PREVENTION OF HIV-1 Infection

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“Telling A Story”

• A beginning

• A middle

• We ABSOLUTELY don’t know the ending
Transmission of HIV-1
Biological Requirements

**Infectious**
- Inoculum (concentration)
- Phenotypic factors

**Susceptibility**
- Hereditary resistance
- Innate resistance
- Acquired (immune) resistance
Probability of HIV Transmission?

~1/1000 episodes for couples?? (Most recently Hughes et. al. JID)

IS 1/1000 AN UNDERESTIMATE??

- "exposed uninfected" partners
- benefits of counseling
- missing amplification factors
## Amplified Transmission of HIV-1

<table>
<thead>
<tr>
<th>Infectiousness</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Viral Load</td>
<td>Genital ulcers</td>
</tr>
<tr>
<td>Genital Tract Viral Load</td>
<td>Inflammatory STDs</td>
</tr>
<tr>
<td><strong>-Inflammatory STDs</strong></td>
<td>Lack of Circumcision</td>
</tr>
<tr>
<td>Viral clade</td>
<td>Cervical ectopy</td>
</tr>
<tr>
<td><strong>ACUTE INFECTION</strong></td>
<td>HLA Haplotype</td>
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<tr>
<td></td>
<td>Cytokine profile</td>
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</tbody>
</table>
HIV-1 Transmission Model

Cohen et al, NEJM, 2011

Inoculum

Mucosa

Recipient

>10^6 virions/ml plasma (Most fit virus $R_0>>1$)

~10^9 infection events

Defective virus

Less fit virus ($R_0\sim1$)

Defective virus

Less fit, attenuated or stochastic event ($R_0<<1$)

Time (days)
Acute HIV-1 Infection

Cohen et al, NEJM, 2011

Transmission

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

Acute Phase Reactants Days -5 to 7

Onset cytokines apoptosis, Day 7

Immune Complexes Day 9

Free Antibody, Day 13

Reservoir

CD8 T Cell Responses

CTL Escape

Autologous Neutralizing Antibody

Autologous Neutralizing Antibody Escape
Four Prevention Opportunities

- Behavioral, Structural
- Vaccines
- ART PrEP
- Microbicides
- ART PEP
- Treatment Of HIV Reduced Infectivity

Cohen et al, JCI, 2008
Cohen IAS 2008
ART to Prevent Sexual Transmission of HIV

• Post-exposure Prophylaxis (PEP) ????

• Pre-exposure prophylaxis (PrEP) ????

• Treatment of the infected person ????
Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women
Quarraisha Abdool Karim, et al.
Science 329, 1168 (2010);
DOI: 10.1126/science.1193748
The PrEP “Conundrum”

*Oral TVF-FTC (Truvada Combination)*

**SUCCESS**
- iPRESX : 42% prevention in MSM
- *TDF2* : 63% protection with high risk
- *PIP*: 73% protection in EU

**FAILURE**
- FEMPREP: Trial in women stopped
- VOICE: Tenofovir in women stopped
- VOICE: Tenofovir gel stopped (????)
- VOICE: TVF-FTC oral ONGOING
Does PrEP WORK and HOW WELL?

- Adherence
- Tissue levels

... Truvada PrEP APPROVED
  - MSM
  - Couples (???)
  - High RISK (????)

INFRASTRUCTURE/LIMITS?
Four Prevention Opportunities

- Behavioral, Structural
- Vaccines
- ART PrEP
- Microbicides

Cohen et al, JCI, 2008
Cohen IAS 2008
Treatment as Prevention
“The Four Questions”

1) Do ART drugs prevent HIV transmission?

2) What do we tell infected people?

3) Can we reduce population HIV incidence?

4) Barriers to “Treatment as Prevention”?
Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm$^3$

Primary Transmission Endpoint
Virally linked transmission events

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death
HPTN 052 Recognition

U.S. Sponsors:
• National Institutes of Health (NIH)
• Division of AIDS (DAIDS), U.S. National Institute of Allergy and Infectious Diseases (NIAID)

HIV Prevention Trials Network (HPTN):
• Network Laboratory, Johns Hopkins University
• Statistical Center for HIV/AIDS Research & Prevention (SCHARP) and University of Washington
• Coordinating and Operations Center, Family Health International (FHI)
• HPTN Leadership

AIDS Clinical Trials Group (ACTG):
• ACTG Leadership and Investigators

Pharmaceutical Companies:
• Abbott Laboratories
• Boehringer Ingelheim Pharmaceuticals, Inc.
• Bristol-Myers Squibb
• Gilead Sciences, Inc.
• GlaxoSmithKline
• Merck & Co., Inc.

