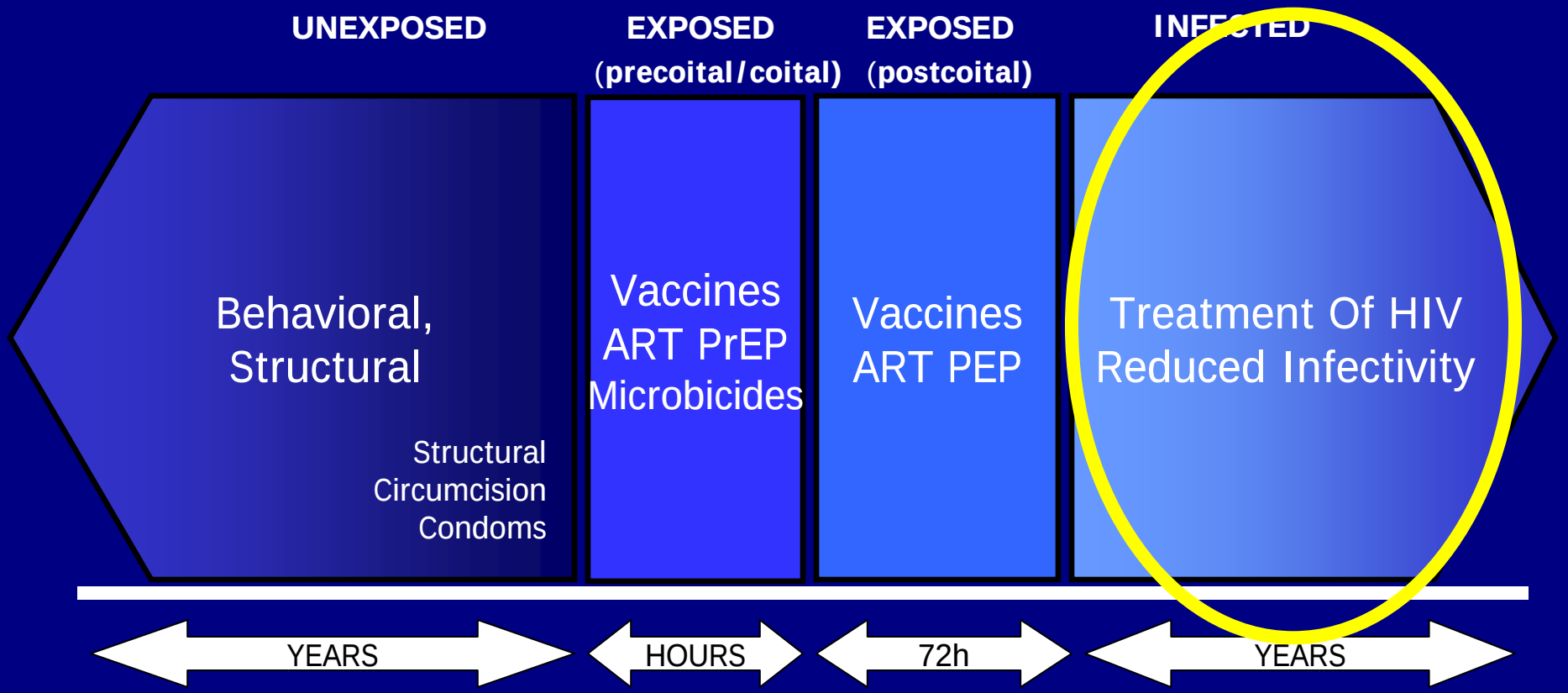
National Institute of Allergy and Infectious Diseases

National Institutes of Health

Department of Health & Human Services · USA

Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008



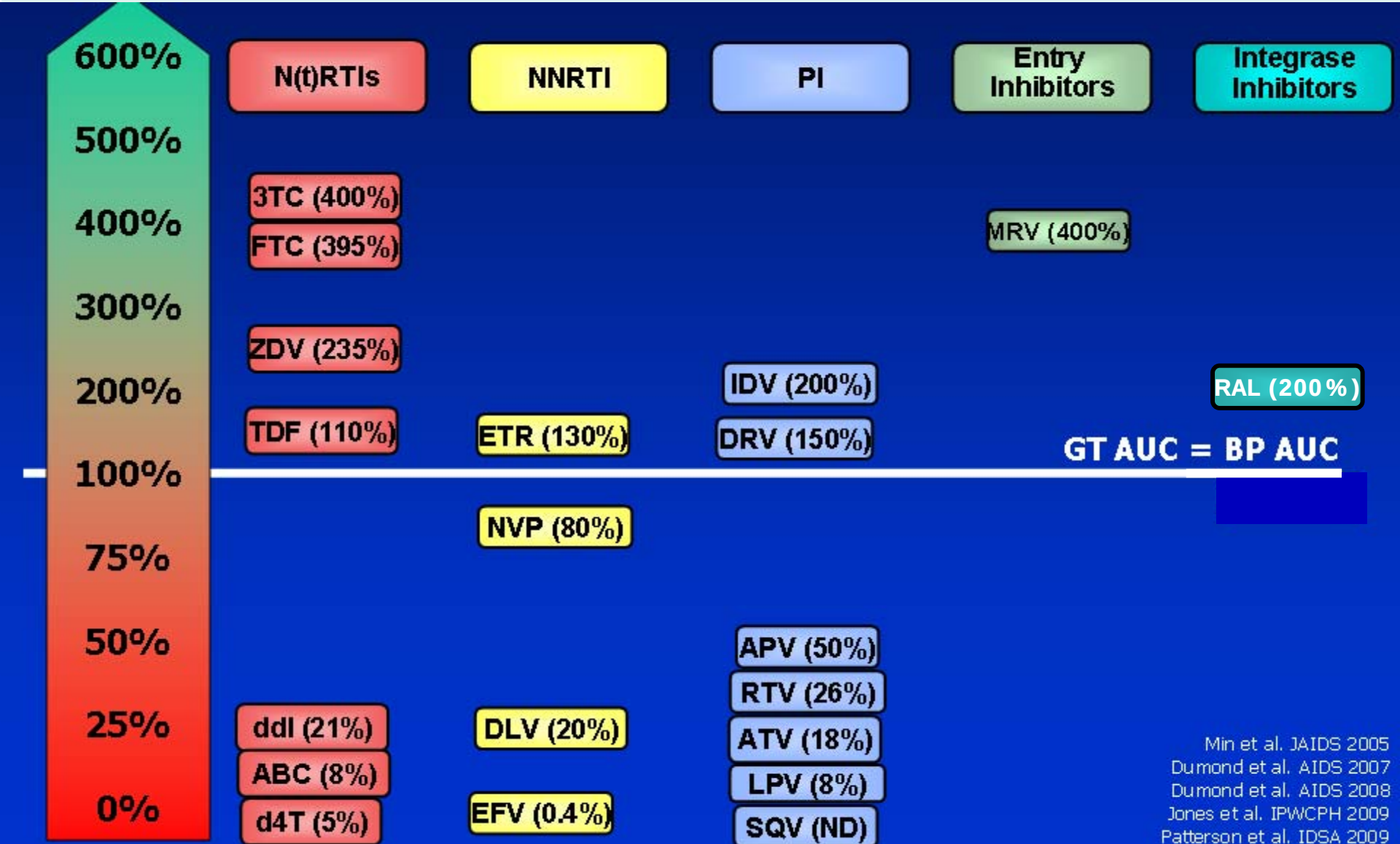
Antiviral Treatment as Prevention

- Extensive biological plausibility
  - The concentration of HIV-1 in blood and genital tract correlates with sexual transmission
  - Antiretroviral agents that concentrate in the genital tract reduce HIV-1 VL

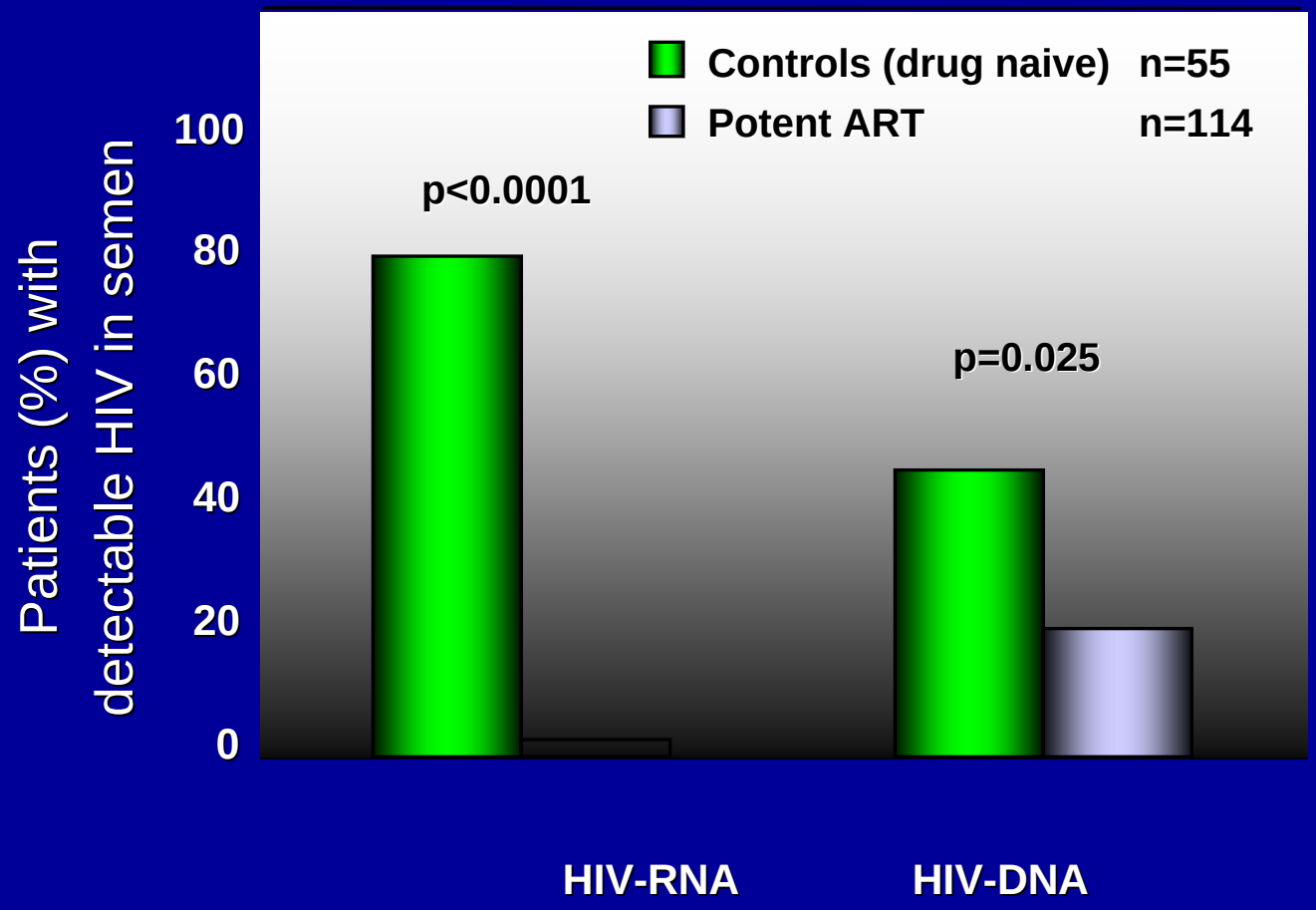
- Most observational reports indicate ART reduces transmission of HIV-1 in couples

