

# **Treatment as Prevention: Great Opportunity, Great Challenge**



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# Treatment for Prevention of HIV

- How did we get here (briefly)?
- Where are we going?
- How do we get there?

# TasP Plausibility

*Smith et al. PLOS Med, 2012*

- Couples studies (11/13)
- Ecological/observational studies
  - Seemingly positive
  - Beware confounding
  - Generalizability?
- One randomized controlled trial

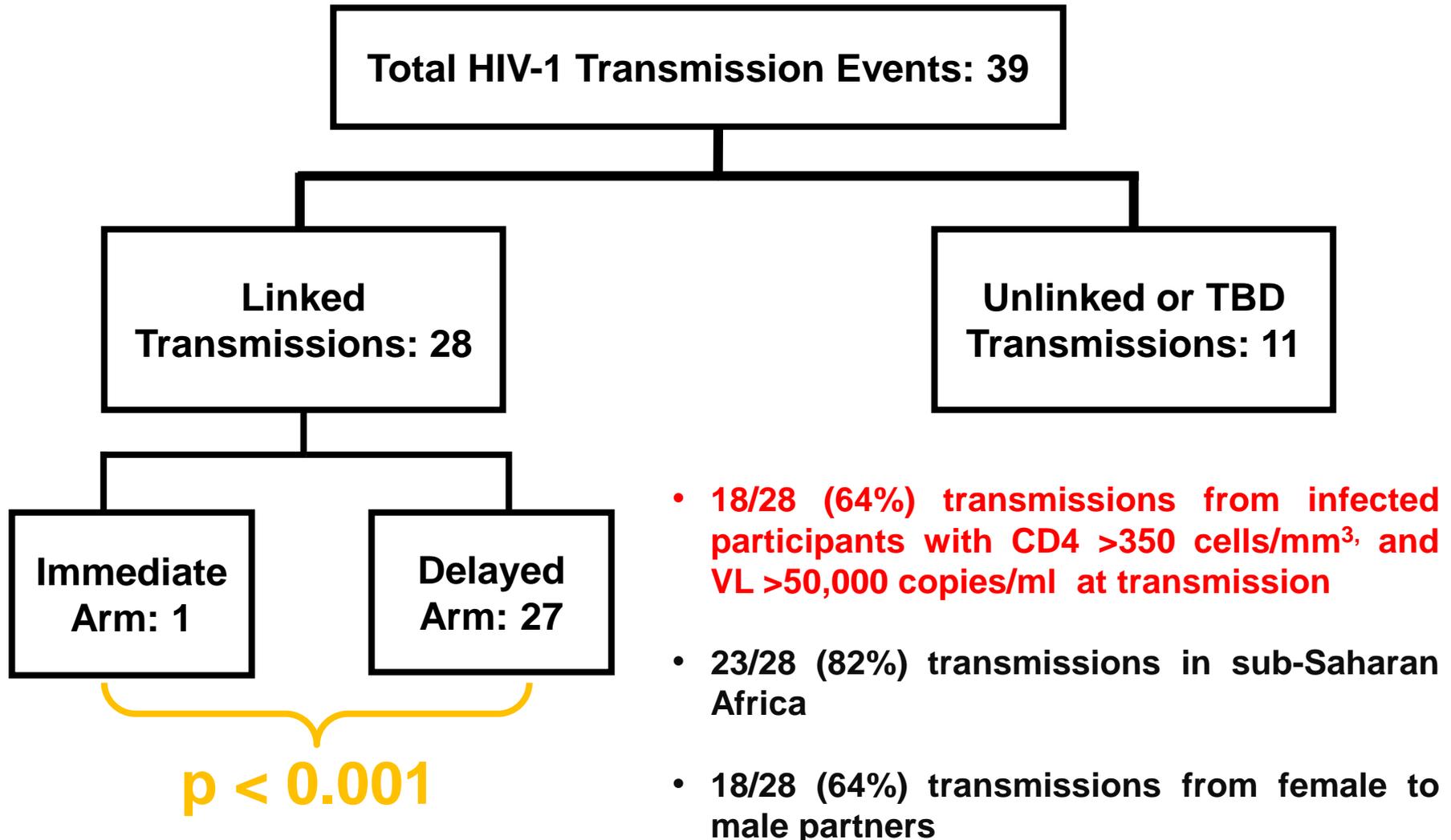
# HPTN 052 Enrollment

*(Total Enrollment: 1763 couples)*



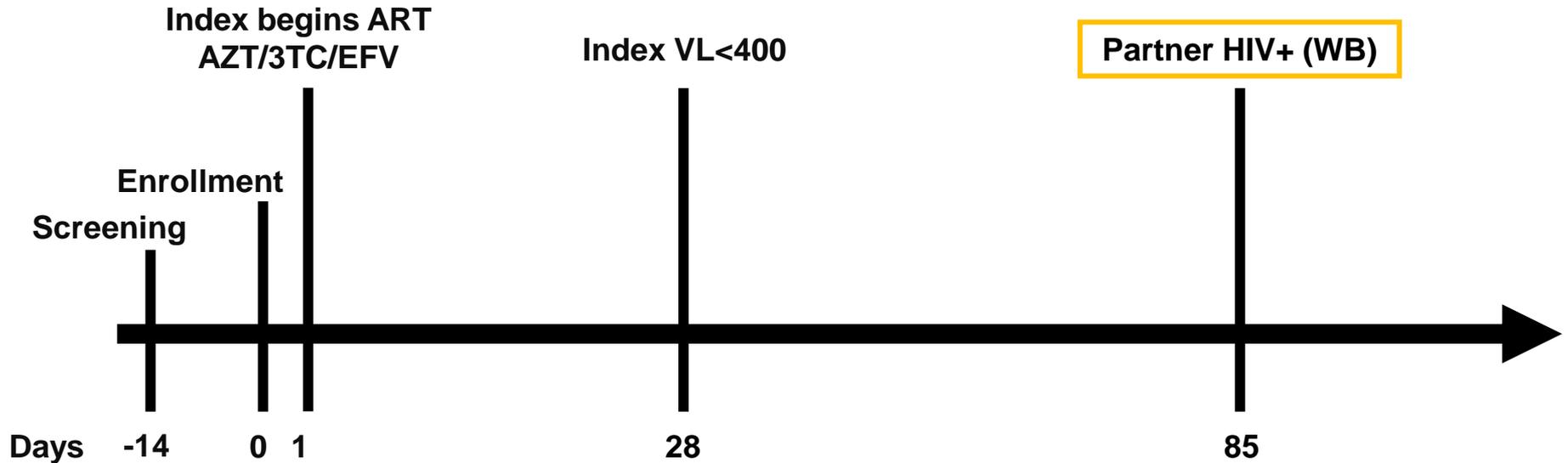
# HPTN 052: HIV-1 Transmission

*NEJM, July 2011*



# A Transmission Event on ART

*Swanstrom et al. PLOS One (in press)*



Partner VL < 400  
Index VL = 87,202

Single Genome Analysis: 1 viruses transmitted

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

# HPTN 052 (2013)

- **The HPTN 052 study is ongoing**
- Retention is > 95% for index cases
- Retention is > 85% for partners (and falling)
- Questions remain:
  - **Durability of the prevention benefit?**
  - **Consequences of delayed ART?**

