Novel Drug Delivery Mechanisms for HIV Treatment and Prevention: what does the future hold?

Tadesse T. Mekonen (MD, MPH, AAF)
Executive Director: Health Care, Education and R&D, AHI
HIVCS, International HIV Conference
Windhoek, Namibia
15-18, August, 2019
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What to cover?

• Novel Drug Delivery Mechanisms (NDDMs) for prevention and treatment:
  • Long acting implants
  • Trans-cutaneous delivery systems
  • Long Acting Injectables

• What is on the horizon for NDDMs
Prevention
Implants and transdermal drug delivery systems for HIV prevention
Long Acting ARV Implants

• **Potential advantages over injectables:**
  • Removable (inert, or early bio-erodible forms)
  • More consistent and predictable drug release
  • PK not dependent on injection site
  • May remain in place for years (inert, non-degradable subcutaneous versions)

• **Potential disadvantages over injectables:**
  • Specialized device required for insertion
  • Minor surgical procedure to remove
  • Should be removed (if not bio-erodible)
  • Regulated as both a drug and a device
  • Difficulty moving to a generic marketplace
Implant Candidate MK-8591 (EFdA): Formulations Release Effective Drug Concentrations for >180 days

- >180-day extended release from solid state implant formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA)

**Unique properties**

- Unique mechanism of action (translocation inhibitor)
- Exceedingly potent (possible dose in humans of <5 mg/day)
- Lack of cross-resistance with most NRTI’s
- Minor impact of M184V
- More active against HIV-2 than other NRTI’s
- Long half-life of intracellular TP (>72 hours) in rhesus macaques
- Possibility of once-weekly oral dosing
- Possibility of implant formulation with dosing interval of >one year
First-in-Human Trial of MK-8591-Eluting Implants Demonstrates Concentrations Suitable for HIV Prophylaxis for at Least One Year
Multiple mechanisms contribute to the high potency of islatravir against HIV-1 and drug-resistant variants and its high barrier to resistance.
ISL Implant Design Similar to Nexplanon®

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

Initial trial uses prototype implant

Polymer + ISL

Projected human Islatravir plasma concentration (mM)

Simulated Human PK Profiles
Translational PK/PD Modeling Supports PrEP Exposure Threshold of 0.05 pmol/$10^6$ Cells ISL-TP

- Threshold of **0.05 pmol/$10^6$ cells** supported by:
  - ISL rhesus macaque SIV study
  - Efficacious concentrations at 0.5 mg

- 0.05 pmol/$10^6$ cells = ~5.0x in vitro IC$_{50}$
  - In vitro WT IC$_{50}$ of ISL-TP is ~0.01 pmol/$10^6$ cells
  - 0.05 pmol/$10^6$ cells ISL-TP also covers in vitro IC$_{50}$ for M184I/V

Goal is to maintain concentrations above 0.05 pmol/$10^6$ cells for the entire duration of implant placement
Study Design

• Double-blind, placebo-controlled trial in healthy individuals
  – Panel A: 54 mg
  – Panel B: 62 mg

• Eight per panel

• Implant placed sub-dermally in upper arm of non-dominant hand

• Implant in place 12 weeks, followed by 4 weeks post-removal

• PK (plasma and PBMC), ECGs, vital signs, safety labs collected throughout

Study Objectives

• Assess safety and tolerability of an islatravir-eluting implant placed for 12 weeks

• Characterize the PK profiles of ISL and ISL-TP, and estimate the time at which the concentration of ISL-TP would fall below 0.05 pmol/10^6 cells
Intracellular ISL-TP PK Threshold of 0.05 pmol/10^6 Cells Maintained Throughout Placement for Both Doses

- Ratio of TP/plasma remains fairly constant at ~1000:1 – consistent with oral dosing
- Half-life after removal of implant similar to half-life of orally dosed ISL
62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months

- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
  - Projected concentration at 12 months: **0.076 pmol/10^6 cells**
  - Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (~16 months)
Safety Summary

Generally Mild Local Tolerability Effects; No Systemic Effects Noted

- Implants generally well tolerated through 12 weeks
  - 16/16 subjects reported at least 1 adverse event (AE)
  - All drug-associated AEs were mild or moderate in severity
  - No serious AEs and no discontinuations due to an AE
  - Types of AEs observed consistent with those observed with other implants; hematoma and pain/tenderness generally noted after placement or removal procedure

