

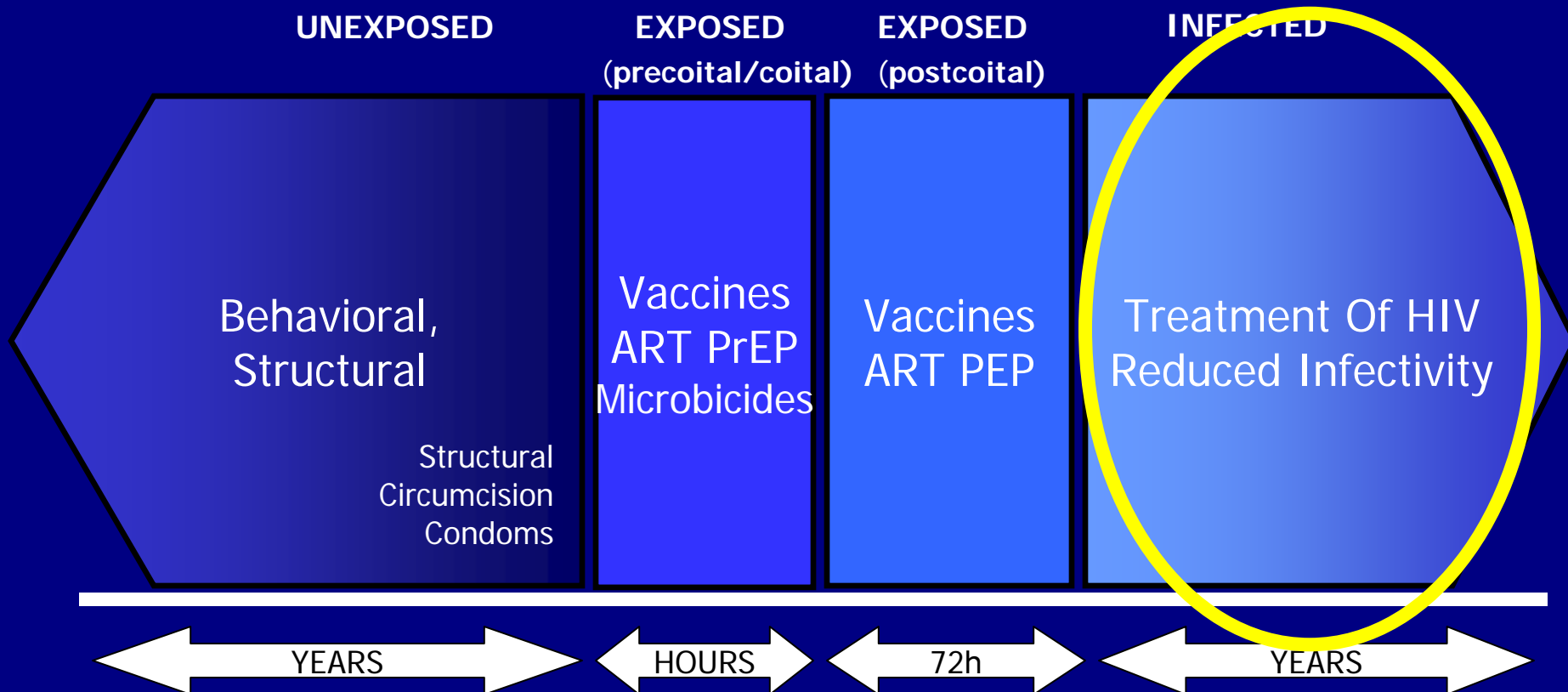
# HIV Treatment as Prevention

Myron S. Cohen, MD



# Four Prevention Opportunities

*Cohen et al, JCI, 2008*  
*Cohen IAS 2008*

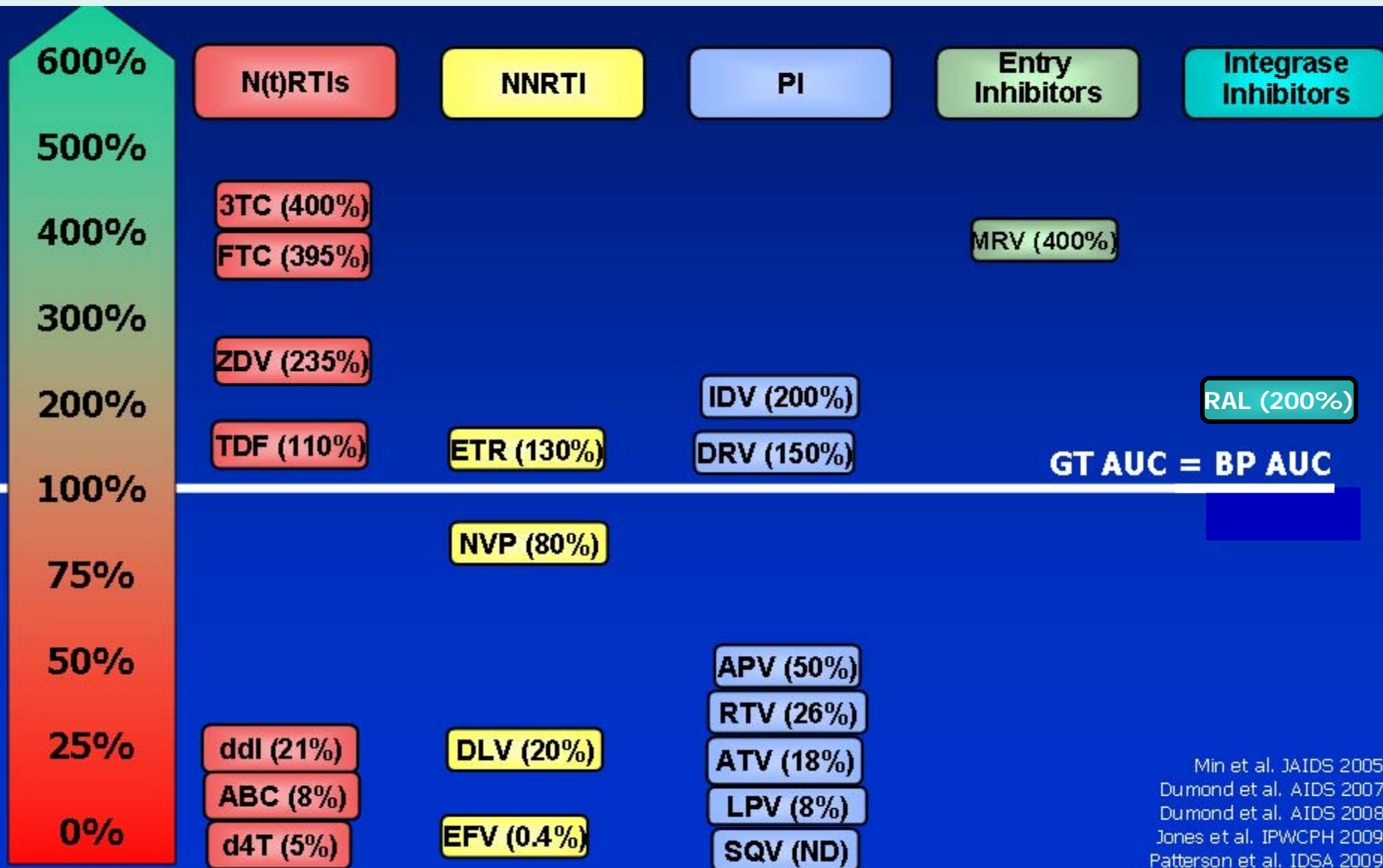


# Antiviral Treatment as Prevention

- 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

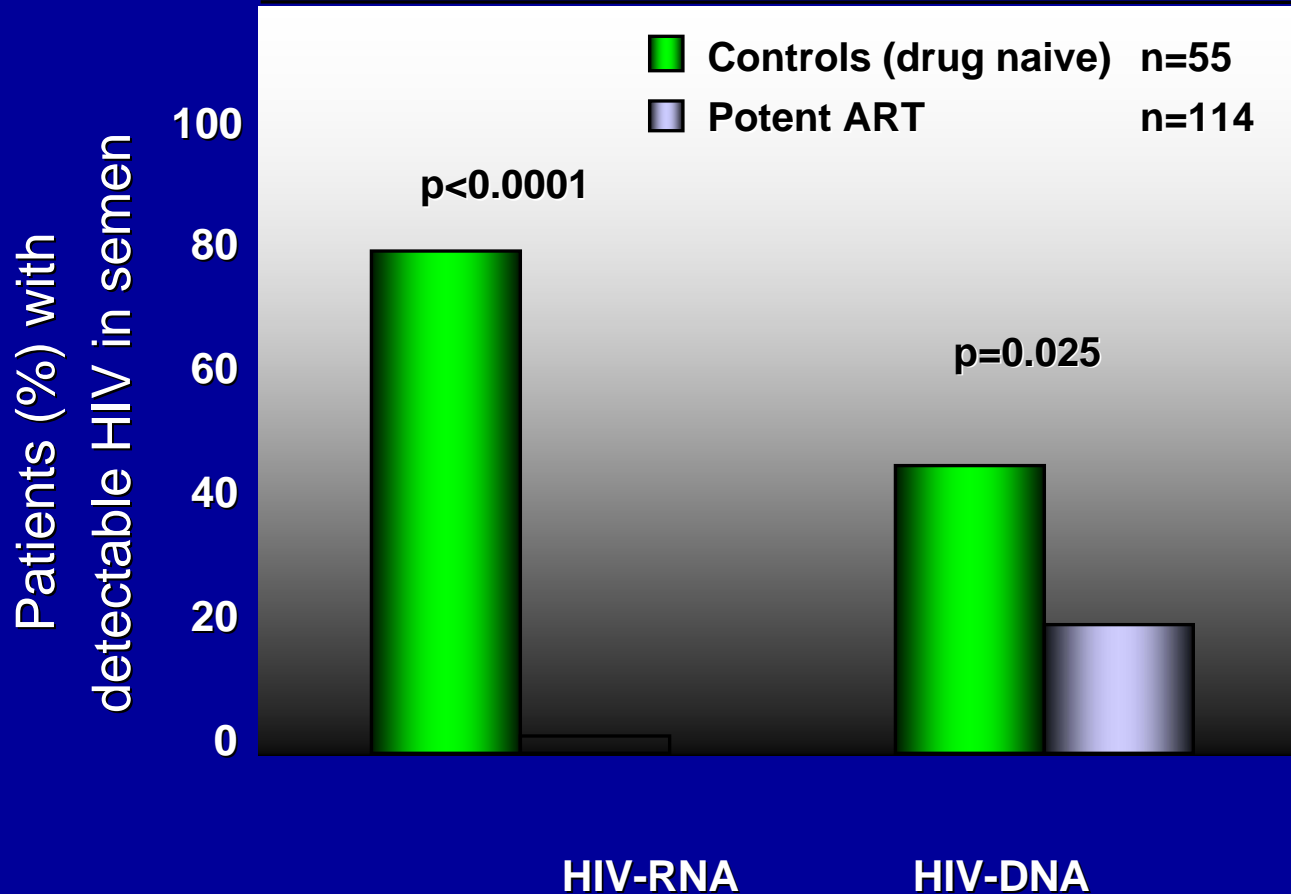
# ART in the Female Genital Tract

*Cohen and Kashuba, Annals Int Med 2007*



Min et al. JAIDS 2005  
 Dumond et al. AIDS 2007  
 Dumond et al. AIDS 2008  
 Jones et al. IPWCPH 2009  
 Patterson et al. IDSA 2009

