Pre-exposure Prophylaxis: Long Acting Agents

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## Component Recommendation

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Risk assessment</td>
<td>▪ PrEP indicated for those at <em>substantial</em> HIV risk</td>
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<tr>
<td>Eligibility</td>
<td>▪ HIV negative, adequate renal function, no HBV</td>
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<tr>
<td>Dosing</td>
<td>▪ 1 FDC tablet, once daily; not intermittent*</td>
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<td>Follow-up</td>
<td>▪ Testing for HIV every 3 mos</td>
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<td>▪ Counseling on risk reduction and testing creatinine at 3 mos and then annually</td>
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<td></td>
<td>▪ Testing for STIs every 6 mos, even if asymptomatic</td>
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<td>Discontinuation</td>
<td>▪ PrEP not meant for lifelong administration but rather for periods of highest risk</td>
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HPTN goals for PrEP

• Optimize use of oral PrEP (FTC/TDF)
  – Better understand populations who will most benefit
  – Optimize dosing
  – An alternative oral agent (maraviroc)?

• Develop novel agents for PrEP
  – Long-acting interventions
    • Injectable antiretrovirals
    • Monoclonal antibodies?

• Next steps
  – Adjunctive developmental studies
  – Phase III trial(s)
INJECTABLE PREP
HPTN 076: EVALUATION OF TMC278LA (RILPIVIRINE LA)

Objectives:
– Safety of long-term dosing
– Tolerability
– Acceptability
– Pharmacokinetics

132* Women (ages 18-45)

88 TMC278LA

44 Placebo

2:1 randomization
active : placebo
CABOTEGRAVIR
GSK1265744 Long Acting (744LA)
Integrase Inhibitor

Favorable attributes for PrEP:
• High barrier to resistance
• Half life of 21-50 days

Muller et al, European Journal of Pharmaceutics and Biopharmaceutics, 2011
Spreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012
CAB LA (GSK744) is an Effective PrEP Agent in Rectal Challenge in Rhesus Macaques

Andrews et al.  20th CROI 2013

8/8 protected
8/8 infected

Drug+virus challenges
Washout

GSK744
GSK744

Percent Aviremic in Plasma

Weeks Post First Challenge

0 2 4 6 8 10 12 14 16

0 20 40 60 80 100

Placebo
GSK744LAP

p<0.0001

Weekly SHIV 162p3 50xTCID50 Intrarectal Challenge in Male Rhesus Macaques (viral challenge weekly 0-7)

Andrews et al.  20th CROI 2013

Drug+virus challenges

GSK744

Range of GSK744 exposure in POC study

Open symbols = point of infection

Plasma GSK744 (µg/mL)

Weeks post first challenge

0 2 4 6 8 10 12 14 16 18

0 0.01 0.001 0.0001 0.001 0.01 1

SHIV 162p3 50xTCID50 Intrarectal Challenge in Male Rhesus Macaques (weekly viral challenge starting at Week 0)

Andrews et al.  21st CROI 2014
HPTN 077: EVALUATION OF GSK1265744

Objectives:
- Safety of long-term dosing
- Tolerability
- Acceptability
- Pharmacokinetics

176 HIV-uninfected men and women (ages 18-65)

132* 744LA
44 placebo

3:1 randomization active:placebo
ÉCLAIR – GSK1265744 in US Men

- N=120
- Randomized 2:1 744:placebo
- Similar structure to 077 (4 week oral lead-in, 3 injections, 52 week follow-up)
- Goal 60% MSM – low-to-moderate risk
- 10 US-based sites

- Aaron Diamond Research Center, NY
- NY Blood Center, NY
- Fenway Institute, Boston
- University of Pennsylvania, Philadelphia
- Gladstone Institute of Virology, SF
- Southwest Care Center: Santa Fe
- Whitman Walker Clinic, DC
- Piedmont Hospital, Atlanta
- Columbia University, NY
- Health Research of Hampton Roads, Newport News

Already enrolling
Long Acting PrEP: Concerns

• Tolerance of two injections (4 ml)
• Safety, as drug “removal” is not possible
• Managing discontinuation
  - subtherapeutic levels of ART threaten resistance if HIV is acquired
Antibodies as an Alternative?
Development of Broad Neutralizing Antibodies (BnABs)

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

The transmitted-Founder virus

Escape virus

HIV-1

Antibody

The initial neutralizing antibody response to HIV "autologous nAb"

Continuum with 10~20% Broadly neutralizing antibodies.
Three BIG BnAB Ideas

• Prevent horizontal/vertical acquisition
  - VRCO1 during breast feeding
• Inform vaccine development
  - PK/PD
• Cure HIV infection?
Three BIG BnAB Ideas

• Prevent horizontal/vertical acquisition (PrEP)
• “Prove” a vaccine will work
• Cure HIV infection?

*i.e. Barouch et al. Nature 503:224, 2013*
Three BIG BnAB Ideas

• Prevent horizontal/vertical acquisition (PrEP)
• “Prove” a vaccine will work
• Cure HIV infection?

Monoclonal Antibodies in Development

- VRCO 1,7 (HVTN104)
- 10E8-Ibalizumab (Aaron Diamond/ Gates)
- PG121 (Ragon/Harvard)
- 3BNC117 (Rockefeller, Cornell)
- Antibody Combinations?
- AAV (Vector, Cal Tech) and PG9 (IAVI)

*West et al. Cell 156, 2014*
*Mascola and Haynes, Immunol Reviews, 2013*
Moving to a PHASE III PrEP Trial

New agents should display:

- Safety advantages
- Administration advantages
- Appropriate tissue penetration
- Limited drug interactions
- Favorable resistance profiles
- Acceptable “cost of goods”
Moving to a PHASE III PrEP Trial

TRIALS MUST

• Focus on accessible and appropriate target population(s) with baseline incidence sufficient to address the questions raised in a timely fashion

• Include proper “comparator” agents

• Meets ethical requirements, and considers and balance equipoise

• Be embraced by the communities involved