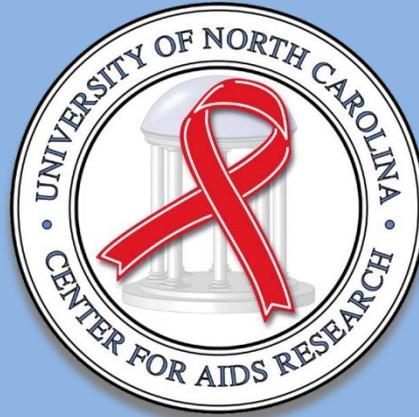


ART and HIV: Treatment as Prevention



Myron S. Cohen, MD

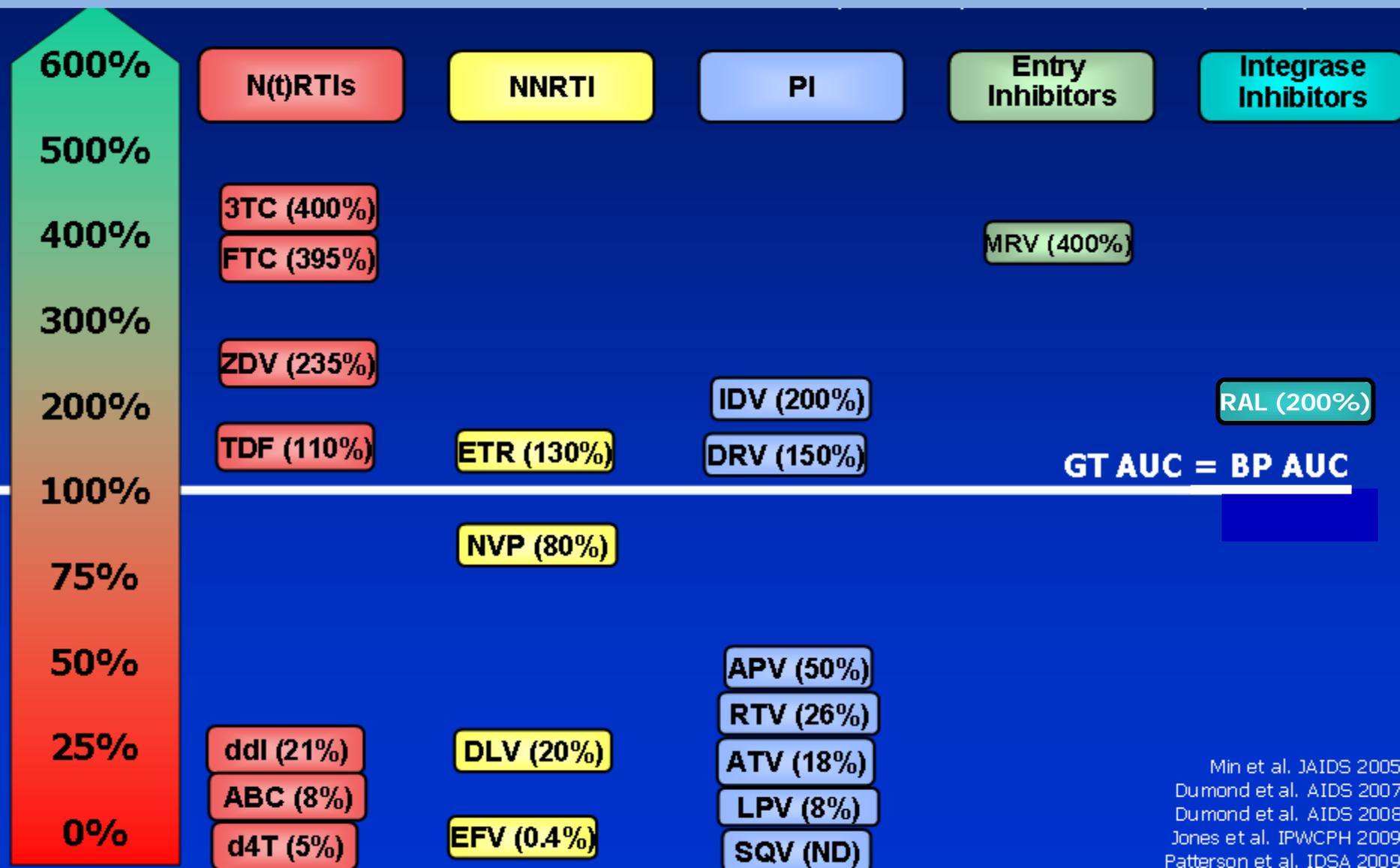
University of North Carolina

Treatment as Prevention

“The Four Questions”