# 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)*

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- 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

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- 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

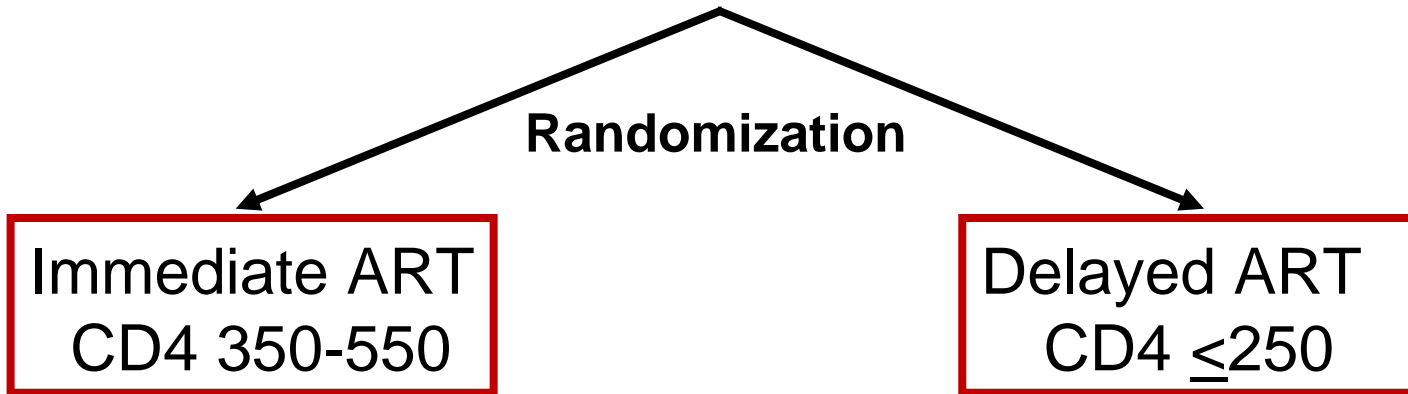
## “The Four Questions”

- 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

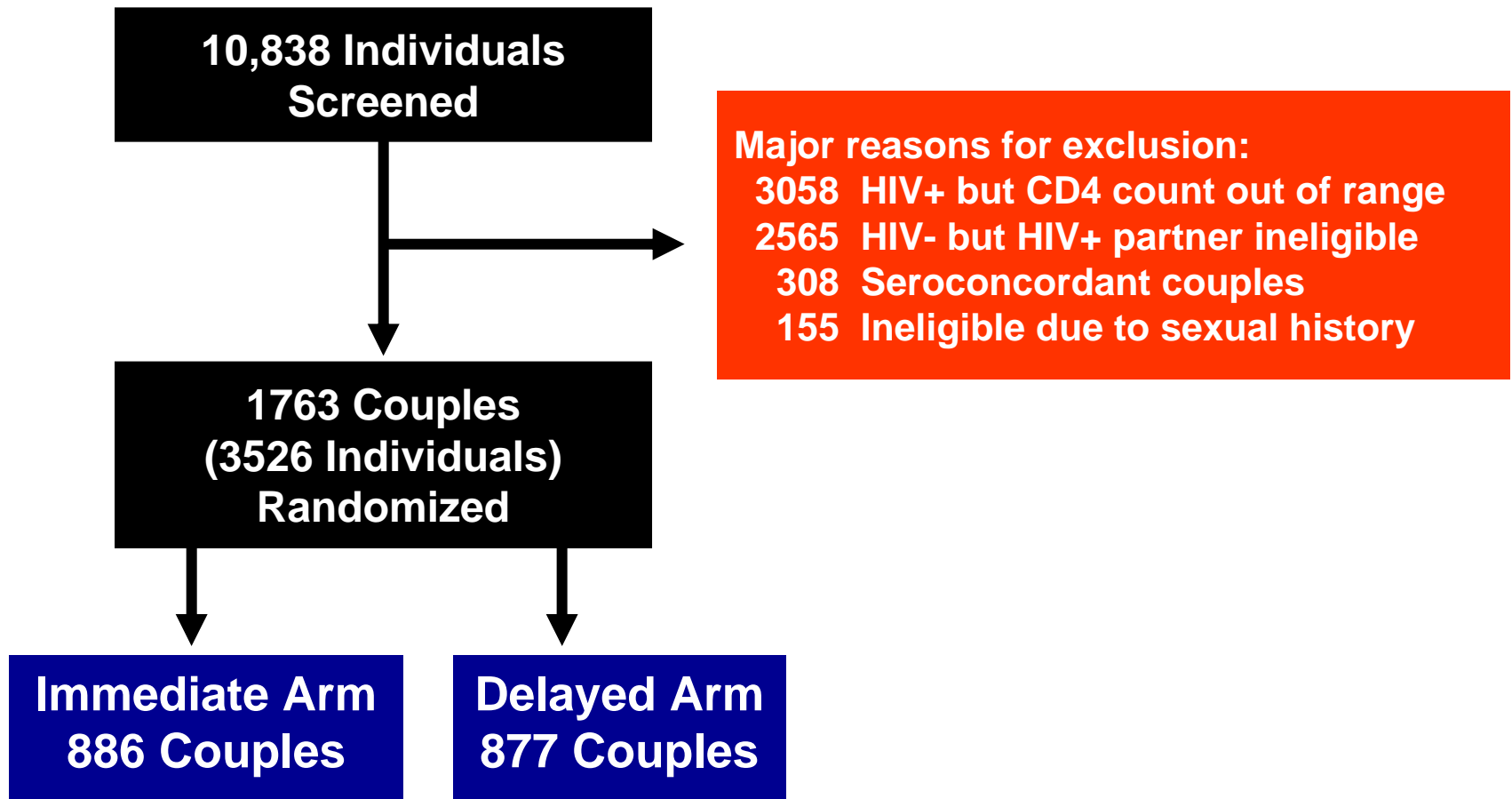
Stable, healthy, serodiscordant couples, sexually active  
CD4 count: 350 to 550 cells/mm<sup>3</sup>



