

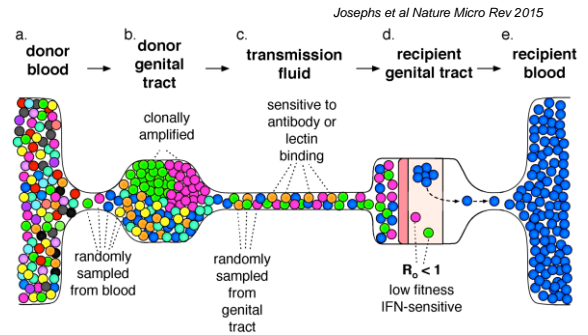
Treatment to Prevent HIV: Does Timing Matter?



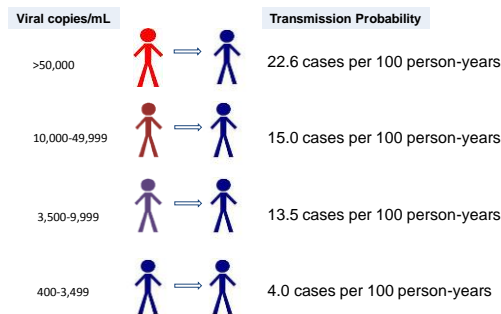
Myron S. Cohen, MD

Yeagan-Bate Eminent Professor
Medicine, Microbiology and Epidemiology
Director, Institute for Global Health & Infectious Diseases

Transmission of HIV



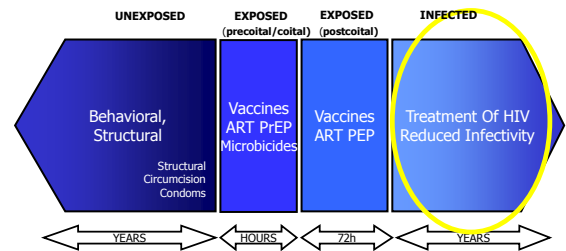
HIV Transmission and Viral Load: IS there a "maximal" level????



Quinn T (2001) N Engl J Med

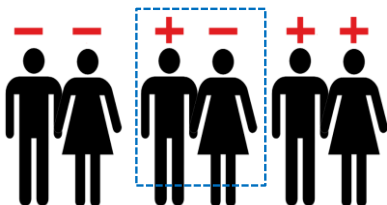
Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008



A Simple Prevention Idea

Reduce HIV in genital secretions with ART!
HIV prevention in discordant couples?



HPTN 052 Study Design (2007)

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 Enrollment (Total Enrollment: 1763 couples)



THE NEW ENGLAND JOURNAL OF MEDICINE

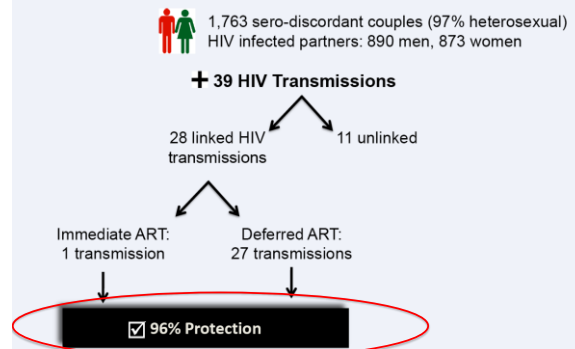
ORIGINAL ARTICLE

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*

Cohen, NEJM. 2011; 365:6

HPTN 052 Study: Key Finding



THE LANCET Infectious Diseases

Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial

Beatriz Grinsztejn, Mina C Hosseinipour, Heather J Ribaudo, Susan Swindells, Joseph Eron, Ying Q Chen, Lei Wang, San San Ou, Majja Anderson, Marybeth McCauley, Theresa Gamble, Nagalingeswaran Kumarasamy, James G Hakim, Johnstone Kumwenda, Jose H S Pilotto, Sheela V Godbole, Suwat Chariyalertsak, Marcinde Gonçalves de Mota, Kenneth H Mayer, Susan H Eshleman, Estelle Piwowar-Manning, Joseph Makhema, Lisa A Mills, Ravindra Panchia, Ian Sanne, Joel Gallant, Irving Hoffman, Taha E Taha, Karin Nielsen-Saines, David Celentano, Max Essex, Diane Havlir, Myron S Cohen, and the HPTN 052-ACG Study Team*

