The Need For LA Therapy

- Adherence to oral antiretrovirals can be variable
- Special populations
  - Drug and alcohol abuse
  - Psychiatric illness
- Antiretroviral stigma
- Consumer preference
LA PrEP in MSM

a. Willingness to use quarterly LAI-PrEP

- Yes: definitely
- Yes: probably
- No: probably not
- No: definitely not
- I don’t know / maybe

b. Preference for route of administration

- Prefer oral pill
- Prefer injection
- Neither acceptable
- I don’t know

Meyers K et al. PLoS ONE 2014
Uses for LA Antiretrovirals

- Treatment of chronic HIV infection
- Prevention of HIV infection
  - Pre-exposure prophylaxis (PrEP)
  - Post-exposure prophylaxis (PEP)
  - Prevention of mother to child transmission (MCT)
- Current development of LA antiretrovirals is for both treatment and prevention indications
Long-Acting Antiretroviral PrEP Candidates
Requirements for LA ARV

- Infrequent dosing (~ 2-3 months)
- Practical injection volume (≤ 4mL)
- Stable formulation ideally without cold chain requirements
- Potential LA antiretroviral products
  - TMC278 LA (Rilpivirine)
  - GSK 744 (Cabotegravir)
  - EFdA
Rilpivirine LA

- NNRTI licensed as Edurant® for the treatment of chronic HIV infection (25 mg)
- PA EC<sub>90</sub>: 12.2 ng/mL
- Plasma trough levels in successful treatment populations: ~70 ng/mL
- Formulation: 300 mg / mL
- PrEP doses evaluated
- 300 - 1200 mg QD & Q8 weeks
Rilpivirine LA PrEP Trials

- Phase 1
  - Dose ranging formulation studies
  - SSAT 040
  - MWRI-01

- Phase 2
  - HPTN 076 Phase 2 study
SSAT 040 Phase I Trial

- Study design
  - HIV-negative volunteers at low risk for HIV
- Single IM dose
  - 20 women per arm at 300 mg, 600 mg or 1200 mg (n=60)
  - 6 men at 600 mg
- Primary objective
  - Characterize plasma, genital and rectal PK

Jackson A et al. Clinical Pharmacology & Therapeutics 2014
Rilpivirine Levels in Plasma

Jackson A et al. Clinical Pharmacology & Therapeutics 2014
MWRI-01 Study

**Baseline Visit**
- Rilpivirine 1200 or 600 mg
- Cervicovaginal Rectal fluid & tissue
- Compartmental PK & explant challenge

**Follow-up Visits**
- Monthly for up to 6 months
  - Cervicovaginal Rectal fluid & tissue
  - Compartmental PK & explant challenge

Rilpivirine PK/PD

Rilpivirine PK/PD

HPTN 076

- Phase 2 study of the safety and acceptability of rilpivirine LA in women
- 136 women enrolled in the US, South Africa, and Zimbabwe
- Oral run in phase followed by six injections of 1200 mg of rilpivirine LA
HPTN 076 Results

**2a.**
Plasma RPV Conc (ng/mL) over visits.

**2b.**
Plasma RPV Conc (ng/mL) over visits.

**3a.**
Attributes LIKED

**3b.**
Attributes DISLIKED
Cabotegravir

- Integrase inhibitor analogue of dolutegravir
- Oral dose ≤ 30mg
- Highly protein bound
  - PA IC$_{90}$: 166ng/mL
- Formulation: 200 mg/mL
- Dosing varies by indication
  - PrEP: 600 mg Q4 x 2 then Q8 weeks
  - Treatment: 400 mg Q4 weeks
Non Human Primate Data

Andrews CD et al. Science 2014 (Rectal)
Andrews CD et al. Sci Trans Med 2015 (Vaginal)
Andrews CD et al. AIDS 2017 (IV)
Cabotegravir LA PrEP Trials

- Phase 1 Program
  - Multiple dose ranging formulation studies\(^1\)
- Phase 2
  - ÉCLAIR study
  - HPTN 077 study
- Phase 3
  - HPTN 083 study
  - HPTN 084 study

\(^1\) McGowan I. Future Virology 2015
ÉCLAIR Study

Phase 2a study conducted at 10 sites in the US
N = 127 HIV-negative men
Three IM injections

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Week 2</th>
<th>Week 4-5</th>
<th>Week 17</th>
<th>Week 29</th>
<th>Week 41</th>
<th>Week 53</th>
<th>Week 65</th>
<th>Week 77</th>
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<tbody>
<tr>
<td>Oral phase</td>
<td>Injection phase</td>
<td>Follow-up phase</td>
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<tr>
<td>Oral cabotegravir 30mg once daily</td>
<td>Long-acting cabotegravir 800mg intramuscular every 12 weeks</td>
<td>Follow-up</td>
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<tr>
<td>Oral placebo once daily</td>
<td>Saline placebo intramuscular every 12 weeks</td>
<td>NA</td>
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</tr>
</tbody>
</table>