**Primary Transmission Endpoint**  
Virally linked transmission events

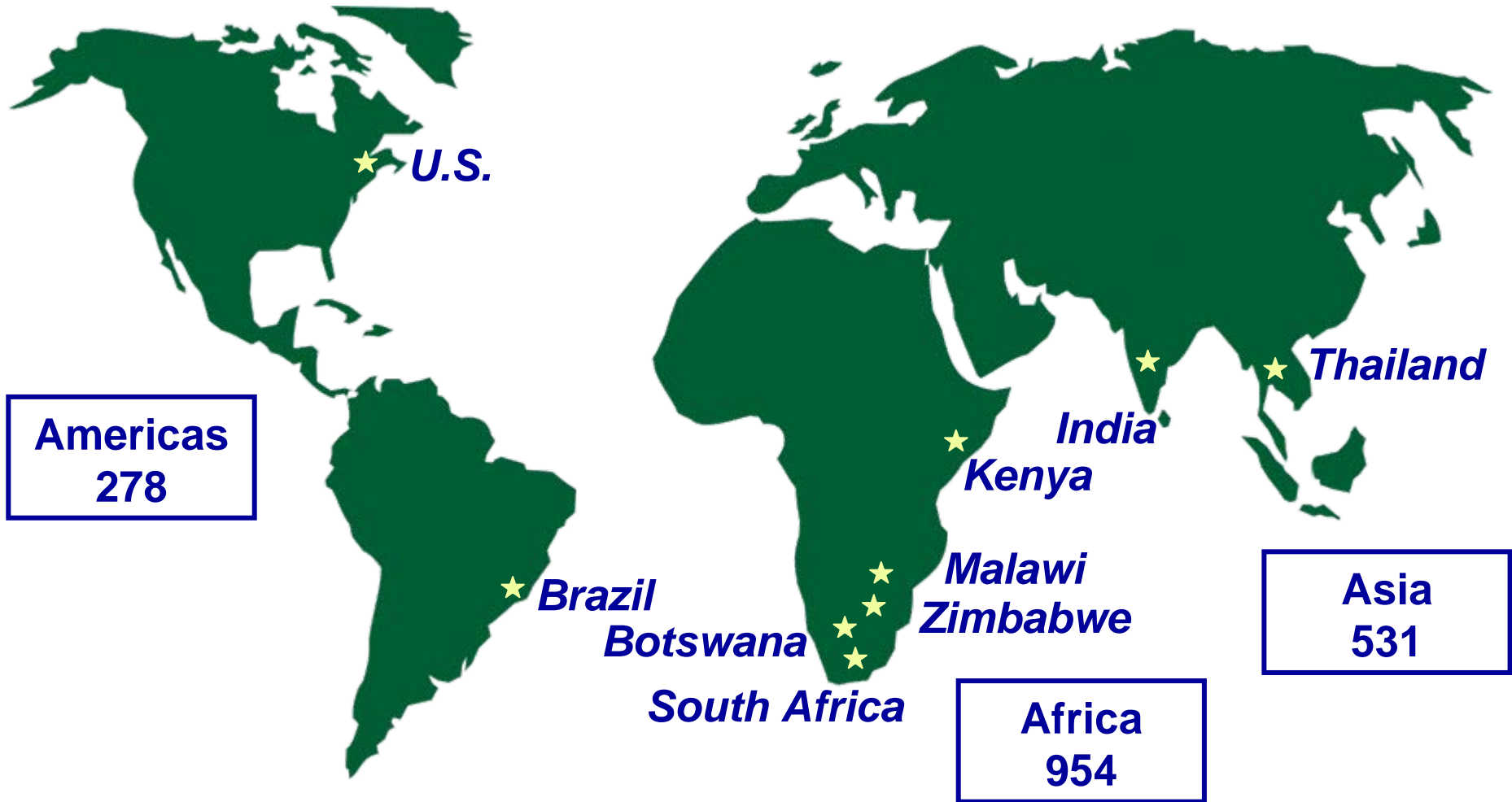
**Primary Clinical Endpoint**  
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