*HPTN 052 is NOW an observational study*

# Will ART at High CD4 Be Resisted?

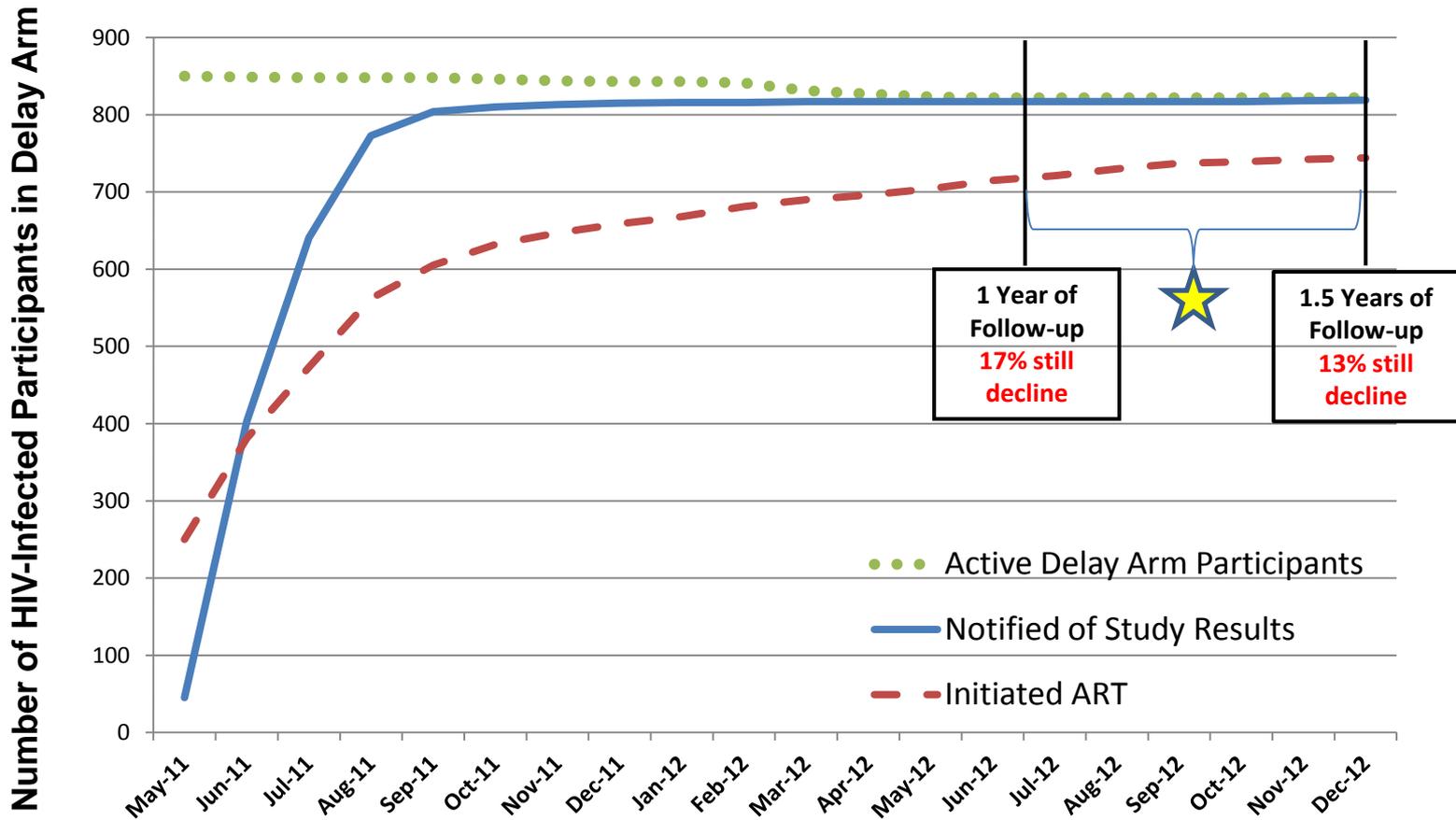
*Adakun, JAIDS 2013*

- Social support
- Infrastructure
- Beliefs?

