Antiretroviral-Based HIV Treatment and Prevention Strategies: Advancing Science into Practice

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Antiretroviral-Based HIV Treatment and Prevention Strategies: Advancing Science into Practice

Sex, Drugs, and Rock and Roll in HIV Prevention
Disclosures

• No antiretroviral medication is currently labeled for prevention of sexual transmission of HIV

• I have received research funding related to PrEP, antiretroviral treatment for HIV prevention, and microbicides from the US National Institutes of Health and the Bill & Melinda Gates Foundation.

• For some research studies, medication has been donated by Gilead Sciences.

• I have no other financial conflicts of interest.
30 years into the HIV epidemic, new research has demonstrated that we now have powerful interventions to prevent new infections.

For the first time, there is rational discussion not just that we can fight HIV, but we stop transmission, on a large scale.
Outline

**SCIENCE**
- Rationale and proof of antiretrovirals for HIV prevention
  - *Sex, Drugs, and Rock and Roll*

**PRACTICE**
- Transitioning from scientific discovery into public health practice – challenges and opportunities
  - *Drugs, Sex, and Getting to Work*
Advancing Science into Practice
Starting point: antiretroviral medications revolutionized HIV care – US

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2006—United States and Dependent Areas

Note. Data have been adjusted for reporting delays.
Global scale-up of antiretroviral treatment is a public health success

A success driven by aggressive roll-out to populations with the greatest HIV burden

WHO, Global HIVAIDS Response, 2011
PMTCT = antiretrovirals as treatment and prophylaxis

The tremendous success of PMTCT in many way presages ART and PrEP for prevention of sexual transmission

Estimated number of children newly infected with HIV in low- and middle-income countries, 2000–2015

Sex
Sex
Sex

*It is 9 am – this is the best that can be depicted for this slide*
Fundamental principles of interventions for prevention of sexual HIV transmission

HIV testing
Behavior change
Condoms
STI treatment

HIV transmission → (infectiousness)

→ HIV acquisition
(infectiousness)

HIV testing
Behavior change
Condoms
STI treatment
Male circumcision
Antiretroviral treatment for HIV prevention: building the hypothesis

• The quantity of HIV in plasma (and genital secretions) is the prime determinant of HIV transmission risk

• Initiation of antiretroviral therapy results in early and sustained reductions in plasma and genital HIV levels

Quinn et al. NEJM 2000
Antiretroviral treatment for HIV prevention

- **Hypothesis:** Treating HIV+ individuals with antiretroviral medications reduces their infectiousness and risk of transmission to partners.
Pre-exposure prophylaxis (PrEP): the hypothesis

- In PrEP, an HIV uninfected individual uses an antiretroviral medication ahead of an HIV exposure. By having the antiretroviral in blood/tissues, PrEP may make it so that HIV is unable to establish infection.

- Analogous to prophylaxis for malaria in travelers.
PrEP for HIV prevention

- Hypothesis: PrEP will reduce HIV susceptibility and risk of infection when taken by HIV- persons.
Sex

Antiretroviral treatment and PrEP were tested for prevention of sexual transmission of HIV based on strong scientific hypotheses.
Drugs
Antiretroviral treatment for HIV prevention: evidence
Observational studies: ART and transmission in HIV serodiscordant couples

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnell 2010</td>
<td>0.08 [0.01, 0.57]</td>
</tr>
<tr>
<td>Melo 2008</td>
<td>0.10 [0.01, 1.67]</td>
</tr>
<tr>
<td>Reynolds 2011</td>
<td>0.10 [0.01, 1.64]</td>
</tr>
<tr>
<td>Sullivan 2009</td>
<td>0.21 [0.08, 0.56]</td>
</tr>
<tr>
<td>Del Romero 2010</td>
<td>0.21 [0.01, 3.75]</td>
</tr>
<tr>
<td>Musicco 1994</td>
<td>0.88 [0.36, 2.16]</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>1.44 [0.85, 2.44]</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0.34 [0.13, 0.92]</td>
</tr>
</tbody>
</table>

Anglemyer et al. Cochrane Reviews 2011
ART and HIV-1 transmission: Partners in Prevention HSV/HIV Study