ART in the Female Genital Tract

Cohen and Kashuba, Annals Int Med 2007



ART Suppresses HIV in Semen: *Biological Plausability*



Vernazza, Cohen *et al.*, AIDS, 2000

Development of HPTN 052

Cohen et al. Current Opinion HIV Research (in press)

- HPTN ART Working Group: 1999
- HPTN 052 Protocol development: 2000
- HPTN 052+ and ACTG 5175: 2001
- HPTN 052 Drug Procurement: 2002-4
- HPTN 052 Pilot: 2005
- HPTN 052 Enrollment 2007-10

A Randomized Controlled Trial

- To determine if ART reduces HIV-1 transmission
  - magnitude?
  - durability of benefit?

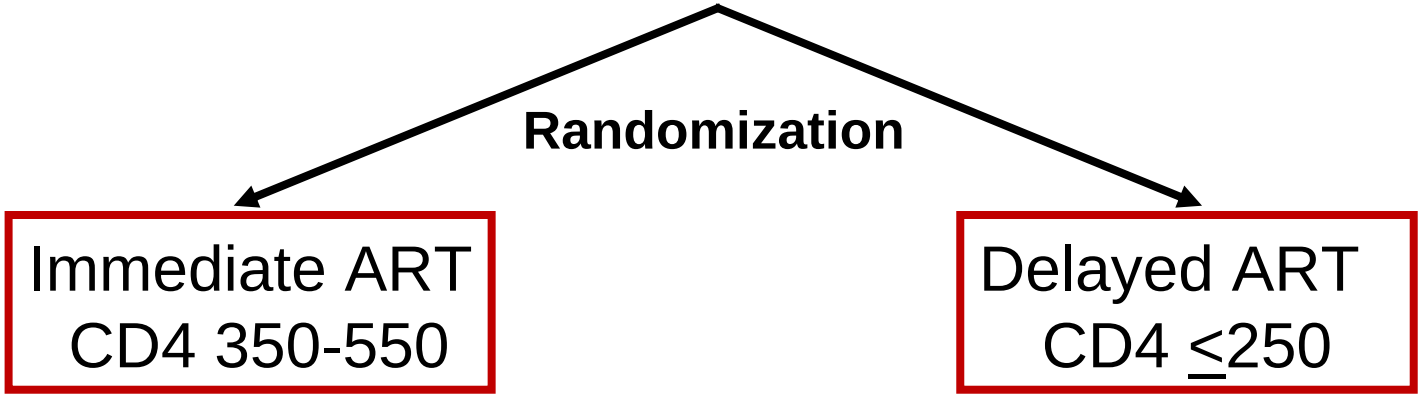
- To determine if ART is used “earlier” to reduce HIV-1 transmission
  - personal health benefit(s)?

Treatment as Prevention
"The Four Questions"

1) How effective are ART drugs to prevent HIV transmission ?
2) What do we tell couples and infected people
3) Can we expect reduced population HIV incidence from ART?
4) What are barriers to "Treatment as Prevention"?

HPTN 052 Study Design

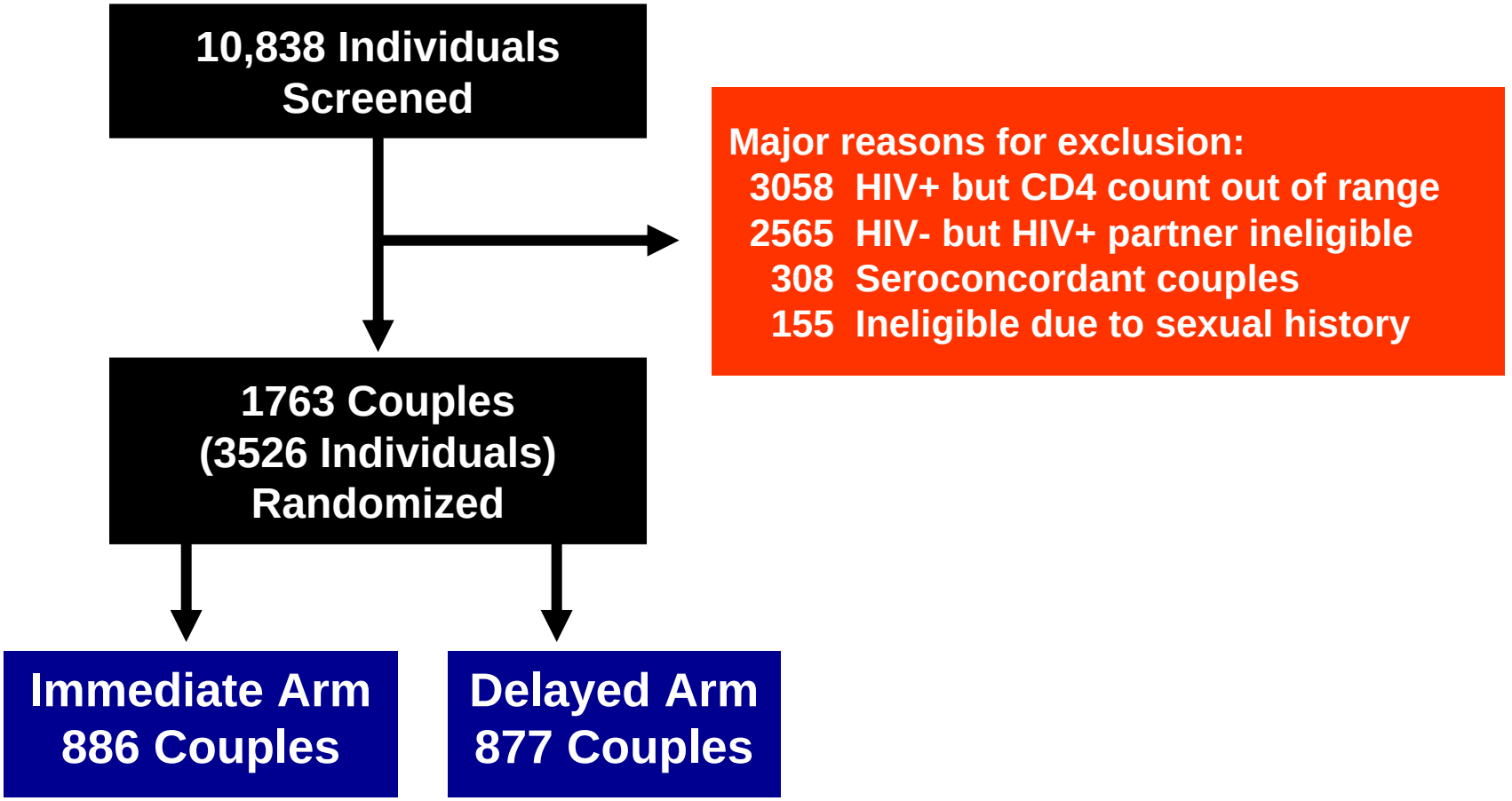
Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm^3



