Long-Acting Parenteral ARVs – where might they fit?

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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/
LA injectables – where might they fit?

- Update on LA injectables for HIV
- Why LA and where might they fit?
- Special populations - Case Histories
- DDIs involving LA injectables
- Summary and conclusion
Long-Acting Anti-Retrovirals

<table>
<thead>
<tr>
<th>Dose frequency</th>
<th>oral</th>
<th>parenteral</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 7 days</td>
<td>Elsulfavirine</td>
<td>Albuvir tide</td>
<td>Cab + RPV-LA</td>
</tr>
<tr>
<td></td>
<td>Islatavir</td>
<td></td>
<td>VRC01 LS (Islatavir)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(GS 6207)</td>
</tr>
<tr>
<td>Q 28 days or longer</td>
<td></td>
<td></td>
<td>Taf implant</td>
</tr>
</tbody>
</table>

CABOTEGRAVIR

RILPIVIRINE LA
Long-Acting Anti-Retrovirals

- UGT1A1 (minor 1A9) metabolism
- Low DDI potential as victim or perpetrator
- Detectable concentrations 1y after single dose

- Terminal T½ 30-90 days (G001)
- CYP3A4 substrate
- Low DDI potential as victim or perpetrator
- Cold chain
- Detectable concentrations 1y after single dose

Spreen HIV-HEPPK 16 and 17
Crawels HIV-HEPPK 16 and 17
Elsulfavirine: Phase 2 Results

- Market authorization in Russia
- NNRTI pro-drug, t½ of active metabolite VM1500A ~8 days
- Evaluated as qd oral dosing – comparable/better than EFV

In development

- q weekly oral dosing
- s.c. formulation for LA administration

Murphy RL et al. CROI, 2017, Seattle, WA
Long-acting Fusion Inhibitor - Albuvirtide

- Synthetic peptide
- High barrier to resistance
- Dosed iv q weekly
- Binds irreversibly to albumin
- Low DDI potential
- TALENT study (Glasgow 2016):
  - Albuvirtide + LPVr vs TDF/ZDV + 3TC + LPVr
- Market authorization in China
- Exploratory: Albuvirtide + 3BNC117

- TALENT week 48 demonstrated **SUPERIOR EFFICACY** of ABT + LPV/r vs LPV/r+TDF/AZT+3TC
- Virologic success: **80.4% in ABT+LPV/r** group vs. 66.0% in the control group

Wu H et al.. Glasgow Congress on HIV Therapy, 2016. Oral abstract O336
Islatravir (MK 8591)

- Novel mechanism of action (immediate/delayed chain termination, mismatched nucleotide incorporation)
- Potent (EC50 0.2nM in PBMCs)
- Intracellular MK8591-TP T½ 103h
- 1 x 10mg po reduced HIV VL by -1.67 log over 10d

In development
- Q-daily with doravirine
- Q-weekly oral dosing
- Parenteral formulations for LA administration / implant

Grobler et al. CROI 2016; Boston, MA. Abstract 98
Grobler et al. Glasgiw 201
Grobler LEAP meeting, Seattle 2019
Capsid Assembly Inhibitor – GS 6207

GS 6207

- Novel action, unique resistance profile
- High antiviral potency (EC50= 50 pM)
- Resistant variants have low fitness
- Low in-vivo clearance
- Poorly soluble
- Half-life: 30-43 days
- Healthy volunteer PK consistent with long-acting potential
- Given as a subcutaneous suspension

Sagar et al. CROI 2019: Abstract 141
Zheng. LEAP meeting Seattle 2019
Broadly Neutralising Antibodies – VRC01LS

- Disrupts interaction of ENV with CD4
- At least 9 bNAbs in clinical development (targeting CD4 binding site, V3 loop, V1/V2 loop or gp41 membrane-proximal external region).
- Response not universal – may require baseline susceptibility testing.
- Changing 2 amino acids increases binding to FcRn, promoting endosomal recycling and extending serum half-life (4x).
- Developed for q 8-12w dosing iv
- ACTG 5357 – Cab (q4w) + VRC01 LS (q12w)

Gaudinski MR et al., PLoS Med 2018; January 24
### Why ‘Long Acting’ and where might they fit?

