Professor Thomas Quinn
Johns Hopkins Center for Global Health, Maryland, USA

6-8 April 2011, Bournemouth International Centre

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Thomas C Quinn M.D.</td>
<td>None declared</td>
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</tbody>
</table>

Date: 1 April 2011
HIV, STIs and Transmission; An Update in Biomedical Prevention

Thomas Quinn, M.D., M.Sc.

Director & Professor of Global Health, Johns Hopkins Univ.
Associate Director for International Research, NIAID

30 Years of AIDS, 30 Million Deaths and 33 Million Infected
2010: A global view of HIV infection
33.3 million people [31.4 – 35.3 million] living with HIV, 2009

22.5 Million

2000: The International Response
Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002–2009

Sub-Saharan Africa

Sub-Saharan Africa

MILLIONS
For Every Person Put on Antiretroviral Therapy in Africa, Two People are Newly Infected with HIV

Biomedical Interventions to Prevent HIV

HIV Sexual Transmission
Transmission Dynamics Model

\[ R_0 = \beta \times C \times D \]

- \( R_0 \): Case reproduction rate
- \( \beta \): Efficiency of transmission (infectiousness of pathogen, prophylaxis)
- \( C \): Mean number of contacts per time (acts, partners)
- \( D \): Duration of infectiousness (natural hx of pathogen, treatment)

HIV treatment reduces viral load and heterosexual transmission

Biological Factors That Affect HIV Sexual Transmission (Infectiousness)

- Level of Blood Viral Load
- Genital Viral Load
- Acute Infection and Advanced Disease
- Immunosuppression
- Genital ulcerations
- Inflammatory STDs
- Cervical ectopy
- Viral Subtype and phenotype X4/R5
- Antiretroviral therapy ↓

Biological Factors That Affect Susceptibility To HIV (Acquisition)

- Viral Load in the Infected Index Case
- Genital ulcers
- Inflammatory STDs
- Cervical ectopy
- Uncircumcised
- HLA Haplotype
- Chemokines/Cytokines
9 Trials of STI Control for HIV Prevention

- **Control of Curable STIs:**
  - Syndromic management or presumptive therapy
  - 5 community randomized trials
  - 1 individually randomized trial
    - Kaul JAMA 2004

- **HSV-2 suppression in HIV-negative participants**
  - 2 randomized trials of acyclovir

- **HSV-2 suppression in HIV-positive participants**
  - 1 randomized trials of acyclovir
    - Celum et al NEJM 2010

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**Trials of STI Control for Prevention of HIV Acquisition**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grosskurth</td>
<td>-0.544</td>
<td>0.191</td>
<td>16.6%</td>
<td>0.58 (0.42, 0.80)</td>
<td></td>
</tr>
<tr>
<td>Wawer</td>
<td>-0.03</td>
<td>0.092</td>
<td>24.3%</td>
<td>0.97 (0.31, 1.16)</td>
<td></td>
</tr>
<tr>
<td>Kamali (pregnant women)</td>
<td>0.131</td>
<td>0.225</td>
<td>11.7%</td>
<td>1.14 (0.73, 1.77)</td>
<td></td>
</tr>
<tr>
<td>Kamali</td>
<td>-0.0843</td>
<td>0.246</td>
<td>10.4%</td>
<td>0.91 (0.56, 1.47)</td>
<td></td>
</tr>
<tr>
<td>Kaul</td>
<td>0.182</td>
<td>0.384</td>
<td>5.2%</td>
<td>1.20 (0.59, 2.45)</td>
<td></td>
</tr>
<tr>
<td>Gregson</td>
<td>0.239</td>
<td>0.364</td>
<td>5.2%</td>
<td>1.27 (0.62, 2.56)</td>
<td></td>
</tr>
<tr>
<td>Celum (HSV-2)</td>
<td>0.149</td>
<td>0.171</td>
<td>15.3%</td>
<td>1.16 (0.83, 1.62)</td>
<td></td>
</tr>
<tr>
<td>Watson-Jones (HSV-2)</td>
<td>0.07666</td>
<td>0.208</td>
<td>9.3%</td>
<td>1.06 (0.64, 1.83)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.96 (0.80, 1.17)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.03$, $Chi^2 = 12.74$, df = 7 ($P = 0.01$), $I^2 = 45\%$

Test for overall effect: $Z = 0.39$ ($P = 0.70$)

- Favora treatment
- Favora control

- **7 negative trials; One RCT showed efficacy in a low HIV incidence/prevalence setting (Mwanza)**
Why were Bacterial STI RCTs largely negative?