# 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
	<b>Total</b>	<b>1763</b>

# HPTN 052: Baseline Characteristics

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

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# **DSMB Recommendation**

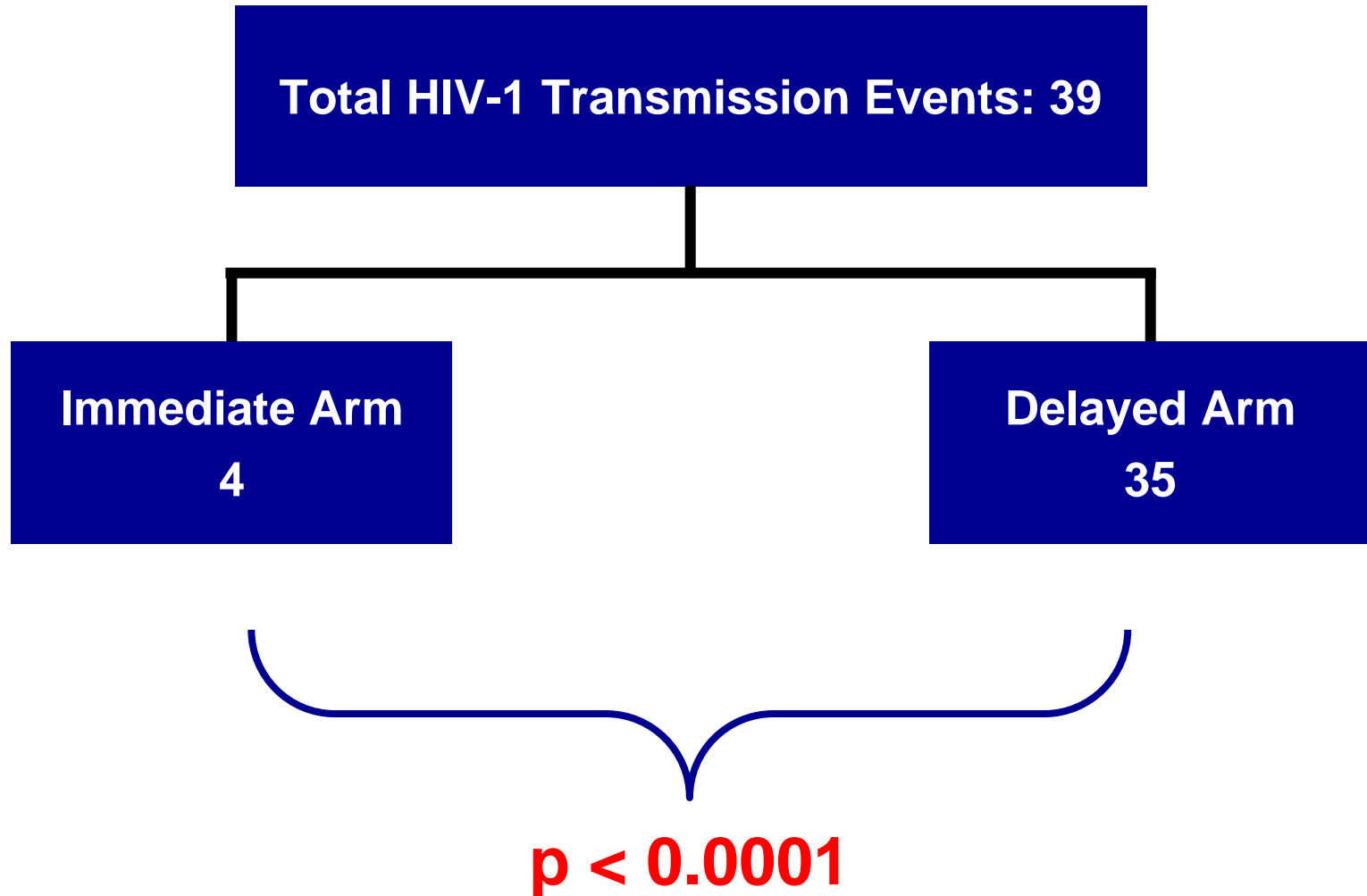
**April 28, 2011**

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**“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*

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## THREE METHODS EMPLOYED

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

# HPTN 052: HIV-1 Transmission

Total HIV-1 Transmission Events: 39

Linked  
Transmissions: 28

Unlinked or TBD  
Transmissions: 11

Immediate  
Arm: 1

Delayed  
Arm: 27

$p < 0.001$

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

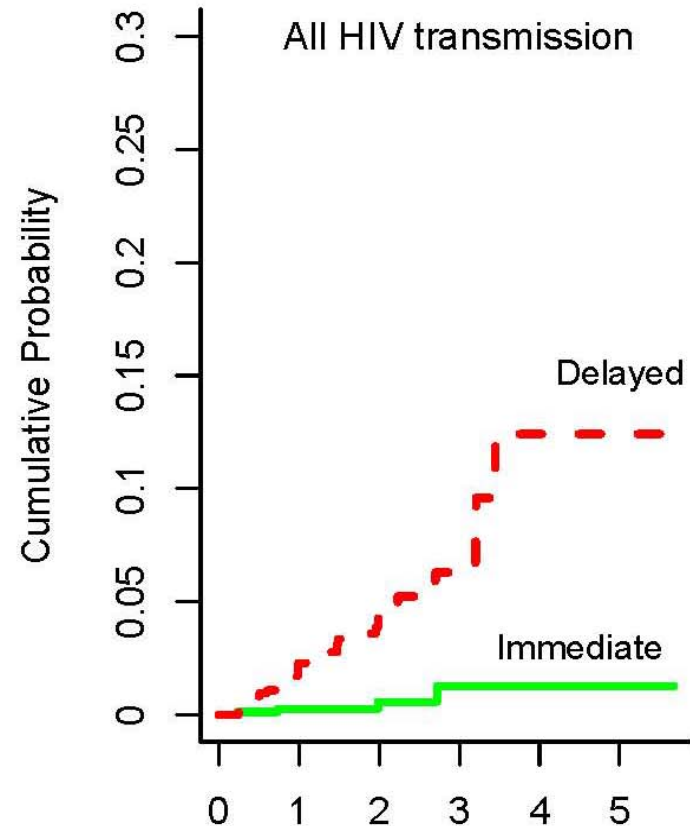
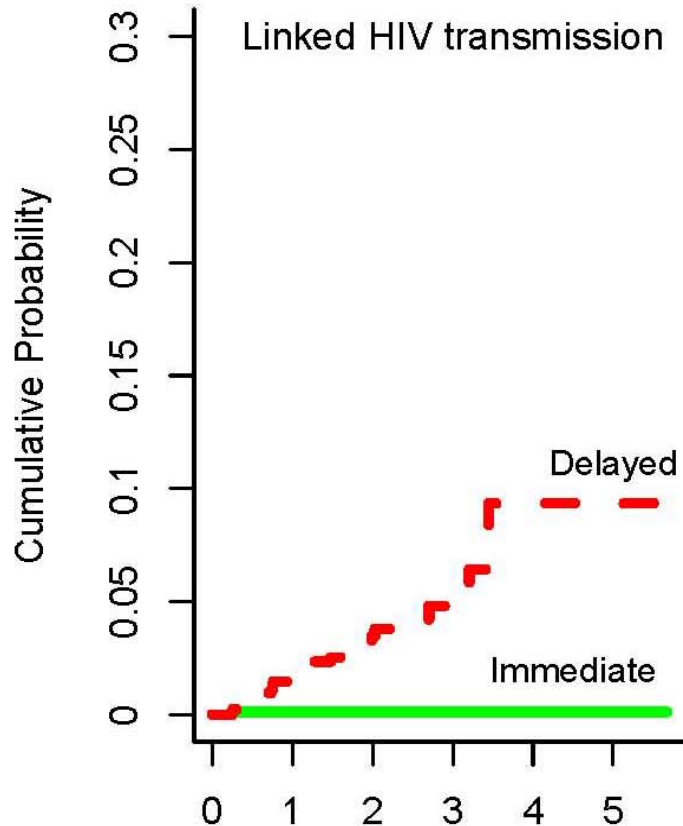
# HPTN 052: HIV-1 Transmission

