HIV Prevention with Long Acting Agents

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Four Prevention Opportunities

- Behavioral, Structural
  - STDS, Circumcision, Condoms
- EXPOSED (precoital/coital)
  - Vaccines, ART PrEP, Microbicides, Antibodies
- EXPOSED (postcoital)
  - Vaccines, ART PEP
- INFECTED
  - Treatment of HIV to Reduce Infectivity

Cohen et al., JCI, 2008
Cohen et al., JIAS, 2008
TDF/FTC was FDA Approved for use for Prevention on July 16, 2012

BUT... success depends on adherence.
Sexually Transmitted Infections

<table>
<thead>
<tr>
<th></th>
<th>Double-Blind</th>
<th></th>
<th>Open-Label</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median FU: 9.3 months</td>
<td>n=400</td>
<td>Median FU: 18.4 months</td>
<td>n=362</td>
</tr>
<tr>
<td>Nb Pt (%)</td>
<td>Nb Cases</td>
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<td>Nb Cases</td>
<td></td>
</tr>
<tr>
<td>Chlamydiae</td>
<td>81 (20)</td>
<td>114</td>
<td>122 (34)</td>
<td>158</td>
</tr>
<tr>
<td>Gonorrheae</td>
<td>88 (22)</td>
<td>123</td>
<td>117 (32)</td>
<td>175</td>
</tr>
<tr>
<td>Syphilis</td>
<td>39 (10)</td>
<td>45</td>
<td>68 (19)</td>
<td>77</td>
</tr>
<tr>
<td>HCV</td>
<td>5 (1)</td>
<td>5</td>
<td>5 (1)</td>
<td>5</td>
</tr>
<tr>
<td>All STIs</td>
<td>147 (37)</td>
<td>287</td>
<td>210 (58)</td>
<td>415</td>
</tr>
</tbody>
</table>

**Incidence rate of first STI**

35.2 vs 40.6 per 100 PY in the double-blinded and OLE phases
## HIV Incidence (mITT Analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (double-blind)</td>
<td>212</td>
<td>6.60 (3.60-11.1)</td>
</tr>
<tr>
<td>TDF/FTC (double-blind)</td>
<td>219</td>
<td>0.91 (0.11-3.30)</td>
</tr>
<tr>
<td>TDF/FTC (open-label)</td>
<td>515</td>
<td>0.19 (0.01-1.08)</td>
</tr>
</tbody>
</table>

Median Follow-up in Open-Label Phase 18.4 months (IQR:17.5-19.1)

97% relative reduction vs. placebo
DAPIVIRINE VAGINAL RINGS

Vaginal rings:

- Potential for better adherence
- Sustained and controlled drug release
- Avoid systemic exposure to drug
- Female controlled

Dapivirine: NNRTI with activity against many HIV subtypes

Limitations: limits of diffusion; age related protection; adherence

2 Phase III RCTs, women 18-45
Monthly replacement of ring

ITT: 27-30% reduction incidence
Open Label Extensions?
Regulatory decisions?
Multipurpose utility?
CABOTEGRAVIR: GSK126744 Long Acting (744LA)

Favorable attributes for PrEP:
• High genetic barrier to resistance
• PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

Muller et al, European Journal of Pharmaceutics and Biopharaceutics, 2011
Sreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012
# HPTN 083: CAB LA 600mg

To Prevent HIV Acquisition in MSM and TGW

Landovitz and Grinsztejn, *Protocol Chairs*

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Daily oral CAB and TDF/FTC placebo</th>
<th>TDF/FTC and oral CAB placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAB LA at two time points 4 weeks apart and every 8 weeks thereafter and TDF/FTC placebo</td>
<td>TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter</td>
</tr>
<tr>
<td>Step 2</td>
<td>Open-label TDF/FTC to cover the PK tail</td>
<td>Open-label TDF/FTC to Cover the PK tail</td>
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**Primary Objective:** Reduce HIV Incidence (*non-inferiority*, double blind, double dummy design)

N=4500; Study duration: Enrollment 24-30 months; follow-up ~ 4.5 years

**Enrollment goals:**
- *Minimum* 50% of US enrollment Black MSM (~ 950)
- Overall minimum 10% TGW (~ 450)
- Overall > 50% under age 30
Status of Site Activation – 43 Sites

• All US sites activated (27)
• South America (11)
  – Brazil: One of 4 sites activated (Rio de Janeiro)
  – Argentina/Peru: Pending
• Asia (4)
  – Thailand: All 3 Sites Activated
  – Vietnam: Activated
• Africa (1)
  – Cape Town Activated
**HPTN 084: CAB LA 600mg**