<table>
<thead>
<tr>
<th>Linked HIV infections</th>
<th>Person Years</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART initiated</td>
<td>102</td>
<td>4558</td>
<td>2.24</td>
</tr>
<tr>
<td>After ART initiation</td>
<td>1*</td>
<td>273</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Unadjusted Relative Risk = 0.17  (95% CI 0.004, 0.94) , p = 0.037
Adjusted* Relative Risk = 0.08  (95% CI 0.002, 0.57),  p = 0.004

* For time on study and CD4 count

Case: *ART-exposed HIV-1 transmission

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>3mo</th>
<th>6mo</th>
<th>9mo</th>
<th>12mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 :</td>
<td>302</td>
<td>201</td>
<td>637</td>
<td></td>
</tr>
<tr>
<td>log_{10} VL :</td>
<td>4.7</td>
<td>4.7</td>
<td>undet.</td>
<td></td>
</tr>
</tbody>
</table>

Donnell et al. Lancet 2010
HPTN 052: randomized clinical trial of immediate vs delayed ART in couples

Total HIV-1 Transmission Events: 39

- Linked Transmissions: 28
  - Immediate ART: 1
  - Delayed ART: 27

- Unlinked or TBD Transmissions: 11

96% reduction in HIV transmission (95% CI 73-99%)

p < 0.001
PrEP for HIV prevention: evidence
Tenofovir-based PrEP

= FTC/TDF (co-formulated emtricitabine + tenofovir)
sold under the trade name Truvada®
It is a daily oral pill.

✓ **Potent:** Broad and potent activity (all HIV subtypes), rapidly active
✓ **Safe:** Favorable safety and tolerability, large experience as treatment
✓ **Easy:** Low pill burden, no food restrictions, few drug interactions
✓ **Evidence:** Animal models of PrEP showed high protection
Two pivotal randomized, placebo-controlled trials of PrEP for HIV prevention

<table>
<thead>
<tr>
<th></th>
<th>iPrEx</th>
<th>Partners PrEP</th>
</tr>
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<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Men who have sex with men</td>
<td>Heterosexual HIV serodiscordant couples</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>US, Brazil, Ecuador, Peru, South Africa, Thailand</td>
<td>Kenya, Uganda</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>2499</td>
<td>4758</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Daily oral FTC/TDF</td>
<td>Daily oral FTC/TDF</td>
</tr>
<tr>
<td><strong>HIV protection due to PrEP (FTC/TDF)</strong></td>
<td><strong>44%</strong> (95% CI 15-63%)</td>
<td><strong>75%</strong> (95% CI 55-87%)</td>
</tr>
</tbody>
</table>

Grant et al N Engl J Med 2010
Baeten et al CROI 2012
Drugs

Clinical trials provide clear and definitive evidence that antiretroviral treatment and PrEP work for the prevention of sexual transmission of HIV.
Rock and Roll

TIME
Top 10 Medical Breakthroughs
1. AIDS Drugs Lower the Risk of HIV Infection

Science
BREAKTHROUGH OF THE YEAR
HIV Treatment as Prevention
Advancing Science into Practice
Challenges and opportunities

Antiretroviral medications – as treatment and as prophylaxis – prevent HIV transmission. We face many challenges and opportunities about how these proven strategies can be put into practice.
Challenges and opportunities

Antiretroviral medications – as treatment and as prophylaxis – prevent HIV transmission. We face many challenges and opportunities about how these proven strategies can be put into practice.

After the sex, drugs, and rock and roll, bound to be some hangover…
Challenges and opportunities

Adherence

Drugs

Adherence and risk behavior

Sex

Uptake and public health implementation

Getting to work
Adherence
Adherence and PrEP

• There is a clear relationship between PrEP use and HIV protection in clinical trials. Divergent PrEP trial results appear to be correlated with PrEP taking behaviors.