- 1) How effective are the current ART regimens?
AND HOW WILL WE MAKE THEM MORE EFFECTIVE?
- 2) What do we tell couples and infected people?
-THE “SWISS STATEMENT” and its consequences
- 3) Can we expect reduced population HIV incidence from ART?
-Can this be measured and monitored?
- 4) What are barriers to “Treatment as Prevention”?
 - Linkage to care
 - Adherence to ART (...and which ART?)
 - HIV resistance (...reflecting drug selection and adherence)
 - Acute, early infection and/or high viral load

ART Drugs Penetrate the Genital Tract But With Different Concentrations and Half-life



AND... HIV Shedding Persists

- **Brown et al (meta-analysis, submitted)**
 - 422 articles, 707 abstracts, 18 ART
- **Cu-Uvin et al (AIDS, Sept. 2010)**
 - 59 women in a longitudinal study
 - endocervix, ectocervix, vagina sampled
 - 54% HIV detection WHEN blood VL<50 copies
 - 6.8% of women were “persistent shedders”

Treatment as Prevention

Discordant Couples?

POSITIVE RESULTS:

- Bunnell (JAIDS, 2007)
- Sullivan (IAS 2008)
- Donnell (Lancet, 2010)
- Romero (BMJ, 2010)

NEGATIVE RESULTS:

- Wang (IAS, 2010, JAIDS, in press)



HIV Treatment as Prevention

Sullivan et al. CROI, IAS 2009

- 2,993 couples studied 2002-2008
- 512 days follow-up (mean)
- 175 transmission events, and 4/175 when the index case was receiving ART!!

80% (?) reduced risk of HIV transmission

-counseling of discordant couples has an impact

-the risk of HIV with ART was NOT zero



The Henan Chinese Couples Study

Wang Lu et al. IAS Oct 2010, JAIDS

Cohen "Test and Treat: To be or not to be" JAIDS

Letters in press

- **1,927 discordant couples in Henan followed 2006-2008**
- **1,396 index cases receiving FREE ART**
- **84 seroconversions distributed equally among subjects on and off ART**
- **Will ART offer "REAL WORLD" benefit???**



Swiss Reduced Condoms Usage

Haase et al. CID, Nov 2010

Cohen, Editorial Comment, Nov 2010

- **7,309 patients (2007-09); >80% on ART**
- **Declining use of condoms during intercourse, in part ascribed to the “Swiss Statement”**
“In for a dime, in for a dollar”

HPTN 052: An RCT in Progress

- To demonstrate DURABLE benefit of ART in prevention of transmission of HIV
- To determine if delayed ART (CD4>250) is comparable to earlier ART (CD4>350<550)
- >1750 couples ENROLLED, entering year 3!!
- Interim analysis DSMB Nov.3, 2010
“No concerns were recognized to limit the integrity of the study”



ART and Population Benefit

- **Modeling, Modeling, Modeling**
 - Assumptions provide answers
- **An absence of empirical results**
 - What about ecological studies?



ART for Prevention: Assumptions=Results

Cohen and Gay, CID

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
<i>Granich (2009)</i>	<i>Universal annual HIV testing & immediate treatment</i>	<i>African HIV epidemic could be ended</i>

Ecological Studies and ART

- **Apparent benefit:**

San Francisco (PloS One, 2010)

British Columbia (Lancet, 2010)

- **No apparent benefit:**

Amsterdam

France

Australia

The measurement of an ecological effect is extremely difficult BECAUSE introduction of ART with benefit does not construe causation



An Ecological Study of ART... and many letters to the Lancet

THE LANCET

Association of highly active antiretroviral therapy coverage, 
population viral load, and yearly new HIV diagnoses in
British Columbia, Canada: a population-based study

*Julio S G Montaner, Viviane D Lima, Rolando Barrios, Benita Yip, Evan Wood, Thomas Kerr, Kate Shannon, P Richard Harrigan, Robert S Hogg,
Patricia Daly, Perry Kendall*

British Columbia and ART???

