Emerging drug delivery systems for the treatment and prevention of HIV

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I have no relevant financial or competing interests to disclose.
Long-acting injectables (LAI) work – now what?

- What about children, adolescents, pregnant women?
- Oral lead in – what, how long, can it be eliminated?
- What is the optimal LA dose and frequency?
- Can injection volumes be reduced?
- How do you manage toxicities and drug-drug interactions, short-term and long term?
- How do you manage missed doses?
- How do you stop therapy?
- How do you manage the long drug exposure after the last dose (PK tail)?
What can we learn from other conditions?

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Oral to Injectable Antipsychotic Therapy

Start your patients on a pathway to INVEGA TRINZA®

<table>
<thead>
<tr>
<th>Paliperidone Formulation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tablets</td>
<td>3-12 mg/day</td>
</tr>
<tr>
<td>Extended release injectable suspension (Sustenna)</td>
<td>39-234 mg once monthly</td>
</tr>
<tr>
<td>Extended release injectable suspension (Trinza)</td>
<td>273-819 mg every 3 months</td>
</tr>
</tbody>
</table>

Slide Courtesy of Courtney V. Fletcher.
Aripiprazole One Day LAI Initiation Regimen

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Tmax</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tablet</td>
<td>3-5 hours</td>
<td>75 hours</td>
</tr>
<tr>
<td>IM suspension, nano particle size (Initio)</td>
<td>16-35 days (27d)</td>
<td>15-18 days</td>
</tr>
<tr>
<td>IM suspension, micron particle size (Aristada)</td>
<td>36 days</td>
<td>54-57 days</td>
</tr>
</tbody>
</table>

With one injection of ARISTADA INITIO and a single dose of oral aripiprazole plus ARISTADA 1064 mg, you can fully dose on day 1 for 2 months of treatment. 

Slide Courtesy of Courtney V. Fletcher.
# Aripiprazole One Day LAI Initiation Regimen

## Recommendations for Missed Doses

<table>
<thead>
<tr>
<th>DOSE OF LAST ARISTADA INJECTION</th>
<th>LENGTH OF TIME SINCE LAST INJECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No supplementation required</td>
</tr>
<tr>
<td>1064 MG EVERY 2 MONTHS</td>
<td>≤10 weeks</td>
</tr>
<tr>
<td>882 MG MONTHLY &amp; EVERY 6 WEEKS</td>
<td>≤8 weeks</td>
</tr>
<tr>
<td>662 MG MONTHLY</td>
<td>≤8 weeks</td>
</tr>
<tr>
<td>441 MG MONTHLY</td>
<td>≤6 weeks</td>
</tr>
</tbody>
</table>
Technology for Drug Delivery

New drug delivery systems for long-acting ART:

➢ Choice
➢ Convenience
➢ Simplify adherence
Characteristics of Successful Long-Acting Agents

- Most developed from oral formulations
  - Low oral dose
  - Medium to long half life
  - Therapeutic concentrations must be low

- Drug development strategies to improve these characteristics: nanoformulations; prodrugs; delivery devices

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily oral dose</th>
<th>Half life</th>
<th>Therapeutic concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA</td>
<td>10 mg</td>
<td>17 h</td>
<td>pg to ng range</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3 mg</td>
<td>20 h</td>
<td>1-5 μg/mL</td>
</tr>
<tr>
<td>Cabotegravir</td>
<td>30 mg</td>
<td>14 h</td>
<td>1.5 μg/mL</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>25 mg</td>
<td>50 h</td>
<td>100 ng/mL</td>
</tr>
</tbody>
</table>
DRUG DELIVERY SYSTEM: VAGINAL RINGS
Multi-Purpose Vaginal Rings: prevention of HIV and contraception

• Could combining contraception plus PrEP increase use and adherence?
  • Antiretroviral for local prevention
  • Progestin hormone for systemic and local pregnancy prevention

• Ongoing trials with tenofovir-levonorgestrel and dapivirine-levonorgestrel
DRUG DELIVERY SYSTEMS:
IMPLANTABLE DEVICES
Implantable devices: Advantages and disadvantages

Advantages
- Removable at end of treatment and for adverse effects
- Potential provide therapy for years with a single insertion
- Potentially improved and more stable pharmacokinetics
- Palpable under skin indicates receipt of drug