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| - Improve adherence, convenience (work, travel, etc)  
- ‘Fragile’ populations **  
- Psychological benefit, pill fatigue etc  
- Eliminates food effects  
- Eliminates gut-based DDIs & AEs  
- Protects privacy  
- Public health benefits – community VLs, transmissions | - Needles, ISR (injection fatigue ?)  
- Resource intensive  
- Managing tail  
- Managing new events, toxicities and morbidities  
- Managing non-adherence (& consequences)  
- Managing DDIs |
Case – ‘R’

23y woman HIV-positive 2015

CD4 615(25%), VL 33,322 copies/mL (Wild Type)
- severe learning difficulties, ADHD (since 5)
- extremely poor adherence
- Binge drinking since 16y
- recreational drug use (cannabis, likely others)

2015 Recurrent STIs – Chlamydia, gonococcal infection
- multiple partners (admits to sex work)
- many discussions about potential for transmission
- willing to take HIV meds, but issues around chaotic life,
- memory, and reluctance to take pills
- clinically asymptomatic from HIV,
- urgently needs TasP

Co-medications
- Ritalin
- DMPA injections
- cannabis
### Case – ‘R’

<table>
<thead>
<tr>
<th>ARV</th>
<th>Start</th>
<th>Stop</th>
<th>Suppressed</th>
<th>Reason for stopping</th>
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</thead>
<tbody>
<tr>
<td>TVD+DRVr</td>
<td>Dec 2015</td>
<td>3 days</td>
<td>N</td>
<td>Diarrhoea, wants STR</td>
</tr>
<tr>
<td>Triumeq</td>
<td>Jan 2017</td>
<td>1 day</td>
<td>N</td>
<td>Hallucination (with cannabis)</td>
</tr>
<tr>
<td>Rezolsta</td>
<td>Aug 2017</td>
<td>On and off</td>
<td>N</td>
<td>Poor adherence</td>
</tr>
<tr>
<td>Genvoya</td>
<td>Oct 2017</td>
<td>On and off</td>
<td>N</td>
<td>Poor adherence (3x/w)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>INI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 2015</td>
<td>WT</td>
<td>WT</td>
<td>(K20I)</td>
<td>WT</td>
<td></td>
</tr>
<tr>
<td>Aug 2017</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
<td></td>
</tr>
<tr>
<td>June 2018</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
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</tr>
</tbody>
</table>
Case – ‘R’

23y woman HIV-positive 2015

severe learning difficulties, ADHD (since 5)
extremely poor adherence
Binge drinking since 16y
recreational drug use

2015  Recurrent STIs
multiple partners
willing to take HIV meds,
issues around chaotic life,
memory, and reluctance to take pills
clinically asymptomatic from HIV
urgently needs TasP

Is this patient a candidate for LA CAB+RPV?

Expanded access to im Cab + RPV approved
Case – ‘R’

23y woman HIV-positive 2015

severe learning difficulties, ADHD (since 5)
extremely poor adherence
Binge drinking since 16y
recreational drug use

2015  Recurrent STIs
multiple partners
willing to take HIV meds,
issues around chaotic life,
memory, and reluctance to take pills
clinically asymptomatic from HIV
urgently needs TasP

What if she stops attending?
What if she becomes pregnant?
Case – ‘K’

Age 65, from Vietnam

2003  HIV+, CD4 nadir 200
      multiple morbidities, polypharmacy, DDI
      Anxiety / depression

2009  Hypertension, ischaemic heart disease
      Hyperlipidaemia

2012  Prostatism

2015  Chronic Kidney Disease (hypertensive)
      Osteoporosis
      GORD

2018  Frailty, falls
      weight loss, sarcopenia
      poor memory, increasingly frail
      VL blips - likely intermittent adherence