Primary Transmission Endpoint
Virally linked transmission events

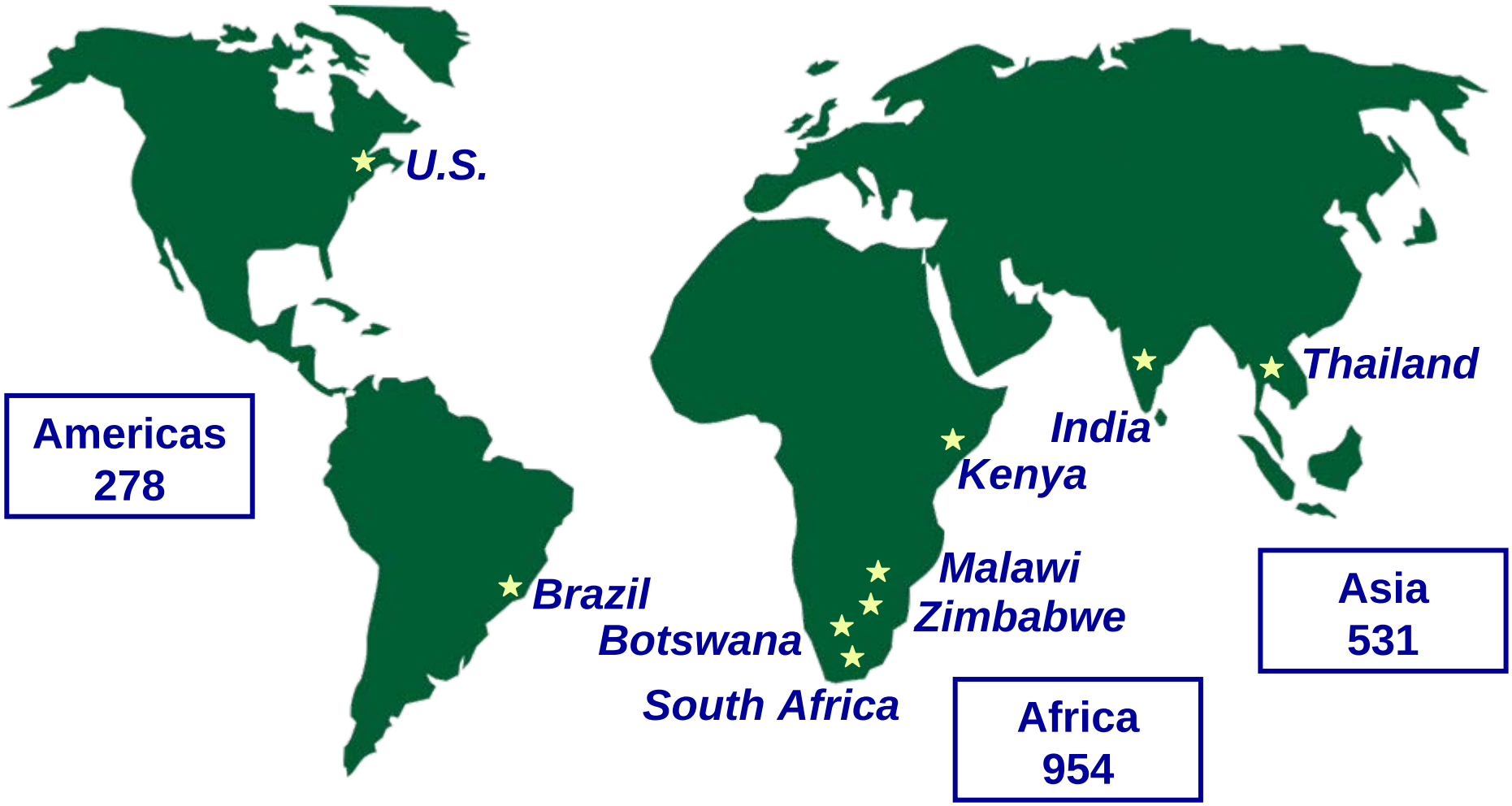
Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

HPTN 052 Enrollment



HPTN 052 Enrollment

(Total Enrollment: 1763 couples)



HPTN 052 Enrollment

Region	Site	Couples
Americas (278)	Porto Alegre, Brazil	90
	Rio de Janeiro, Brazil	186
	Boston, United States	2
Asia (531)	Chennai, India	250
	Pune, India	175
	Chiang Mai, Thailand	106
Africa (954)	Gaborone, Botswana	77
	Kisumu, Kenya	60
	Blantyre, Malawi	230
	Lilongwe, Malawi	251
	Johannesburg, South Africa	46
	Soweto, South Africa	50
	Harare, Zimbabwe	240
	Total	**1763**

HPTN 052: Baseline Characteristics

	Index		Partner	
	Immediate N = 886	Delayed N = 877	Immediate N = 893	Delayed N = 882
Female	49%	50%	49%	47%
Age (median)	33	32	32	32
Married	94%	95%	93%	94%
Any unprotected sex	6%	8%	8%	8%
CD4 (median [IQR])	442 [373-522]	428 [357-522]	---	---
HIV RNA $\log_{10}$ (median [IQR])	4.4 [3.8-4.9]	4.4 [3.9-4.9]	---	---

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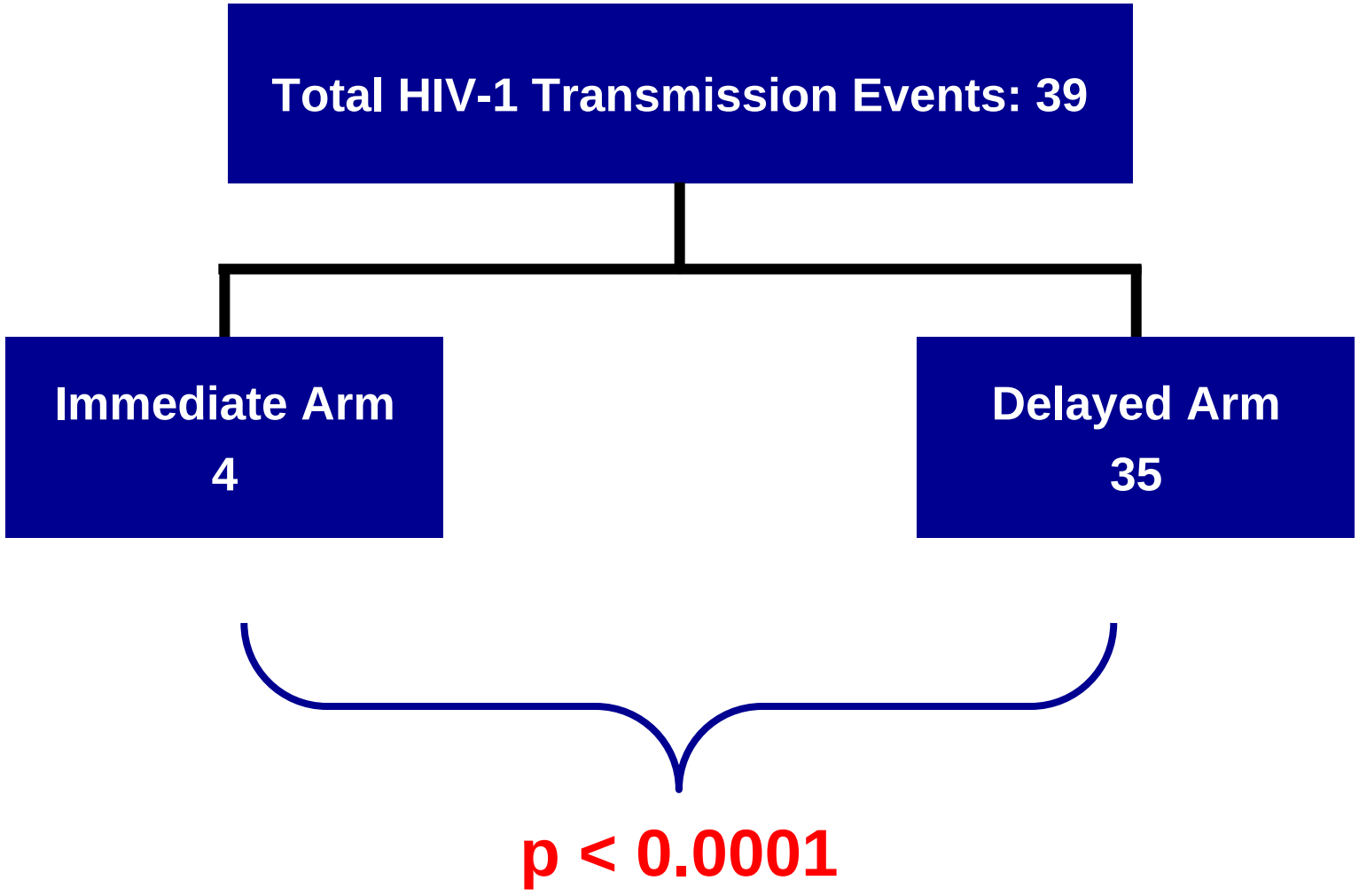
DSMB Recommendation
April 28, 2011

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

HPTN 052 continues to follow couples, but all HIV-infected participants are being offered ART

HPTN 052: HIV-1 Transmission



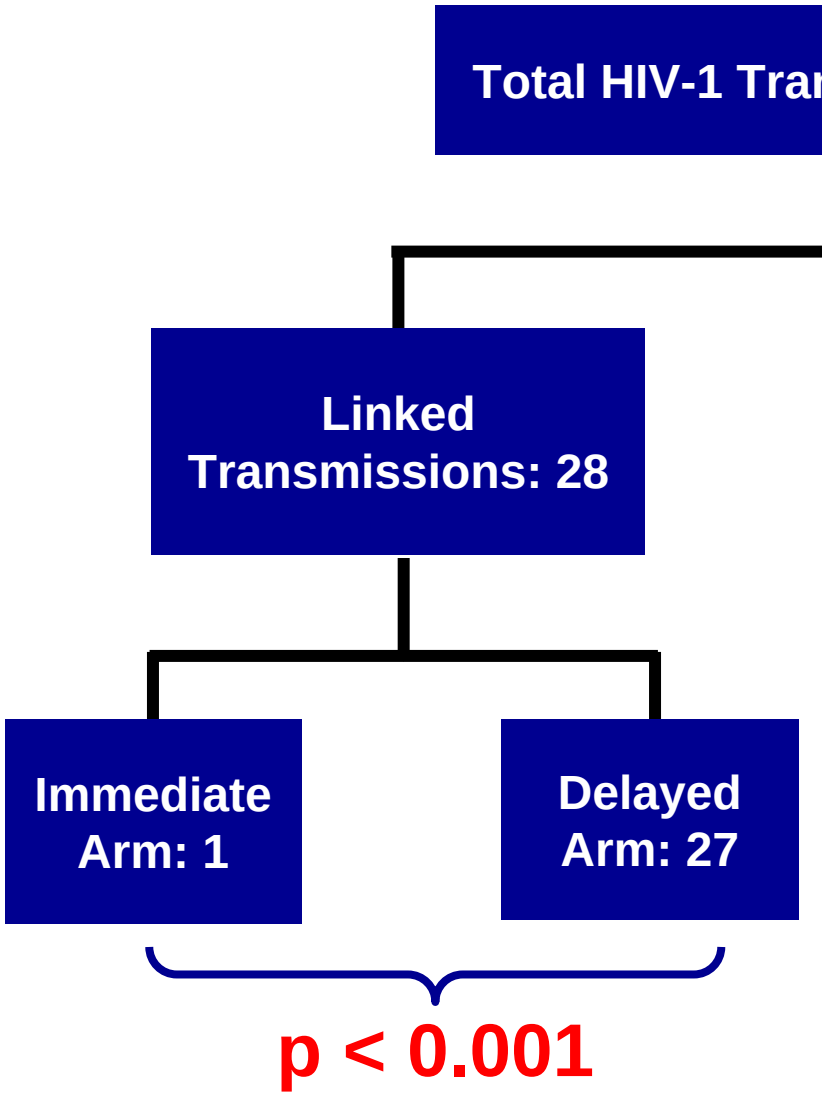
HPTN 052 Linkage

Eshelman et al. JID in press

THREE METHODS EMPLOYED

- Boot strap analysis with *pol* gene
- Local statistical comparison
- NextGen (454) Sequences

