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 Plausability

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

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 and VL >50,000 copies/ml at transmission
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

p < 0.001
A Transmission Event on ART

Swanstrom et al. PLOS One (in press)

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

Number of HIV-Infected Participants in Delay Arm

- Active Delay Arm Participants
- Notified of Study Results
- Initiated ART

Dictated by information about CD4 count
HPTN 052: Clinical Endpoints

Grinsztejn et al (in review)

Number of subjects experiencing ≥1 event

<table>
<thead>
<tr>
<th>Event</th>
<th>Delayed</th>
<th>Immediate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>34 (4%)</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Serious bacterial infection</td>
<td>13 (1%)</td>
<td>20 (2%)</td>
</tr>
<tr>
<td>WHO Stage 4 event</td>
<td>19 (2%)</td>
<td>9 (1%)</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HIV-related encephalopathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Herpes simplex, chronic</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CNS Lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HIV Wasting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
HIV-1 RNA and CD4 Over Time (ITT)

CD4 (cells/mm$^3$)

Immediate

Delayed

Proportion <400 copies/ml

Subjects contributing data

Years since randomization

0 1 2 3 4

883 785 390 134 37

873 785 390 138 34
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
COHERERE Study 1998-2010

Relationship between current CD4 and AIDS-defining illness with a CD4 count ≥500 cells/μL: relationship with current viral load and antiretroviral treatment

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>ARV naive</th>
<th>First 6 mo cART</th>
<th>VL &lt; 400</th>
<th>VL ≥ 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>2271 648 265</td>
<td>522 145 73</td>
<td>626 144 52</td>
<td>1191 407 170</td>
<td>1030 242 92</td>
</tr>
</tbody>
</table>

![Graph showing the relationship between CD4 counts and different patient groups with viral load (VL) values.](chart)

A. Mocroft, et al., Oxford Journal, August 2013
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
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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*

- **Transmission**
- **Virus Concentration in Extracellular Fluid or Plasma (Copies/ml)**
- **Time Post Exposure (days)**

**Key Events**
- **T0**
- **Reservoir**
- **Eclipse**
- **Onset cytokines apoptosis, Day 7**
- **Free Antibody, Day 13**
- **Immune Complexes Day 9**
- **CD8 T Cell Responses**
- **CTL Escape**
- **Acute Phase Reactants Days -5 to -7**
- **Autologous Neutralizing Antibody**
- **Autologous Neutralizing Antibody Escape**

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Reservoir Size in Treated AHI

\[ \log_{10} \text{infected resting CD4}^+ \text{ T cells} \]

\[ \log_{10}(A_1^V + A_2^V) \]

\[ r = 0.62 \]
\[ p = 0.0006 \]

Archin … Margolis, Cohen, Perelson PNAS 2012
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
Assuming transmission is almost completely suppressed in 75% of CHI cases and 75% of EHI cases:

Transmission suppressed in:
- 75% CHI + 0% EHI cases
- 75% CHI + 75% EHI cases

No intervention
HIV Treatment is NOT Static

• Before 1987, NO ART
• Before 1996, AZT alone
• 1996, triple drug therapy
• 2006, single daily doing
• 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