<table>
<thead>
<tr>
<th>Adverse Event (mild unless noted)</th>
<th>Placebo (N=4)</th>
<th>54 mg Implant (N=6)</th>
<th>62 mg Implant (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant site hematoma</td>
<td>4 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Implant site pain/tenderness</td>
<td>2 (50%)</td>
<td>3 (50%); 1/3 moderate</td>
<td>6 (100%); 2/6 moderate</td>
</tr>
<tr>
<td>Implant site erythema</td>
<td>0 (0%)</td>
<td>2 (33%)</td>
<td>5 (83%); 1/5 moderate</td>
</tr>
<tr>
<td>Implant site induration</td>
<td>0 (0%)</td>
<td>5 (83%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Implant site pruritus</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>5 (83%)</td>
</tr>
</tbody>
</table>

- In pooled analysis of vital signs, ECG parameters, and safety laboratory studies, there were no clinically significant differences between the placebo group and the 2 implant groups
- No clinically significant outlying values in any individual set of vital signs, ECG parameters, or safety laboratory studies
Conclusions

• ISL prototype implants were generally well tolerated, with no discontinuations due to an AE and no severe implant-related AEs
  – No laboratory or other signs of systemic reactions
  – Local tolerability (erythema, induration) generally mild and possibly dose dependent

• Both implants (54 and 62 mg) had concentrations above PK threshold at 12 weeks
  – 62 mg implant projected to be well above threshold at 12 months and likely for several months beyond

Supports potential of the ISL implant as a once-yearly PrEP option
Transcutaneous ARV Delivery Systems
Fig. 4. Digital microscopic images of PLGA NMP-loaded bilayer microneedles. (A) Conical MN arrays (19 × 19). (B) Conical arrays (12 × 12). (C) Pyramidal (14 × 14) arrays.

- Vora LK et al. *J Contr Release* 2017
What is it like to wear a microneedle patch?
Transcutaneous ARV Delivery Systems

- Potential advantages over injectables
  - Removable
  - Can be applied by the patient or family member
  - PK not dependent on placement site
  - May remain in place for days or weeks
  - Also appropriate for short-duration drug delivery (per day or week)

- Potential disadvantages over injectables
  - Limited number of drug candidates
  - Complex manufacturing
  - Expensive to manufacture
  - Regulated as both a drug and a device
  - Difficulty moving to a generic marketplace
Estimated cabotegravir concentrations after applying a 30-60 cm$^2$ microneedle patch (adults)

- Rajoli et al. CROI 2018
Long Acting Injectable Agents for PrEP
Effectiveness of Daily TDF/FTC in Clinical Trials

SS Abdool Karim, personal communication
Long-Acting Injectables: Rilpivirine

- Rilpivirine LA is a long-acting nanosuspension for delivery via IM injection (regulatory approvals for HIV treatment in combination with other ART agents – in development with CAB LA)

- **Agent class:** Non-nucleoside reverse transcriptase inhibitor

- **Half-life:**
  - *Oral:* 45 hours
  - *Injectable:* 90 days
**Objective:** To evaluate the safety and acceptability of rilpivirine LA in healthy, HIV-uninfected females.

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>52</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
<td>Daily oral RPV</td>
<td>Six injections of RPV LA 1200 mg every 8 weeks</td>
<td>Follow-up phase (tail phase)</td>
</tr>
<tr>
<td>N = 91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 2</td>
<td>Daily oral placebo</td>
<td>Six injections of placebo every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>N = 45</td>
<td></td>
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</table>
HPTN 076: Phase 2 Safety Results

- Two 2mL IM injections every 8 weeks were safe, well-tolerated, and acceptable to women

- Lower quartile RPV concentrations were consistently above the IC$_{90}$ 8 weeks post injection at all time points

- Cold chain required

Bekker LG, CROI 2017. Abstract 421 LB.
Seroconversion during pharmacokinetic tail after 300 mg IM dose

Summary: Drug Levels, Viraemia, Resistance

HIV RNA (copies/mL)

- Viral load
- Plasma [RPV]
- K101E (%)

Days post RPV injection

HIV exposure

Plasma RPV concentration (ng/mL)

ART = antiretroviral therapy

Penrose K, et al. HIVR4P 2014. Abstract OA27.01
Long-acting Injectables: Cabotegravir

- **Cabotegravir LA** is a long-acting suspension for delivery via IM injection (Currently in advanced development for Maintenance of virologic suppression [with RPV LA] and PrEP-monotherapy)

- **Agent class:**
  Strand-transfer integrase inhibitor

- **Half-life:**
  *Oral*: 40 hours
  *Injectable*: 40-65 days
CAB LA in Development: HPTN 077

Objective: To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.