Grinsztejn, Lancet Infect Dis. 2014; 14:281

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



Bruce Alberts,
editor of Science



HIV-Infected Participants in HPTN 052

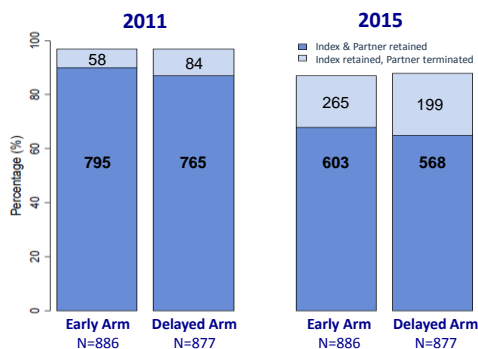
2010: 1,763 enrolled (HIV-infected)

2011: 1,642 remained in the trial (96%)
-All infected subjects offered ART

2015: 1,535 remained in the trial (87%)

Overall: 9,822 person-years follow-up

Retention of Couples in HPTN 052



Partner Infections (ITT)

	April 2005 - May 2011			May 2011 - May 2015			Overall		
	CY t/u	All partner infections # (rate)	Linked partner infections # (rate)	CY t/u	All partner infections # (rate)	Linked partner infections # (rate)	CY t/u	All partner infections # (rate)	Linked partner infections # (rate)
Total	3482	46 (1.32)	37 (1.06)	5012	32 (0.64)	9 (0.18)	8494	78 (0.92)	46 (0.54)
Early arm	1751	4 (0.23)	1 (0.06)	2563	15 (0.59)	2 (0.08)	4314	19 (0.44)	3 (0.07)
Delayed arm	1731	42 (2.43)	36 (2.08)	2449	17 (0.69)	7 (0.29)	4180	59 (1.41)	43 (1.03)
Rate ratio		0.09	0.03		0.86	0.28		0.31	0.07
Risk reduction		91%	97%		14%	72%		69%	93%

Rate = # of events/ 100 PY
Risk reduction = 1 - rate ratio

Linked = index to partner transmission

Explaining Linked Partner Infections

8 linked partner infections diagnosed AFTER the index partner started ART: WHY?

4 infections were diagnosed soon after the index partner started ART; these infections likely occurred before or soon after ART initiation

4 infections occurred after the index failed ART

NO INFECTIONS WERE OBSERVED WHEN HIV REPLICATION WAS SUPPRESSED

NOT SO FAST

BIG BARRIERS:

"When to Start" ART?

Acute/Early HIV infection?

The Economist, June 2011



START ART NOW!!!

IAS-USA; DHHS Guidelines

- HIV replication has negative consequences
- Earlier ART prolongs survival
- ART blocks HIV transmission

CIPRA HAITI, NEJM 2010

HPTN 052, NEJM 2011, Lancet ID 2014

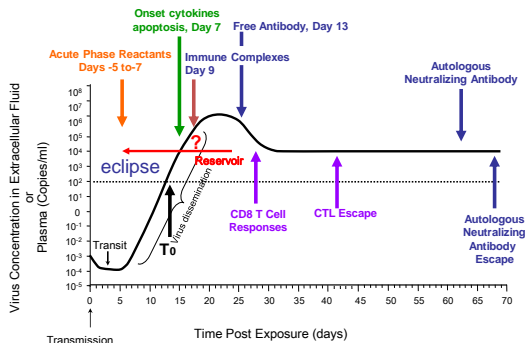
"TEMPERANO" NEJM 2015

"START" NEJM 2015

UNIVERSAL TEST AND TREAT (WHO 2015)!!!!