• PREMISE: PrEP cannot work if it is not taken.
## Divergent oral PrEP efficacy trial results

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2499</td>
<td>44% efficacy FTC/TDF</td>
</tr>
<tr>
<td>TDF2 Study</td>
<td>Young men and women</td>
<td>1200</td>
<td>62% efficacy FTC/TDF</td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>Heterosexual couples</td>
<td>4758</td>
<td>67% efficacy TDF 75% efficacy FTC/TDF</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Women</td>
<td>2021</td>
<td>6% efficacy FTC/TDF</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>3021</td>
<td>No efficacy TDF FTC/TDF ongoing</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>IDUs</td>
<td>2400</td>
<td>TDF ongoing</td>
</tr>
</tbody>
</table>
Adherence and efficacy in PrEP trials

<table>
<thead>
<tr>
<th>Study</th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>81%</td>
<td>75%</td>
</tr>
<tr>
<td>TDF2</td>
<td>79%</td>
<td>62%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>26%</td>
<td>6%</td>
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</table>

There is a clear dose-response between evidence of PrEP use & efficacy

Donnell et al CROI 2012
Grant et al N Engl J Med 2010
Van Damme et al CROI 2012
Paxton et al FDA 2012
### Tenofovir levels and HIV protection

- And when PrEP was taken (=detected in blood), protection was very high

<table>
<thead>
<tr>
<th></th>
<th>% with tenofovir detected</th>
<th>HIV-1 relative risk reduction: detection versus no detection of tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>92%</td>
</tr>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>81%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010
Adherence and perfection

- Imperfect, but still regular adherence, might still provide substantial HIV protection, although PrEP is still as a daily medication

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Estimated HIV risk reduction (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>2 doses/week</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>(56-96%)</td>
</tr>
<tr>
<td>4 doses/week</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>(90-&gt;99%)</td>
</tr>
<tr>
<td>7 doses/week</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>(96-&gt;99%)</td>
</tr>
</tbody>
</table>

Anderson et al. CROI 2012
Pharmacokinetics and PrEP adherence

- PK studies offered one possible mechanism for lower HIV protection in women: oral tenofovir results in >10x higher concentrations in rectal tissue than cervical and vaginal tissue.
## Partners PrEP Study:
PrEP does work in high-risk subpopulations

<table>
<thead>
<tr>
<th></th>
<th>Incidence placebo</th>
<th>FTC/TDF Efficacy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2.0</td>
<td>75%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>2.8</td>
<td>66%</td>
<td>0.01</td>
</tr>
<tr>
<td>Couples w/ HIV+ partner had viral load ≥50,000 c/mL</td>
<td>3.9</td>
<td>77%</td>
<td>0.008</td>
</tr>
<tr>
<td>Couples with key high-risk characteristics*</td>
<td>5.0+</td>
<td>78%</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Baeten et al CROI 2012 Abstract 29
**Kahle et al CROI 2012 Abstract 1102 and unpublished
Divergent PrEP trials: it stems from adherence

Adherence

Biology
marginal vaginal concentrations, inflammation, acute HIV in partner, etc. could make PrEP more sensitive to imperfect adherence, particularly in women, which could have influenced some PrEP trial results

Dilution of effect
very low adherence (missed doses, missed visits) diminishes statistical power in some clinical trials to evaluate HIV protection from PrEP

PrEP Efficacy
Adherence and antiretroviral treatment

- In a way very similar to PrEP, antiretroviral treatment requires high adherence in order to achieve prevention benefits.
  - *Viral suppression is the biologic pathway to efficacy*
  - *The results from HPTN 052 are very clear in this regard – and were an optimized test of the biologic hypothesis that ART diminishes HIV infectiousness*
Adherence and HPTN 052

In HPTN 052, viral suppression was near-universal, reflecting intensive strategies to achieve near-perfect adherence.

Proportion of participants with VL<400 copies/ml

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

Months
Cohen et al. NEJM 2011
Adherence and HPTN 052

In HPTN 052, viral suppression was near-universal, reflecting intensive strategies to achieve near-perfect adherence.

![Graph showing adherence and viral load suppression over time.]

Proportion of participants with VL<400 copies/ml

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

Adherence → efficacy

Cohen et al. NEJM 2011
Putting this all together

<table>
<thead>
<tr>
<th>HIV prevention effect with high adherence</th>
<th>Antiretroviral treatment for HIV prevention</th>
<th>PrEP for HIV prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96%</td>
<td>90-92%</td>
</tr>
<tr>
<td></td>
<td>(HPTN 052, near-perfect adherence)</td>
<td>(Tenofovir levels in iPrEx and Partners PrEP)</td>
</tr>
</tbody>
</table>

Two incredibly powerful prevention strategies – when adherence is high
Adherence Matters

*(Drugs)*
Adherence, adherence behavior, and risk behavior (sex)
Adherence, adherence behavior, and risk behavior

For PrEP:

What do adherence patterns look like in PrEP trials?