**-Mixed Messages**

# HPTN 052 Results and ART Initiation

## Gamble et al. CROI, 2013

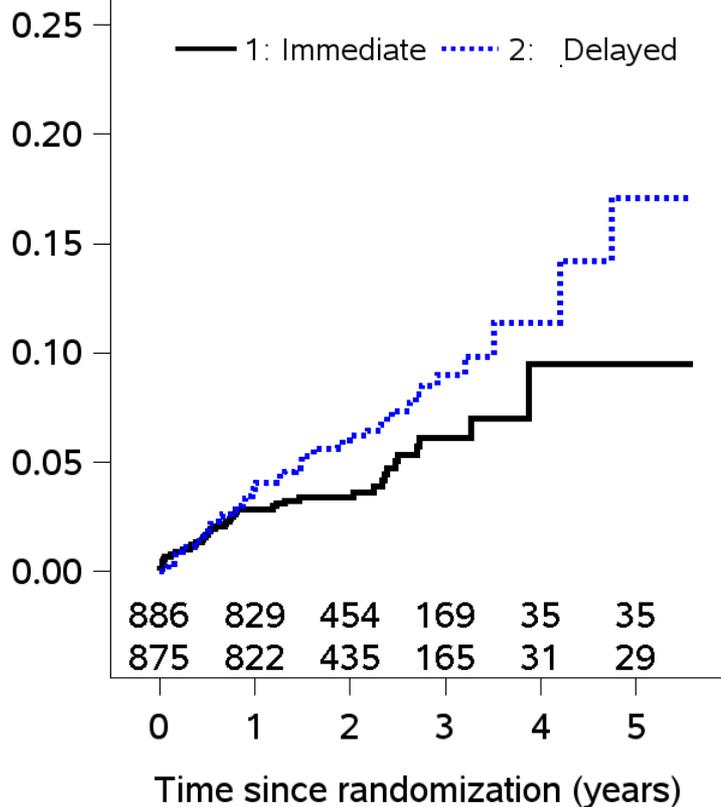


# HPTN 052: Clinical Endpoints

*Grinsztejn et al (in review)*

Time to first AIDS defining disease

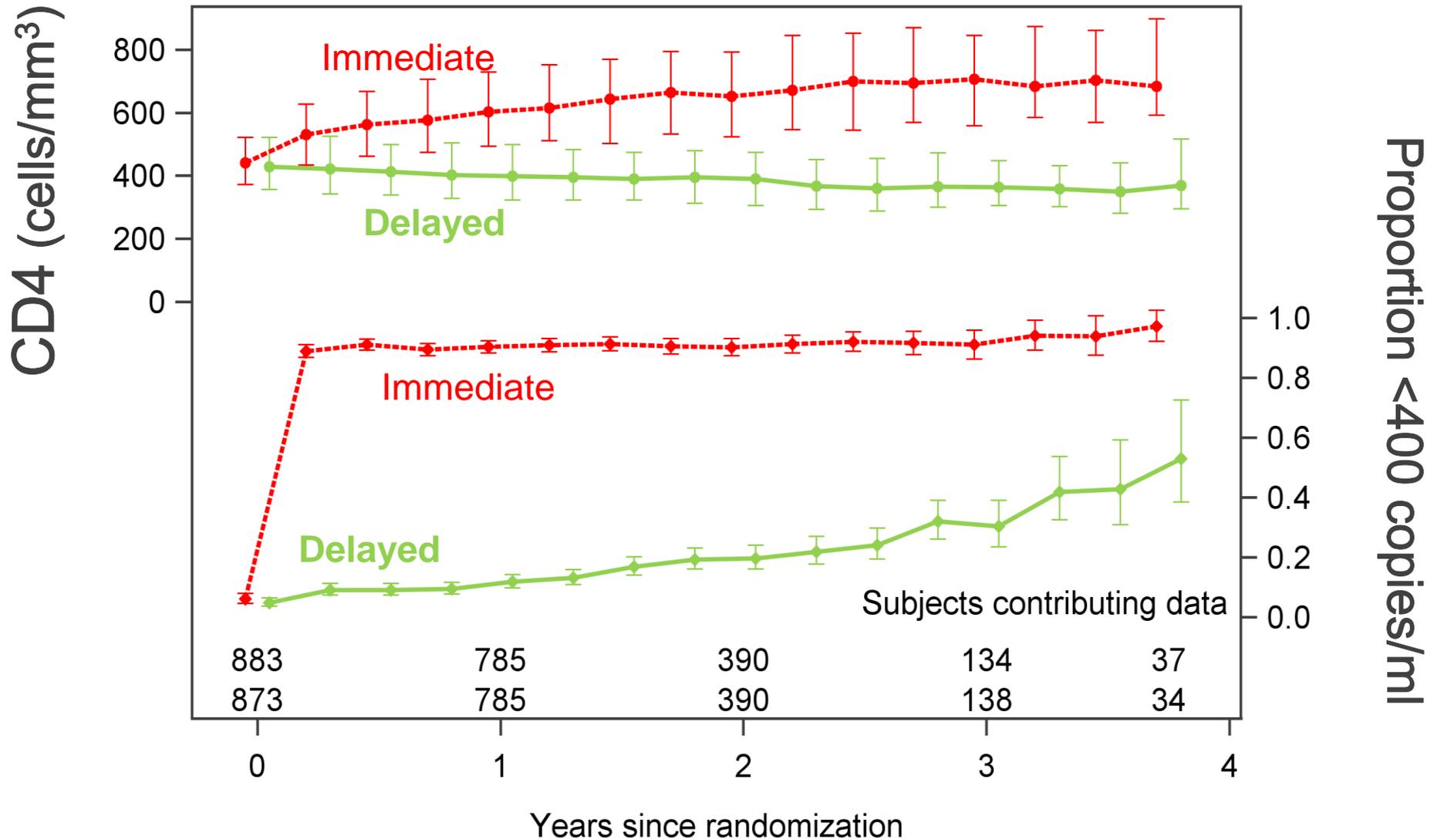
Logrank p= 0.03



Number of subjects experiencing  $\geq 1$  event

	Delayed	Immediate
<b>Tuberculosis</b>	<b>34 (4%)</b>	<b>17 (2%)</b>
Serious bacterial infection	13 (1%)	20 (2%)
<b>WHO Stage 4 event</b>	<b>19 (2%)</b>	<b>9 (1%)</b>
Oesophageal candidiasis	2	2
Cervical carcinoma	2	0
Cryptococcosis	0	1
HIV-related encephalopathy	1	0
<b>Herpes simplex, chronic</b>	<b>8</b>	<b>2</b>
Kaposi's sarcoma	1	1
CNS Lymphoma	1	0
Pneumocystis pneumonia	1	0
Septicemia	0	1
HIV Wasting	2	0
Bacterial pneumonia	1	2

# HIV-1 RNA and CD4 Over Time (ITT)



# HPTN 052 Cost Effectiveness

*Walensky et al. NEJM (in press)*

- In South Africa, over the short term, early ART is “**cost-saving**”
- Over time ART in INDIA and South Africa proves “**very cost effective**”

But we must also consider “cost-benefit”