HPTN077: CAB $C_t$ Following Each Injection

Adapted from Landovitz, R. IAS. 2017

CAB LA 800 mg IM Q12W

Males

- 23% ≥4x PA-IC$_{90}$
- 65% 1x – 4x PA-IC$_{90}$
- 68% <1x PA-IC$_{90}$

Females

- 23% ≥4x PA-IC$_{90}$
- 95% 1x – 4x PA-IC$_{90}$
- 100% <1x PA-IC$_{90}$

CAB LA 600 mg IM Q8W

Males

- 95% ≥4x PA-IC$_{90}$
- 80% 1x – 4x PA-IC$_{90}$
- 84% <1x PA-IC$_{90}$

Females

- 79% ≥4x PA-IC$_{90}$
- 95% 1x – 4x PA-IC$_{90}$
- 87% <1x PA-IC$_{90}$
HPTN 084

A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

Sinead Delany-Moretlwe
Mina Hosseinipour

NIAID/DAIDS DSMB
November, 2018
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)

- Not pregnant or breastfeeding
- No previous enrollment in vaccine trial and no co-enrollment in other HIV prevention trials
- No contraindications to either agent
Enrollment

- Almost halfway!
- Current enrolment $n=1535$
- Since activation of all 20 sites, average enrolment/month 160
- Accrual targeted to complete e/o April 2020

Source: SDMC, data to May 16, 2019
Theoretical Infection-Exposure-Resistance Relationships

- No Drug
- No Resistance
- Infection
- No Infection
- No Resistance

Drug Exposure

Fraction infected or resistant

Markowitz et al, Lancet HIV 2017;4:e331-40
Treatment
LAI: CAB+RPV

• Optimal viral success

• Excellent acceptance
  • Baseline ACCEPT score higher than other chronic conditions
  • ACCEPT score significantly better after switch to CAB/RPV (all time points)
  • Acceptability of ISR’s and pain scored ‘totally/very acceptable’ by 90% and 86%
  • Withdrawals due to ISR’s :4 (1%)

• Preference question: 97% (266/273) of responding participants preferred CAB/RPV*
LA CAB/RPV IM: Still to be answered-Pharmacology

• How long to cover tail?
• What happens to drug levels if renal or hepatic impairment occurs on CAB/RPV?
• What happens to drug levels if TB drugs are used?
• Imputation of DDIs from oral CAB
• Discarding the oral lead in
• Missed doses and oral bridging
LA CAB/RPV IM: Still to be answered - Other

- What about the L74I polymorphism?
- Longer term data
- Long term toxicity
- Pregnancy
- Children and adolescents
- Poorly adherent patients
- Implementation
- Ensuring LMIC roll out
What does the landscape for Novel Delivery mechanisms look like?

### IV or subcutaneous Injectable entry inhibitors
- Ibalizumab
  - CD4
- Levonlimab (PRO140)
  - CCR5
- Albuviridite
  - GP41
- bNABs
  - VRC01
  - 3BNC117
  - 10-1074
  - PGT121
- Combinectin

### Long-acting IM injectables
- GS-6207:
  - Capsid inhibitor
- Elsulfavirine
  - NNRTI
- Raltegravir
  - INSTI
- Atazanavir
  - PI
- Ritonavir
  - PI

### Potential implant/ Biodegradable devices
- MK8591 implant:
  - NRTTI
- TAF implant:
  - NRTI
- GS-9131 implant:
  - NRTI
- DTG polymer device
  - INSTI

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Key Points

• NDDS may transform PrEP and Treatment
  • Better adherence and prevention outcome

• Several questions will still need to be answered
  • PK tail, risk of infection and subsequent resistance is an issue with LAI