What does that mean for implementation?

How does adherence relate to risk?
Sustained use (and non-use) of PrEP: Partners PrEP Study

At Month 1, ~80% had tenofovir detected

Donnell et al CROI 2012
Sustained use (and non-use) of PrEP: Partners PrEP Study

Those who had no tenofovir at Month 1 tended to have no tenofovir throughout

Donnell et al CROI 2012
Sustained use (and non-use) of PrEP: Partners PrEP Study

Those who had tenofovir at Month 1 tended to have tenofovir throughout

Exception: pregnancies

Donnell et al. CROI 2012
Adherence and habit

- In contrast to clinical trials, which followed every person randomized regardless of continued interest in PrEP, implementation of PrEP will focus on those who continue to return for PrEP refills.
- Those who don’t use PrEP won’t come back & will receive no benefit, but also incur no costs.
- Those who use PrEP will achieve prevention benefits. PrEP as habit may be important for sustained use.
What motivates PrEP use?

• **Risk perception** is a potentially powerful driver of adherence

• Partners PrEP = serodiscordant couples
  • Known HIV+ partner, ongoing exposure, decision to maintain relationship, high adherence

• FEM-PrEP = young women
  • 70% perceived themselves to be at little or no HIV risk, very low adherence

• **Understanding interface of risk perception & HIV prevention is key for any strategy**
Men who practiced unprotected receptive anal intercourse had higher PrEP use than other men, and received HIV protection (subgroup efficacy = 58%).

Grant et al IAS 2011, FDA 2012
Risk behavior and pill taking in iPrEx

- Men who practiced unprotected receptive anal intercourse had higher PrEP use than other men, and received HIV protection (subgroup efficacy = 58%)
- Men not having sex were least likely to take PrEP

<table>
<thead>
<tr>
<th>Sexual Behavior</th>
<th>No Sex</th>
<th>Sex No URAI</th>
<th>URAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time points with tenofovir detected (%)</td>
<td>38%</td>
<td>42%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Drug detected
No drug detected

Grant et al IAS 2011, FDA 2012
# Risk behavior and pill taking in Partners PrEP

## Multivariate predictors of low adherence by unannounced pill count

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (increase in year)</td>
<td>0.96 (0.93-1.00)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>0.8 (0.5-1.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>1.1 (0.9-1.4)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Sex risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sex</td>
<td>4.2 (1.9-9.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>100% protected</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>&lt; 100% protected</td>
<td>1.7 (0.9-3.3)</td>
<td></td>
</tr>
<tr>
<td>Sex with other partner only</td>
<td>1.4 (0.3-6.1)</td>
<td></td>
</tr>
<tr>
<td>Sex with other + protected with index</td>
<td>2.2 (1.1-4.6)</td>
<td></td>
</tr>
<tr>
<td>Sex with other + unprotected with index</td>
<td>3.3 (1.3-8.7)</td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>2.3 (1.1-4.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Months on PrEP</td>
<td>0.98 (0.96-1.01)</td>
<td>0.27</td>
</tr>
<tr>
<td>Age difference ≥10 years</td>
<td>0.3 (0.1-1.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Haberer et al IAPAC 2012
The Next Condom Conundrum

Why use a rubber when you can just pop a pill? That’s what HIV-negative guys across the country are asking themselves -- and their doctors.
No evidence of risk compensation in PrEP clinical trials

iPrEx

Partners PrEP

Follow-up time (Month)

Proportion of HIV – participants with any unprotected sex (%)

Percent Reporting URAI

Weeks Since Randomization

TDF  FTC/TDF  Placebo
HIV prevention benefits in the context of potential risk compensation

Risk compensation is an important question.

However, pretty substantial increases in risk-taking would have to occur to substantially impact PrEP prevention effects.

Adherence, adherence behavior, and risk behavior

For ART:

What does real world adherence to antiretroviral therapy look like?