HPTN 052: HIV-1 Transmission



- 18/28 (64%) transmissions from infected participants with CD4 >350 cells/mm^3
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

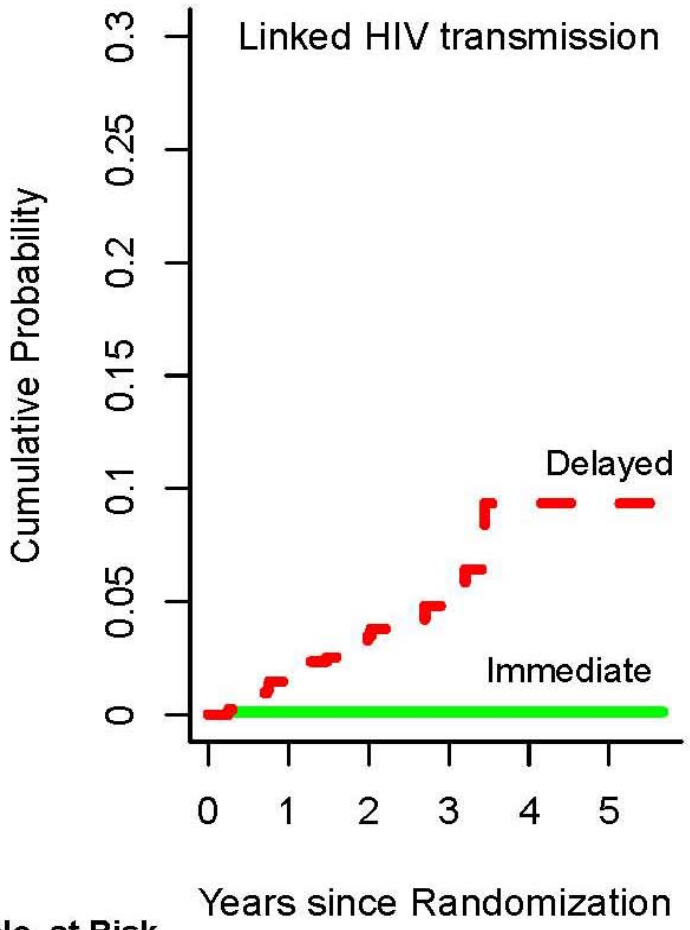
HPTN 052: HIV-1 Transmission

Study Arm	Follow-up (PY)*	Incidence/100PY [95% CI]	
		Linked	Overall
Immediate	1585	0.1 [0.0 – 0.4]	0.3 [0.1 – 0.6]
Delayed	1567	1.7 [1.1 – 2.5]	2.2 [1.6 – 3.1]

***Person-years specific for transmission events**

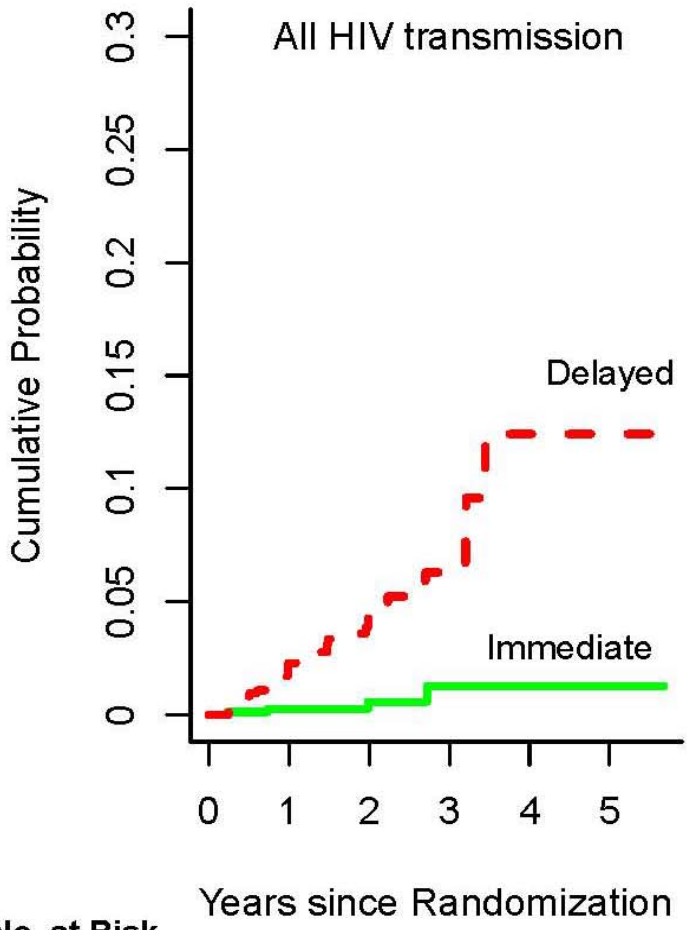
Median follow-up: 1.7 years

HPTN052: HIV-1 Transmissions



No. at Risk

Immediate	893	658	298	79	31	24
Delayed	882	655	297	80	26	22



No. at Risk

Immediate	893	658	298	79	31	24
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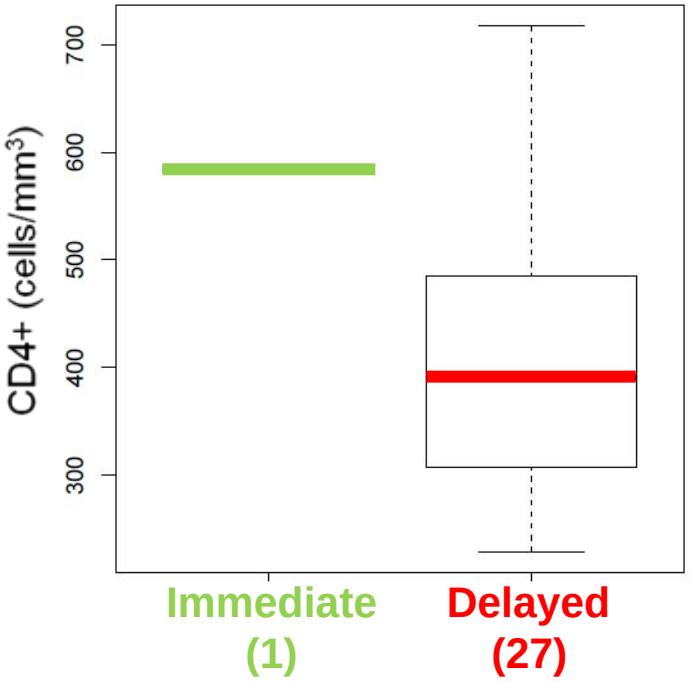
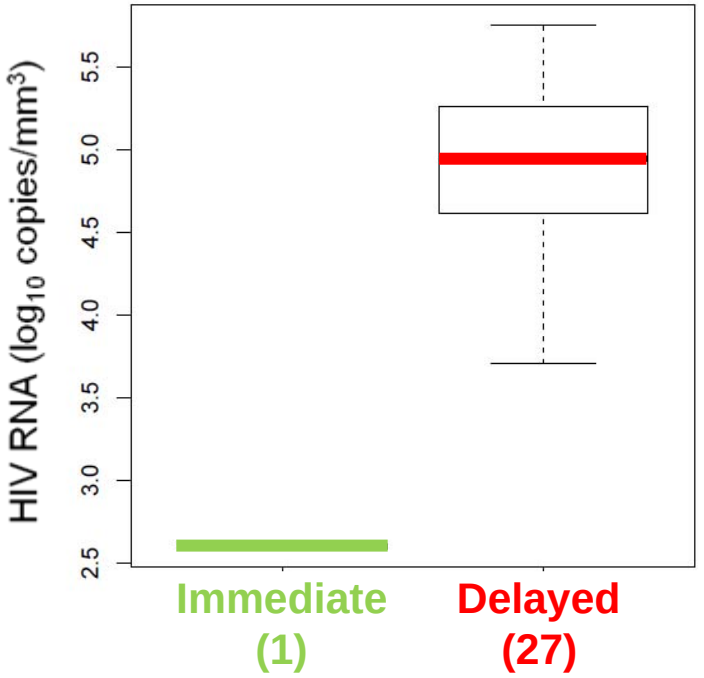
HIV Transmission and Viral Load