Markowitz M et al. Lancet HIV 2017
Approximately 66% of participants had Week 12 cabotegravir levels < than the target PK (4 x PA-IC90)

Markowitz M et al. Lancet HIV 2017
HPTN 077: Safety, tolerability and pharmacokinetics of injectable cabotegravir (CAB) in men and women

Primary objective: Evaluate the safety and tolerability of the injectable CAB in HIV-uninfected men and women.
EFdA

- Potent nucleoside RTI originally derived from soy
- 10 mg dose associated with 1.64 log reduction in viral load
  - 2 log drop seen in GI and FRT tissue in humanized animal models*
- PK profile might allow for once weekly dosing
- An LA formulation might last 1 year

*Shanmugasundaram U et al. PLoS One 2017
BLT Mouse EFdA Study Design

*Shanmugasundaram U et al. PLoS One 2017*
BLT EFdA Data

*Shanmugasundaram U et al. PLoS One 2017
Ongoing LA Therapy Trials

- The Antiretroviral Therapy as Long Acting Suppression (ATLAS) study
- The First Long-Acting Injectable Regimen (FLAIR) study
  - N = 570, Global study
  - Rilpivirine 600mg & Cabotegravir 400mg
  - Monthly dosing
- Primary data availability July/August 2018
Adherence and Tolerability of LA Antiretrovirals
Adherence to LA Antiretrovirals

- Rilpivirine LA and cabotegravir LA have only been evaluated in the context of clinical trials
- Adherence data may vary in the real world and be influenced by treatments indication
  - Treatment versus prevention
- Adherence may be better when LA antiretrovirals are used for treatment
The Patient’s Perspective

- It seems to me that it’s much better because you simply don’t have to worry about anything. If you go on a trip, you don’t have to bring your pills or take anything at all along. It’s just that. You come once a month and you’re done. You follow your “normal life”. You come once a month. You get the shot and it’s over. You don’t have to be thinking everyday …oh I forgot to take the pill. Or …when did I take it last… You just don’t worry about anything. In reality, taking the pill everyday keeps it present [HIV]…you have it more present…and the shot is just once a month…you remember it when you come in and the rest of the time you can basically forget it.-Spain, MSM

LATTE-2 Study
“I’m thinking why not do injectable PrEP because there could be that one night where you’re not even planning for that, you’re like oh wait I have to take pills for a week before I even consider doing this. Because for men who have sex with men, being spontaneous is there. The hookup culture is so prevalent, where I think it’s just smarter to take injectable PrEP.” -MSM, SF
Tolerability of LA Antiretrovirals
MWRI-01 Study

- Participants reported acceptable levels of anxiety related to injections
- Anxiety was significantly lower among women than men
- Barriers to uptake
  - Costs and potential side effects
  - Fear of needles not a major concern
Injection Site Reactions Over Time

Overall ISR AE Incidence

Looking Towards the Future
Implantable PrEP

Tenofovir alafenamide silicone tubing implant

Biodegradable Implants

Tenofovir alafenamide polycaprolactone biodegradable implant

Solid drug core

Dissolved drug (saturated)

Thin-film polymer membrane

Biological fluid in

Dissolved drug out

Schlesinger EB et al. Pharma Research 2016
Subcutaneous Implant Trocar
Options for Clinical Phase
Challenges of LA PrEP

- Safety
- Acceptability
- Adherence
- Pharmacokinetics
- Resistance
- Operational complexity
The LA PrEP PK Tail

Female participant receiving a single 1200 mg dose of rilpivirine
Persistence of Rilpivirine LA

- RPV was detectable in 7/7 (100%) of plasma samples collected a mean of 541 days after single dose exposure to 1200 mg of RPV LA

McGowan I et al. AIDS Conference 2016
Operational Complexity

One month oral run in phase

Exposure to LA PrEP every 2-3 months
Two IM injections

PrEP Cessation
12 months of Oral PrEP

HPTN-083
Delivery of LA PrEP
LA PrEP and HIV Resistance

Penrose K et al. JID 2016
Resistance

- HIV infection during periods of declining drug exposure may result in the development of resistance.
- NNRTI resistance seen in a SSAT040 study participant who received a 300 mg dose of rilpivirine and who seroconverted.
- Loss to follow-up during implementation may generate large pool of individuals at risk of HIV infection and the development of resistance.
Summary

- Cabotegravir LA and rilpivirine LA have progressed through Phase 1/2 studies
  - Both generally safe and acceptable but ISR common
- Efficacy signals seen for both products
  - Cabotegravir: NHP model
  - Rilpivirine: Explant model
- Phase 3 cabotegravir LA studies ongoing
- The extended PK tail and the potential risk of resistance is the primary concern associated with LA PrEP
Acknowledgments

The study participants

- Study Teams
  - SSAT 040
  - HPTN-076
  - HPTN-077
  - HPTN-083
  - MWRI-01
  - ÉCLAIR
  - LATTE

- Funders
  - NIH/NIAID/DAIDS
  - Bill and Melinda Gates Foundation