- **Population Attributable fraction of HIV due to STIs**
  - STIs play a modest role in HIV acquisition at a population level?
  - Trials were not powered to detect modest effects

![Graph showing population attributable fraction of HIV acquisition due to treatable STDs](image)

- **HSV-2 Suppression in HIV+ co-infected persons to prevent transmission**

  - **4 RCTs with Intermediate end points**
    - HIV shedding, genital and plasma viral load

  - **One RCT with a HIV end point:**
    - (Celum et al, NEJM 2010)
14 Sites for HSV-HIV Transmission Trial

HSV-2 Suppression in HIV+ Co-infected Partners in Serodiscordant couples

- 3408 HIV-serodiscordant couples
- Co-infected HIV+ partners treated with acyclovir 400mg bid
- Primary endpoint HIV transmission

Results

- HIV transmission: $HR = 0.92 \ (0.60-1.41)^{na}$
- HSV-2 GUD: $HR = 0.27 \ (0.20-0.36) <0.001$
- Plasma viral load: $-0.25 \ log_{10} \ cps/mL <0.001$

(Celum et al NEJM 2010.)
Kaplan-Meier Curve for mITT analysis (Linked Transmissions)

HR* 0.92 (95% CI 0.60-1.41); p=0.70

*HR stratified by site

What about...“The STD Paradox”? 

Only 1/9 STD intervention RCTs have led to reduced transmission of HIV

So... either STDs do not “amplify” HIV transmission OR (MORE LIKELY) the interventions were inadequate??

BUT Successful intervention requires that.....
  ✓ The “RIGHT” STD(S) are treated
  ✓ At JUST the right time
  ✓ In JUST the right people (HIV positive or negative)
  ✓ With VERY EFFECTIVE drug(s)
  ✓ For the RIGHT duration of time

And treating STDs has a benefit far BEYOND the effects of HIV prevention
Four Prevention Opportunities

Cohen et al. JCI 2008; Cohen. IAS 2008

The Effect of Circumcision on Acquisition and Transmission of HIV and STIs
Randomised controlled trials of male circumcision to reduce HIV infection (>50% Effectiveness)

Rakai, Uganda
Gray et al. (2007) Lancet; 657 – 66

Kisumu, Kenya

Orange Farm, South Africa
Auvert et al. (2005) PLoS Med; e298

HIV incidence during and after the RCT in Trial Participants

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<tr>
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<td>Trial (N=4,996)</td>
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Gray et al Lancet 2007
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<td><strong>Post-Trial Period</strong></td>
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<td>All Men</td>
<td>0.54</td>
<td>1.66</td>
<td>0.33 (0.18-0.59)</td>
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*Post-trial effectiveness ~ 67%*

*Kong et al CROI 2011*

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</tr>
<tr>
<td>Control Arm Men</td>
<td>0.53</td>
<td>1.65</td>
<td>0.32 (0.15-0.65)</td>
</tr>
</tbody>
</table>

*Post-trial effectiveness ~ 67%*

*Kong et al CROI 2011*
MC Effect on HIV Incidence Post Trial

Cox model: Hazard Ratio=0.32 (0.17-0.61)

Potential Biologic Mechanisms of Protection In Circumcised Males

Circumcision
Anatomic effect by removal of foreskin
Reduced HIV Target cells
Reduced GUD, STI cofactor Effects
Protective Efficacy of MC for STIs

MEN

- GUD
  - RR = 0.53 (0.43-0.64)
- HSV-2
  - RR = 0.72 (0.56-0.92)
- Pro-inflam anaerobes
  - RR = 0.28 (P=0.014)
- HPV
  - RR = 0.65 (0.46-0.90)

FEMALE PARTNERS

- GUD
  - RR = 0.78 (0.63-0.97)
- Trichomonas
  - RR = 0.52 (0.05-0.98)
- Severe BV
  - RR = 0.39 (0.24-0.64)
- HPV
  - RR = 0.72(0.60-0.85)

Antiretroviral Therapy as HIV Prevention

- Prevention of mother-to-child transmission
- Post-exposure prophylaxis
- Pre-exposure prophylaxis
- Treatment of chronic infection
The Impact of ART on HIV Transmission

- ART offered in 7 African countries (part of the Partners in Preventions trial on ACV)
- 3381 HIV serodiscordant couples followed
- 349 “index cases” receiving ART (median CD4=198)
- In spite of counseling, 103 seroconversions occurred, but only 1 seroconversions were with partner on ART (18 days after starting ARVs)
- **ART leads to 92% reduction in HIV transmission**


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Mathematical Modeling

**Universal Test and Treat**

**Utopian Assumptions**

- High uptake of annual testing by all individuals >15 year old
- Treat all HIV+
- 99% decrease in infectiousness
- High adherence and low failure with 1st line ART

Is it practical; is it affordable; what about resistance

*Granich P et al* *Lancet* 2009; 373:48-57
Antiretroviral Therapy as HIV Prevention

- Prevention of mother-to-child transmission
- Post-exposure prophylaxis
- Pre-exposure prophylaxis
- Treatment of chronic infection

TIME
Top 10 Medical Breakthroughs
1. AIDS Drugs Lower the Risk of HIV Infection
CAPRISA 004: Urban and Rural sites

CAPRISA Vulindlela Clinic  
KwaZulu-Natal Midlands

CAPRISA eThekwini Clinic  
Durban City Centre

HIV infection rates in the tenofovir and placebo gel groups: Kaplan-Meier survival probability

