Injectable Pre-exposure Prophylaxis

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Transmission of HIV

TDF/FTC was FDA Approved for use for Prevention on July 16, 2012

Success depends entirely on adherence
Alternatives to daily dosing are possible
Truvada PrEP uptake has been limited to date
Perhaps longer acting agents will prove more attractive?
<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>
</tr>
<tr>
<td>Eligibility</td>
<td>▪ HIV negative, adequate renal function, no HBV</td>
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<tr>
<td><strong>Dosing</strong></td>
<td>▪ 1 FDC tablet, once daily; not intermittent* (??)</td>
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<tr>
<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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<tr>
<td></td>
<td>▪ Testing for STIs every 6 mos, even if asymptomatic</td>
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<tr>
<td>Discontinuation</td>
<td>▪ PrEP not meant for lifelong administration but rather for periods of highest risk</td>
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</table>
Optimization of FTC/TDF in MSM

- IPERGAY (CROI 2015)
- PROUD (CROI 2015)
- HPTN 067: varying dosage schedule for FTC/TDF (R4P, Late Breaker IAS)
- HPTN 073: Client centered care coordination (C4) to enhance update and adherence with FTC/TDF among Black MSM
Cabotegravir and Rilpivirine As Two-Drug Oral Maintenance Therapy: LATTE Week 96 Results

David A. Margolis,1 Cynthia C. Brinson,2 Graham H.R. Smith,3 Jerome de Vente,4 Debbie P. Hagins,5 Sandy K. Griffith,1 Marty H. St. Clair,1 Kimberly Smith,6 Peter E. Williams,7 William R. Spreen1

1GlaxoSmithKline, Infectious Diseases, Research Triangle Park, NC, USA; 2Central Texas Clinical Research, Austin, TX, USA; 3Maple Leaf Medical Clinic, Toronto, ON, Canada; 4Living Hope Foundation, Long Beach, CA, USA; 5Chatham County Health Department, Savannah, GA, USA; 6ViiV Healthcare, Research Triangle Park, NC, USA; 7Janssen R&D, Beerse, Belgium
Long-acting rilpivirine for HIV prevention

Akil Jacksona and Ian McGowan

Curr Opin HIV AIDS 2015, 10:253–257
Clinical Pharmacology & Therapeutics

A Compartmental Pharmacokinetic Evaluation of Long-Acting Rilpivirine in HIV-Negative Volunteers for Pre-Exposure Prophylaxis

AGA Jackson, LJ Else, PMM Mesquita, D Egan, DJ Back, Z Karolia, L Ringner-Nackter, CH Higgs, BC Herold, BG Gazzard and M Boffito

Clin Pharmacol Ther. 314, 2014
Selection of Resistance: The Tail

Penrose KJ, Parikh UM, Hamanishi KA, Panousis C, Else L, Back D, Boffito M, Jackson A, Mellors JW.

Selection of rilpivirine resistant HIV-1 in a seroconverter on long-acting rilpivirine (TMC278LA) from the lowest dose arm of the SSAT 040 trial.

HIV R4P Meeting 2014, Cape Town, South Africa, Abstract OA27.01.
HPTN 076: EVALUATION OF TMC278LA (RILPIVIRINE LA)

132* Women (ages 18-45)

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

2:1 randomization
active : placebo
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 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 Vaginal Challenge in Rhesus and Pigtail Macaques

SHIV 162p3 300xTCID50 Intravaginal Challenge in Female Rhesus Macaques, with DMPA (viral challenge Week 1, 5 and 7)

Andrews et al. 21st CROI 2014

SHIV 162p3 50xTCID50 Intravaginal Challenge in Female Pigtail Macaques, no DMPA (biweekly viral challenges x 22)

Radzio et al. 21st CROI 2014
CAB LA (GSK744) is an Effective PrEP Agent in Rectal Challenge in Rhesus Macaques

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

Andrews et al. 20th CROI 2013

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

Andrews et al. 21st CROI 2014
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

Nearing Completion leading to HPTN 083
HPTN 077 – 8 Sites

US Sites
- Los Angeles, California
- San Francisco, California
- Washington, DC
- Chapel Hill, North Carolina

International Sites
- Soweto, South Africa
- Durban, South Africa
- Lilongwe, Malawi
- Rio de Janeiro, Brazil
A Phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, Cabotegravir, in HIV-uninfected Men and Women

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>ARM 1</th>
<th>ARM 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N = 132</td>
<td>N = 44</td>
</tr>
<tr>
<td>4</td>
<td>Daily Oral 744</td>
<td>Daily Oral Placebo</td>
</tr>
<tr>
<td>41</td>
<td>Injections of 744LA at 3 timepoints (every 12 weeks)</td>
<td>Injections of 744LA placebo at 3 timepoints (every 12 weeks)</td>
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<tr>
<td>81</td>
<td>Follow-up Phase (Tail Phase)</td>
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Primary objective: Evaluate the safety and tolerability of the cabotegravir LA injectable through Week 41 in HIV-uninfected men and women
Current Status
HPTN 077

As of August 1, 2015:

• 7/8 sites activated and enrolling; Lilongwe to be activated soon

• 60/176 enrolled to date (34%), 25 men and 35 women

Note: These numbers will change since enrollment is currently ongoing
HPTN 083

PHASE 2B/3 DOUBLE BLIND SAFETY AND EFFICACY STUDY
OF QUARTERLY INJECTABLE GSK 1265744
(CABOTEGRAVIR) COMPARED TO DAILY ORAL
TENOFOVIR/EMTRICITABINE (TRUVADA), FOR
PRE-EXPOSURE PROPHYLAXIS IN HIV UNINFECTED MSM
AND TRANSGENDER WOMEN
HPTN 083 STUDY SCHEMA

4500 HIV-uninfected MSM in North & South America, Asia will be randomized 1:1 to:

Step 1: Oral TDF/FTC or Oral 744 30 mg daily x 5 weeks (DB)

Step 2: Oral TDF/FTC daily or Injectable 744 800 mg every 3 months (DB)
Continues until 286 seroconversions reached (mean 3.5 py)

Step 3: Open label TDF/FTC daily to cover PK “tail” / post-trial access if locally unavailable

Blinded study duration 101-231 weeks
PK “tail” coverage/OLE 48 weeks

ARM A
1:1
ARM B
Long Acting PrEP: Concerns

• Tolerance of two injections (4 ml)
• Safety, as drug “removal” is not possible
• Managing discontinuation (the tail)
  - subtherapeutic levels of ART threaten resistance if HIV is acquired
THANK YOU