Treatment as prevention
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Acknowledgement: Julio Montagner, Helen Rees, Mike Cohen, HPTN/NIH, Ian Sanne, Connie Cellum
Is sex now safe?
Why should we worry?

• All HIV spread is from a discordant couple
• Discordant couples > concordant HIV couples
Effect of HAART on HIV Transmission

HAART stops HIV replication

↓

HIV levels fall to undetectable in blood as well as sexual fluids

↓

Sharp reduction in HIV transmission
HIV-1 levels & HIV-1 infectiousness

- High plasma HIV-1 RNA concentrations are associated with increased HIV-1 transmission risk.
- Plasma and genital HIV-1 levels are correlated (coefficient ~0.5-0.6)
  - But, genital HIV-1 more variable than plasma and tight correlation not found in all individuals.

Thanks Connie Cellum
HIV-1 levels & HIV-1 infectiousness

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  - But, genital HIV-1 more variable than plasma and tight correlation not found in all individuals.

Quinn et al NEJM 2000

Thanks Connie Cellum
Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

So how does transmission work?
Multiple targets

Usually a single virus!

Cohen et al, NEJM, 2011
Cohen et al, NEJM, 2011
How does this help us?
## Routes of Exposure and HIV

### INFECTION ROUTE

#### SEXUAL TRANSMISSION

<table>
<thead>
<tr>
<th>Route</th>
<th>Risk of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Female-to-male transmission</td>
<td>1 in 700 to 1 in 3,000</td>
</tr>
<tr>
<td>b. Male-to-female transmission</td>
<td>1 in 200 to 1 in 2,000</td>
</tr>
<tr>
<td>c. Male-to-male transmission</td>
<td>1 in 10 to 1 in 1,600</td>
</tr>
<tr>
<td>d. Fellatio</td>
<td>.0 %</td>
</tr>
</tbody>
</table>

It is hard to get HIV!

### PARENTERAL TRANSMISSION

<table>
<thead>
<tr>
<th>Route</th>
<th>Risk of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Transfusion of infected blood</td>
<td>95 in 100</td>
</tr>
<tr>
<td>b. Needle sharing</td>
<td>1 in 150</td>
</tr>
<tr>
<td>c. Needle stick</td>
<td>1 in 200</td>
</tr>
<tr>
<td>d. Needle stick /AZT PEP</td>
<td>1 in 10,000</td>
</tr>
</tbody>
</table>

### TRANSMISSION FROM MOTHER TO INFANT

<table>
<thead>
<tr>
<th>Route</th>
<th>Risk of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Without AZT treatment</td>
<td>1 in 4</td>
</tr>
<tr>
<td>b. With AZT treatment</td>
<td>Less than 1 in 10</td>
</tr>
</tbody>
</table>

Adapted from Royce, Sena, Cates and Cohen, NEJM 336:1072-1078, 1997
HIV ‘natural history’

- Needs ARV’s
- Gets HIV!
- CD4
- 8 to 10 years
Sexual Transmission of HIV


Risk of Transmission Reflects **Genital** Viral Burden

1/30 - 1/200

1/1000 - 1/10,000

1/500 - 1/2000

1/100 - 1/1000

1\textsuperscript{st} 5/12: 50% of all transmissions!!!!!

(Wawer, 2005)

HIV RNA in Semen (Log\textsubscript{10} copies/ml)
What is the biggest news of the year?

- HPTN 052
HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm³ (N = 1763 couples)

Immediate ART
Initiate ART at CD4+ cell count 350-550 cells/mm³ (n = 886 couples)

Delayed ART
Initiate ART at CD4+ cell count ≤ 250 cells/mm³* (n = 877 couples)

*Based on 2 consecutive values ≤ 250 cells/mm³.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

DSMB recommended release of results as soon as possible following April 28, 2011, review; follow-up continues but all HIV-infected partners offered ART after release of results.