To Prevent HIV Acquisition in Women
Delaney-Moretlwe and Hosseinipour, *Protocol Chairs*

<table>
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<th>Step 1</th>
<th>Daily oral CAB and TDF/FTC placebo</th>
<th>Oral TDF/FTC and oral CAB placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CAB LA and oral TDF/FTC placebo at two time points 4 weeks apart and every 8 weeks thereafter</td>
<td>Oral TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter</td>
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| Step 2 | Open-label oral TDF/FTC to cover the PK tail | Open-label oral TDF/FTC to cover the PK tail |

**Primary Objective:** Reduce HIV Incidence *(superiority, double blind, double dummy design)*

**Study duration:** Enrollment 24 months; follow-up up to 4.5 years, N=3200
Status of Site Activation – 20 Sites

- 6 Sites Activated
  - Gabarone
  - Soweto PHRU
  - Ward 21
  - St. Mary’s
  - Parirenyatwa
  - Zengeza

- Remaining 14 to be activated after the next protocol training in April 2018
While much is said about other designs:
- OPEN label was not recommended by FDA
- STDS are not necessarily a surrogate
- STDS may (or may not) effect the efficacy of the experimental agent
- Historical incidence may be flawed with expansion of ART
- Exposure is not predictable
Subcutaneous PrEP Implants

- Many strategies
- Simple insertion AND removal
- Long-acting (months to years)
- PrEP + contraception?
- Current development:
  - TAF, EFdA (MK-8591), Cabotegravitir

Preclinical assessment of MK-8591 as PrEP

Martin Markowitz M.D.
Anna and George Professor of Clinical Infectious Diseases
Aaron Diamond AIDS Research Center
New York, New York
Development of Broad Neutralizing Antibodies (BnABs)

The initial neutralizing antibody response to HIV "autologous nAb" with 10~20% Broadly neutralizing antibodies.

HIV-1

The transmitted-Founder virus

Escape virus

Antibody

The initial neutralizing antibody response to HIV "autologous nAb"
Current mAbs are More Potent and Broadly Reactive than Previous mAbs

190 diverse Env-pseudoviruses

CAVD David Montefiori (PI)
NVITAL Bailar, Louder et al.
Passive Antibody Prevention
Phase IIB Efficacy Studies

AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults: MSM in Americas & Heterosexual Women in sub-Saharan Africa?

Chairs: Lawrence Corey, HVTN
Myron S. Cohen, HPTN

Co-chairs: Srilatha Edupuganti
Nyaradzo Mgodi
The AMP Studies: Highlights

• Placebo controlled trial of VRC01 mAb (IV), given on q2 month schedule

• Two cohorts:
  - 2,400 MSM + TG in North & South America (increased to 2800)
  - 1,500 Women in sub-Saharan Africa

• Powered to detect 60% efficacy; and to associate VRC01 plasma level with protection

• Both trials opened in April/May 2016

• Both trials near full enrollment!!
AMP Research Sites
47 sites in 11 countries

HVTN 704/HPTN 085, MSM + TG
HVTN 703/HPTN 081, Women
Enrollment and Retention Updates

7u03/081
African Women

- 1,491 enrolled
- 78%
- 95% retention through 13981 clinic visits
- 99% adherence of 7167 infusions

704/085
MSM + TG

- 2157 enrolled
- 80%
- 94% retention through 23639 clinic visits
- 100% adherence of 11779 infusions
bnAbs prevent HIV-1

Combinations of bnAbs and a trispecific antibody can bind to virions and prevent HIV-1 mucosal infection and elicit antiviral responses in deeper tissue. It is hoped this multitarget approach will prevent resistant breakthrough.

bnAbs in epithelial mucosa
A mixture of two bnAbs, PGDM1400 and PGT121, or a trispecific bnAb prevent infection of CD4 T cells from HIV-1.

bnAbs in deeper tissue
bnAbs can also protect tissues from HIV-1 infection through natural killer cells or other phagocytic cells, with no latent or persistent viral replication in lymphoid tissue.
BnAB Additional Considerations

**Criticism:** No product will evolve, results can only be used to inform vaccine development

**Criticism:** A negative result cannot be interpreted

**Criticism:** Only a subcutaneous formulation is commercially viable

**Criticism:** BnABS are too expensive and complex to be of any public health benefit

**Response:** But...industry seems attracted to BnABS (PG121, N6, others); they must know something the critics don’t know
Acknowledgements

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• Study participants and participating communities

• Site investigators, staff, and community representatives

• BMGF, USAID, PEPFAR/OGAC, ViiV, Gilead and other industry partners