28 Linked Transmissions

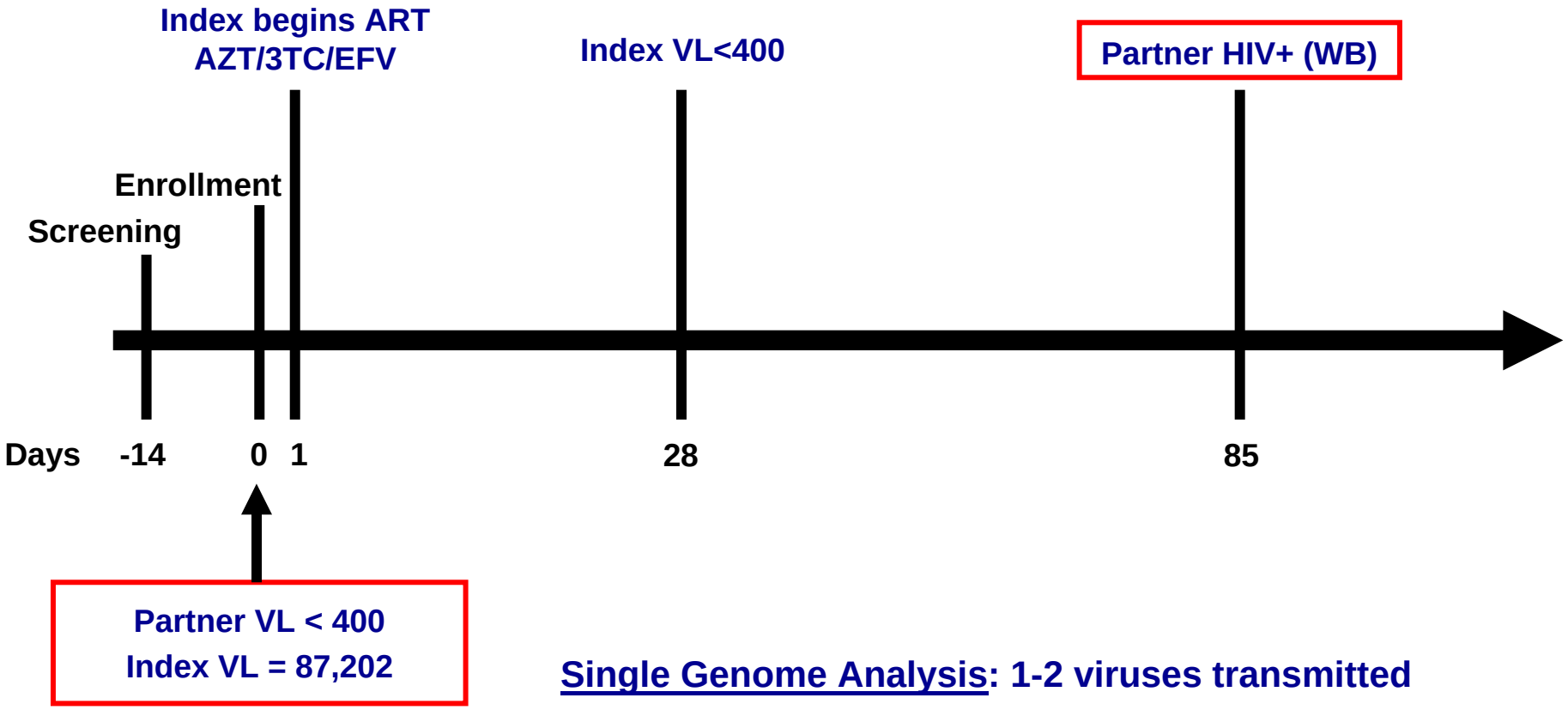




Median proximal CD4 (range): 400 (229-858)
Immediate arm: 584 (584-584)
Delayed arm: 391 (229-858)

Median proximal log_{10} VL (range): 4.9 (2.6-5.8)
Immediate arm: 2.6 (2.6-2.6)
Delayed arm: 4.9 (2.6-5.8)

One Transmission Event on ART



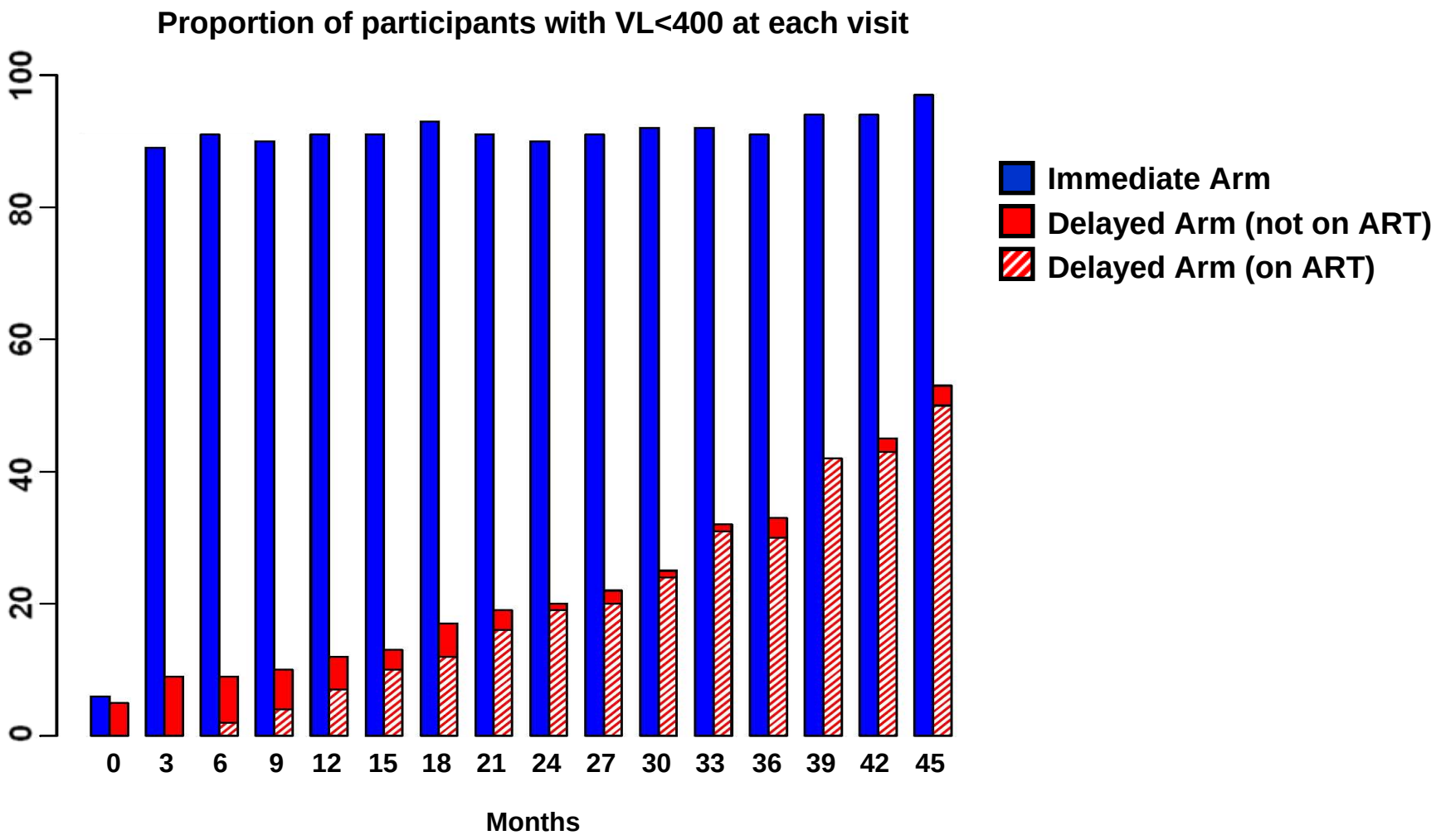
Single Genome Analysis: 1-2 viruses transmitted

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

Multivariate Analysis – Linked Transmission

Variable	Hazard Ratio	95% Confidence Interval
Treatment (immediate vs. delayed)	0.04	[0.01 - 0.28]
Baseline CD4 (per 100 CD4 Increment)	1.24	[1.00 - 1.54]
Baseline VL (per unit log increment)	2.84	[1.51 - 5.41]
Baseline condom use (100% vs. <100%)	0.33	[0.12 - 0.91]
Gender (HIV +) (male vs. female)	0.73	[0.33 - 1.65]

HPTN 052: Consistent Use of ART



Effects of Early versus Delayed Initiation of Antiretroviral Therapy (ART) on HIV Clinical Outcomes: Results from the HPTN 052 Randomized Clinical Trial

Beatriz Grinsztejn, MD
Site Investigator
Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz
6th IAS Conference, Rome, Italy
July 18, 2011