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

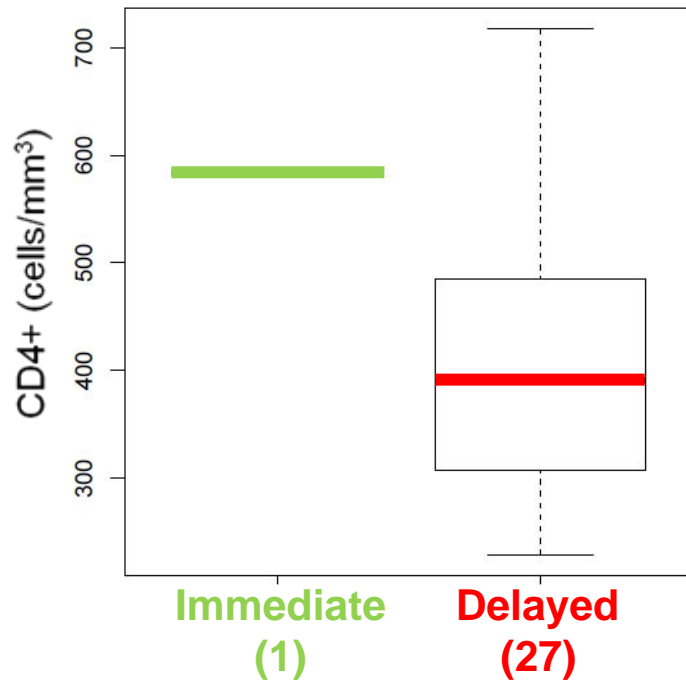
No. at Risk

Immediate 893 658 298 79 31 24

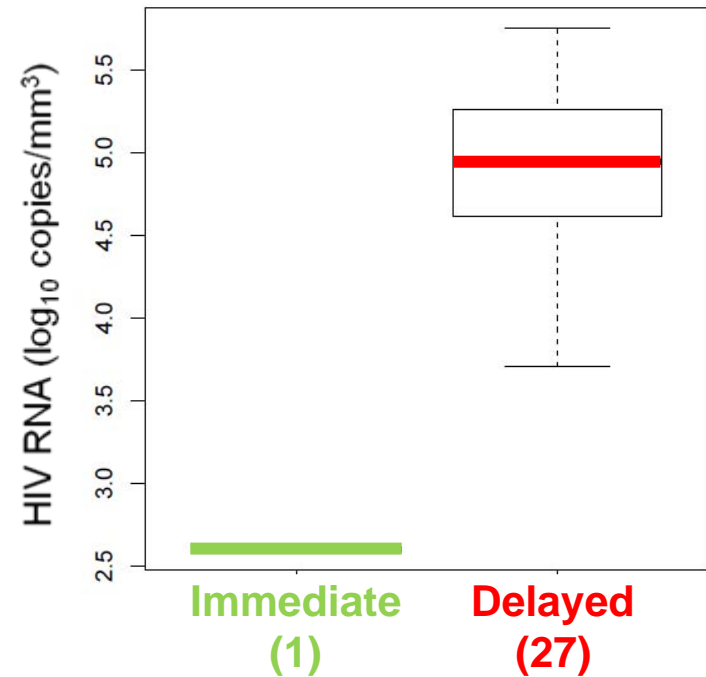
Delayed 882 655 297 80 26 22

# HIV Transmission and Viral Load

## 28 Linked Transmissions

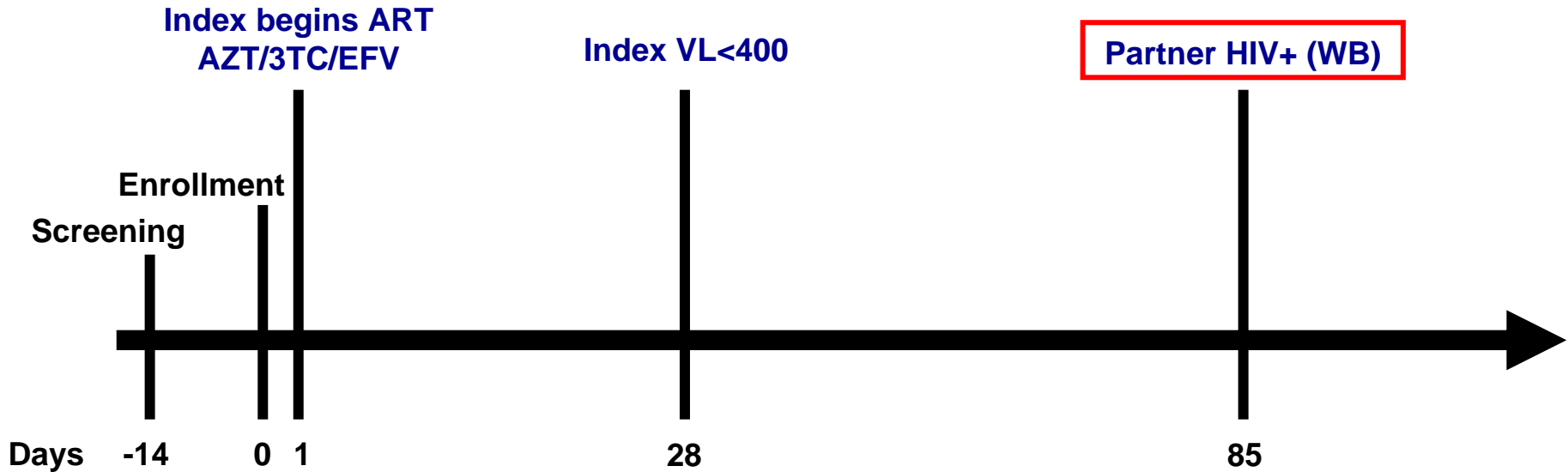


Median proximal CD4 (range): 400 (229-858)  
Immediate arm: 584 (584-584)  
Delayed arm: 391 (229-858)



Median proximal log<sub>10</sub> 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



Partner VL < 400  
Index VL = 87,202

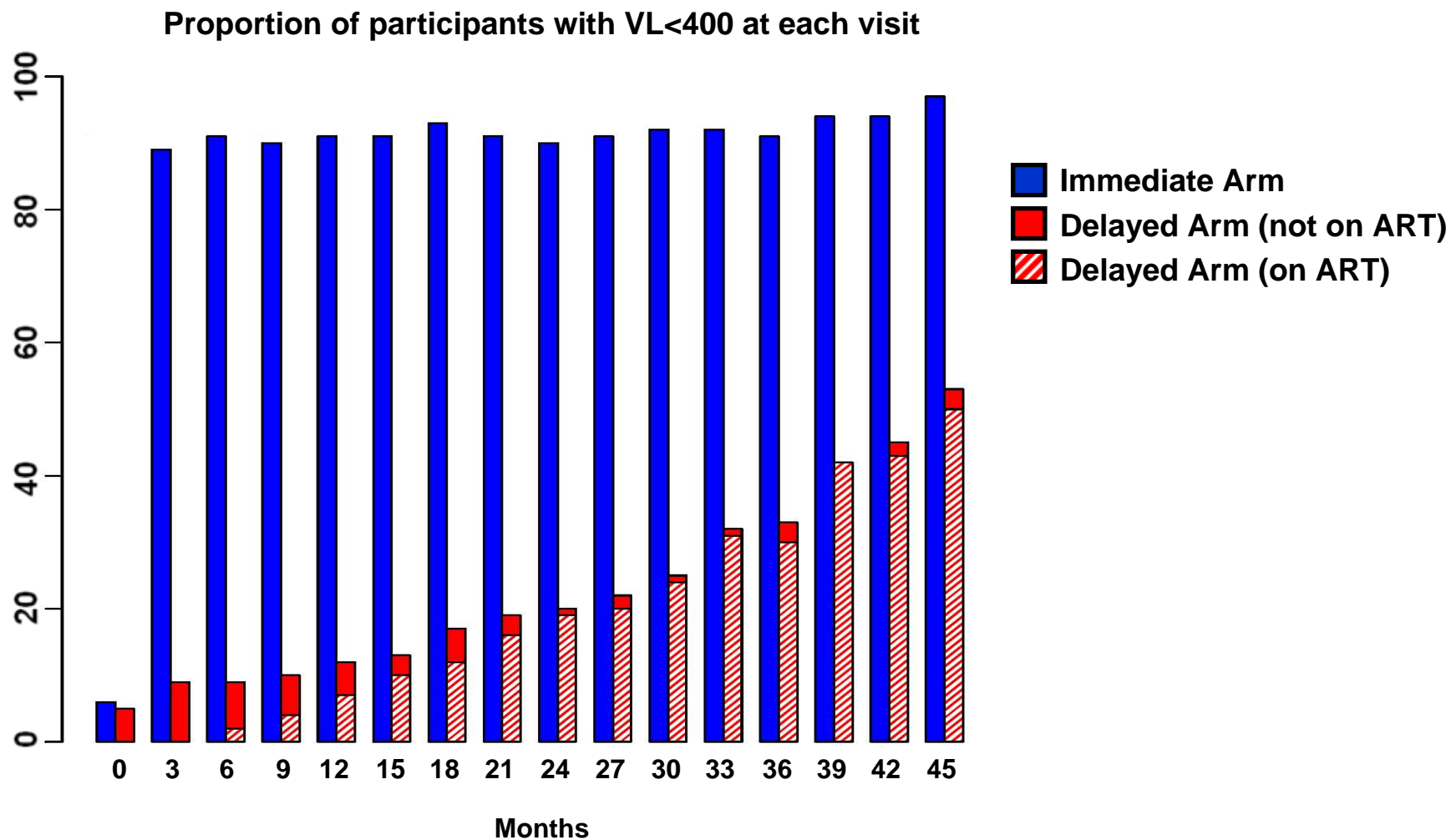
Single Genome Analysis: 1-2 viruses transmitted

