Treatment to Prevent HIV: Does Timing Matter?

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Medicine, Microbiology and Epidemiology
Director, Institute for Global Health & Infectious Diseases

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

<table>
<thead>
<tr>
<th>Viral copies/mL</th>
<th>Transmission Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50,000</td>
<td>22.6 cases per 100 person-years</td>
</tr>
<tr>
<td>10,000-49,999</td>
<td>15.0 cases per 100 person-years</td>
</tr>
<tr>
<td>3,500-9,999</td>
<td>13.5 cases per 100 person-years</td>
</tr>
<tr>
<td>400-3,499</td>
<td>4.0 cases per 100 person-years</td>
</tr>
</tbody>
</table>


A Simple Prevention Idea
Reduce HIV in genital secretions with ART!
HIV prevention in discordant couples?

Transmission of HIV
Josephs et al Nature Rev 2015

Four Prevention Opportunities
Cohen et al, JCI, 2008
Cohen IAS 2008

HPTN 052 Study Design (2007)
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
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

Prevention of HIV-1 Infection with Early Antiretroviral Therapy


Cohen, NEJM. 2011; 365:6

Grinsztejn, Lancet Infect Dis. 2014; 14:281
Retention of Couples in HPTN 052

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58%</td>
<td>84%</td>
</tr>
<tr>
<td>2015</td>
<td>795</td>
<td>765</td>
</tr>
<tr>
<td></td>
<td>285</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td>603</td>
<td>568</td>
</tr>
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</table>

Partner Infections (ITT)

<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td>CY (#)</td>
<td>All partner infections # (rate)</td>
<td>Linked partner infections # (rate)</td>
</tr>
<tr>
<td>Total</td>
<td>3482</td>
<td>37 (1.00)</td>
<td>46 (1.32)</td>
</tr>
<tr>
<td>Early arm</td>
<td>1751</td>
<td>1 (0.06)</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td>Delayed arm</td>
<td>1731</td>
<td>42 (2.43)</td>
<td>36 (2.08)</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>0.09</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>91%</td>
<td>97%</td>
<td>14%</td>
</tr>
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</table>

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

The Economist, June 2011

NOT SO FAST

BIG BARRIERS:

“When to Start” ART?
Acute/Early HIV infection?

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)!!!
Transmission Virus Concentration in Extracellular Fluid
or Plasma (Copies/ml)

Reservoir Transit eclipse

Immune Complexes Day 9
Autologous Neutralizing Antibody

Acute Phase Reactants
Days 5 to 7
CD8 T Cell Responses Day 8
CTLA escape

Onset cytokines apoptosis, Day 7
Fow Antibody, Day 13

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

73 Accredited Health Districts as of December 14, 2012

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

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<th>Population</th>
<th>Prevalence</th>
<th>Reference</th>
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<td>Malawi: STI clinic patients</td>
<td>1.1%-1.8%</td>
<td>Pilcher 2004</td>
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<td>Powers 2007</td>
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<td>Rutstein 2014</td>
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<td>Uganda: Suspected malaria</td>
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<td>Bebell 2010</td>
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<td>Mozambique: Fever</td>
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<td>Serna-Bolea 2010</td>
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<td>South Africa: Outpatients</td>
<td>1.1%</td>
<td>Bassett 2011</td>
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<tr>
<td>Kenya: Fever and risk score</td>
<td>1.7%</td>
<td>Sanders 2014</td>
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DETECTION OF HIV RNA BEFORE SEROCONVERSION

90 individual HIV antibody negative specimens

9 intermediate pools (10 specimens)

1 master pool (90 specimens)

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1 master pool (90 specimens)

DETECTION OF HIV RNA BEFORE SEROCONVERSION

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Acute HIV in African Clinics

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CONSEQUENCES OF AHI

• Health Consequences
• Public Health Consequences

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


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

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<th>Published Studies</th>
<th>Viremic control</th>
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<td>VISCONTI (n=32) ART during PHI (Hocqueloux L, AIDS 2010)</td>
<td>15.6% had VL &lt; 50 for &gt; 6 years</td>
</tr>
<tr>
<td>Swiss HIV Cohort Study (n=32) ART during acute vs. Chronic HIV (Giannella S, Antiviral Therapy 2011)</td>
<td>3 of 32 (9%) had VL &lt; 50 at 1 year</td>
</tr>
<tr>
<td>Primo-SHM (n=173) No ART vs. 24 weeks vs. 60 weeks ART (Gijsen ML, PLoS Medicine 2012)</td>
<td>4 of 79 (5%) in ART arms had VL &lt; 100 at wk 24</td>
</tr>
<tr>
<td>ANRS C06 PRIMO (n=164) ART during PHI (Goujard C, Antiviral Ther 2012)</td>
<td>VL &lt; 50</td>
</tr>
<tr>
<td>CASCADE (n=259) ART during PHI (Lodi S, Arch Intern Med 2012)</td>
<td>11% at 1 year, 8.5% at 2 years</td>
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Transmission Related to Early HIV

<table>
<thead>
<tr>
<th>Study</th>
<th>Population / Setting</th>
<th>Early HIV definition</th>
<th>% new cases due to early HIV</th>
</tr>
</thead>
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<tr>
<td>Yerly (2001)</td>
<td>Mixed/Switzerland</td>
<td>First 3-12 months</td>
<td>29%</td>
</tr>
<tr>
<td>Pao (2005)</td>
<td>Mostly MSM/UK</td>
<td>First 6 months</td>
<td>34%</td>
</tr>
<tr>
<td>Brenner (2007)</td>
<td>Mixed/Quebec</td>
<td>First 6 months</td>
<td>49%</td>
</tr>
<tr>
<td>Lewis (2008)</td>
<td>MSM/UK</td>
<td>First 6 months</td>
<td>25%</td>
</tr>
<tr>
<td>Wilson (2009)</td>
<td>MSM/Australia</td>
<td>First 3-5 months</td>
<td>19%</td>
</tr>
<tr>
<td>Fisher (2010)</td>
<td>MSM/UK</td>
<td>First 6 months</td>
<td>27%</td>
</tr>
<tr>
<td>Bezemere (2010)</td>
<td>MSM/Netherlands</td>
<td>First 7 months</td>
<td>25%</td>
</tr>
<tr>
<td>Leigh Brown (2011)</td>
<td>MSM/UK</td>
<td>First 6 months</td>
<td>20% of those in large clusters</td>
</tr>
<tr>
<td>Ambrosioni (2012)</td>
<td>Mixed/Switzerland</td>
<td>First 12 months</td>
<td>?</td>
</tr>
<tr>
<td>Little (2014)</td>
<td>Mostly MSM/San Diego</td>
<td>First 6 months</td>
<td>52%</td>
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Treatment as Prevention in Malawi


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

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.

AHI & ENDLESS DEBATE

Programmatic implications of acute and early HIV infection
Suthar, Granich, Montaner, Williams, JID Aug 26, 2015

Higher viral load matters (or not)?
Cluster growth matters (or not)?
AHI compromises TasP... (or not)?

Treatment as Prevention Trials


- 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

Trial Design

- 3 arm cluster-randomised trial with 21 communities (N = 1.2 million total population)
- 9 communities in South Africa
- 12 communities in Zambia
- 21 communities in 3 arms

- 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
Heartfelt thanks to all the many trainees and faculty that have worked with me and our group, and the many selfless volunteers who made our research possible.