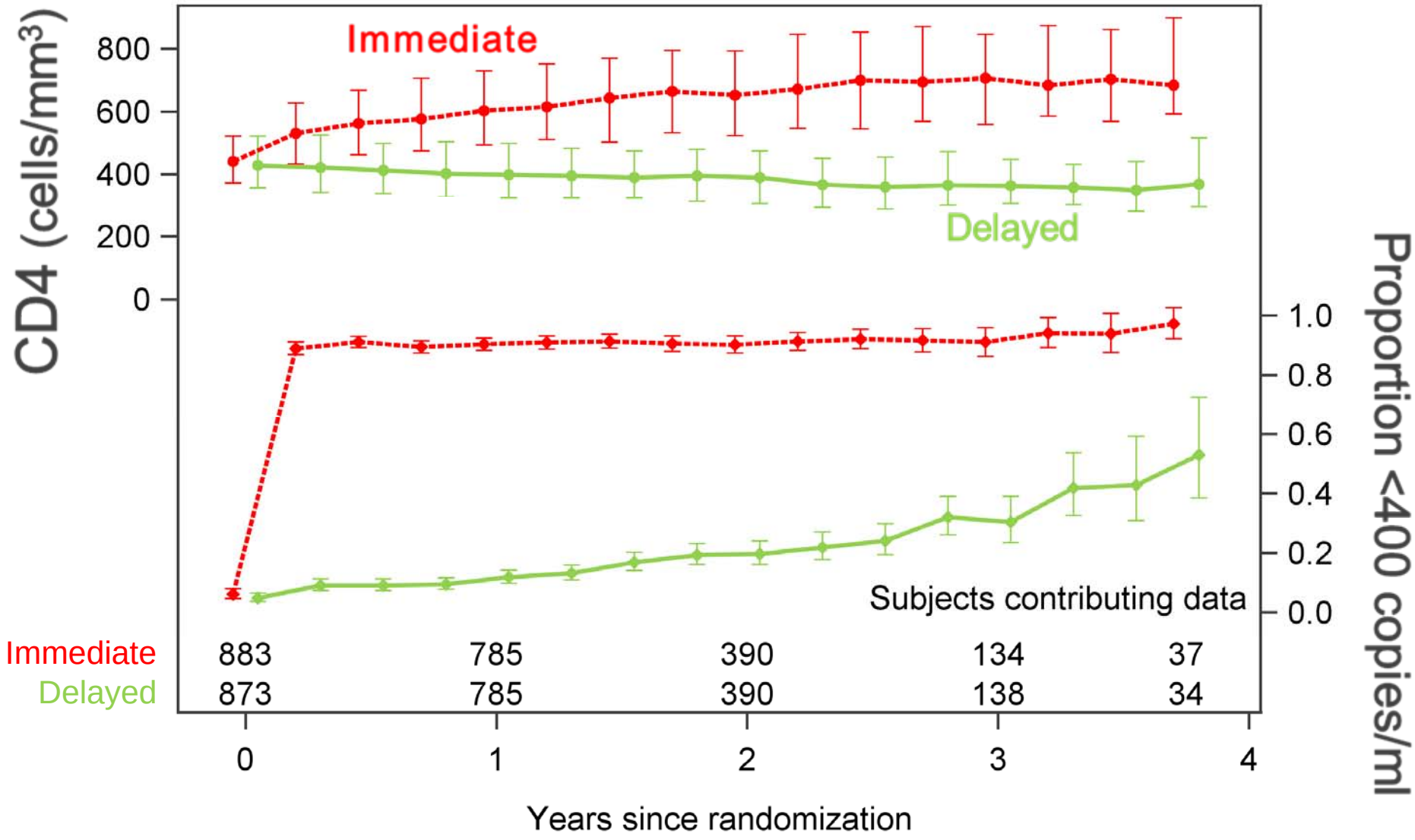
HIV Prevention Trials Network

National Institute of Allergy and Infectious Diseases

National Institutes of Health

Department of Health & Human Services · USA

HIV-1 RNA and CD4 Over Time (ITT)



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

All Primary Clinical Events (N = 129)

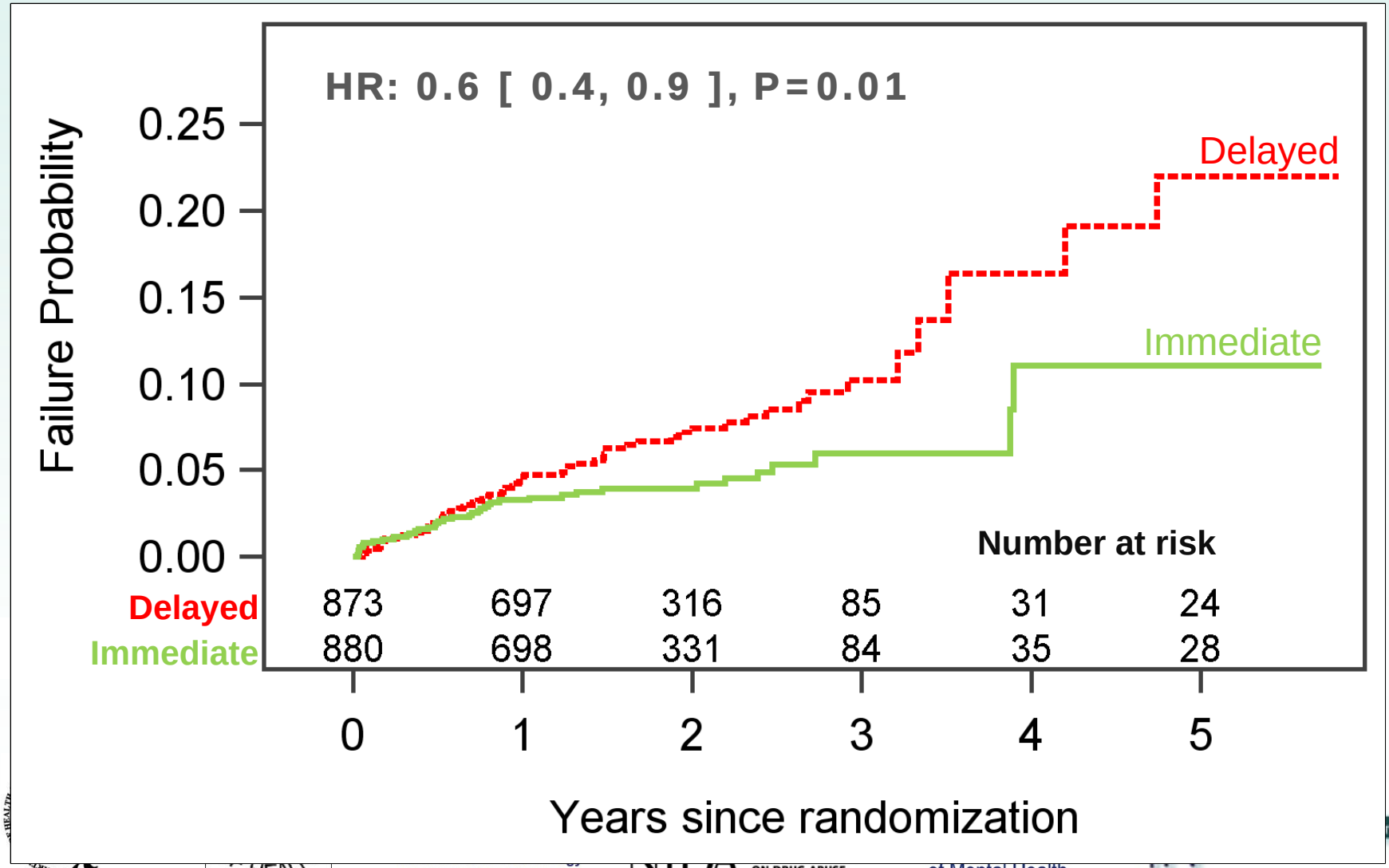
17 subjects experienced >1 primary clinical event

	Immediate		Delayed	
Total (N=129)				
Tuberculosis	**17**		**33**	
Severe bacterial infection	**16**		**11**	
Death	**10**		**13**	
Chronic herpes simplex	**3**		**7**	
Bacterial pneumonia (recurrent)	**2**		**2**	
Oesophageal candidiasis	**2**		**2**	
Cervical carcinoma	**0**		**2**	
Kaposi's sarcoma	**1**		**1**	
Wasting syndrome	**0**		**2**	
Other*	**2**		**3**	

** Extrapulmonary crypto, HIV-related encephalopathy, lymphoma, PCP, septicemia (recurrent)*

Probability of Primary Clinical Event

(Death, WHO stage 4 clinical event, pulmonary TB or severe bacterial infection)



ART STOPS HIV Transmission

NEJM Aug 11, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

HPTN 052: What's NEXT

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

  -DURABILITY OF PREVENTION?

  -DELAYED ART, CLINICAL OUTCOMES?
- MSM?