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

# Multivariate Analysis – Linked Transmission

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

# HPTN 052: Consistent Use of ART





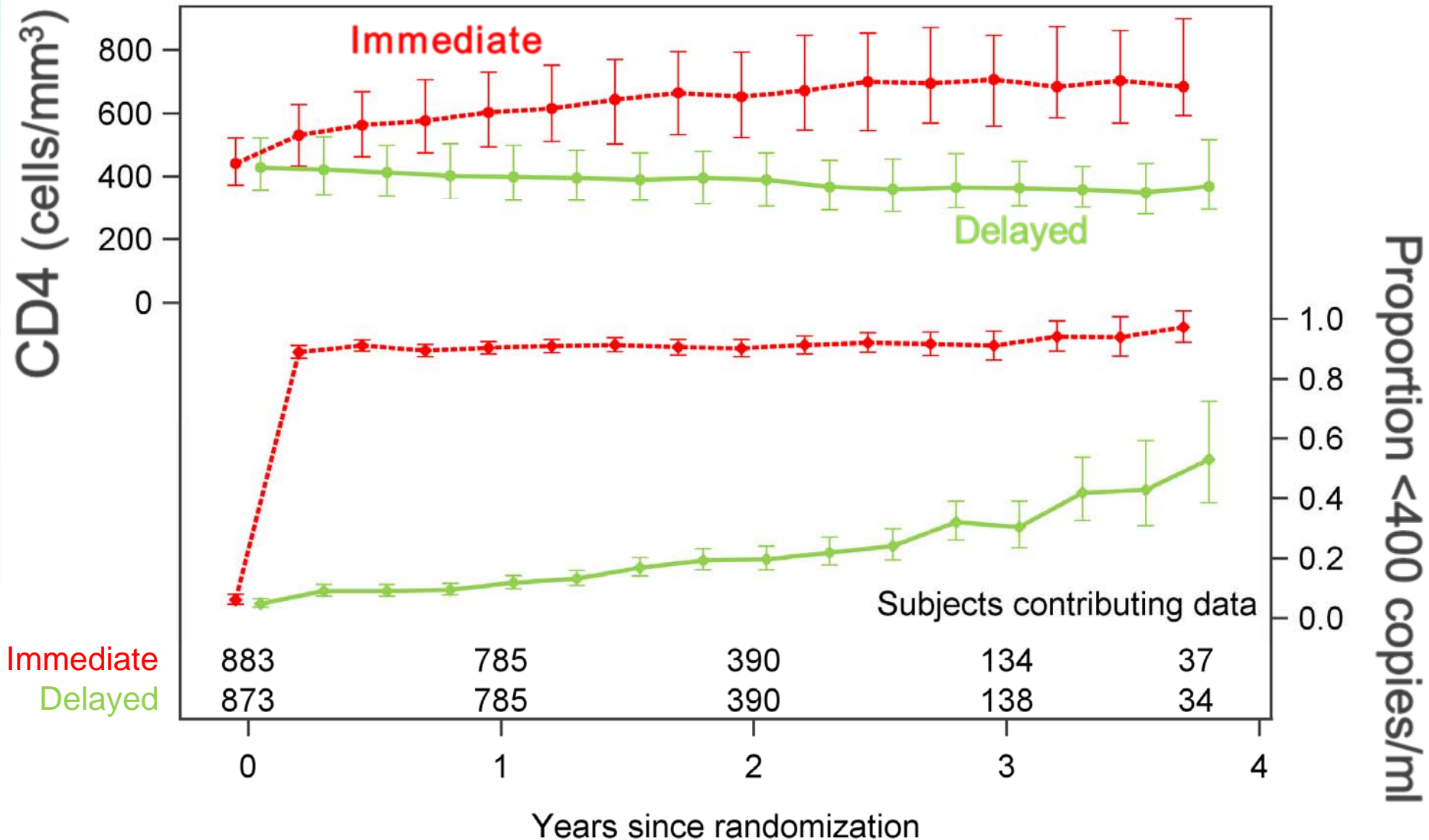
# Effects of Early versus Delayed Initiation of Antiretroviral Therapy (ART) on HIV Clinical Outcomes: Results from the HPTN 052 Randomized Clinical Trial

Beatriz Grinsztejn, MD  
Site Investigator

Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz  
6<sup>th</sup> IAS Conference, Rome, Italy  
July 18, 2011



# 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)

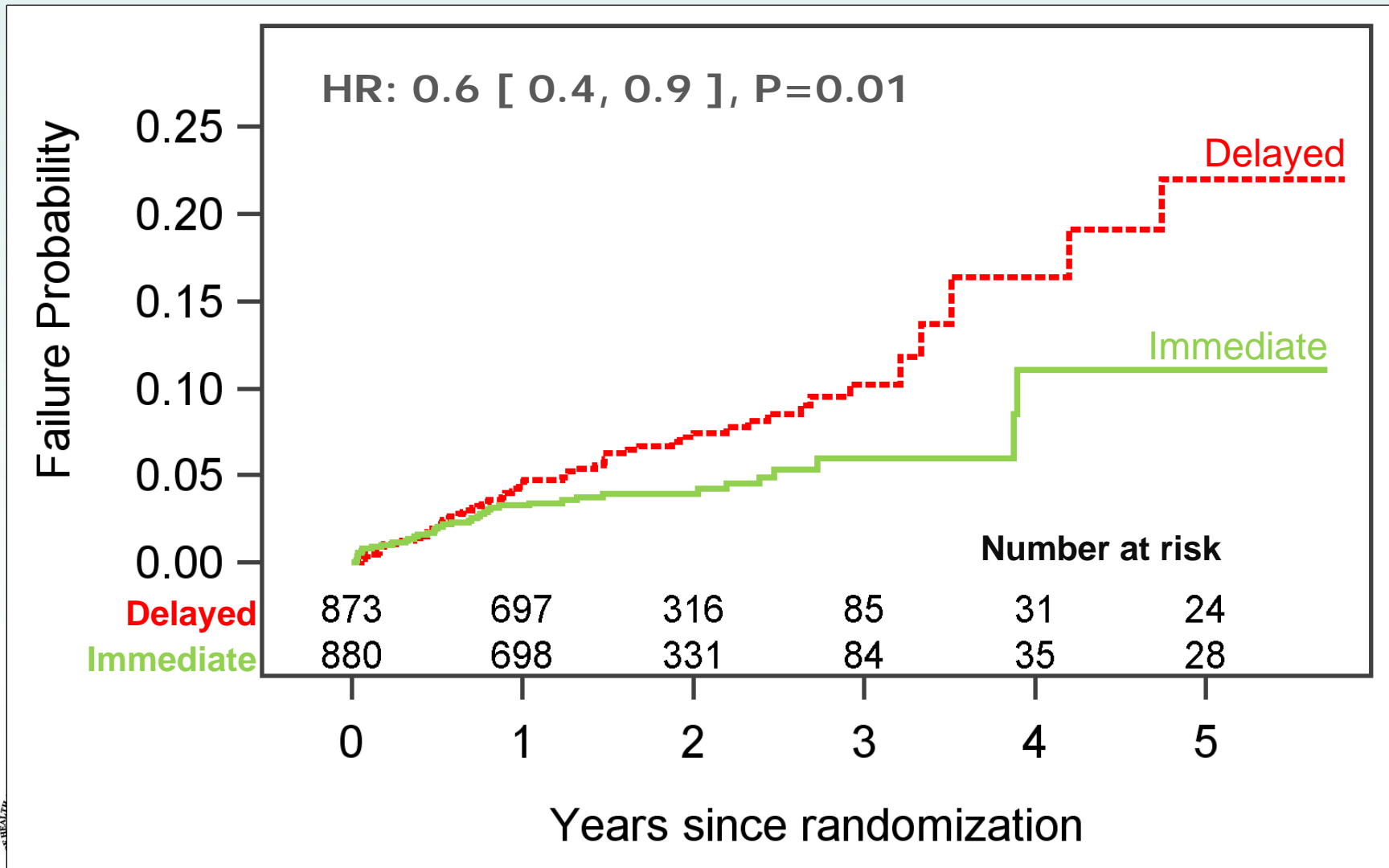
17 subjects experienced >1 primary clinical event

Total (N=129)	Immediate		Delayed	
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 Charialertsak, 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?

