HIV Treatment as Prevention

Myron S. Cohen, MD
Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008

BEHAVIORAL, STRUCTURAL
- Structural
- Circumcision
- Condoms

VACCINES
- ART PrEP
- Microbicides

EXPOSED (precoital/coital)

VACCINES
- ART PEP

EXPOSED (postcoital)

INFECTED
- Treatment Of HIV
- Reduced Infectivity

YEARS

HOURS

72h

YEARS
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 Suppresses HIV in Semen: Biological Plausability

Vernazza, Cohen et al., AIDS, 2000
Development of HPTN 052

- 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/mm³

Randomization

Immediate ART
CD4 350-550

Delayed ART
CD4 <250

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

10,838 Individuals Screened

Major reasons for exclusion:
- 3058 HIV+ but CD4 count out of range
- 2565 HIV- but HIV+ partner ineligible
- 308 Seroconcordant couples
- 155 Ineligible due to sexual history

1763 Couples (3526 Individuals) Randomized

Immediate Arm
- 886 Couples

Delayed Arm
- 877 Couples
HPTN 052 Enrollment
(Total Enrollment: 1763 couples)
# HPTN 052 Enrollment

<table>
<thead>
<tr>
<th>Region</th>
<th>Site</th>
<th>Couples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas</td>
<td>Porto Alegre, Brazil</td>
<td>90</td>
</tr>
<tr>
<td>(278)</td>
<td>Rio de Janeiro, Brazil</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>Boston, United States</td>
<td>2</td>
</tr>
<tr>
<td>Asia</td>
<td>Chennai, India</td>
<td>250</td>
</tr>
<tr>
<td>(531)</td>
<td>Pune, India</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td>Chiang Mai, Thailand</td>
<td>106</td>
</tr>
<tr>
<td>Africa</td>
<td>Gaborone, Botswana</td>
<td>77</td>
</tr>
<tr>
<td>(954)</td>
<td>Kisumu, Kenya</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Blantyre, Malawi</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Lilongwe, Malawi</td>
<td>251</td>
</tr>
<tr>
<td></td>
<td>Johannesburg, South Africa</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Soweto, South Africa</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Harare, Zimbabwe</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>1763</strong></td>
</tr>
</tbody>
</table>
# HPTN 052: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Index</th>
<th></th>
<th></th>
<th>Partner</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate</td>
<td>Delayed</td>
<td>Immediate</td>
<td>Delayed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 886</td>
<td>N = 877</td>
<td>N = 893</td>
<td>N = 882</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49%</td>
<td>50%</td>
<td>49%</td>
<td>47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (median)</td>
<td>33</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>94%</td>
<td>95%</td>
<td>93%</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any unprotected sex</td>
<td>6%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA log_{10} (median [IQR])</td>
<td>4.4 [3.8-4.9]</td>
<td>4.4 [3.9-4.9]</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
</tbody>
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<tr>
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<tr>
<td></td>
<td>Immediate (N = 886)</td>
<td>Delayed (N = 877)</td>
</tr>
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</tr>
<tr>
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<td>33</td>
<td>32</td>
</tr>
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</tr>
</tbody>
</table>
“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

Total HIV-1 Transmission Events: 39

Immediate Arm
4

Delayed Arm
35

p < 0.0001
THREE METHODS EMPLOYED
- Bootstrap analysis with pol gene
- Local statistical comparison
- NextGen (454) Sequences
HPTN 052: HIV-1 Transmission

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28
- Immediate Arm: 1
- Delayed Arm: 27

Unlinked or TBD Transmissions: 11
- 18/28 (64%) transmissions from infected participants with CD4 >350 cells/mm³
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

p < 0.001
HPTN 052: HIV-1 Transmission

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Follow-up (PY)*</th>
<th>Incidence/100PY [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Linked</td>
</tr>
<tr>
<td>Immediate</td>
<td>1585</td>
<td>0.1 [0.0 – 0.4]</td>
</tr>
<tr>
<td>Delayed</td>
<td>1567</td>
<td>1.7 [1.1 – 2.5]</td>
</tr>
</tbody>
</table>