Disadvantages
- Minor sterile medical procedure required for insertion (and removal)
- Palpation will not determine duration of use
- Complicated regulatory environment
Biodegradable TAF implant for PrEP

• Sustained release implant for >6 months
  • Users preferred 2 rods for 1 year, 1 rod for 6 months, biodegradable, flexible
  • Existing Sino-implant II applicator for subcutaneous insertion

• Graph demonstrates PK over 2 months
  • Dashed line is predicted concentration for PrEP effectiveness
    • Red circle: plasma TAF
    • Blue dot plasma TFV
    • Green diamond: PBMC TFV-DP

Gratto et al. CROI 2018.
TDF-FTC combination implants

- Potential for refillable implants?
  - Administration demonstrate adequate intracellular TFV-DP and FTC-TB exposure over 83 days.

MK-8591 (EFdA): Prolonged Release After Parenteral Administration

- > 180 day release from a solid formulation after single injection in the rat.
- Ongoing non-human primate study suggests implants can deliver sustained therapeutic concentrations.

Rat


Slide Courtesy of Courtney V. Fletcher.
Extending these characteristics to an Implant

- Bio-erodible and non-erodible implants demonstrate desirable MK-8591 (EFdA) plasma and intracellular concentrations over 6 months

- Stable exposure projected to be similar to weekly oral administration

In situ forming implant development

- Dolutegravir solution injected subcutaneously, within 48 hours forms solid “globule”
  - Stable concentrations from the first day after administration through 9 months
  - Rapid elimination of drug after removal

Kovarova et al. Nature Communications. 2018; 9:4156
DRUG DELIVERY SYSTEMS:
LONG-ACTING ORAL PRODUCTS
Antiretroviral Oral Drug Sustained Release Delivery System

Antiretroviral Oral Drug Delivery System: proof of concept

DRUG DELIVERY SYSTEMS:
PATCHES
MICRONEEDLE PATCHES

• Patch size comparable to a nicotine patch (25 cm²)
• Needles are made up of nanoparticle drug + dissolvable polymer
• USAID supported collaboration for CAB-LA for PrEP:
  • Queen’s University, PATH, ViiV Healthcare, the Population Council and LTS Lohmann Therapie-Systeme AG

https://daro.qub.ac.uk/hiv-microneedles-patch
Novel ARV Drug Delivery: needs and some opportunities to improve patient care

- Long acting fixed dose combinations
  - Combination products to achieve sustained drug delivery

- New drugs
  - Highly potent, selective agents with novel mechanisms of action and additive-to-synergistic with existing agents

- Targeted delivery
  - To achieve improved tissue/organ distribution such as to brain and lymphoid tissues

- Pediatric formulations
  - New formulations and combinations

- Scalable manufacturing is critical to make these products widely accessible

Slide adapted with permission from Courtney V. Fletcher.
Benefits of Choice: An example in contraception

- **Increased choice is** associated with:
  - 12% increase in contraception uptake per additional method offered
  - Better health outcomes (fewer pregnancies, STIs)
  - Longer continuation of the method

- Contraceptive needs and choices vary over a women’s reproductive life
- Preferred methods vary by regions
- Education about methods and reducing financial barriers improve uptake

<table>
<thead>
<tr>
<th></th>
<th>South Africa</th>
<th>Zimbabwe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td>Insert</td>
<td>35%</td>
<td>18%</td>
</tr>
<tr>
<td>Film</td>
<td>13%</td>
<td>45%</td>
</tr>
<tr>
<td>Gel</td>
<td>25%</td>
<td>8%</td>
</tr>
</tbody>
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Novel ARV Drug Delivery: a focus on women

- Are there differences in drug dosing?
  - Differences in drug absorption from IM or subcutaneous injections
- Are there important drug interactions and how do we manage them?
  - Minimally, contraception and other hormone therapies
- Are they safe and effective in pregnancy?
  - If unsafe, how can they be quickly discontinued, and safely transitioned to a new therapy?
  - If safe, do they maintain adequate exposure for both mom and baby?

Finding the solutions to these questions:
1. Start early: consider sex differences during animal studies
2. Early clinical evaluations: enroll a diverse, reflective patient population
3. At all times: ask the right questions a priori and present the findings stratified by sex
Emerging information on long acting formulations: www.leapresources.org

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