Sites (Investigators of Record):
• Porto Alegre, Brazil (Breno Santos)
• Rio de Janeiro, Brazil (Beatriz Grinsztejn)
• Boston, United States (Kenneth Mayer)
• Chennai, India (N. Kumarasamy)
• Pune, India (Sheela Godbole)
• Chiang Mai, Thailand (Suwat Chariyalertsak)
• Gaborone, Botswana (Joseph Makhema)
• Kisumu, Kenya (Lisa Mills)
• Blantyre, Malawi (Johnstone Kumwenda)
• Lilongwe, Malawi (Mina Hosseinipour)
• Johannesburg, South Africa (Ian Sanne)
• Soweto, South Africa (Guy De Bruyn)
• Harare, Zimbabwe (James Hakim)

Study Participants
HPTN 052 Timeline: The Fast Track?

- ART for prevention of HIV 1993- THE PRESENT
HPTN 052 Enrollment

10,838 Individuals Screened

1763 Couples (3526 Individuals) Randomized

Immediate Arm 886 Couples

Delayed Arm 877 Couples

Major reasons for exclusion:
- 3058 HIV+ but CD4 count out of range
- 2565 HIV- but HIV+ partner ineligible
- 308 Seroconcordant couples
- 155 Ineligible due to sexual history
HPTN 052 Enrollment
(Total Enrollment: 1763 couples)
“The Board recommends that the results of the trial be announced as soon as possible”
HPTN 052: HIV-1 Transmission

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28
- Immediate Arm: 1
- Delayed Arm: 27
  - 18/28 (64%) transmissions from infected participants with CD4 >350 cells/mm³ and VL >50,000 copies/ml at transmission

Unlinked or TBD Transmissions: 11
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

p < 0.001
Results of the HPTN052 trial announced on 12 May 2011 show that if an HIV-positive person adheres to an effective antiretroviral therapy regimen, the risk of transmitting the virus to their uninfected sexual partner can be reduced by 96%.

“Treatment for prevention is a game changer”.

Michel Sidibe
Executive Director of UNAIDS
HPTN 052: ADHERENCE MATTERS

Proportion of participants with VL<400 at each visit

- Immediate Arm
- Delayed Arm (not on ART)
- Delayed Arm (on ART)

Months

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45

Proportion (%)
One Transmission Event on ART

Analysis of Transmission: >50 days earlier (84 – 190 days)

Single Genome Analysis: 1-2 viruses transmitted

Partner VL < 400
Index VL = 87,202
HPTN 052 Clinical Results

- **105 morbidity and mortality events (p<.01)**
  - 65 in delayed arm
  - 40 in immediate arm

- **20 cases of extrapulmonary TB (p= 0.0013)**
  - 17 in delayed arm
  - 3 in immediate arm

- **23 deaths (NS)**
  - 13 in delayed arm
  - 10 in immediate arm
HIV-1 RNA and CD4 Over Time (ITT)

- Immediate
- Delayed

CD4 (cells/mm³)

- 0
- 200
- 400
- 600
- 800

Years since randomization

- 0
- 1
- 2
- 3
- 4

Subjects contributing data

- 883
- 785
- 390
- 134
- 37

Proportion <400 copies/ml

- 0.0
- 0.2
- 0.4
- 0.6
- 0.8
- 1.0
21% initiated therapy
- Mostly (75%) triggered by a decline in CD4 count

Median time to initiation was 3.5 years

Median CD4 at initiation was 225 cells/mm$^3$
- Q1–Q3: 199 – 247
THE HPTN 052 TRANSITION...
BEFORE AND AFTER APRIL 28
HPTN 052: An Ethical Odyssey
HPTN 052 and the New York Times

Early H.I.V. Therapy Sharply Curbs Transmission
By DONALD G. McNEIL Jr.
Published: May 12, 2011

Dr. Fauci and Dr. Myron Cohen, an AIDS specialist at the University of North Carolina at Chapel Hill and the study’s principal investigator, collected since the study began data on safety review panels. The upfront cost of treatment is minimal compared to the cost of non-treatment.

Drugs Stop AIDS. Take Your Medicine.
By DONALD G. McNEIL Jr.
Published: May 21, 2011

With an estimated 34 million people infected with the virus, the risk that the epidemic will be controlled is low. But the infected person who was treated with drugs immediately, the risk of transmission to an uninfected partner was cut by 96 percent. The upfront cost of treating the infected person would be enormous, but in the long run it could well save money by greatly reducing the number of people who become infected and need treatment.

When Treatment Is Also Prevention
Published: May 22, 2011

The discovery of a near-perfect way to halt the transmission of the most common strains of the virus could spell the end of the epidemic. The epidemic will be controlled if an infected person is treated with drugs immediately, the risk of transmission to an uninfected partner is cut by 96 per cent. The upfront cost of treating the infected person would be enormous, but in the long run it could well save money by greatly reducing the number of people who become infected and need treatment.

Editorial
No Time to Let Up on the Fight
Published: June 5, 2011

Dr. Bernhard Schwartländer, the agency’s chief of strategy, said AIDS had seen a “game-changing year in science,” noting especially a study showing that people on drugs lowered by 96 percent their chances of passing on the infection. And he highlighted areas where progress had been made.