# Immediate ART??

*Cohen et al Lancet (in press)*

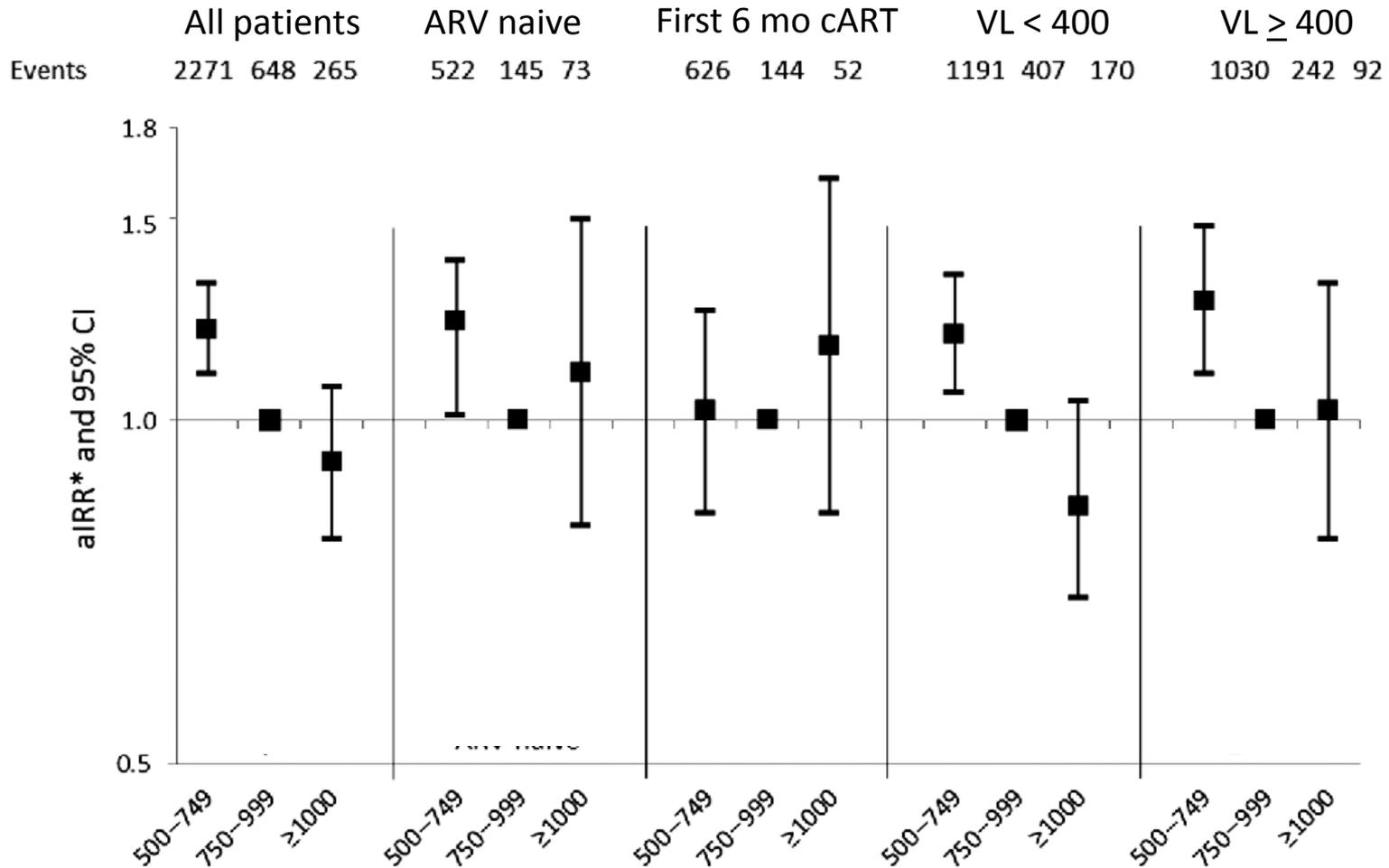
- The consequences of replication (?)
- Reduced long-term survival (?)
- Ongoing HIV transmission (+++)
- Micro and macroeconomic analysis (+)

*The arguments for delay include*

- Anticipated detection of “harm” (?)
- Ongoing search for “benefit” (?)
- Intense focus on logistical challenges
- START and TEMPERANO

# COHERE Study 1998-2010

Relationship between current CD4 and AIDS-defining illness with a CD4 count  $\geq 500$  cells/ $\mu$ L: relationship with current viral load and antiretroviral treatment



# Who Might We Treat?

- Couples (WHO standard)
- Pregnant women (Option B+)
- CD4 cells > 500 (WHO)
- Acute infection (?)

