ART and HIV: Treatment as Prevention

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Presented at the 5th International Workshop on HIV Transmission
Uses of ART for HIV Prevention


• Pre-exposure prophylaxis:
  - 21,000 subjects in PrEP trials
  - CAPRISA 004 on July, 19, 2010

• Post-exposure prophylaxis

• Treatment as prevention

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HIV TRANSMISSION PARADIGM

Infectivity
- Inoculum (concentration)
- Phenotypic factors

Susceptibility
- Hereditary resistance
- Innate resistance
- Acquired immunity

*communicability and virulence are two different concepts

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Treatment as Prevention

• Can ART *reliably* prevent HIV transmission?
• How should infected people/couples be counseled (based on the question above)?
• How important is acute infection to population spread of HIV (an “inconvenient truth”)?
• If ART results in population level prevention benefit(s) how can this ACTUALLY be proven?

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Treatment as Prevention: The Promise

• Biological plausibility (...incomplete)
• Discordant Couples (...sometimes)
• Ecological Studies (...sometimes)
• Modeling (...with just the right assumptions)
TITLE: ART FOR PREVENTION: Disclaimer

...I am a BIG ADVOCATE


CONCLUSION 1997 (AND 2011):
TREATMENT CAN BE DEVELOPED AS PREVENTION ..IF (BIG IF) WE PAY ATTENTION TO the DETAILS
BUT With ART HIV Shedding PERSISTS

• Semen (many studies...and we still don’t know THE SOURCE of the transmitted virus)
• Female genital Secretions (many, many studies...Cu-Uvin, AIDS in press, Brown et al)
• Does detection of HIV RNA copies suggest “infectious units”???

REMEMBER THESE ARE QUESTIONS THAT CAN EVOKE DRUG DISCOVERY
3 Distinct Patterns Observed Between Blood and Semen

Anderson et al. PLOS Pathogen (in press)
BUT With ART HIV Shedding PERSISTS

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ART Prevents HIV Transmission?

Five recent prospective observational cohort studies in discordant couples, mostly short term:

**POSITIVE RESULTS:**
- Bunnell (JAIDS, 2007)
- Sullivan (IAS 2008)
- Donnell (Lancet, 2010)
- Romero (BMJ, 2010)

**NEGATIVE RESULTS:**

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Spanish Couples Study 1998-2008

Romero et al, BMJ 2010

• 341 couples, no ART
  – 11,000 sexual exposures
  – 50 pregnancies
  – 5 seroconversions

• 144 couples, ART provided
  – 7,000 sexual exposures
  – 47 pregnancies
  – No seroconversions

The authors conclude condoms and ART offer substantial protection from seroconversion
HIV Treatment as Prevention

Sullivan et al. CROI, IAS 2009

- 2,993 couples studied 2002-2008
- 512 days follow-up (mean)
- 175 transmission events, but “only” 4 when the index case received ART
- Less risk behavior in the index case
- 80% reduced risk of HIV transmission
  i) counseling of discordant couples has an impact
  ii) risk of HIV with ART was NOT zero

Presented at the 5th International Workshop on HIV Transmission
Chinese Couples Study

Wang Lu et al. IAS 2010, JAIDS in press
Cohen “Test and Treat: To be or not to be” JAIDS in press

• 1,927 discordant couples in Henan followed 2006-2008
• 1,396 index cases receiving free ART
• 84 seroconversions distributed equally among this on and off ART
• Will ART offer “REAL WORLD” population benefit???
HPTN 052: An RCT in Progress

• To demonstrate DURABLE benefit of ART in prevention of transmission of HIV from an infected person to their sexual partner
• To determine if delayed ART (CD4>250 is comparable to earlier ART (CD4>350<550)
• 12 sites, 9 countries with more than 800 couples in Africa
• 1750 couples ENROLLED; entering year 2