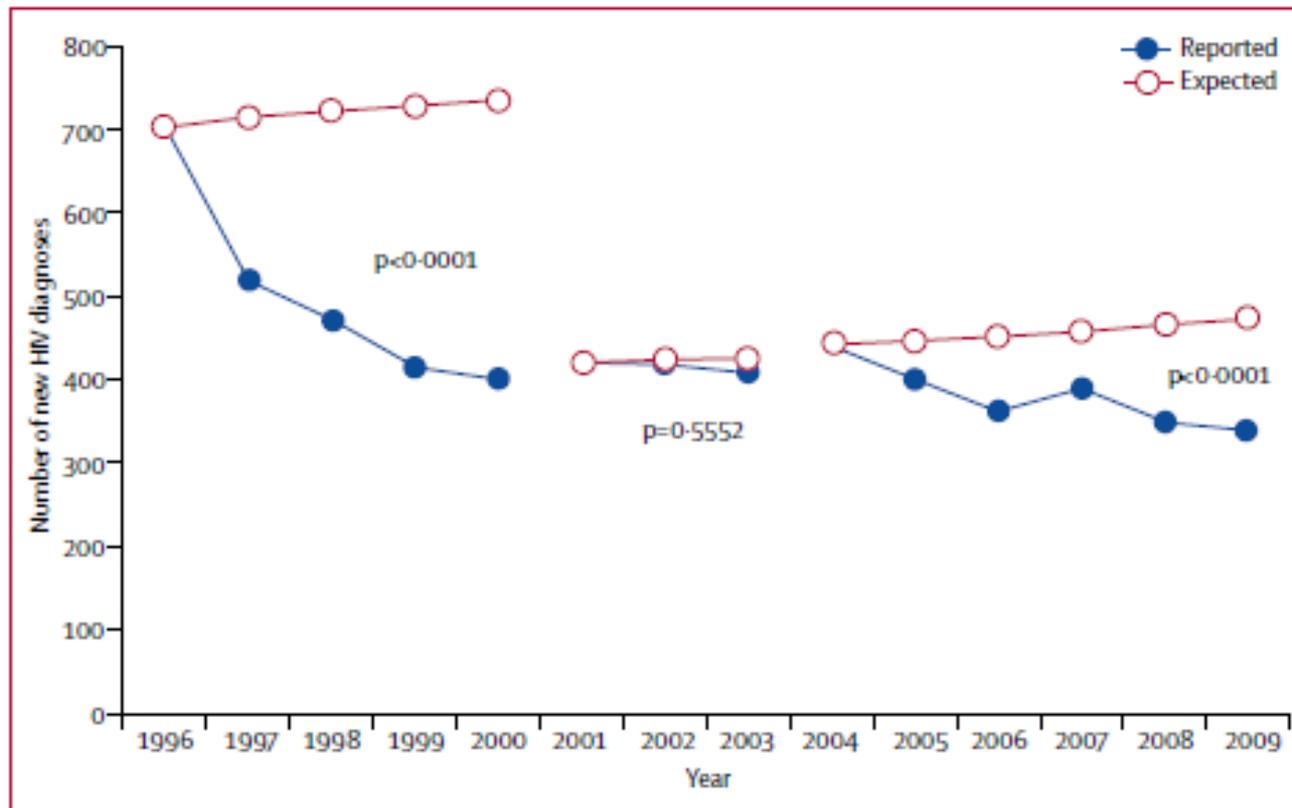


Figure 2: Reported and expected number of new HIV diagnoses per year in British Columbia, Canada, during the three phases of the study, 1996-2009

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.

Treatment as Prevention

The “Test and Treat” Movement

THE HORSE IS OUT OF THE BARN

- Botswana cohort MP3 pilot (*Essex*)
-Plos One Nov 2010
- US HPTN 062 in NYC, DC, (*El-Sadr, Mayer*)
- Population ART in Tanzania (*Fiddler, Hayes*)
- HPTN 064, Africa (*Hodder and others*)
- Kisumu, Kenya (*Little*)
- ANRS (*Dabas and others*)