**WHO IS LEFT TO TREAT?**

# **Will Treatment Serve as Prevention?**

# HIV Prevention and MSM

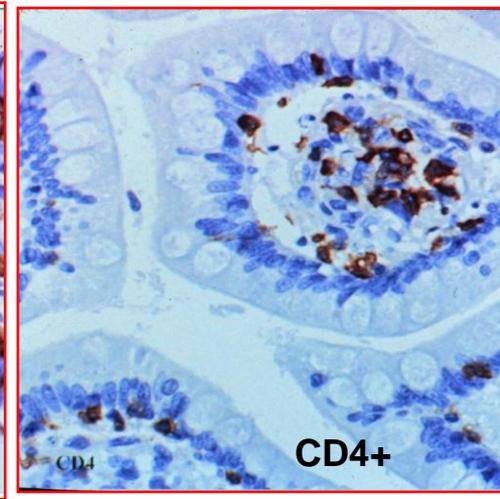
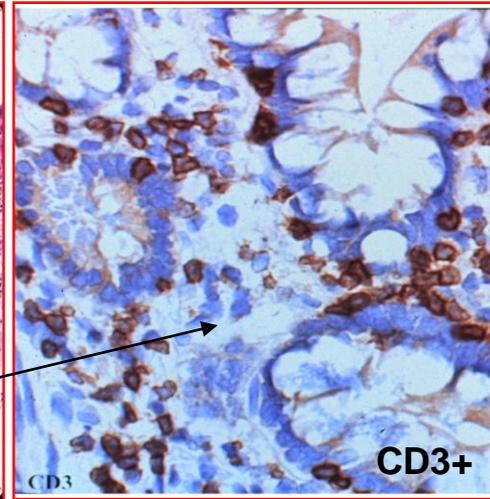
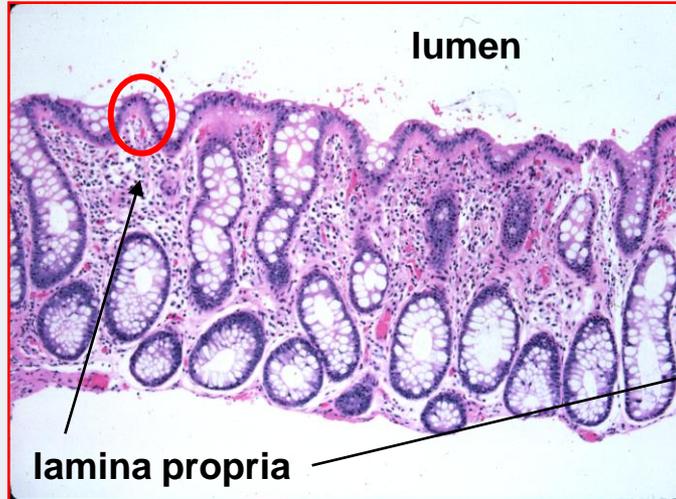
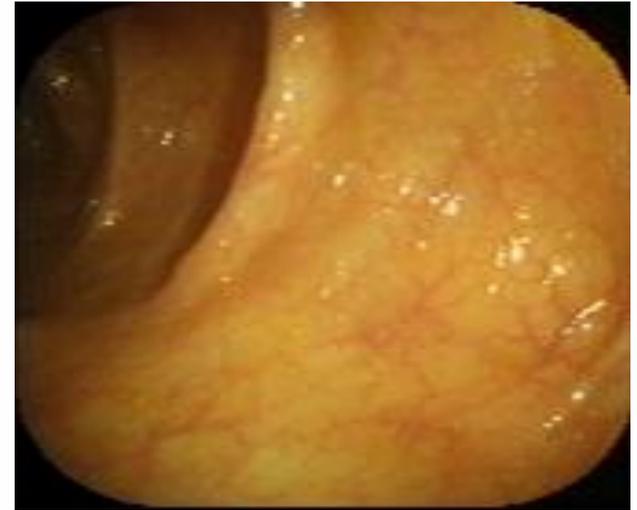
*Muessig, AIDS 2012; Wilson 2012; Philips 2012*

Increase in ART has not reduced HIV

- *ART does not stop anal transmission?*
- MSM on ART are not suppressed?
- Untested/untreated people?
  - increase in condom-less sex?

# Rectal HIV Prevention

Large, tubular surface area  
Physiologically dynamic  
Physiologically inflamed  