EDITORIAL
Still Fighting Against AIDS
Published: November 27, 2011

New Cases of AIDS Hit Plateau
By DONALD G. McNEIL Jr.
Published: November 27, 2011

This month, a randomized clinical trial in the United States and South Africa — the gold standard in medicine — showed that the drugcombination substantially reduced the risk of HIV transmission to an uninfected partner by 96 per cent. This month, a randomized clinical trial in the United States and South Africa — the gold standard in medicine — showed that the drug combination substantially reduced the risk of HIV transmission to an uninfected partner by 96 per cent.
The Economist

INSIDE THIS WEEK: TECHNOLOGY QUARTERLY

The trap for Turkey
Wall Street’s plumbing problem
Lady Gaga, Mother Teresa and profits
Brazil’s boiling economy
The farce that is FIFA

The end of AIDS?

How 5 million lives have been saved, and a plague could now be defeated
Bruce Alberts, Editor of Science explains the choice of this work

“The results have galvanized efforts to end the world’s AIDS epidemic in a way that would been inconceivable even a year ago”
HPTN 052: What’s Happened Next

- All HIV infected subjects offered ART
- Continued follow-up in HPTN 052

- 1682 index cases / 1763 (96% retention)
- 1502 discordant couples (85% retention)
- 1561/1682 index cases are NOW on ART

DURABILITY OF PREVENTION?
DELAYED ART & CLINICAL OUTCOMES?
HPTN 052 and IAS 2012

- Mayer et al: Sexual Behavior
- Grinjzstein et al: WHEN TO START (A1 Evidence)
- Walensky et al: ART in India and Africa (CE or CS?)
- ART for heterosexual discordant couples
- Treat HIV before CD4 count falls below 350
- Does ART prevent HIV transmission in…
  - MSM couples?
  - IDU transmission?
TnT: Aspiration Meets Reality

Smith et al. PLOS MED (in press)

ECOLOGICAL STUDIES
OBSERVATIONAL STUDIES
ACUTE INFECTION
“THE CASCADE”
British Columbia and ART?

*Lancet, Montaner, 2010: “NEW DIAGNOSIS”*

![Graph showing reported and expected number of new HIV diagnoses per year in British Columbia, Canada, during the three phases of the study, 1996-2009. P values refer to the total reported number of HIV diagnoses compared with the total expected number of HIV diagnoses at the end of each study phase.](image-url)
New HIV Diagnosis in North Carolina 2006-10

WHAT DOES THIS MEAN?

* Range of estimates reflects the proportion of all transmissions during an individual's entire infectious period that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI at the population level will depend on the epidemic phase and the distribution of sexual contact patterns in the population.

** Transmission probabilities were drawn from the population category shown, but the reported estimates result from a range of hypothetical sexual behavior parameters that do not necessarily reflect a specific population.

† The range of estimates shown was extracted from the endemic-phase portion of graphs showing the proportion of new infections due to EHI over calendar time.
HIV Rx “Cascade”: Aspiration Meets Reality

850,000 HIV+ Americans (72%) lack viral control

Refs: MMWR 2011; see also Gardner CID 2011; Burns CID 2010
HPTN 065 (TLC-Plus) Provider Survey
Study Population and Participants

- ART-prescribing providers at 38 participating HPTN 065 care sites in Bronx, NY and Washington, DC
- Internet-based survey (anonymous)

Kurth et al, TASP 2012
Glimmers of Hope
ART coverage 2004-2011

- **ART coverage** = proportion of the total HIV-infected population receiving ART

- **Patients on treatment:** Individual, geo-located DOH programme adult patients actively on treatment in June (2004-2011)

- **HIV-infected:** Individual, geo-located, HIV positive adults identified through population-based HIV surveillance data (2004-2011)

*Using a standard Gaussian kernel of radius 3km*
Adjusted HIV acquisition hazard by ART coverage category

Adjusted for age, sex, community-level HIV prevalence, urban vs. rural locale, marital status, >1 partner in last 12 months, and household wealth index.
Treatment as Prevention
The “Test and Treat” Movement
(Granich t al Current Opinion in HIV)

More than 50 studies described!!

- US HPTN 065 Linkage in NYC, DC, (El-Sadr)
- ANRS PILOT in South Africa (Newell)
- THE PEPFAR Combination Prevention Trials:
  - CDC- BOTSWANA (Essex)
  - NIH HPTN 071 -South Africa, Zambia (Hayes)
  - USAID JHU-Tanzania (Celentano)
HPTN 071 Intervention Package

Community HIV Care Providers (CHiPs team):

- Counselling, condom provision, syndromic STI Rx
- Referral of pregnant women for ANC/PMTCT services
- Universal voluntary HIV testing house-to-house
- HIV-uninfected men offered circumcision
- HIV-infected persons
  - Arm A: **Immediate ART** (analogous to HPTN 052)
  - Arm B: **“Enhanced” Standard of Care** (CD4<350)
  - Arm C: **Standard of Care** (CD4<350)
Clinton speech November 8, 2011