HIV Treatment As Prevention?

Myron S. Cohen, MD

J. Herbert Bate Distinguished Professor
Medicine, Microbiology and Public Health
Director, Institute for Global Health & Infectious Diseases
Associate Vice Chancellor for Global Heath
Modeling???
# ART for Prevention: Assumptions Determine Results

*Cohen and Gay, CID (in press)*

<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>
The HIV-1 Transmission Event
ART Prevention Models Ignore Acute Infection

Transmission

Virus Concentration in Extracellular Fluid or Plasma (c/ml)

Window of Opportunity?
Established Infection

Time Postexposure (days)

0 5 10 15 20 30 35 40 45 50 55 60 65 70

Set Point

Limit of detection for HIV RNA

Symptoms

Reservoir

Virus dissemination

“ACUTE INFECTION”

eclipse

Transit

Transmission
HIV variants are 750X more contagious!

- far fewer viral units required for tmx

Fewer defective copies of HIV?

Lack of antibodies or antibody antigen complexes that block transmission?

OTHER?
Does Acute/Early HIV Spread HIV?

*Powers et al. in press*

![Graph showing proportion of new infections due to 'early' index for different populations](image)
Messages to HIV Discordant Couples?
The “Swiss Statement”

…After ART suppression for several months, and in the absence of an STD, the risk for HIV transmission is so low that unprotected sex can be permitted

• Discussion, Debate and Aspiration
  • Hirschel B. HIV9, Glasgow 2008
  • Spire B. HIV9, Glasgow 2008
HIV Treatment as Prevention

*Sullivan et al. CROI, IAS 2009*

- 2993 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 is NOT zero
And ART Suppression is NOT Reliable

- Women receiving ART shed HIV
  - 15-50% detection of HIV in cross section
  - 65% of women HIV in secretions at least once in 21 months in a longitudinal study
  - 64% of women with HIV in secretions at least once during pregnancy

2. Fiore et al. 2003
3. Kovacs et al. 2001
4. Si-Mohammed et al. 2000
5. Vettore et al. 2006
6. Neely et al. 2007
7. DeBiaggi et al. 2001
8. Tuomola et al. 2002
Don’t We Need Prospective Data?

- About when to start ART?
- About Whether ART prevents transmission?
HPTN 052...an RCT

1,750 couples, 8 countries and 12 sites

Randomization

Immediate ART
- 350-550 cells/μL
- AZT+3TC+EFV/ATV

Deferred ART
- CD4 <250-200

Endpoints: i) Transmission Events
ii) OIs and Clinical Events-WHO 2,3,4
iii) ART Toxicity
Pharmacology Really Matters

The genital tract and blood are not the same
ART in cervical and vaginal secretions?
ART in semen?
Female Genital Tract Exposure
(median percent of blood plasma)

GT exposure within 2 hrs of dosing

Min et al. JAIDS 2005
Dumond et al. AIDS 2007
Dumond et al. AIDS 2008
Jones et al. IPWCPH 2009
Patterson et al. IDSA 2009
Male Genital Tract Exposure

*Can We Get ARV to Recipient’s Cells Before HIV?*

**N(t)RTIs**
- 3TC (600%)
- TDF (500%)
- ZDV (200%)

**NNRTI**
- NVP (70%)

**PI**
- IDV (100%)

**Entry Inhibitors**
- APV (20%)
- ATV (14%)
- LPV (5%)
- RTV (3%)
- SQV (3%)

**Integrase Inhibitors**
- RAL (TBD)
- DRV (TBD)
- ETR (TBD)

GT AUC = BP AUC

GT exposure within 1 hr of dosing
Conclusions

- It seems likely that ART will reduce transmission of HIV
- The exact magnitude of ART transmission suppression and its durability are unknown
- ART combinations designed for HIV prevention can be developed
- The population benefit of ART depends on 
  - transmission suppression
  - the contribution of acute HIV infection