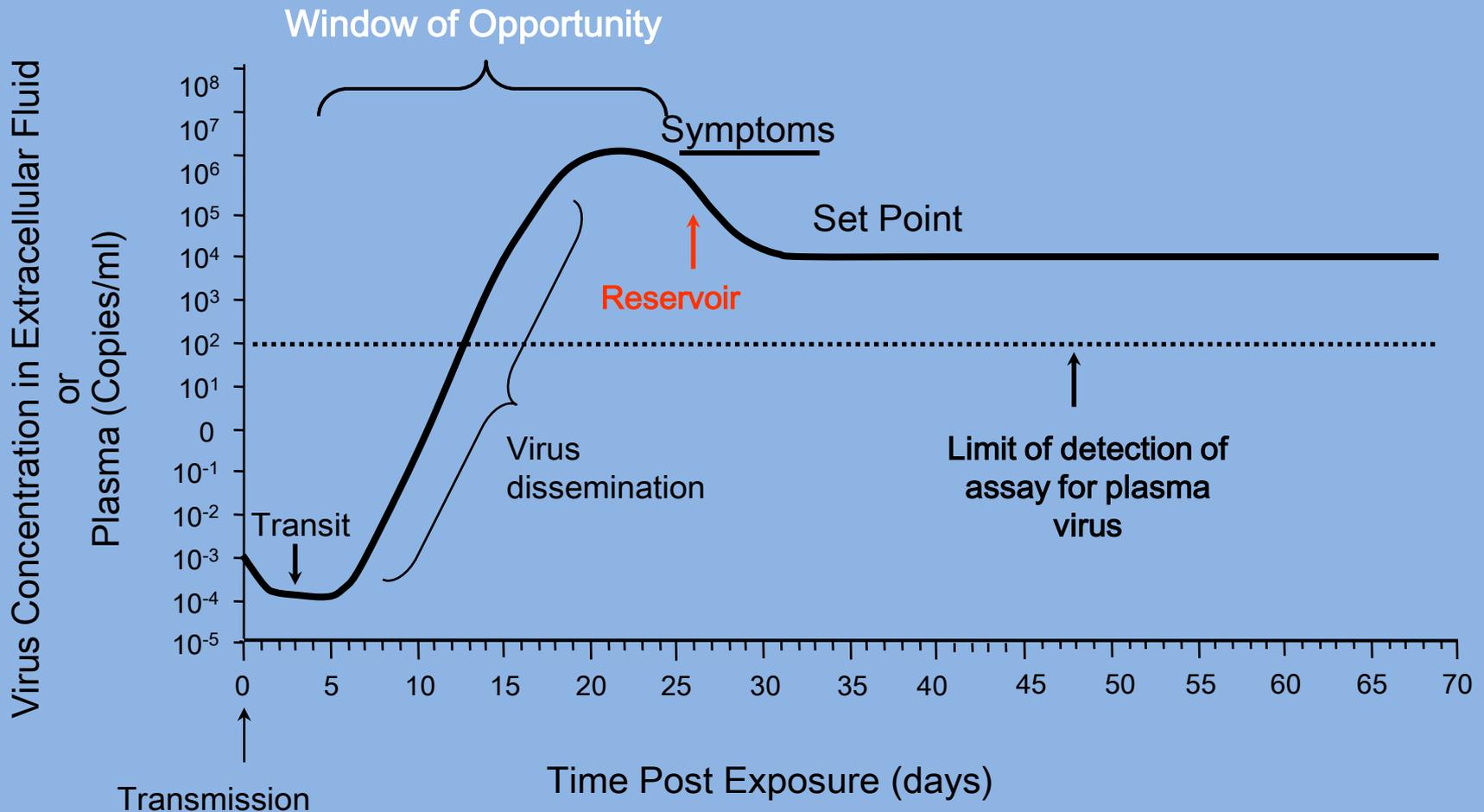
Treatment as Prevention

“Inconvenient Truths”

- **What is the role of acute and early infection?**
 - viral load, viral phenotype, host response?
- **Will drug resistant limit ART population benefit, or even threaten treatment?**

Acute HIV-1 Infection

McMichael et al Nature Imm 2009
Ma, J. Virology 2009 (SHIV)