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Total HIV-1 Transmission Events: 39
(4 in immediate arm and 35 in delayed arm; \( P < .0001 \))

Linked Transmissions: 28

Delayed Arm: 27

Immediate Arm: 1

Unlinked or TBD Transmissions: 11

Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to HIV-1 RNA suppression

\( P < .001 \)
HPTN 052 (www.hptn.org)

HR = 0.37 or 96.3% reduction in transmission
No difference whether index pt was M or F

To be presented at IAS-Rome, July 2011
HPTN 052 (www.hptn.org)

Extra-Pulmonary TB
Deferred: 17 cases
Immediate: 3 cases
84% Reduction

M & M
To be presented at IAS-Rome, July 2011
## Most Prevalent Secondary Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Delayed (N=317)</th>
<th>Immediate (N=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>87</td>
<td>72</td>
</tr>
<tr>
<td>Moderate unexplained weight loss*</td>
<td>61</td>
<td>76</td>
</tr>
<tr>
<td>Popular puritic eruption</td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td><strong>Herpes zoster</strong></td>
<td><strong>53</strong></td>
<td><strong>17</strong></td>
</tr>
<tr>
<td>Smear positive malaria</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td><strong>Oral Candidiasis, persistent</strong></td>
<td><strong>47</strong></td>
<td><strong>22</strong></td>
</tr>
<tr>
<td>Unexplained severe weight loss</td>
<td>21</td>
<td>37</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td><strong>Seborrhoeic dermatitis</strong></td>
<td><strong>18</strong></td>
<td><strong>7</strong></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Oral ulcerations</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>
HPTN 052 Enrollment
(Total Enrollment: 1763 couples)
Clinical trial evidence for preventing sexual HIV transmission – 14 July 2011

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for prevention (Africa, Asia, America’s)</td>
<td>96% (73; 99)</td>
</tr>
<tr>
<td>PrEP for discordant couples (Partners PrEP)</td>
<td>73% (49; 85)</td>
</tr>
<tr>
<td>PrEP for heterosexuals (Botswana TDF2)</td>
<td>63% (21; 48)</td>
</tr>
<tr>
<td>Medical male circumcision (Orange Farm, Rakai, Kisumu)</td>
<td>54% (38; 66)</td>
</tr>
<tr>
<td>PrEP for MSMs (America’s, Thailand, South Africa)</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>STD treatment (Mwanza)</td>
<td>42% (21; 58)</td>
</tr>
<tr>
<td>Microbicide (CAPRISA 004 tenofovir gel)</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>HIV Vaccine (Thai RV144)</td>
<td>31% (1; 51)</td>
</tr>
</tbody>
</table>
What’s not to like????
• Sex is inherently risky – ‘safe sex’ is nonsense

But the vast majority of us think its very, very worth it.
Does ART prevent HIV transmission among MSM?

Kathryn E. Muessig\textsuperscript{a}, M. Kumi Smith\textsuperscript{b}, Kimberly A. Powers\textsuperscript{a,b}, Ying-Ru Lo\textsuperscript{c}, David N. Burns\textsuperscript{d}, Andrew E. Grulich\textsuperscript{e}, Andrew N. Phillips\textsuperscript{f} and Myron S. Cohen\textsuperscript{a,b,g}

Transmitted infections (STIs). Additional studies are needed on the impact of ART on HIV sexual risk behaviors and transmission among MSM outside of developed countries in North America, western Europe, and Australia.

Conclusion: The benefits of treatment as prevention for MSM are highly plausible, but not certain. In the face of these unknowns, treatment guidelines for earlier ART initiation should be considered within a combination prevention strategy that includes earlier diagnosis, expanded STI treatment, and structural and behavioral interventions.
052 was a **clinical trial**

- Will we get adherence like this?
- If it’s not your partner?
- Disinhibition?
- Transmission events disproportionately came from Africa (!!!)
The authors estimated that only about 19% of HIV infected individuals in the USA have an undetectable HIV-1 RNA level.
Several questions

- Will people take it for their own health?
- Will it have a population impact? (noting the transmission dynamic in acute seroconversion)
- Will it actually work? Randomised studies
Treatment as prevention

- Incredibly exciting BUT
- Will require huge investment in health systems
- For discordant couples – yes (but how?)
- For general roll-out? We need more data