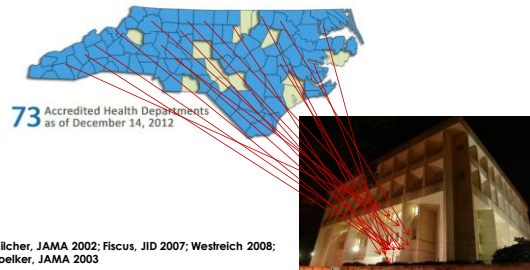
Acute HIV-1 Infection

Cohen et al, NEJM, 2011



SCREENING FOR AHI IN NC

Assuring the health of North Carolina through local health department accreditation



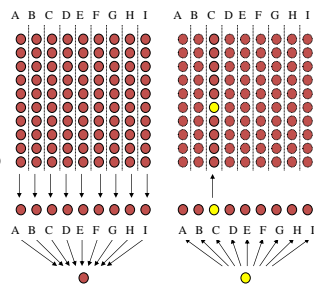
¹Pilcher, JAMA 2002; Fiscus, JID 2007; Westreich 2008; Voelker, JAMA 2003

DETECTION OF HIV RNA BEFORE SEROCONVERSION

90 individual HIV antibody negative specimens

9 intermediate pools (10 specimens)

1 master pool (90 specimens)



SCREENING FOR AHI 2003-2012

- 1,799,865 HIV results reported from the NC SLPH
- 6634 (0.4%) diagnosed with established HIV
- 235 (0.01%) confirmed to have AHI
- Overall, AHI represents 3.4% of HIV+ cases
- **Now, alternative third and fourth generation ag/ab assays for detection of acute HIV infection available**

Targeted HIV Screening

Powers et al. AIDS21:2237-42, 2007

	aPOR (95% CI)	Risk score
Self-reported behaviors/demographics		
>1 sex partner in past 2 mos	4.11 (1.10, 15.60)	1
Self-reported ARS symptoms		
Diarrhea in past month	4.69 (0.55, 24.54)	2
Fever in past month	2.28 (0.64, 7.48)	1
Body ache in past month	2.61 (0.70, 8.56)	1
Clinical examination findings		
Genital ulcer disease	6.04 (1.76, 21.59)	2
Discordant rapid-test results	41.04 (6.86, 191.08)	4

Acute HIV in African Clinics

Population	Prevalence	Reference
Malawi: STI clinic patients	1.1%-1.8%	Pilcher 2004 Powers 2007 Rutstein 2014
Uganda: Suspected malaria	0.8%	Bebell 2010
Mozambique: Fever	3.3%	Serna-Bolea 2010
South Africa: Outpatients	1.1%	Bassett 2011
Kenya: Fever and risk score	1.7%	Sanders 2014

CONSEQUENCES OF AHI

- Health Consequences
- Public Health Consequences

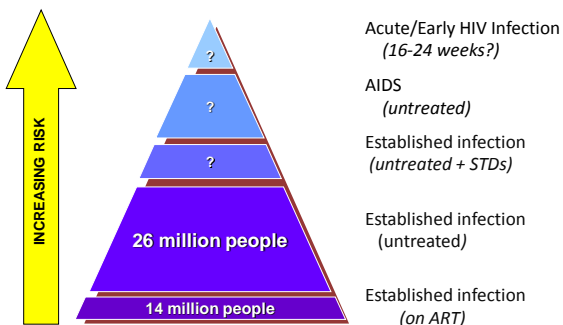
PNAS

Immediate antiviral therapy appears to restrict resting CD4⁺ cell HIV-1 infection without accelerating the decay of latent infection

Nancie M. Archin, Naveen K. Vaidya, JoAnn D. Kuruc, Abigail L. Liberty, Ann Wiegand, Mary F. Kearney, Myron S. Cohen, John M. Coffin, Ronald J. Bosch, Cynthia L. Gay, Joseph J. Eron, David M. Margolis, and Alan S. Perelson

Proc Natl Acad Sci USA. 2012 Jun 12;109(24):9523-8

HIV Transmission RISK???



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enhanced CD4⁺ T-Cell Recovery with Earlier HIV-1 Antiretroviral Therapy

Tuan Le, M.D., Dr.P.H., Edwin J. Wright, M.D., Davey M. Smith, M.D., Weijing He, M.D., Gabriel Catano, M.D., Jason F. Okulicz, M.D., Jason A. Young, Ph.D., Robert A. Clark, M.D., Douglas D. Richman, M.D., Susan J. Little, M.D., and Sunil K. Ahuja, M.D.