And, again, its relation to sex?
Real-world adherence to antiretroviral treatment

- Systematic review of adherence (Mills et al JAMA 2006)
  - 28,689 patients in 228 studies

  Resource-Rich Country: 54.7% (95 CI: 48.0-61.3%)
  Resource-Poor Country: 77.1% (95 CI: 67.3-85.6%)
Real-world adherence to antiretroviral treatment

- Systematic review of adherence (Mills et al JAMA 2006)
  - 28,689 patients in 228 studies

<table>
<thead>
<tr>
<th>Country Type</th>
<th>Adherence Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource-Rich Country</td>
<td>54.7% (48.0-61.3%)</td>
</tr>
<tr>
<td>Resource-Poor Country</td>
<td>77.1% (67.3-85.6%)</td>
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</table>

Contrast to HPTN 052
Treatment cascade: US

Of 1.1 million with HIV infection in the US, only 328,000 (28%) have suppressed HIV RNA

MMWR (60), 2011
Willingness to start antiretrovirals

- Soweto, South Africa:
  - 7287 adults tested for HIV
  - 2562 (35%) HIV infected
  - 743 (29%) eligible for ART (CD4<200***)
  - 148 (20%) refused

- Most common reason for refusal was feeling well

Katz et al. AIDS 2011
Willingness to start antiretrovirals

- Soweto, South Africa:
  7287 adults tested for HIV
    2562 (35%) HIV infected
    743 (29%) eligible for ART (CD4<200***)
    148 (20%) refused

  - Most common reason for refusal was feeling well
  - What might this look like for those with CD4>200, >350?

Katz et al. AIDS 2011
Retention rates after starting antiretroviral therapy

We have little experience with starting ART in asymptomatic persons….

- Mixed methods work in Thika, Kenya among 772 members of HIV-1 serodiscordant couples in the Partners PrEP Study

**Survey question:** Would you be willing to start antiretrovirals before your CD4 count reaches 350 if it would lower your chance of giving HIV to your partner?

**Top concerns about initiating early ART for HIV-1 prevention:**
- Side effects (51.4%)
- Stigma (20.8%)
- Pill burden (19.4%)
- Potential for earlier development of antiretroviral resistance (18.1%)
What does it mean to patients to start ART?

Focus group discussions among HIV+ members of HIV serodiscordant couples from Thika, Kenya

“Now if you start [ARVs] and you haven’t reached 350, you will feel like you have reached another stage.”

“You know the mentality that is there when you take the ARVs, it means you are at the lowest stage and that is why people fear ARVs.”

“Like me, if I am given ARVs I will think I am nearing the grave.”

Risk behavior after starting ART

• Some data suggest that risk behaviors do not increase substantially in those starting ART (Berhan et al AIDS Res and Ther 2012)

• But little long-term data or data on those starting ART at higher CD4 counts. In several studies, pregnancy incidence increases with antiretroviral therapy.

• Incomplete genital HIV suppression with ART could mean some amount of ongoing infectious risk (Politch AIDS 2012)
## Parallel challenges, parallel opportunities

<table>
<thead>
<tr>
<th>Adherence</th>
<th>ART for HIV prevention</th>
<th>PrEP for HIV prevention</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Necessary for efficacy</td>
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### Parallel challenges, parallel opportunities

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<tr>
<td><strong>Sexual risk-taking</strong></td>
<td>Mixed evidence</td>
<td>Limited evidence, key theoretical concern</td>
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*Principal question is whether risk-taking would be sufficient to undermine prevention benefits*
### Parallel challenges, parallel opportunities

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<tr>
<td></td>
<td><em>Principal question is whether risk-taking would be sufficient to undermine prevention benefits</em></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretroviral resistance</strong></td>
<td>Established risk, associated with poor adherence, rising in Africa</td>
<td>So far, only with use in acute infection but a key theoretical question</td>
</tr>
</tbody>
</table>
### Parallel challenges, parallel opportunities

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<td>Target to those at highest risk. Time-limited for periods of highest risk.</td>
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## Parallel challenges, parallel opportunities

<table>
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<td><strong>Who will pay?</strong></td>
<td>Rising need = rising costs</td>
<td>Where fit in the priority list?</td>
</tr>
</tbody>
</table>
What does this all mean for implementation?

Getting to work
“The potential short term gains … may be far outweighed …. In Africa, a higher proportion of patients are likely to fall into the category of potential poor adherers unless resource intensive adherence programmes are available.”