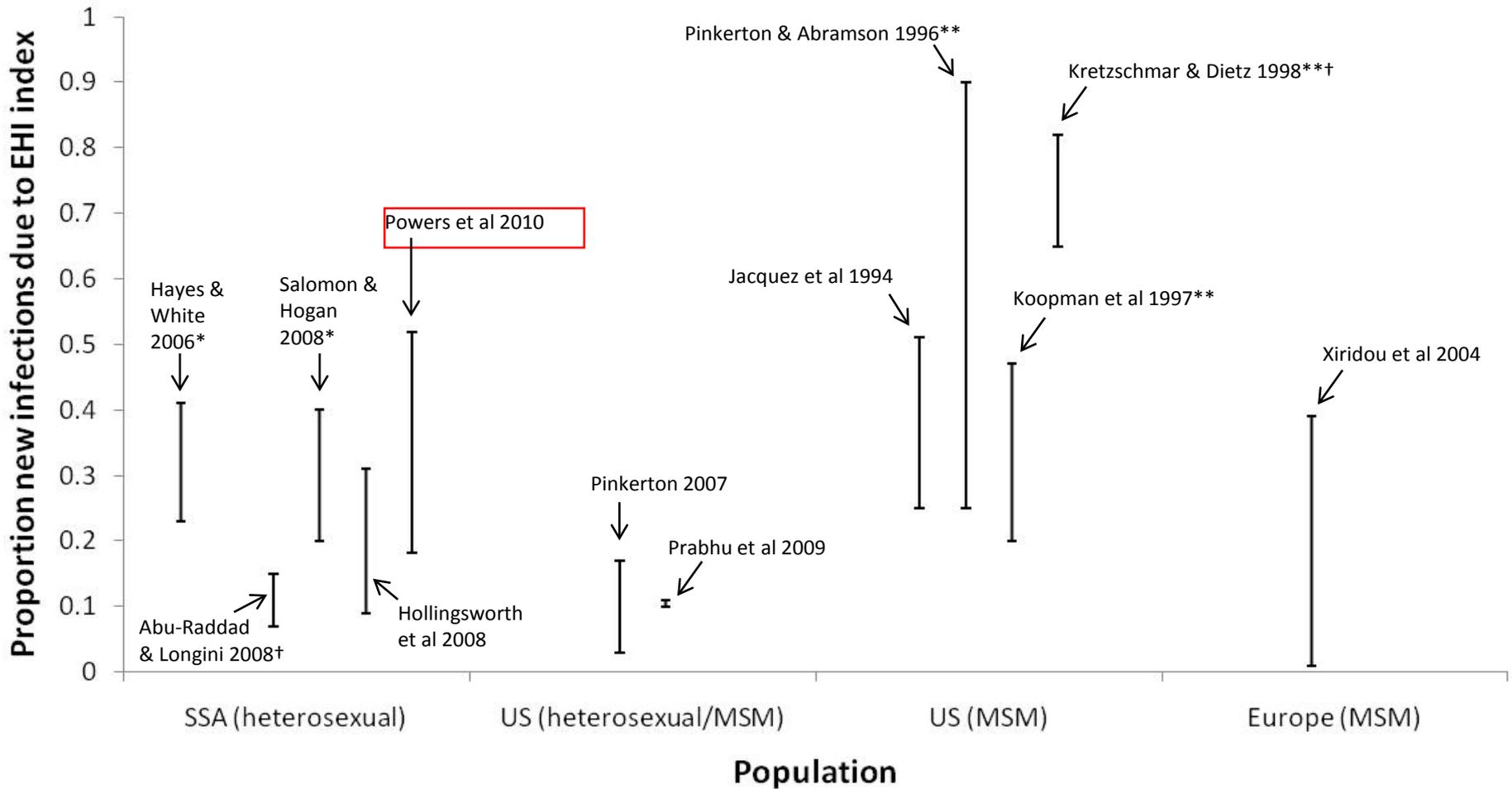


Acute HIV Infection Spreads HIV?

- HIV phylogenetic clusters “acute to acute”
 - Brenner et al in Montreal
 - Little et al in San Diego
 - Hurt in Chapel Hill