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HPTN 052: A Brief History

- Extensive plausibility studies (1989-2000)
- 2000: AIDS Meeting in Durban- ART for Africa POSSIBLE?
- 2002: HPTN Planning Summit, Washington DC
- 2003-5: Protocol development; OBTAIN THE DRUGS!!
- 2005-6: HPTN052 Pilot completed (network recompetition)
- 2007: Trial enrollment begins
- April 16, 2010: Final target of 1750 couples ENROLLED!
HPTN052 and Industry

- 1750 people who need treatment
- ART costs >10,000/year (true cost)
- ART for 5 years minimum
- Industry contribution over 7 years: >$15,000,000
THINGS CHANGE

• NEW BELIEFS
  - TREATMENT IS PREVENTION, END OF STORY
  - EARLIER ART IS BETTER, END OF STORY

These beliefs dominate President Obama’s 2010 Plan
TEST AND TREAT?

• Not so Fast...
ART and Population Benefit

• Modeling, Modeling, Modeling
• The ASSUMPTIONS provide the answer
### ART for Prevention: Assumptions=Results

_Cohen and Gay, CID 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>
Ecological Studies and ART

• Apparent benefit:
  San Francisco (PloS One, 2010)
  British Columbia (CROI 2010)

• No apparent benefit:
  Amsterdam
  France
  Australia

*But...the measurement of an ecological effect is extremely difficult BECAUSE introduction of ART with benefit does not construe causation*
TEST AND TREAT??

Easier, less toxic, and more potent therapy..
Leads to part of the rationale for EARLIER ART
Earlier ART: The ACTUAL results

- The benefits of ART at CD4 200-350 in cohorts (n=4) are modest (HR=1.3)
  - CD4 effects are very unlikely to be linear, so CD4 250 may be very different than CD4 200
  - HPTN 052 is measuring something different than the cohort studies and may not see a difference in early vs. delayed ART
  - cohort studies from developed countries may not be entirely relevant to resource constrained studies
- CIPRA Haiti (NEJM, July 2010) reiterate the DANGER of CD4<200; “early” subjects started ART at median CD4=287
- Proving ART benefit at CD4 >500 will be difficult
Treatment As Prevention: The Concerns

1) ART does NOT reliably stop viral shedding in the male or female tract regardless of results in the blood viral load (Cu-Uvin, in press)
   • ART evokes resistance and it is possible that resistant variants will be transmitted
   • In the “real world” ART may not provide the transmission prevention expected (Wang)
   • Acute infection is a powerful force (Powers)
**Test & Treat:** predicted prevalence for Wild-Type (blue) & Drug-Resistant (red)

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

Bradley G. Wagner, Justin T. Okano, James S. Kahn and Sally Blower. “A ‘Test and Treat Strategy in South Africa is Likely to Lead to a Self-Sustaining Epidemic of Only NNRTI Resistant Strains’.”

17th Conference on Retroviruses and Opportunistic Infections, abstract #966.
Acute HIV Infection, ART and Prevention

Clusters of HIV spread in Montreal reflect early infections (to be presented by Wainberg)

Lilongwe, Malawi empirical results (to be presented by Powers)

~40% of HIV in Lilongwe can be ascribed to spread from subjects with AHI

-ART can only be maximally effective IF we can prevent transmission derived from subjects with AHI
Conclusions

• ART has the power reduce transmission of HIV, but the exact magnitude of ART transmission suppression and its durability are unknown.

• The population benefit of ART depends on:
  – durable transmission suppression
  – PREVENTING transmitted resistance
  – the contribution of acute HIV infection

WE KNOW HOW TO MAKE AND USE ART:
- Maternal-child transmission is <1% with ART
- PrEP and topical microbicides are moving forward GUIDED BY RESULTS(!!!) and very strong “plausibility infrastructure”

TEST AND TREAT OUGHT TO WORK IF WE AVOID HYERBOLE AND SHORTCUTS (WHICH ARE REAL THREATS) AND APPLY RIGOR TO THE CHALLENGE