Protective mucus, bacterial, innate systems  
Single cell epithelia  
**Easily damaged *and* repaired**  
**Unique pharmacology**  
*Patterson et al. Sci Trans Med*



# HIV Prevention and MSM

*Muessig, AIDS 2012; Wilson 2012; Philips 2012*

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# Treatment as Prevention

## Clues from Observational Studies

An “imperfect” intervention may be sufficient?

*Tanser et al. Science 2013*

And yet randomized clinical trials for “proof”??

- **HPTN071 (POPART)**
- CDC Botswana
- ANRS Africa Center

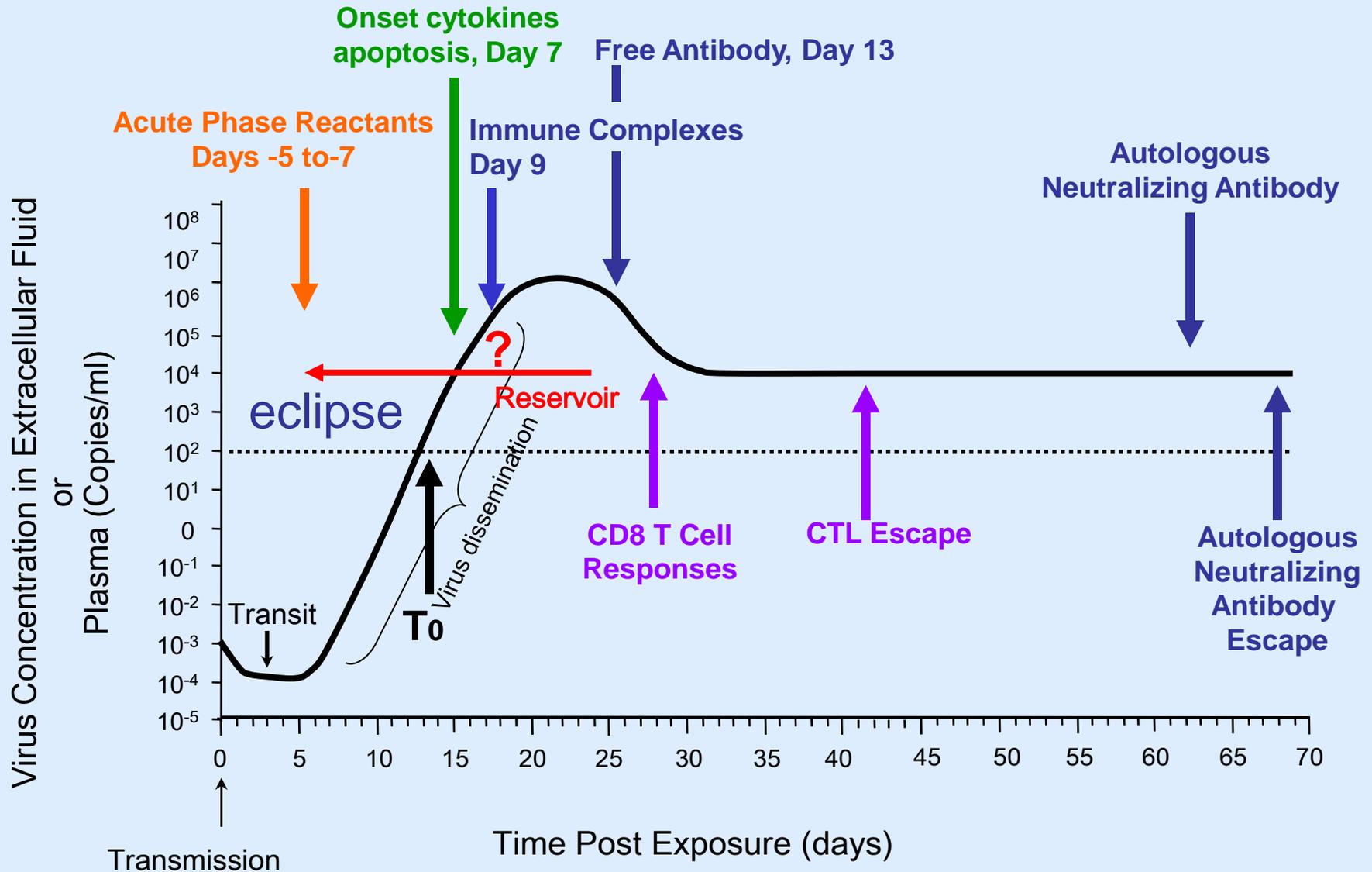
# Why Are We Unsure?