N Engl J Med. 2013 Jan 17;368(3):218-30

Clinical Trials of ART during Acute/Primary HIV Infection followed by ART Interruption

Published Studies	Viremic control
VISCONTI (n=32) ART during PHI (Hocqueloux L, AIDS 2010)	15.6% had VL < 50 for > 6 years
Swiss HIV Cohort Study (n=32) ART during acute vs. Chronic HIV (Gianella S, Antiviral Therapy 2011)	3 of 32 (9%) had VL < 50 at 1 year
Primo-SHM (n=173) No ART vs. 24 weeks vs. 60 weeks ART (Grijnsen ML, PLoS Medicine 2012)	4 of 79 (5%) in ART arms had VL < 100 at wk 24
ANRS CO6 PRIMO (n=164) ART during PHI (Goujard C, Antiviral Ther 2012)	VL < 50 11% at 1 year, 8.5% at 2 years
CASCADE (n=259) ART during PHI (Lodi S, Arch Intern Med 2012)	VL < 50 8.2% at 1 year and 5.5% at 2 years

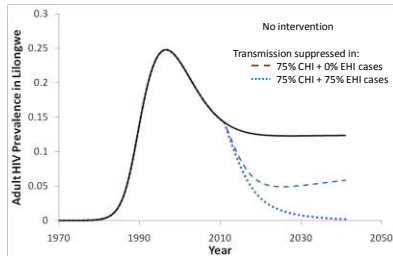
Transmission Related to Early HIV

Study	Population / Setting	Early HIV definition	% new cases due to early HIV
Yerly (2001)	Mixed/Switzerland	First 3-12 months	29%
Pao (2005)	Mostly MSM/UK	First 6 months	34%
Brenner (2007)	Mixed/Quebec	First 6 months	49%
Lewis (2008)	MSM/UK	First 6 months	25%
Wilson (2009)	MSM/Australia	First 3-9 months	19%
Fisher (2010)	MSM/UK	First 6 months	27%
Bezemer (2010)	MSM/Netherlands	First 7 months	25%
Leigh Brown (2011)	MSM/UK	First 6 months	20% of those in large clusters
Ambrosioni (2012)	Mixed/Switzerland	First 12 months	?
Little (2014)	Mostly MSM/San Diego	First 6 months	52%

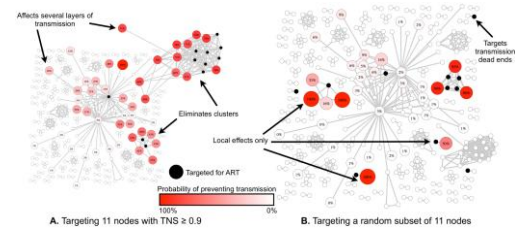
Treatment as Prevention in Malawi

Powers et al. *Lancet*, 2011

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



ART Targeting in Networks



ART initiated <12 weeks after infection resulted in less transmission than initiation later in infection.

Targeting ART to individuals with highest transmission network score is much more effective than targeting ART to individuals at random.

Little et al., *PLOS One*, 2014

PLOS MEDICINE

Review

HIV Treatment as Prevention: Debate and Commentary—Will Early Infection Compromise Treatment-as-Prevention Strategies?

Cohen MS, Dye C, Fraser C, Miller WC, Powers KA, Williams BG. *PLoS Med.* 2012;9(7):e1001232.
doi:10.1371/journal.pmed.1001232.

AHI & ENDLESS DEBATE

Programmatic implications of acute and early HIV infection

Suthar, Granich, Montaner, Williams, *JID* Aug 26, 2015 epub

Higher viral load matters (or not)?

Cluster growth matters (or not)?

AHI compromises TasP...(or not)?

Treatment as Prevention Trials

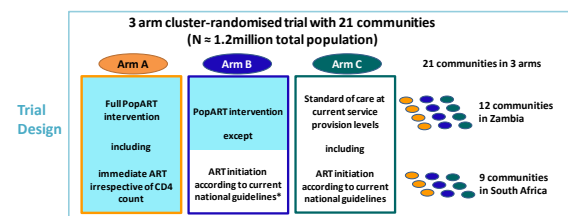
Cohen et al. *Lancet*, 2013

- HPTN071 (POPART)
- CDC Botswana
- ANRS Africa Center
- SEARCH Uganda
- *New South Wales (a new study)*

...and many smaller studies



Primary objective: Measure the impact of PopART intervention on HIV incidence



- Average population of ~50,000 in each cluster (~50% adults)
- Intervention delivered annually, door-to-door by field workers
- Incidence measured in *Population Cohort (PC)*: (52,000 individuals) 2,500 adults in each cluster, followed up after 1, 2 and 3 years