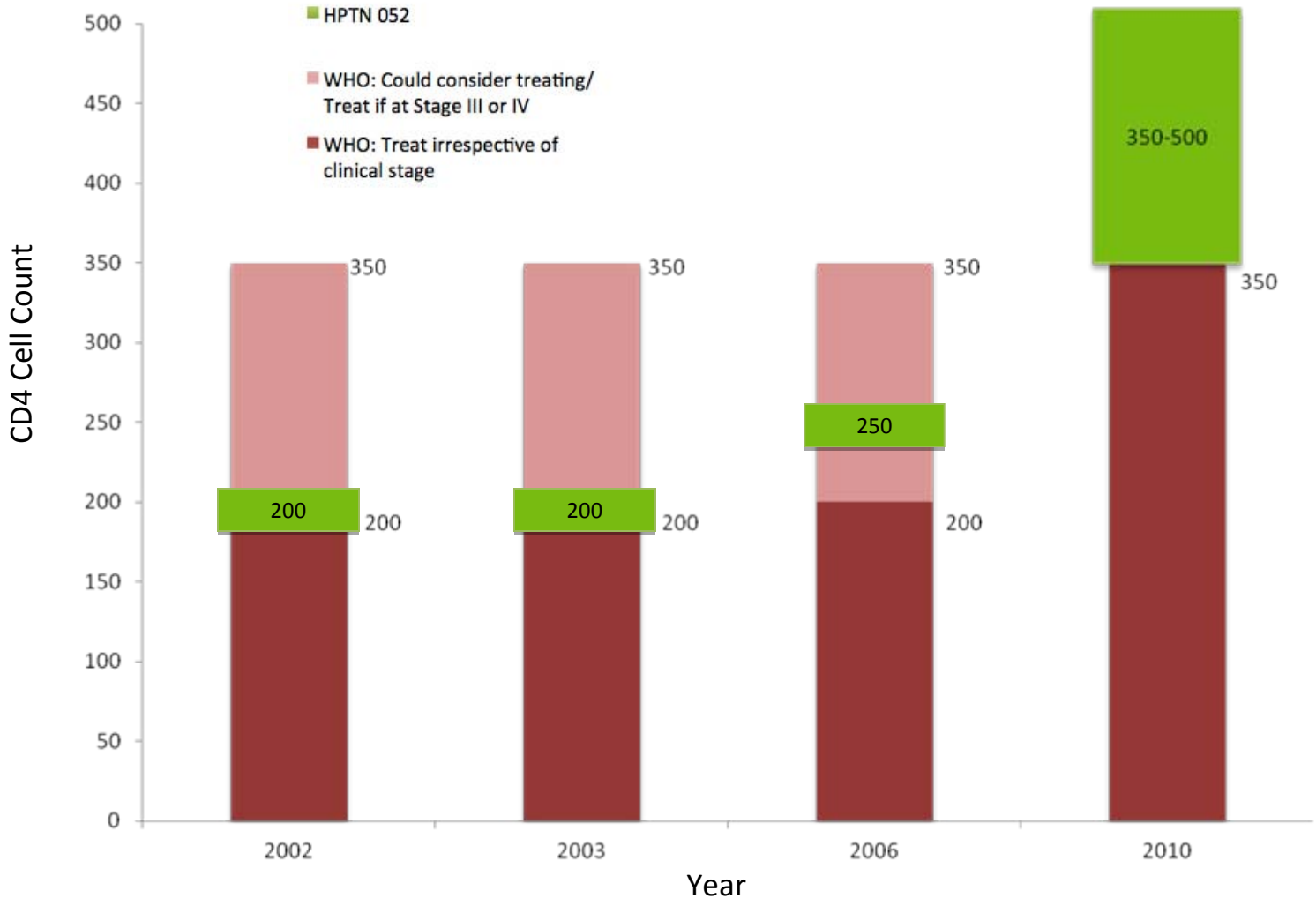


Figure 1. WHO recommended CD4 cell counts at which to initiate antiretroviral treatment irrespective of clinical stage (dark red), WHO recommended CD4 cell counts at which antiretroviral treatment could be considered given the patient's clinical condition (light red), and CD4 cell counts at which HTPN 052 study protocol indicated antiretroviral treatment initiation.

The Economist

June 4, 2011

ART for Prevention: Assumptions=Results

Cohen and Gay, 2010

1st author (yr)	Key assumptions	Results
Blower (2000)	Steady risk behavior levels; low resistance rate; 50% - 90% ART coverage	substantial ↓in HIV incidence
Lima (2008)	75% - 100% ART coverage when CD4 < 200; stable adherence	37% - 62% ↓ in HIV incidence
Law (2001)	2X-10X ↓ in infectiousness; 40% - 70% ↑ in unsafe sex	Behavioral disinhibition could limit preventive benefit
Fraser (2004)	Viral load suppression on ART limits transmission; 66% ↑ in risk behavior	Behavioral disinhibition could limit preventive benefit
Wilson (2008)	Effective ART reduces viral load to < 10 copies / mL; decreased condom use	Behavioral disinhibition could limit preventive benefit
Baggaley (2006)	Treatment of all w/ AIDS & pre-AIDS; decreased risk-taking	Only small number of infections averted
Granich (2009)	Universal annual HIV testing & immediate treatment	African HIV epidemic could be ended

Ecology and ART

- San Francisco

  Das et al. PLoS One, 2010

- British Columbia

  Montaner et al Lancet, 2010

These studies lack:

-True assessment of HIV prevalence

-The number of people "suppressed" on ART

-Measurement of HIV "incidence"

…and Australia, the Netherlands and the US (Plos One, August 2011) see NO DECREASE in HIV incidence in spite of widespread usage of ART!

British Columbia and ART?

Lancet, Montaner, 2010: "NEW DIAGNOSIS"

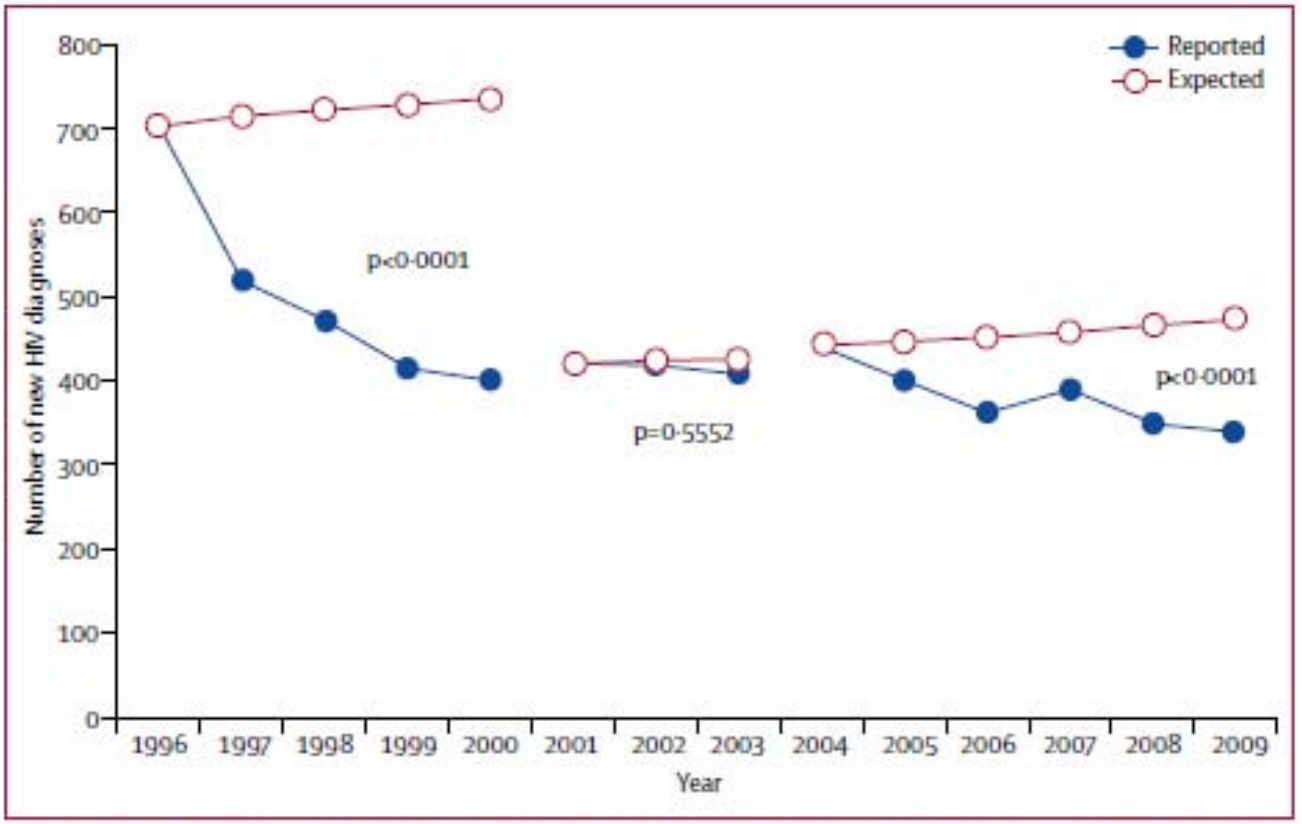


Figure 2: **Reported and expected number of new HIV diagnoses per year in British Columbia, Canada, during the three phases of the study, 1996–2009**

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.