*Cohen Lancet (in press)*

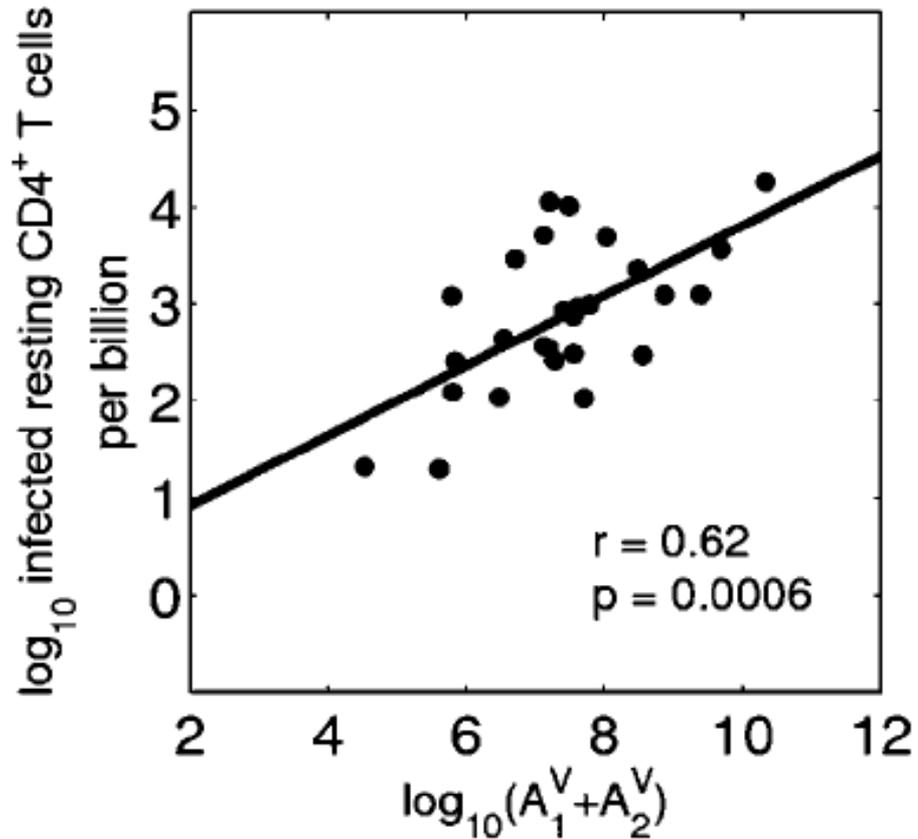
- Very considerable logistical challenges
- Acute HIV infection
- History repeats itself

# Acute HIV-1 Infection

Cohen et al, NEJM, 2011



# Reservoir Size in Treated AHI



# Possible HIV Eradication Strategies

*Margolis and Hazuda, Current Opinion HIV, 2013*

- “Kick and Kill” strategy with Vorinostat
- Argos dendritic vaccine
- Therapeutic DNA vaccine
- Cytotoxic T cell therapy
- Transplantation strategies

# Acute HIV Infection and RAPID CD4 Fall

*Novitsky et al. AIDS, 2011*

- 77 patients with acute HIV infection
- 34% >100,000 copies at set point
- CD4 fall <350 88 vs. 691 days!