*Pre-determining failure has not been productive in the past…*
The new challenge is the ability to scale-up ART sufficiently to have an impact on the epidemic:

- Testing $\rightarrow$ linkage to care $\rightarrow$ ART initiation $\rightarrow$ sustained use

- Most HIV-infected persons currently have high CD4 counts and lack of clinical disease

- Large community-randomized trials to gauge impact of HIV testing and earlier ART implementation to be done (HPTN 071, Botswana, Africa Centre, Irigina)
  - But we need not wait for these to work on figuring out how to deliver ART better
ART implementation, 2012

• Innovative, envelope-pushing implementation is already underway. These make sense to do & evaluate.

  – US DHHS guidelines evolving to higher CD4 counts, in parallel with knowledge of clinical benefits, prevention benefits, medication tolerability
    
    • Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
      
      - CD4 count <350 cells/mm$^3$ (AI)
      - CD4 count 350 to 500 cells/mm$^3$ (AII)
      - CD4 count >500 cells/mm$^3$ (BIII)

  – San Francisco and New York public health departments recommending universal treatment

  
  SF Endorses New Policy for Treatment of H.I.V.- ‘start HAART as soon as found to be infected’

  NY Times
  By SABIN RUSSELL
  Published: April 2, 2010

  – Countries making policies to increase earlier access to ART: WHO Option B+ for pregnant women (Malawi), immediate initiation for HIV serodiscordant couples (Rwanda)
Ecological evidence: San Francisco

Das et al. PLoS One 2010
Scaling up antiretroviral therapy for HIV prevention

- The greatest treatment (and prevention) impact is with delivery of ART to those with lower CD4 counts – and scale-up is not sufficient yet for this group

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Transmissions</th>
<th>Person-Years</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 200</td>
<td>8</td>
<td>91</td>
<td>8.8</td>
</tr>
<tr>
<td>CD4 200-350</td>
<td>41</td>
<td>1467</td>
<td>2.8</td>
</tr>
<tr>
<td>CD4 350-500</td>
<td>24</td>
<td>1408</td>
<td>1.7</td>
</tr>
<tr>
<td>CD4 ≥ 500</td>
<td>29</td>
<td>1592</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Donnell et al. Lancet 2010
PrEP implementation, 2012

• Unlike ART, the research questions here are brand-new

• Multiple open-label projects, in and outside of the US, are planned, for oral PrEP

• Primary goals: can PrEP be done?
<table>
<thead>
<tr>
<th>Topic</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeting</td>
<td>Who to prioritize for PrEP?</td>
</tr>
<tr>
<td>Uptake</td>
<td>Do those who might benefit most from PrEP want it?</td>
</tr>
<tr>
<td>Adherence</td>
<td>Who takes PrEP? Do they take it often enough?</td>
</tr>
<tr>
<td>Sexual behavior</td>
<td>PrEP use as relates to behavior?</td>
</tr>
<tr>
<td>Impact</td>
<td>HIV incidence? Resistance? Costs?</td>
</tr>
</tbody>
</table>
FDA review of PrEP for HIV prevention

- The US FDA is currently reviewing a label indication for emtricitabine/tenofovir (Truvada®) for HIV prevention. On 10 May 2012 an Advisory Committee to the FDA recommended that the label indication be added.

- If approved (FDA decision expected in June), would be the first medication indication for prevention of sexual transmission of HIV.

AIDS RESEARCH

FDA Panel Recommends Anti-HIV Drug for Prevention

Science Magazine May 2012
Next-generation PrEP research

- Pill
- Gel
- Vaginal film
- Vaginal ring
- Injectable
Changing the conversation

How do we talk about the benefits for treatment and PrEP?

(after years of telling people not to get HIV because antiretrovirals are awful)
Changing the conversation

- **Antiretroviral therapy**
  - Treatment is health-preserving and not reflecting late-stage sickness

- **PrEP**
  - PrEP is not life-long – targeted months/years of PrEP might avoid 40+ years of treatment
Guidance will come – for ART, for PrEP, for both as they relate to each other
It is not ART vs. PrEP, or ART or PrEP – greatest impact with implementing effective strategies together

From Cohen Science 2011, model from Cremin and Hallett
Our thoughts for next steps in couples
Partners PrEP: PrEP among heterosexual men and women

☑️ 4758 couples, in which HIV+ partner not yet eligible for ART, randomized 1:1:1 to daily oral TDF or FTC/TDF vs placebo

