Injectable cabotegravir for HIV prevention – status and updates

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Outline

• Rationale: injectable cabotegravir for PrEP

• Phase II study updates

• Phase III study updates

• Lessons learned
Cabotegravir

- Integrase inhibitor
- LA formulation is low solubility crystalline drug suspended in aqueous vehicle for intramuscular injection
- High genetic barrier to resistance and long half life makes it favourable for PrEP
- HIV treatment studies (with rilpivirine) demonstrate potent anti-HIV activity and high resistance barrier
- NHP studies demonstrate high levels of protection against rectal, vaginal, parenteral or penile SHIV challenges

Source: Andrews, 2014; Radzio, 2015; Andrews, 2015; Andrews, 2017; Dobard, 2018
CAB LA development programme

Early Phase

- Treatment (adults)
  - LATTE (n=243)
  - LATTE-2 (n=309)
- Treatment (<18 yrs.)
  - MOCHA\textsuperscript{a} (n\approx155)
- Prevention MSM/TGW
  - ECLAIR (n=127)
- Prevention women
  - HPTN 077 (n=199)

Phase 2

- LATTE (n=243)
- LATTE-2 (n=309)
- MOCHA\textsuperscript{a} (n\approx155)
- ECLAIR (n=127)
- HPTN 077 (n=199)

Phase 3

- FLAIR (n\approx620)
- ATLAS (n\approx570)
  - Q4W dosing
- ATLAS 2M (n\approx1020)
  - Q8W dosing

Phase 3b

- HPTN 083 (n\approx4500)
- HPTN 084 (n\approx3200)
Objective: To evaluate the safety and tolerability of the injectable agent in HIV uninfected US men.

- Oral phase
  - Oral cabotegravir 30mg once daily
  - Oral placebo once daily
- Injection phase
  - Long-acting cabotegravir 800mg intramuscular every 12 weeks
  - Saline placebo intramuscular every 12 weeks
- Follow-up phase
  - Follow-up
  - NA
- Follow-up

Two x 2-ml injections IM
ECLAIR: predicted vs. observed CAB LA PK

Only 30-37% achieved target concentrations $\geq 4 \times PAIC_{90}$

Markowitz et al, Lancet HIV 2017
**Objective:** To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.

### CAB LA Phase II – HPTN 077

#### Cohort 1
- **3:1 Randomization**
- **Oral Phase**
  - 30mg CAB PO QD
- **Injection Phase**
  - 800mg long-acting CAB every 12 weeks
- **Tail Phase**
  - Tail phase
- **Visit Week**
  - 0, 2, 5, 9, 13, 17, 23, 29, 35, 41, 53, 65, 77, 81

#### Cohort 2
- **3:1 Randomization**
- **Oral Phase**
  - 30mg CAB PO QD
- **Injection Phase**
  - 600mg long-acting CAB every 8 weeks
- **Tail Phase**
  - Tail phase
- **Visit Week**
  - 0, 2, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 53, 65, 77, 81
HPTN 077: CAB LA $C_T$ following each injection

Landovitz, PLoS Medicine 2018
CAB LA Ph II: safety and acceptability

HPTN 077: proportion reporting any injection site reactions

- Ph II acceptability studies show high preference for injection vs. pills
  - despite ISR because of convenience and perceived adherence advantage
  - Very few discontinuations d/t ISR
- In 077, injection preference increased with time and was higher in non-US sites (95%)
ADVANCE: Percentage change in weight over time: women

Weight gain more severe in female patients, and with lower CD4+ counts and higher viral loads

Moorhouse, IAS 2019; Venter, NEJM 2019
HPTN 077: No differences in weight gain

- Distributions did not vary by race, sex at birth, BMI category, smoking status or geographic region

Landovitz, CID 2019
CAB LA - the PK tail

• When administering agents with long t1/2 in non-removable method

• May have prolonged sub-therapeutic tail; great concern for poorly adherent

Markowitz, Lancet HIV 2017; Slide modified from John Mellors, FDA 2012
HPTN 077: CAB LA PK tail

Week 60
- Males: 78% <LLOQ, 15% LLOQ - 1x PA-IC90, 8% >4x PA-IC90
- Females: 37% <LLOQ, 40% LLOQ - 1x PA-IC90, 23% >4x PA-IC90

Week 76
- Males: 87% <LLOQ, 13% LLOQ - 1x PA-IC90, 0% >4x PA-IC90
- Females: 58% <LLOQ, 31% LLOQ - 1x PA-IC90, 11% >4x PA-IC90

HPTN 083 and 084: Phase III for CAB LA PrEP

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)

