Novel Drug Delivery Systems

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Declaration of Interests

www.hiv-druginteractions.org & www.hep-druginteractions.org
Receives sponsorship from AbbVie, Merck, BMS, Janssen, Gilead, ViiV.
Editorial content remains independent.
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See https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/external-engagement/
Menu

1. The ‘long-acting’ concept

2. Injectables & implants
   - properties
   - variability
   - drug interactions
   - devices for delivery

3. Oral delivery
   - simple → complex
   - modifications to existing ARVs
   - nanoformulations
   - new devices
Long – Acting Antiretrovirals

Why ‘long-acting’?

- Improve adherence, convenience (work, travel, etc)
- ‘Fragile’ populations
- Psychological benefit, pill fatigue etc
- Improves bioavailability
- PK ‘smoothing’, reduced variability
- Eliminates food effects
- Eliminates gut-based DDIs
- Improve GI tolerability
- Public health benefits – community VLs, transmissions
Long – Acting Antiretrovirals

- **Terminology**
  - ‘..... - *acting*’ is not the same as
  - ‘.....- *release*’ (prolonged, modified, sustained, controlled)

- **Pharmacology**
  - drug potency
  - rational drug combinations
  - physiochemical characteristics, solubility, release characteristics
  - injection volume and drug loading
  - formulation characteristics
  - route of administration s/c, im, iv, oral
  - oral formulation available (lead-in, lead-out, bridging)
  - tissue partitioning (for PreP)
Long – Acting Formulations

**CABOTEGRAVIR**
- UGT1A1 (minor 1A9) metabolism
- Low DDI potential as victim or perpetrator
- PK optimised for Q4w or Q8w
- Detectable concentrations 1y after single dose

**RILPIVIRINE LA**
- Terminal T½ 30-90 days (G001)
- CYP3A4 substrate
- Low DDI potential as victim or perpetrator
- Cold chain
- Detectable concentrations 1y after single dose
Modifying existing drugs for LA use

- Modifying solubility
  - paloperidone → palmitate
  - triamcinolone diacetate → acetonide
  - olanzepine → pamoate

- Prodrugs
Modifying existing drugs for LA use

• **ProTides**

Mehellou. Chem Med Chem 2016;11:1114
# Tissue Distribution of TFV after Oral TDF or Tenofovir Alafenamide (TAF, GS 7340)*

<table>
<thead>
<tr>
<th>Tissue or Fluid</th>
<th>TDF conc</th>
<th>TAF conc</th>
<th>TAF:TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>88</td>
<td>80</td>
<td>0.9</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.50</td>
<td>4.34</td>
<td>8.2</td>
</tr>
<tr>
<td>Inguinal lymph nodes</td>
<td>0.28</td>
<td>4.12</td>
<td>15</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.63</td>
<td>8.13</td>
<td>12.8</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt; LOD</td>
<td>&lt; LOD</td>
<td>-</td>
</tr>
<tr>
<td>Ileum</td>
<td>0.50</td>
<td>4.61</td>
<td>9.2</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.24</td>
<td>2.14</td>
<td>9.1</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.20</td>
<td>2.05</td>
<td>10.2</td>
</tr>
</tbody>
</table>

* Male beagle dogs.
Ratio of Intracellular Concentrations in Lymph Node MNCs to PBMCs

Quantitative Whole Body Autoradiography of [14C]MK-8591 in Male Rats at 0.5 Hours

Grobler JA, et al.
Abstract #435, CROI 2017
Myristoylated DTG and CAB

DTG and MDTG concentrations after a single im dose of nanoformulated MDTG to macaques

redistribution of MCAB from depot into immune cells?

Zhou et al. Biomaterials 2018;151:53-65
McMillan et al. JAC 2018;62:e01316-17
Nanotechnologies being explored in drug delivery

**Solid Drug Nanoparticles** (SDNs; aka nanocrystals, nanosuspensions, nanodispersions)

- **“Bottom-Up”**
  - Precipitation of solutions
  - Particles in liquid

- **“Top-Down”**
  - Breaking large solids

**Nanocarrier systems** (extremely diverse in composition)

- **Lipid-based carriers**
- **Polymer-based carriers**
- **Inorganic carriers**
- **Biological**
Do LA formulations reduce inter-patient variability?