*Person-years specific for transmission events

Median follow-up: 1.7 years
HPTN052: HIV-1 Transmissions

Linked HIV transmission

No. at Risk
Immediate 893 658 298 79 31 24
Delayed 882 655 297 80 26 22

All HIV transmission

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 log₁₀ 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

Index begins ART
AZT/3TC/EFV

Enrollment
Screening

Days -14 0 1

Index VL<400

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (immediate vs. delayed)</td>
<td>0.04</td>
<td>[0.01 - 0.28]</td>
</tr>
<tr>
<td>Baseline CD4 (per 100 CD4 Increment)</td>
<td>1.24</td>
<td>[1.00 - 1.54]</td>
</tr>
<tr>
<td>Baseline VL (per unit log increment)</td>
<td>2.84</td>
<td>[1.51 - 5.41]</td>
</tr>
<tr>
<td>Baseline condom use (100% vs. &lt;100%)</td>
<td>0.33</td>
<td>[0.12 - 0.91]</td>
</tr>
<tr>
<td>Gender (HIV +) (male vs. female)</td>
<td>0.73</td>
<td>[0.33 - 1.65]</td>
</tr>
</tbody>
</table>
HPTN 052: Consistent Use of ART

Proportion of participants with VL<400 at each visit

- Immediate Arm
- Delayed Arm (not on ART)
- Delayed Arm (on 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-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

<table>
<thead>
<tr>
<th>Event</th>
<th>Immediate</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Severe bacterial infection</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Chronic herpes simplex</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Bacterial pneumonia (recurrent)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* 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)

HR: 0.6 [0.4, 0.9], P=0.01

Failure Probability

Number at risk

- **Immediate**
  - Years since randomization:
    - 0: 873
    - 1: 880
    - 2: 697
    - 3: 316
    - 4: 85
    - 5: 31

- **Delayed**
  - Years since randomization:
    - 0: 880
    - 1: 698
    - 2: 331
    - 3: 84
    - 4: 35
    - 5: 28
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 HPTN 052 study protocol indicated antiretroviral treatment initiation.
The Economist

June 4, 2011

The end of AIDS?

How 5 million lives have been saved, and a plague could now be defeated
## ART for Prevention: Assumptions=Results

*Cohen and Gay, 2010*

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


- 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment for prevention</strong></td>
<td>96% (73; 99)</td>
</tr>
<tr>
<td>(Africa, Asia, America’s)</td>
<td></td>
</tr>
<tr>
<td><strong>PrEP for discordant couples</strong></td>
<td>73% (49; 85)</td>
</tr>
<tr>
<td>(Partners PrEP)</td>
<td></td>
</tr>
<tr>
<td><strong>PrEP for heterosexuals</strong></td>
<td>63% (21; 48)</td>
</tr>
<tr>
<td>(Botswana TDF2)</td>
<td></td>
</tr>
<tr>
<td><strong>Medical male circumcision</strong></td>
<td>54% (38; 66)</td>
</tr>
<tr>
<td>(Orange Farm, Rakai, Kisumu)</td>
<td></td>
</tr>
<tr>
<td><strong>PrEP for MSMs</strong></td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>(America’s, Thailand, South Africa)</td>
<td></td>
</tr>
<tr>
<td><strong>STD treatment</strong></td>
<td>42% (21; 58)</td>
</tr>
<tr>
<td>(Mwanza)</td>
<td></td>
</tr>
<tr>
<td><strong>Microbicide</strong></td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>(CAPRISA 004 tenofovir gel)</td>
<td></td>
</tr>
<tr>
<td><strong>HIV Vaccine</strong></td>
<td>31% (1; 51)</td>
</tr>
<tr>
<td>(Thai RV144)</td>
<td></td>
</tr>
</tbody>
</table>

The chart shows the efficacy of different interventions in preventing sexual HIV transmission, with effect sizes and confidence intervals provided.
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