Primary outcome: HIV incidence
HPTN 083 – enrolment progress

43 sites across USA, S. America, Asia, Africa

N=4345 enrolled
Age <30 65%
TGW 12%
US AA 50%
HPTN 084 - study Population

3,200 women who have sex with men
- Female
- HIV negative
- Age 18-45 years
- Sexually active (vaginal intercourse twice in past 30 days)
- Modified VOICE Risk Score 3
- Not pregnant or breastfeeding
- No previous enrollment in vaccine trial and no co-enrollment in other HIV prevention trials
- No contraindications to either agent
HPTN 084 – enrolment progress

- 49% ≤ 25 years,
- 45% not living with partner,
- 33% partner status positive or unknown
- 54% 2+ partners
- High prevalence curable STIs

N=2183

### NTD Prevalence Difference by Exposure

**Source:** Zash, IAS 2018

<table>
<thead>
<tr>
<th>NTDs/Exposure</th>
<th>NTDs</th>
<th>Exposures</th>
<th>% with NTD (95% CI)</th>
<th>Prevalence Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG-Conception</td>
<td>4</td>
<td>426</td>
<td>0.94% (0.37%, 2.4%)</td>
<td>ref (-0.24%, -2.3%)</td>
</tr>
<tr>
<td>Any Non-DTG ART-Conception</td>
<td>14</td>
<td>11,300</td>
<td>0.12% (0.07%, 0.21%)</td>
<td>-0.82% (-0.31%, -2.3%)</td>
</tr>
<tr>
<td>EFV-Conception</td>
<td>3</td>
<td>5,787</td>
<td>0.05% (0.02%, 0.15%)</td>
<td>-0.89% (-0.35%, -2.4%)</td>
</tr>
<tr>
<td>DTG Started During Pregnancy</td>
<td>0</td>
<td>2,812</td>
<td>0.00% (0.00%, 0.13%)</td>
<td>-0.94% (-0.27%, -2.3%)</td>
</tr>
<tr>
<td>HIV-Neg</td>
<td>61</td>
<td>66,057</td>
<td>0.09% (0.07%, 0.12%)</td>
<td>-0.85% (-0.27%, -2.3%)</td>
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</table>
CAB LA in women of reproductive potential

- **HPTN 084 protocol modified LOA #3**
  - Require women to be on a long-acting contraceptive at enrolment
  - No evidence of drug-drug interactions with contraceptives
    - Will expand the dataset to include data on DMPA, NET-EN and etonorgestrel
  - Target pregnancy incidence <3%

- **For those that become pregnant**
  - Unblinding at confirmed pregnancy visit
  - Referral for early ultrasound and follow up
  - Plan for co-enrolment in a protocol to assess CAB PK in breastmilk and infant plasma
Contraceptive use at most recent visit  
(n=2145)

- DMPA: 52%  
- Implant: 31%  
- NET-EN: 9%  
- IUCD: 6%  
- Sterilisation: 1%  
- COC*: 1%  

*COC users all transitioned to TDF/FTC

Source: SCHARP report, 9 SEPT 2019
**NTD Prevalence by Exposure**

Since May 2018
1 NTD/1275 additional exposures to DTG at conception

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>5/1683</th>
<th>15/14792</th>
<th>3/7959</th>
<th>1/3840</th>
<th>70/89372</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.30% (0.13, 0.69)</td>
<td>0.10% (0.06, 0.17)</td>
<td>0.04% (0.01, 0.11)</td>
<td>0.03% (0.0, 0.15)</td>
<td>0.08% (0.06, 0.10)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>0.20% (0.01, 0.59)</td>
<td>0.26% (0.07, 0.66)</td>
<td>0.27% (0.06, 0.67)</td>
<td>0.22% (0.05, 0.62)</td>
</tr>
</tbody>
</table>
What have we learned

- >6,500 ppl across diverse geographies enrolled in these trials
- High risk i.e. PrEP eligible
- Injections appear highly acceptable
- Stigma observed with oral PrEP (and ART) still present in many communities
- Risk factors that shape HIV e.g. gender-based violence, alcohol and substance use, STIs are highly prevalent
  - Influence participation and need for services
What have we learned

• 2\textsuperscript{nd} generation trial with two active products
  – More complex design
  – Consideration of AE attribution
  – Need to be attentive to effects of long acting product
    • Needed if effective?
  – Effects on conventional HIV testing algorithms
    • Need for new approaches
    • Education of health care providers and participants
Next steps

• Protocol revisions for both trials underway
• Addition of adolescent sub-studies
• Complete trials and plan for success
  – Learn lesson from oral PrEP introduction
  – E.g. Biopic initiative to consider questions that can be addressed in current trials or trials post-licensure
  – Future products
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  Network partners
  SMC, DSMB

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