Co-medications

- Amlodipine
- Pravastatin
- Calcichew D3
- Lansoprazole
- Tamsulosin
- Citalopram
- Aspirin
<table>
<thead>
<tr>
<th>Previous HIV Medication</th>
<th>Start</th>
<th>Stop</th>
<th>Reason Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATVr</td>
<td>01/06/2006</td>
<td>01/02/2007</td>
<td>Intolerant (jaundice)</td>
</tr>
<tr>
<td>LPVr</td>
<td>18/11/2007</td>
<td>29/11/2012</td>
<td>Declining renal function</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>29/11/2012</td>
<td>15/11/2016</td>
<td>Switched to Cobicistat</td>
</tr>
<tr>
<td>Darunavir/c</td>
<td>15/11/16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2019  neurocognitive impairment, multiple morbidities, multiple DDIs sarcopenia

*Is he a candidate for LA CAB+RPV?*

2019  Admitted with swallowing difficulties, AF / CVA and starts dabigatran

*Is he a candidate for LA CAB+RPV?*

2019  He develops post-CVA partial seizures, started on oxcarbazepine

*Is he a candidate for LA CAB+RPV?*
DDIs in PLWHIV with Multi-morbidities

Study included 1073 PLWH (mean age 52 years) from the POPPY cohort

- Comorbidities co-occur in specific patterns
- Better understanding how comorbidities cluster together would enable the development of targeted interventions and guidelines addressing specifically the needs of PLWH with multiple comorbidities
Co-morbidity clusters – DDI potential

Liverpool DDI Database - % Amber or Red

Boosted ATV, DRV, EVG
47-61%

Boosted ATV, DRV, EVG
37-55%

Boosted ATV, DRV, EVG
28-53%

Interaction Potential (%)

Mental Health
Cardiovascular Diseases
Metabolic Disorders

ATV/r  DRV/r  DRV/c  EVG/c

Gibbons et al. EACS 2019 (oral abstract)
Prevalence of ‘Clinically Significant’ DDIs in HIV Cohorts by Calendar Year
definitions vary, generally equivalent to Amber / Red in Liverpool tool

% Clinically Significant DDIs

Europe
USA
SS Africa

Year

% with DDI


Barcelona (1,259)
INI use 14.5%
- Statins
- Antidepressants
- Anxiolytics
- Methadone
- Analgesia
- Anti-platelets

UK (4,360)
INI use 27%
- Sildenafil
- Quetiapine
- PPIs
- OHCs

Swiss (9,034)
INI use 65%
- Steroids (25%)

France (9,076)
INI use 48%
- Steroids (29%)
- PPI (27%)
- Lercanidipine (11%)
- Alfuzosin (9%)
- Amiodarone (3%)
- Simvastatin (3%)
- DOAC (3%)

Madrid (22,945)
INI use 51%
- Steroids (51% of Red DDIs)
- Quetiapine (14% of Red DDIs)
- Clopidogrel (7% of Red DDIs)
- Domperidone (7% of Red DDIs)
- Simvastatin (6% of Red DDIs)

DDIs associated with $2,693 additional cost per year
Same, more, less or different? - DDIs

NOTE
Neither CAB-LA nor RPV-LA are licensed, and no regulatory guidance on DDIs are available. The DDI calls (brackets) are ‘Guesswork’ – informed and otherwise .....
Same, more, less or different? – Special Populations

NOTE
Neither CAB-LA nor RPV-LA are licensed, and no regulatory guidance on Special Populations are available.

Pregnancy
- RPV-LA – likely unchanged? (oral - no safety signal, [RPV]↓ in T3)
- CAB – no data

Chronic Renal Impairment
- RPV-LA – likely unchanged? (oral – caution with ESRF, not significantly removed by HD)
- CAB – unlikely to be significantly affected

Chronic Liver Disease
- RPV-LA – likely unchanged? (oral – normal dose with CPT A,B, unstudied with CPT C)
- CAB – unlikely to be significantly affected in mild – mod liver impairment
Summary of injectable LA therapy for HIV

- **Transformative** for other diseases, potentially also in treatment and prevention of HIV
  - Evidence of success with contraception, osteoporosis, schizophrenia

- **LA orals, and new devices** will augment this repertoire

- **Pragmatic arrangements for clinical deployment** yet to be fully worked out

- Some key **unanswered Qs** remain (e.g. pregnancy)

- Will not suit everyone

- Potential use in ‘fragile’ populations will need to be evaluated in Phase 4
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