82 HIV infections

17 TDF
13 FTC/TDF
52 placebo

Reduction in HIV acquisition:
TDF = 67% (95% CI 44%-81%)
FTC/TDF = 75% (95% CI 55%-87%)
Rationale for evaluation of PrEP in heterosexual HIV-1 serodiscordant couples

• Public health relevance
  • In Africa and worldwide, a substantial proportion of new HIV-1 cases occur in coupled relationships.
  • Serodiscordant couples are common: half of partners of HIV-1 infected persons are HIV-1 uninfected
  • PrEP is a strategy under the control of an HIV-1 uninfected person

Discordant couples brochure, Uganda
High adherence to PrEP in HIV serodiscordant couples

PrEP Resolves Tension in a Committed HIV Discordant Sexual Relationship

“Discordance dilemma”

PrEP adherence is opportunity to mitigate tension and strengthen relationship

Ware et al. JAIDS 2012
PrEP and HIV-1 serodiscordant couples

• Both PrEP and ART have been demonstrated to provide substantial protection against HIV infection
  • ART is clearly the priority for HIV+ partners with lower CD4 counts
  • Not all HIV+ partners will start ART, or can/will start immediately
  • PrEP could be used as a time-limited “bridge” to ART start
HPTN 052: HIV transmissions

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28

Immediate Arm: 1

Delayed Arm: 27

Unlinked or TBD Transmissions: 11

PrEP and HIV-1 serodiscordant couples

- Staged use of PrEP, as a bridge to ART, could be an effective and cost-effective public health strategy.

Demonstration project work for PrEP and antiretrovirals for HIV-1 prevention

• Subset of Partners PrEP Study sites in Kenya and Uganda

• Open-label demonstration project among new, high-risk HIV-1 serodiscordant couples

• Assess interest in, uptake of, and adherence to FTC/TDF PrEP & ART (provided according to national guidelines)
  • PrEP as bridge to ART initiation

• Timeline: mid-2012 to 2015
Demonstration project approach – PrEP as bridge to ART in couples

Recruit higher-risk HIV-1 serodiscordant couples

Offer/refer for ART for HIV-1+ partners according to current national guidelines

Accepts ART

Offer PrEP for 6 months to HIV-1- partner

Continue to counsel HIV-1+ partner on ART

Declines ART

Offer PrEP to HIV-1- partner

Not yet eligible for ART

Offer PrEP to HIV-1- partner

Follow HIV-1+ partner and refer for ART when eligible

Timeline: 2012 to 2015

Funding: NIMH/NIH, Bill & Melinda Gates Foundation
Conclusions
Summary

• The **science** is clear: clinical trials provide clear and definitive evidence that antiretroviral treatment and PrEP work for the prevention of sexual transmission of HIV.

• Translating science into **practice** is the priority. PrEP and ART face parallel challenges – including adherence, risk behavior, costs.
Next steps

ART:
• Can we deliver more ART and deliver it better?
• Can we show, through large-scale research and operations, the big impact we expect?
• Will people take it? Especially at higher CD4

PrEP:
• Can we figure out how to deliver this promising strategy in real-world settings?
• Will people take it? For how long? How can motivation be increased?

ART & PrEP together:
• Can we maximize the benefits of these complimentary and revolutionary interventions?
Now is the time to implement what works for HIV prevention. We are at a rare moment – we have a powerful package of interventions for HIV prevention that have the potential to change the direction of the epidemic.
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This is transformative: Let’s Rock and Roll
Thank you

**Partners PrEP Study team**
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- Jinja, Uganda (Makarere U, UW): Patrick Ndase, Elly Katabira, Fridah Gabona
- Kabwohe, Uganda (KCRC): Elioda Tumwesigye, Rogers Twesigye
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- Thika, Kenya (KNH/U Nairobi, UW): Nelly Mugo, Kenneth Ngure
- Tororo, Uganda (CDC, TASO): Jim Campbell, Jordan Tappero, Aloysious Kakia

**Adherence in Partners PrEP Study:** David Bangsberg, Jessica Haberer, Craig Hendrix, Norma Ware, Monique Wyatt, Steve Safren, Christina Psaros

**Additional work on ART & PrEP modeling and preferences:** Katie Curran, Tim Hallett, Renee Heffron, Ann Kurth, Bettina Shell-Duncan

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**Research participants**