Injectable Antiretrovirals
The Promise and the Peril

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The Promise
Long Acting Formulations

- Have been used to improve adherence and prevent missed doses/treatment fatigue in several therapeutic areas
- Contraception: (Depo Provera)
- Schizophrenia: 6 long-acting antipsychotics available (e.g. risperidone, olanzapine, aripiprazole)
- LA ARV products being developed for PrEP and treatment indications
Acceptability of LA PrEP

(a) Willingness to use quarterly LAI-PrEP

(b) Preference for route of administration

Meyers K et al. PLoS ONE 2014
Prevention Product Preference

- VOICE-D study
- In depth interview (N = 68)
- Women asked to make hypothetical choices about product preference

Ariane van der Straten and the VOICE-D Team
Injectable PrEP
Requirements for LA ARV

- Potency and PK profile allowing infrequent dosing (~ 2-3 months)
- Practical injection volume (~ 4mL)
- Stable formulation ideally without cold chain requirements
- Potential products
  - TMC278 LA (Rilpivirine)
  - GSK 744 (Cabotegravir)
  - Monoclonals (Ibalizumab, 3BNC117, 10-1074)
Nanosuspension Formulations

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower injection volumes

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>GSK1265744A (d50 ~200 nm)</td>
<td>Active</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Tonicity agent</td>
</tr>
<tr>
<td>Surfactant System</td>
<td>Wetting/Stabilizer</td>
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<td>TMC278 (d50 ~200 nm)</td>
<td>Active</td>
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<tr>
<td>Glucose</td>
<td>Tonicity agent</td>
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TMC278-LA (Rilpivirine)

- Non Nucleoside Reverse Transcriptase Inhibitor
- Oral rilpivirine licensed as Edurant® for the treatment of chronic HIV infection (25 mg)
- EC$_{50}$: <0.4 ng/mL
- Plasma trough levels in successful treatment populations: ~70 ng/mL
SSAT 040 Phase I Trial

- Study design
  - HIV-negative volunteers, between 18–50 years, 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 objectives
  - Plasma PK through Day 84 post dose
  - PK in genital tract and rectal fluids/tissues

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

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>F 300 mg (n=20)</th>
<th>F 600 mg (n=20)</th>
<th>F 1200 mg (n=20)</th>
</tr>
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<tbody>
<tr>
<td>$C_{\text{max}}$ ng/mL</td>
<td>33.7 (27.8–39.6)</td>
<td>81.9 (68.7–95.1)</td>
<td>160.2 (137.5–182.9)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ day</td>
<td>7.9 (4.2–11.5)</td>
<td>6.0 (3.4–8.6)</td>
<td>6.2 (4.3–8.1)</td>
</tr>
<tr>
<td>$C_{28}$ ng/mL</td>
<td>19.3 (16.0–22.6)</td>
<td>44.2 (33.6–54.7)</td>
<td>82.9 (66.6–99.1)</td>
</tr>
<tr>
<td>$C_{56}$ ng/mL</td>
<td>9.1 (7.7–10.6)</td>
<td>22.6 (19.1–26.1)</td>
<td>45.3 (35.8–54.9)</td>
</tr>
<tr>
<td>$C_{84}$ ng/mL</td>
<td>6.4 (5.5–7.3)</td>
<td>16.2 (13.0–19.3)</td>
<td>30.2 (23.7–36.6)</td>
</tr>
<tr>
<td>AUC$_{84}$ ng.day/mL</td>
<td>1231.0 (1053.9–1408.1)</td>
<td>2934 (2568.5–3300.4)</td>
<td>5981.6 (5155.9–6807.4)</td>
</tr>
</tbody>
</table>

Jackson A et al. Clinical Pharmacology & Therapeutics 2014
Pharmacodynamic Data

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

Screening Visit

Baseline Visit
- Rilpivirine 1200 mg or 600 mg
- Female (N=12)
- Male (N=6)
- Cervicovaginal Rectal fluid & tissue
- Compartmental PK & explant challenge

FU Visit + 1 month

Monthly FU Visits + 2 months to + 6 months
Compartment

Plasma

Cervicovaginal & rectal fluid

Cervicovaginal & rectal tissue

1200 mg

600 mg

[Graphs showing drug concentration over time for different compartments and dosages]
MWRI-01 Explant Data

Log$_{10}$ [p24] pg/mg

Dose Effect $P = 0.0009$
Visit Effect $P < 0.0001$
Dose*Visit Interaction $P = 0.2131$

McGowan I et al. HIV R4P 2014
MWRI-01 PK/PD

600 mg Single Dose  1200 mg Single Dose

A  Tissue  $P < 0.0001$

B  Plasma  $P < 0.0001$

C  Fluid  $P < 0.001$

D  Tissue  $P = 0.72$

E  Plasma  $P = 0.59$

F  Fluid  $P = 0.68$

G  Tissue  $P = 0.39$

H  Plasma  $P = 0.90$

I  Fluid  $P = 0.35$

Rectal  Cervical  Vaginal
Rilpivirine Development

- Complete MWRI-01 multiple dosing phase
  - 1200 mg every 2 months
- Complete Phase 2 evaluation
  - HPTN-076
- Rilpivirine unlikely to advance to Phase 3 development for prevention
  - Resistance and cold-chain requirement
  - Failure to suppress explant infection
- Also being developed for Rx indication
GSK 744 (Cabotegravir)

- Integrase inhibitor
- Analogue of dolutegravir
- Oral dose ≤ 30mg
- $IC_{50}$: 0.22 nmol/L
- Highly protein bound
- PA $IC_{90}$: 166ng/mL
- LA formulation has 200 mg/mL
Non Human Primate Study

Andrews CD et al. Science 2014
PK Profile of Cabotegravir

- Mean Plasma S/GSK1265744 (μg/ml)
- Time (weeks)

Legend:
- 200mg IM
- 400mg IM
- 800mg IM
- 200mg SC
- 400mg SC
- 4X PAIC<sub>90</sub>
- PAIC<sub>90</sub>

W. Sreen, et al, 19<sup>th</sup> IAC July 2012. Abstract TUPE040
Tissue Concentration Analysis

- Median split, unsplit (range) individual tissue:plasma ratios were
  - 0.16, 0.20 (NQ – 0.40) in cervical tissue
  - 0.19, 0.28 (NQ – 0.70) in vaginal tissue
  - NQ, 0.08 (NQ – 0.20, 0.10) in rectal tissue
Cabotegravir Development

- **Phase 1**
  - Multiple Phase 1 safety studies completed*

- **Phase 2**
  - HPTN-077
    - Brazil, Malawi, South Africa, and the US
    - Currently enrolling

- **Phase 3**
  - HPTN-083
    - In development

*Jackson A and McGowan I Current Opinion HIV and AIDS 2015
The Perils
The Perils of LA PrEP

- Safety
- Acceptability
- Adherence
- Pharmacokinetics
- Resistance
- Operational complexity
Pharmacokinetics
Female participant receiving a single 1200 mg dose of rilpivirine
Resistance

- HIV infection during periods of subtherapeutic 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 vulnerable individuals
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
Implantable Products
Implantable Formulations

Tenofovir alafenamide implant

Gunawardana M et al.
Antimicrob Agents Chemother 2015

Van der Straten A
USAID Grant
In Progress
Summary

- GSK744 and TMC278 have progressed through Phase 1 studies
  - Generally safe and acceptable but ISR common
- Efficacy signals seen for both products
  - GSK744: NHP model
  - TMC278: Explant model
- Phase 2 studies ongoing
- Phase 3 GSK744 study planned
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Thank You