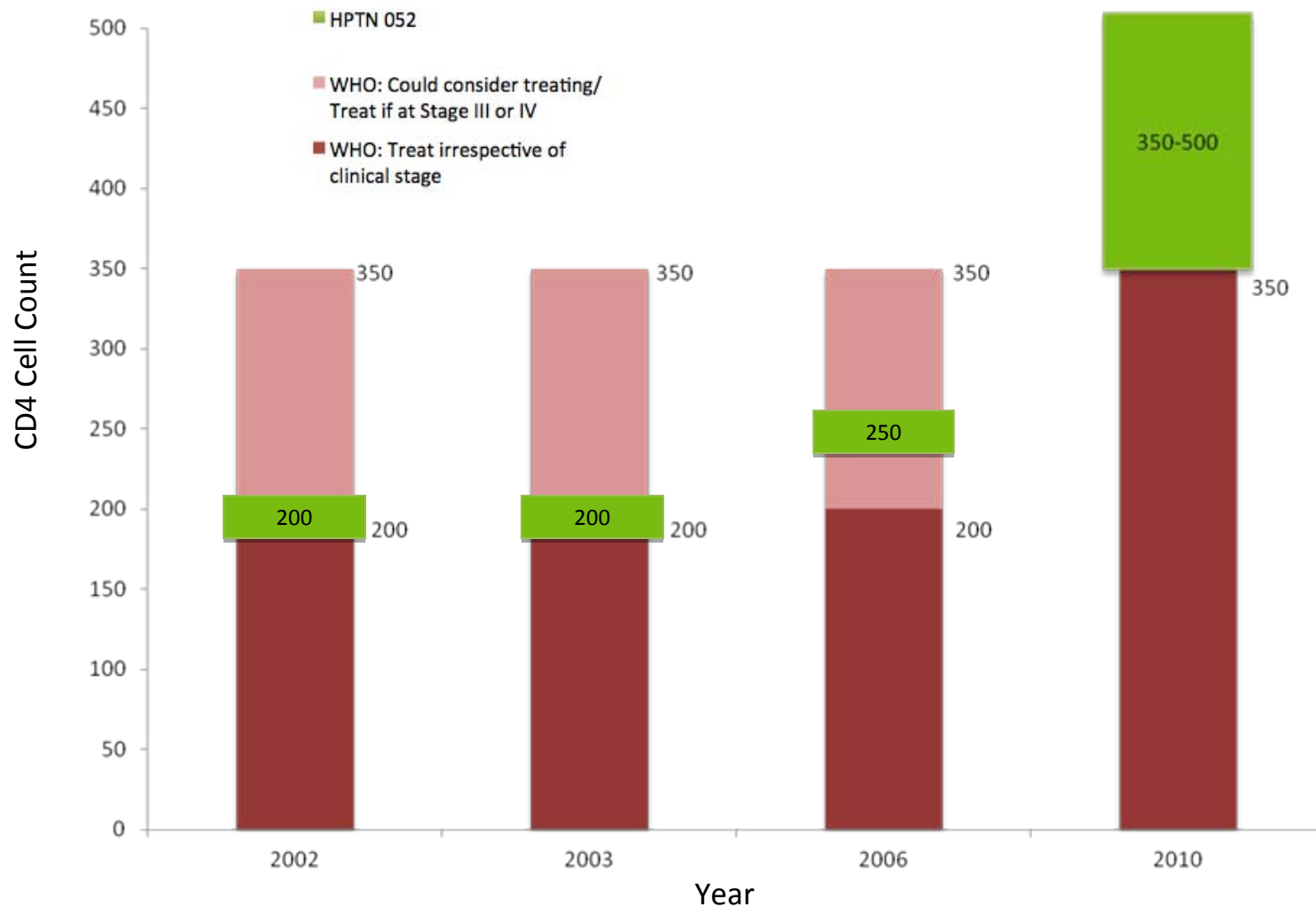


Figure 1. WHO recommended CD4 cell counts at which to initiate antiretroviral treatment irrespective of clinical stage (dark red), WHO recommended CD4 cell counts at which antiretroviral treatment could be considered given the patient's clinical condition (light red), and CD4 cell counts at which HTPN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



# The Economist

June 4, 2011



# ART for Prevention: Assumptions=Results

*Cohen and Gay, 2010*

1 <sup>st</sup> 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

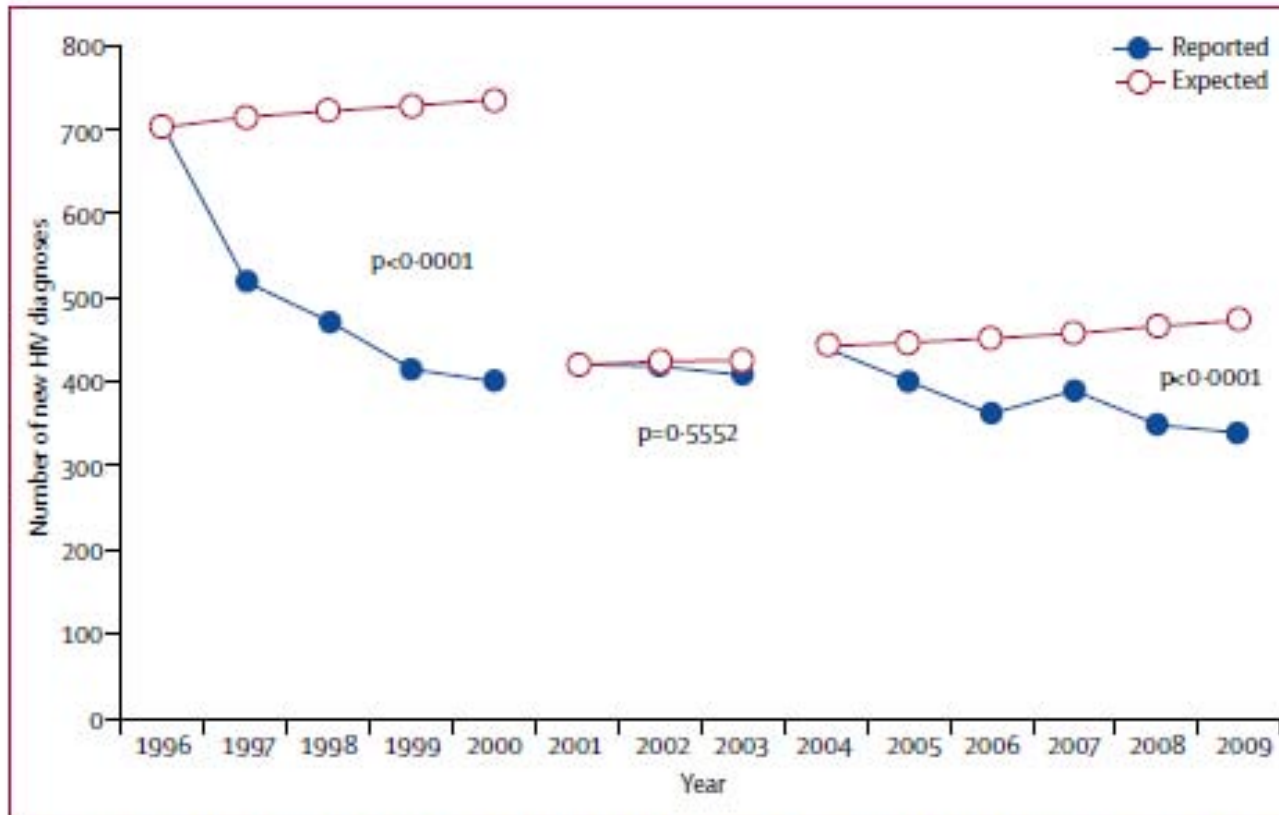
- The number of people “suppressed” on ART