The "Test and Treat" Movement
THE HORSE IS OUT OF THE BARN

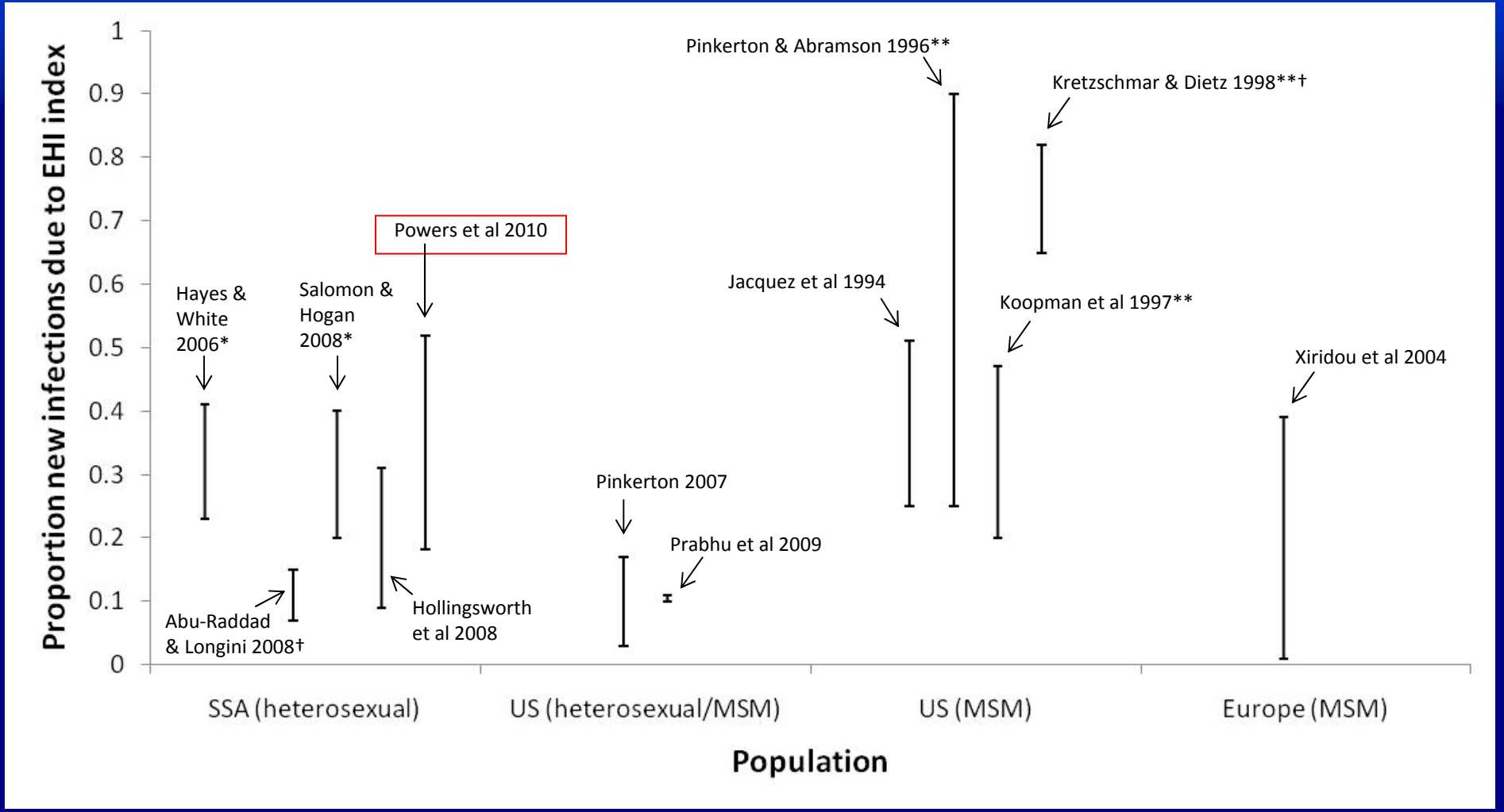
Cohen et al. Current Opinion HIV, 2011

- US HPTN 065 : NYC, DC (*El-Sadr*)
- ANRS South Africa (*Newell*)
- Combination Prevention Trials:
  - CDC Award: Botswana (Essex)
  - HPTN 071: "POPART" (Hayes)

Test and Treat Limitations

Effect of Acute and Early HIV Infection on Spread

Cohen et al, NEJM, 2011



* 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.

Test, Link and Treat: The Reality

Gardner et al CID, 2011

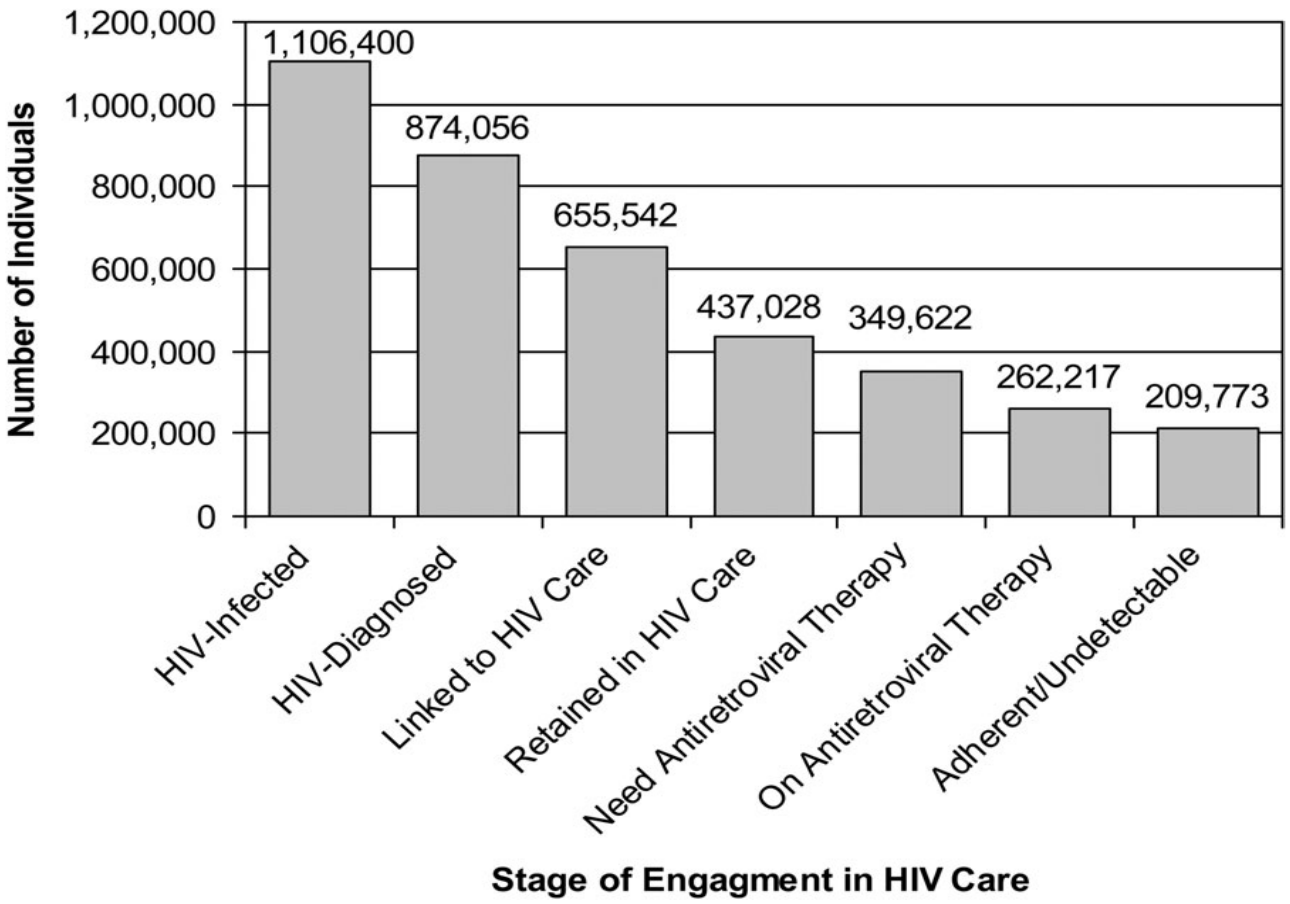
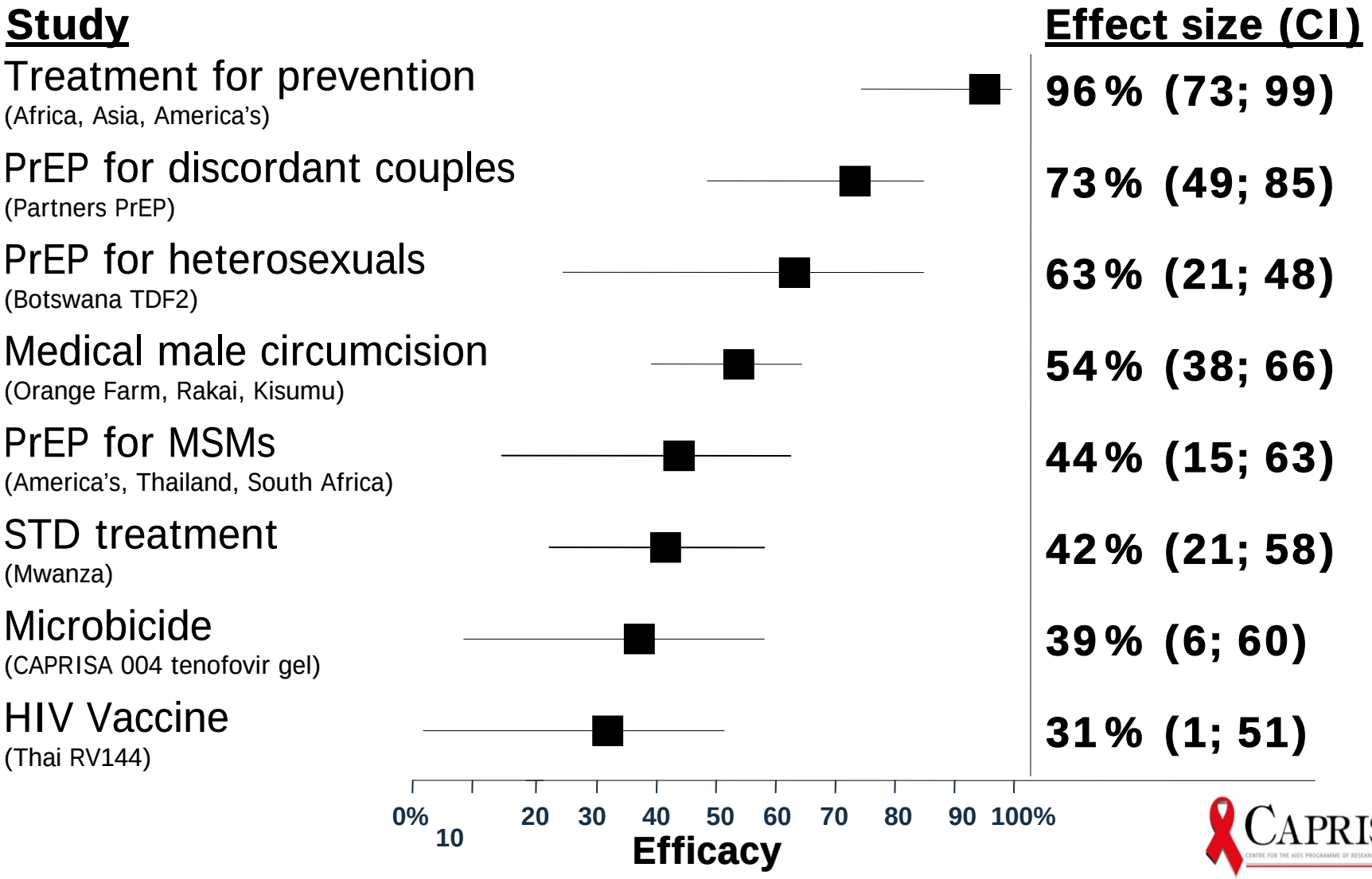


Figure 2. The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to full engagement in care, receipt of antiretroviral therapy, and achievement of complete viral suppression. We estimate that only 19% of HIV-infected individuals in the United States have an undetectable HIV load.

Clinical trial evidence for preventing sexual HIV transmission



CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

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