Predicting the Effect of Acute and Early HIV Infection on The Spread of Disease

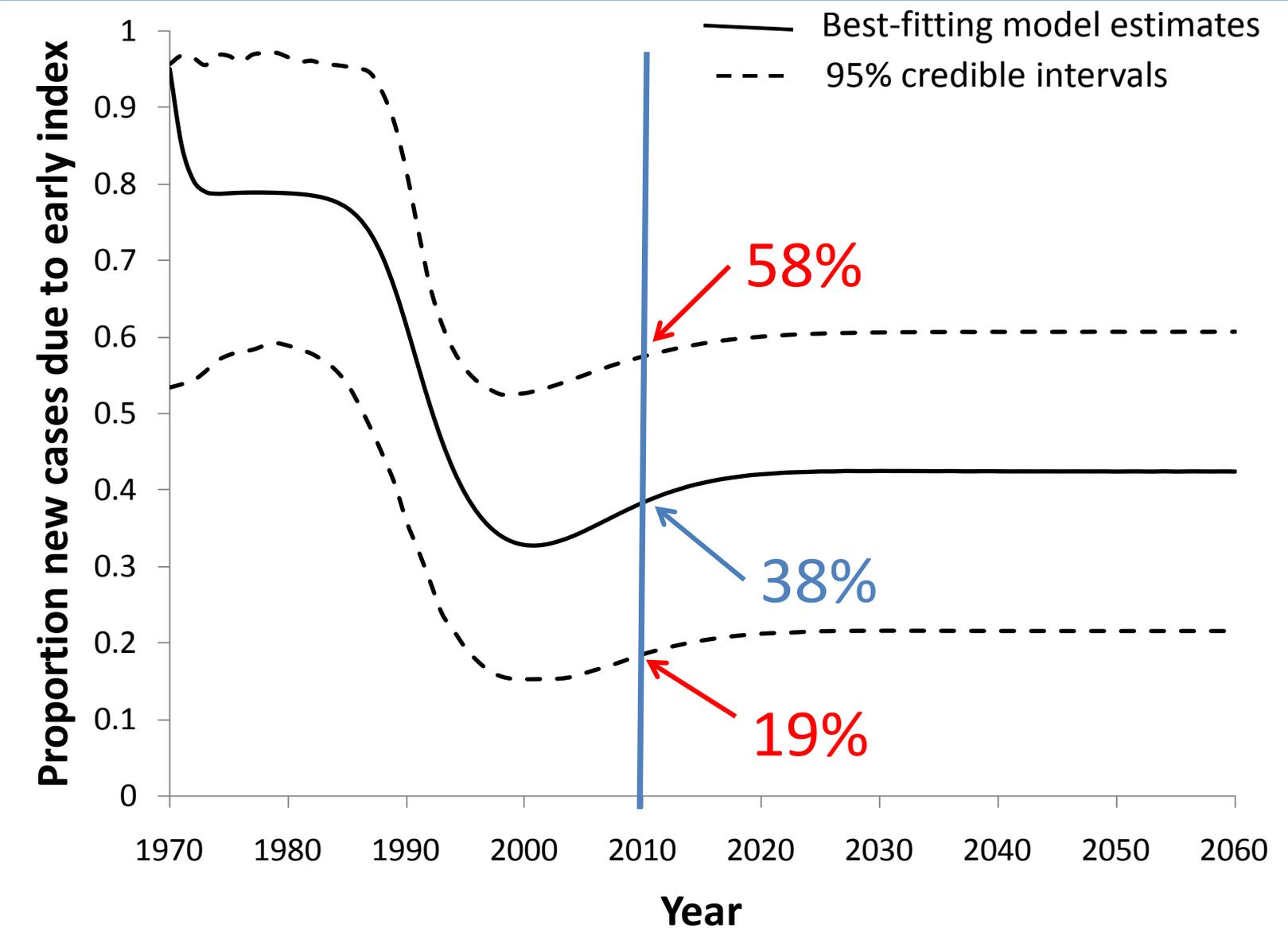


* Range of estimates reflects the proportion of all transmissions *during an individual's entire infectious period* that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI *at the population level* will depend on the epidemic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

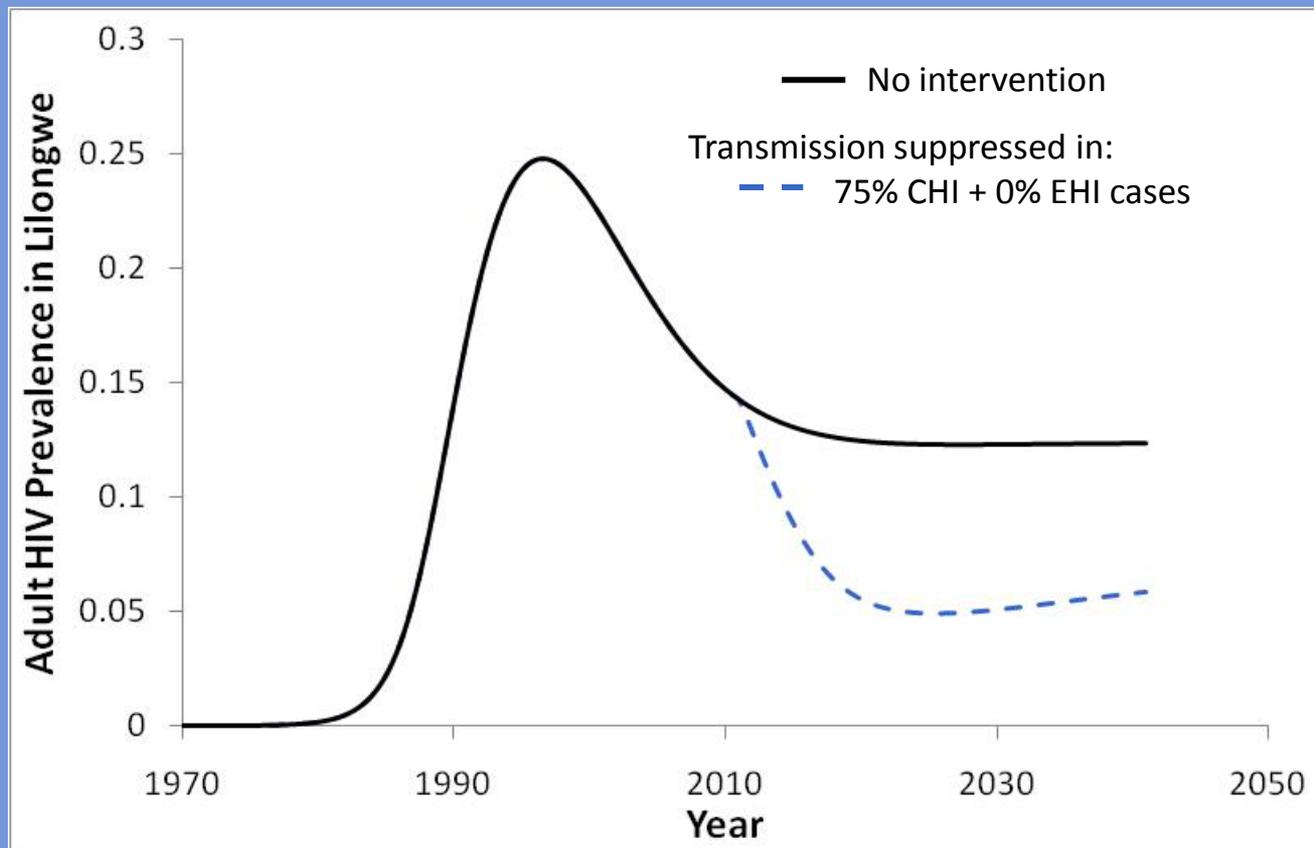
† The range of estimates shown was extracted from the endemic-phase portion of graphs showing the proportion of new infections due to EHI over calendar time.