LA formulations appear to be as variable in terms of PK as their oral counterparts:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral PK variability (AUC CV%)</th>
<th>LA PK variability (AUC CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>26%</td>
<td>50%</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>52%</td>
<td>34%</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>39%</td>
<td>52%*</td>
</tr>
<tr>
<td>Cabotegravir</td>
<td>27%</td>
<td>39%</td>
</tr>
</tbody>
</table>

What are the mechanisms for drug absorption following depot administration?
PK Variability after i.m dosing

Plasma **diazepam** 90min after im injection with 3cm vs 4cm needle

**Cephradine** concentrations after 475mg im in males and females

Steady-state **dapsone** serum concentrations after 375mg im oily injection

CAB LA: Factors influencing drug exposure

<table>
<thead>
<tr>
<th>Gender</th>
<th>BMI 50th Percentile (10th, 90th) (kg/m²)</th>
<th>Mean Estimate of Ka LA (h⁻¹) by BMI Quantile (Relative Difference from 50% Ka LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26.8 (22.8, 30.3)</td>
<td>0.00114 (1.35) ↑35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.000845 (1.00) ↓20%</td>
</tr>
<tr>
<td>Female</td>
<td>26.3 (21.7, 30.4)</td>
<td>0.000407 (1.43) ↑43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.000285 (1.00) ↓24%</td>
</tr>
</tbody>
</table>

Population PK model (oral N=346; LA N=121)
Two compartment model
Covariate analysis (stepwise): age, gender, race, BMI, BSA, weight, HIV status, route, injections/dose
Gender & BMI retained as significant covariates in final model

Ford et al. ICAAC 2014; Abstr H-645
RPV – LA PK and gender

MWRI-01 study (healthy volunteers)
RPV-LA 600mg & 1200mg i.m. single dose
(1200mg data shown below)

- 17% ↓ in males (cf SSAT040, and oral RPV pop PK models)
- High variability
- Levels lower than seen with SSAT040

McGowan et al. Lancet HIV 2016; Sept 16
Jackson et al CPT 2014;96:314
im Gluteal injections – truly ‘intramuscular’?

Karnataka Study

- 700 abdo CTs examined
- 476M, 224F; aged 3-91 years
- Mean gluteal fat 1.98cm (M), 3.0cm (F)
- Average length of a 20-22G needle is 40mm in UK

b) Inflammation s/c plane
c) & d) partially calcified granuloma

Dayananda et al. J Postgrad Med 2014;60:175-78
DDIs involving LA – same or different?

- **First-pass metabolism bypassed**
- **Hepatic metabolism** may be modified by ‘flip-flop’ kinetics

In-silico (PBPK) modelling

Cabotegravir (400 mg) IM monthly at steady state

Rifampicin

Rajoli et al. CROI 2018; # 458
Microneedles: A New Frontier in Nanomedicine Delivery

Potential to Deliver:
• Drug & drug combinations
• Smart insulin patch- glucose sensing
• Vaccines

Yu et al. PNAS 2015;112(27):8260
Taf Implants

Thin-film polymer device
- Tunable (thickness/ surface area)
- stable

Subdermal implant
- Tunable (thickness/ surface area)
- stable

Gunawardana et al AAC 2015
Schesinger et al CROI 2017
‘Gastric-Resident’ dosing for oral delivery

Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy

Other new drugs

**MK8591 (EFdA)**
- Translocation inhibitor
- Potent, extremely long half-life

**GS9131**
- Prodrug of GS9148 - ↑↑↑ intracellular accumulation
- Long i-c half-life

**Atazanavir/ritonavir**
- Encased in folate polymers for macrophage targeting

**Albuvirtide**
- Peptide fusion inhibitor
- Conjugates to serum albumin
- $T_{1/2}$ 11d
- Once-weekly IV with LPVr
- TALENT data presented
Challenges

- **Long-acting formulations**
  - acceptability, consistency & reproducibility of injections
  - special groups - children, low BMI
  - Pregnancy
  - PK variability – does it matter ?
  - Pharmacogenetics
  - Drug interactions
  - Managing the tail
  - missed dosing

- **Targeting the reservoir**
  - can nanomedicines deliver ?
  - are we at ceiling with existing compounds ?
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