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative HIV endpoints</td>
<td>37</td>
<td>65</td>
<td>88</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Cumulative women-years</td>
<td>432</td>
<td>833</td>
<td>1143</td>
<td>1305</td>
<td>1341</td>
</tr>
<tr>
<td>HIV incidence rates (Tenofovir vs Placebo)</td>
<td>6.0 vs 11.2</td>
<td>5.2 vs 10.5</td>
<td>5.3 vs 10.2</td>
<td>5.6 vs 9.4</td>
<td>5.6 vs 9.1</td>
</tr>
<tr>
<td>Effectiveness (p-value)</td>
<td>47%  (0.069)</td>
<td>50%  (0.007)</td>
<td>47%  (0.004)</td>
<td>40%  (0.013)</td>
<td>39%  (0.017)</td>
</tr>
</tbody>
</table>
Impact of adherence on effectiveness of tenofovir gel

<table>
<thead>
<tr>
<th></th>
<th>HIV incidence</th>
<th></th>
<th></th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># HIV</td>
<td>N</td>
<td>TFV</td>
<td>Placebo</td>
</tr>
<tr>
<td>High adherers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;80% gel adherence)</td>
<td>36</td>
<td>336</td>
<td>4.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Intermediate adherers</td>
<td>(50-80% adherence)</td>
<td>20</td>
<td>181</td>
<td>6.3</td>
</tr>
<tr>
<td>Low adherers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;50% gel adherence)</td>
<td>41</td>
<td>367</td>
<td>6.2</td>
<td>8.6</td>
</tr>
</tbody>
</table>

2010: A landmark year for oral PrEP for HIV-1 prevention with iPrEx

- 2499 MSM, randomized 1:1 daily oral FTC/TDF vs placebo
- 11 sites (Brazil, Ecuador, Peru, South Africa, Thailand, US)
- Young high risk MSM:
  - 50% <25 yrs
  - Median 18 partners in 12 wks prior to enrollment
- Completed 2010; excellent safety profile
  - ↑ nausea 1st month
  - Small decrease in bone mineral density (Mulligan CROI 94LB)
Updated iPrEx Efficacy

131 infections after randomization

48 on FTC/TDF
83 on placebo

Updated efficacy estimate (mITT):
42% reduction in HIV acquisition (95% CI 18%-60%)

No reduction in HSV-2 acquisition (Lama, CROI 1002)
- TDF-DP drug levels in blood << EC50 for HSV

iPrEx: Adherence is critical to efficacy

Efficacy by as-treated analysis (data as of Feb 21, 2011)

High (≥ 90% adherence; 49% of visits)  
68% efficacy

Intermediate (50-90% adherence; 33% of visits)  
34% efficacy

Low (< 50% adherence; 18% of visits)  
16% efficacy

- 9% of seroconverters had detectable drug at first HIV+ visit vs 51% of nonseroconverters

Grant et al, NEJM 2010
I split the text into different boxes so it would be easier to manipulate

got better photo from article

tmaddox, 09/02/2011
Investigation:
Ongoing PrEP efficacy studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Sponsor/ Funder</th>
<th>Population</th>
<th>N</th>
<th>PrEP Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>CDC</td>
<td>IDU</td>
<td>2400</td>
<td>TDF</td>
<td>Fully enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results 2012</td>
</tr>
<tr>
<td>Kenya, Uganda</td>
<td>UW / BMGF</td>
<td>HIV discordant couples</td>
<td>4758</td>
<td>TDF, FTC/TDF</td>
<td>Fully enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results 2012</td>
</tr>
<tr>
<td>Kenya, South Africa, Tanzania, Zimbabwe</td>
<td>FHI / USAID &amp; BMGF</td>
<td>Women</td>
<td>3900</td>
<td>FTC/TDF</td>
<td>49% enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results 2013</td>
</tr>
<tr>
<td>South Africa, Uganda, Zimbabwe</td>
<td>MTN / NIH</td>
<td>Women</td>
<td>5000</td>
<td>TDF, FTC/TDF, Vaginal tenofovir gel (daily)</td>
<td>65% enrolled</td>
</tr>
</tbody>
</table>

Safety, efficacy, resistance & costs of TDF & FTC-TDF will inform choice of drugs for PrEP roll-out

Key challenges in future implementation of PrEP: impact on study design

• Is it safe to give ARV drugs to healthy people?

• Will those who get infected have HIV that is resistant to the PrEP antiretrovirals? Will this affect their subsequent care and choice of ARV treatment?

• Will healthy people be willing to take medication everyday or at the time of sex for long periods?

• Is this an affordable and practical HIV prevention strategy for scale-up if it is efficacious?

• Will there be behavioral disinhibition / risk compensation?
Successes In Prevention

• ARVs for PMTCT (>90%)
• ARVs for Discordant Couples (>90%)
• Male Circumcision (>68% and lifelong)
• PrEP (42%) (up to 73% if >90% adherent)
• Microbicide (39%, but >54% if 80% adherent)
• Thai vaccine (31%)

Combination, high impact HIV prevention

Should be evidenced-based for a given population, targeted, integrated & achieve...

- Synergies of partially effective interventions from combining interventions that
  - Reduce HIV infectiousness (eg ART), and
  - Reduce HIV susceptibility (eg male circumcision, PrEP, vaccine)
- High coverage

Coates, Lancet 2008