Effect of Acute/Early Infection in Lilongwe, Malawi



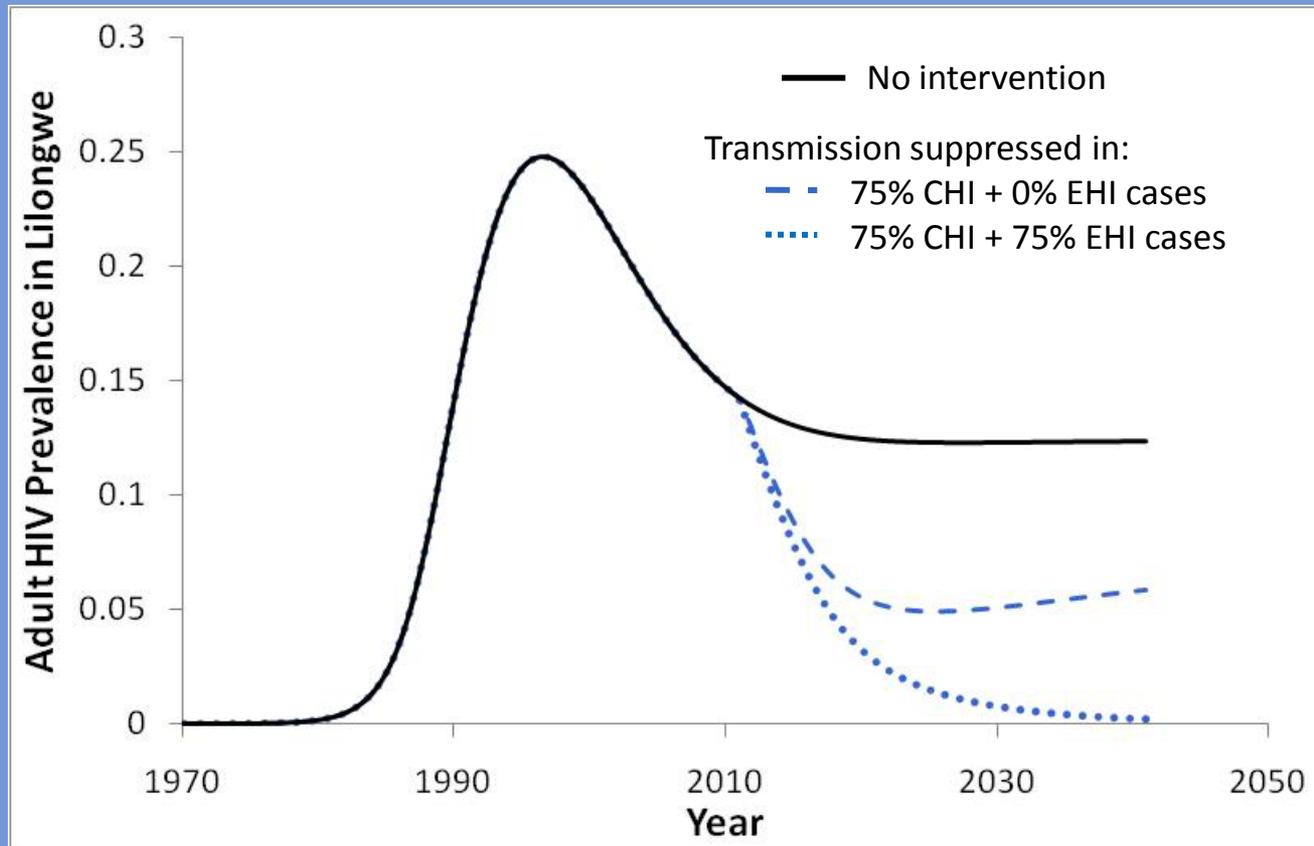
CHI-only Prevention Strategy

Assuming transmission is almost completely suppressed in 75% of CHI cases only (beginning to end of CHI):



75% CHI coverage, 75% EHI coverage

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



Benefits of treating AHI?