- 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

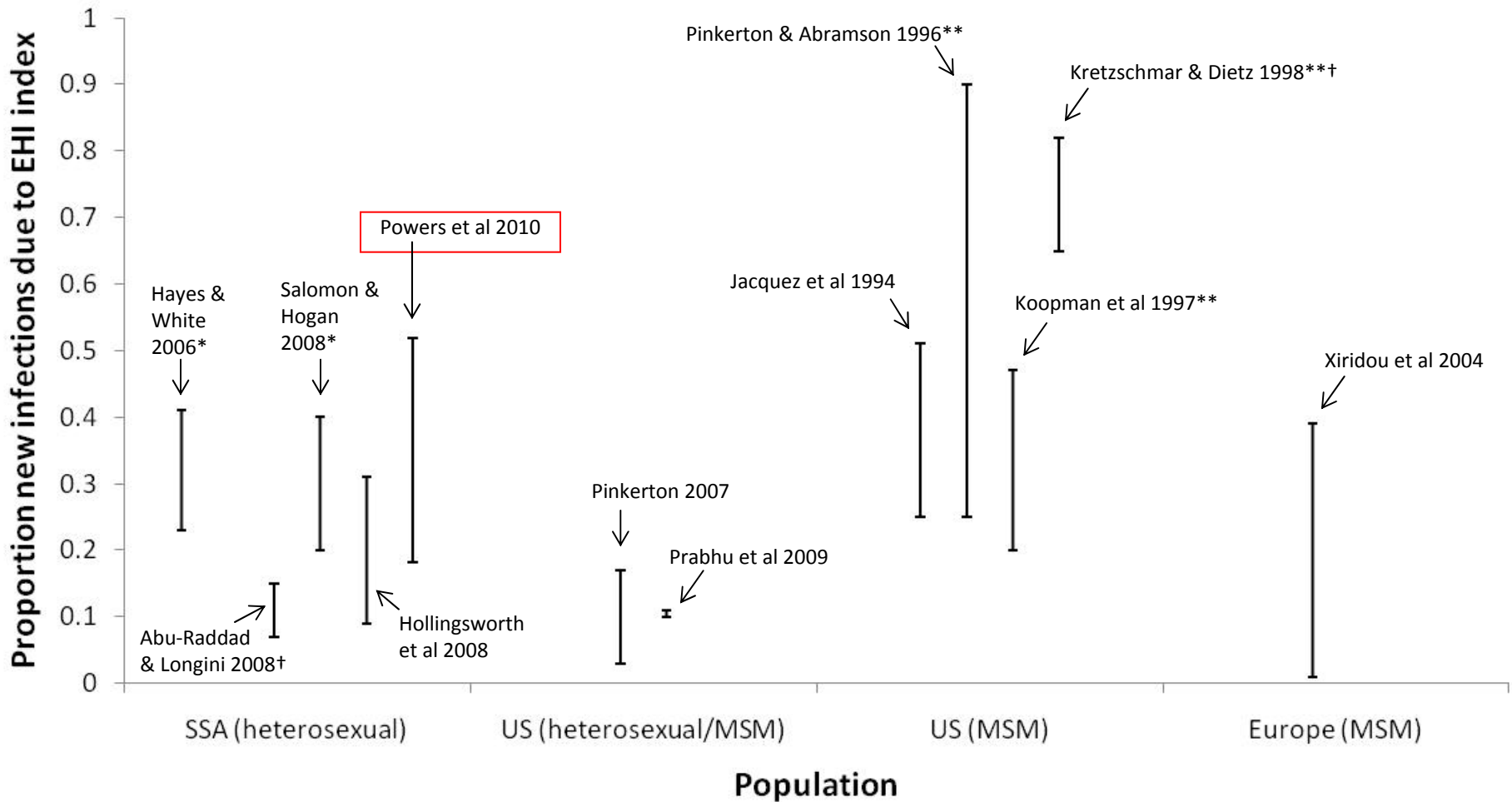
*Cohen et al. Current Opinion HIV, 2011*

- 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



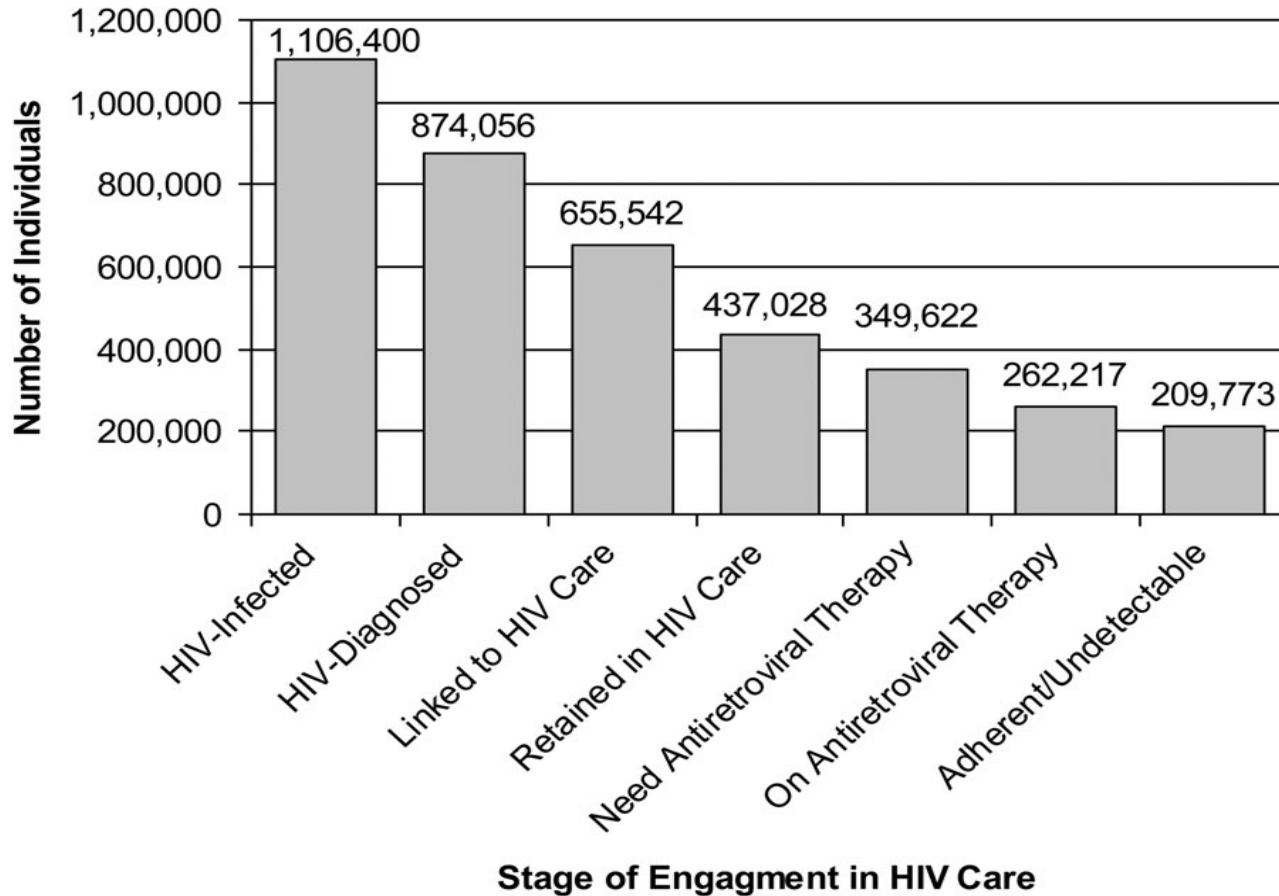
\* Range of estimates reflects the proportion of all transmissions *during an individual's entire infectious period* that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI *at the population level* will depend on the epidemic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

## Study

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)

## Effect size (CI)

96% (73; 99)

73% (49; 85)

63% (21; 48)

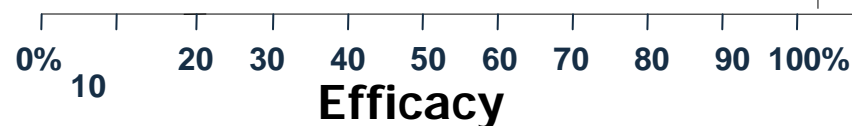
54% (38; 66)

44% (15; 63)

42% (21; 58)

39% (6; 60)

31% (1; 51)



# 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