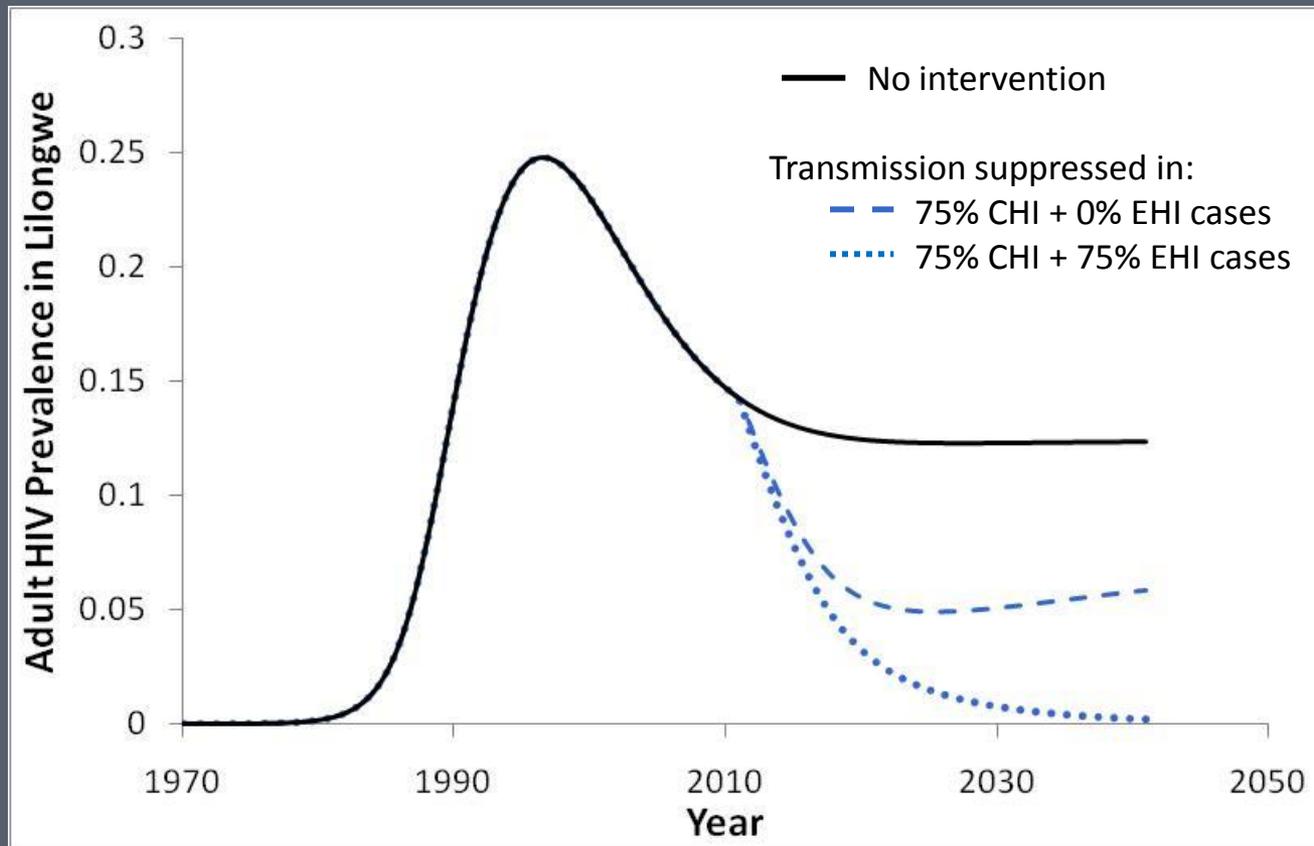
And failure to treat acute infection jeopardizes complete recovery of CD4 cell count, and allows some degree of harm

*Tuan et al. NEJM, 2013, Jain et al. JID, 2013*

# Treatment of Acute Infection

*Powers, Lancet 2011*

Assuming transmission is almost completely suppressed in 75% of CHI cases and 75% of EHI cases:





# **HIV Treatment is NOT Static**

- Before 1987, NO ART
- Before 1996, AZT alone
- 1996, triple drug therapy
- 2006, single daily dosing
- 2013, long acting agents
- 2015??

**THIS IS GOOD NEWS!**

# But..History Repeats Itself

**We have been here before**

TasP for Tuberculosis  
*Tubercle Editorial, late 1950s*

TASP for syphilis  
*“No Magic Bullet”, Allan Brandt*  
*“Syphilis in China”, Cohen et al. JID 1995*

# Treatment as Prevention

**AXIOM: ART improves health, blocks transmission**  
BUT the AIDS Free Generation is only an aspiration

## The Challenge

- Humility as we go forward, *but with confidence*
  - remember, HIV is the most studied pathogen in history!
- Redouble research and implementation efforts NOW
- Identify and focus on the most critical questions
- Prepare for a “long march”: tenacity, tenacity, tenacity
- Failure is NOT an option