(adapted from Bell et al. JID 2010)

Rosenberg et al 2000

Virologic control

Desquilbet et al 2004

No difference in virologic control

Kaufmann et al 2004

Limited virologic control

Streeck et al 2006

No difference in virologic control

Hecht et al 2006

Mixed outcomes

Lampe et al 2007

Virologic control

Fidler et al 2007

Mixed outcomes

Steingrover et al 2008

Mixed outcomes

Pantazis et al 2008

No difference in viral load set point

Seng et al 2008

No CD4 cell count benefit

Prazuck et al 2008

Virologic control and CD4 cell count benefit

Goujard et al 2009

Virologic control

Volberding et al 2009

Virologic control

Koegl et al 2009

Mixed outcomes

Hogan et al 2010

Slower disease progression



Global HIV Vaccine
Enterprise



CHAVI
CENTER FOR HIV/AIDS VACCINE IMMUNOLOGY

National Institute of Allergy and Infectious Diseases



Treatment as Prevention

Drug Resistance?

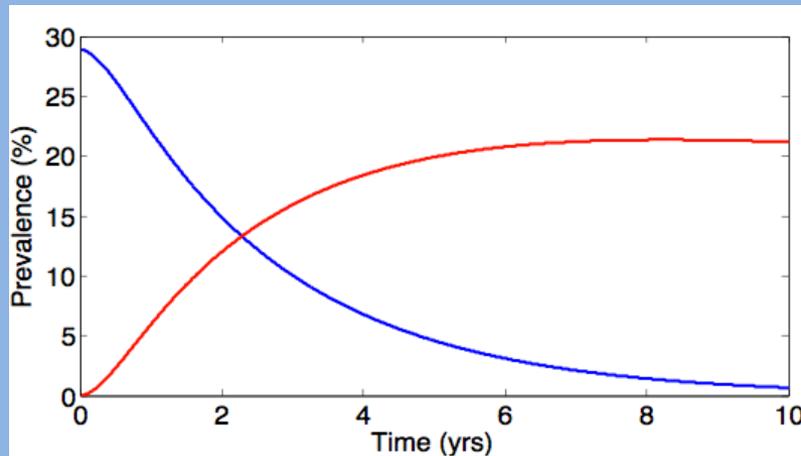
- Transmitted drug resistance is easily detected
 - "fitness cost" will limit the impact?
- Mathematical modeling is cautionary

Test and Treat, and Drug Resistance?

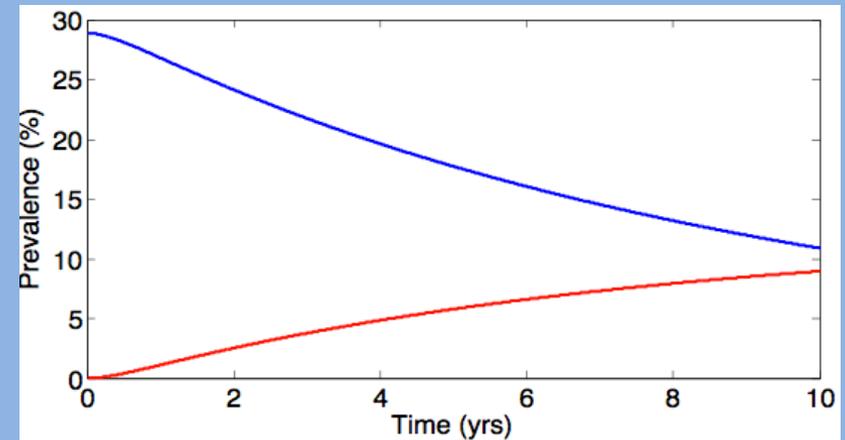
Based on Granich *et al.* (Lancet, 2009) assumptions:

- 95% treatment rate
- Individuals with undetectable viral loads are non-infectious

**Moderate adherence
(70% of daily doses)**



**High adherence
(95% of daily doses)**



Notably: prevalence of drug resistance is highest at moderate levels of adherence

Test and Treat

Conclusions 2010

- ART has the power to reduce transmission of HIV, but the magnitude is unknown
- The population benefit of ART will depend on
 - durable transmission suppression
 - preventing transmitted resistance
 - dealing with acute HIV infection
- *We ought to commit resources to the essential research to DEVELOP treatment as prevention, avoiding the pitfalls of hyperbole and wishful thinking*

