New Delivery Systems and Long Acting Antiretroviral Drugs

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University of Liverpool
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Disclosures

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• Educational grants for www.hep-druginteractions.org and www.hiv-druginteractions.org from AbbVie, BMS, Gilead, Janssen, Merck, ViiV
Overview

1. The Changing Face of Treatment.
2. Oral Nanoformulations of ARVs
3. I.M. Long Acting Nanoformulations of ARVs
4. Long Acting Implants of ARVs
Overview

1. The changing face of treatment.
2. Oral Nanoformulations of ARVs
3. I.M. Long Acting Nanoformulations of ARVs
4. Long Acting Implants
Antiretroviral Therapy: Past, Present & Future

1983 HIV-1 discovered
1987 ZDV monotherapy
1996 Triple drug therapy
2006 Single tablet regimens
2012/13 The Integrase era
2018 & beyond

1. New Drugs
2. 2 Drug Regimens (2DR)
3. New Delivery Systems
### Newer ART Agents (partial list)

<table>
<thead>
<tr>
<th></th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI (CCR5, CD4)</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recently Approved</td>
<td></td>
<td>Doravirine <em>(FDA approved as STR and alone)</em></td>
<td></td>
<td>Ibalizumab <em>(Mab; FDA approved)</em> Albuvirtide <em>(Approved in China)</em></td>
<td>Bictegravir <em>(FDA and EMA approved)</em></td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cabotegravir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fostemsavir PRO140 UB421</td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Apricitabine</td>
<td>Festinavir Dexelvucitabine</td>
<td>BILR 355 Elsulfavirine</td>
<td>Cenicriviroc PF-232798</td>
<td></td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>MK-8591</td>
<td>Elsulfavirine</td>
<td>TMC 310911</td>
<td>VRCO1 UB-421</td>
<td></td>
</tr>
</tbody>
</table>
## Differentiating Efavirenz, Rilpivirine, Doravirine

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz</th>
<th>Rilpivirine</th>
<th>Doravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (h)</td>
<td>40-55</td>
<td>45</td>
<td>11-16</td>
</tr>
<tr>
<td>Food requirement</td>
<td>Recommended on empty stomach</td>
<td>Must be taken with food</td>
<td>Administer without regard to food</td>
</tr>
<tr>
<td>DDI potential as Perpetrator</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>DDI potential as a victim</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
| Key trial data  | Drive-Forward ART-naïve: DOR + 2NRTIs vs DRV/r + 2NRTIs  
Drive-Ahead ART-naïve: DOR/3TC/TDF vs EFV/FTC/TDF  
Drive-Shift Switch to DOR/3TC/TDF in suppressed pts  
Drive-Beyond DOR/3TC/TDF in tx-naïve pts with NNRTI resistance | | | |
Ibalizumab

TROGARZO™ (ibalizumab-uiyk) injection, for intravenous use
Initial U.S. Approval: [2018]

------------- INDICATIONS AND USAGE -------------
TROGARZO, a CD4-directed post-attachment HIV-1 inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen. (1)

------------- DOSAGE AND ADMINISTRATION -------------
TROGARZO is administered intravenously (IV) as a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks after dilution in 250 mL of 0.9% Sodium Chloride Injection, USP. (2.1)
# Integrase Inhibitors: Profile

<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR</th>
<th>ELVITEGRAVIR</th>
<th>DOLUTEGRAVIR</th>
<th>BICTEGRAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical dose</strong></td>
<td>400 mg BID* OR 1200 mg QD</td>
<td>150 mg QD with cobi and F/TDF or F/TAF</td>
<td>50 mg QD</td>
<td>50 mg QD with F/TAF</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>UGT1A1</td>
<td>CYP3A (major), UGT1A1/3 (minor)</td>
<td>UGT1A1 (major), CYP3A (minor; &lt;15%)</td>
<td>UGT1A1 and CYP3A (equal)</td>
</tr>
<tr>
<td><strong>DDI Potential</strong></td>
<td>Least</td>
<td>Highest</td>
<td>Slightly greater than RAL</td>
<td>Slightly greater than DTG</td>
</tr>
</tbody>
</table>

Interaction Classification (Green, Amber/Yellow, Red) in Liverpool Database for Integrase Inhibitors

Green: No interaction; Amber: Caution; Red: Contraindicated/not recommended

Raltegravir: 95%
EVG/cobi: 53%
Dolutegravir: 93%
Bictegravir: 86%

Note: Data from ~700 co-meds (excluding ARV-ARV interactions) in www.hiv-druginteractions.org
Why 2-Drug Regimens (2DR)?

- Why take 3 (or 4) drugs, when 2 can do?
- Potential preservation of future treatment options
- Fewer drugs - Potential to reduce DDIs Important with Aging patients and Comorbidities
- Reduce impact of long-term exposure to multiple ARVs Less potential for AEs?
- Less API Cost?
- Establish new treatment paradigms and evolve SoC.

AE, adverse event; ARV, antiretroviral; DDI, drug-drug interaction; HCP, healthcare professional; SoC, standard of care; 2DR, two-drug regimen.

Slide courtesy of Viiv Healthcare
### Some Key Pharmacological Considerations for 2DR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DTG + 3TC</th>
<th>DTG/RPV</th>
<th>CAB + RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half lives; Balance &amp; Forgiveness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tissue Penetration</td>
<td>? – any issue of removing 3&lt;sup&gt;rd&lt;/sup&gt; agent</td>
<td>? – any issue of removing 3&lt;sup&gt;rd&lt;/sup&gt; agent</td>
<td>?- any issue of removing 3&lt;sup&gt;rd&lt;/sup&gt; agent</td>
</tr>
<tr>
<td>DDI profile</td>
<td>low</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>TB Coinfection</td>
<td>DTG bid (<strong>INSPIRING</strong>)</td>
<td>Contraindicated with RIF</td>
<td>Likely contraindicated with RIF</td>
</tr>
<tr>
<td>Use in Pregnancy</td>
<td>Potentially yes…but</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Use in Renal Impairment</td>
<td>Problematic for STR due to 3TC exposure.</td>
<td>Yes – but caution in ESRD</td>
<td>No data</td>
</tr>
<tr>
<td>Use in Chronic HBV</td>
<td>Need additional HBV tx</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Initial therapy; High VLs?</td>
<td>Yes – 20% pts in Gemini 1 &amp; 2</td>
<td>Need data</td>
<td>Need data</td>
</tr>
</tbody>
</table>
Overview

1. The changing face of treatment.
2. Oral Nanoformulations of ARVs
3. I.M. Long Acting Nanoformulations of ARVs
4. Long Acting Implants of ARVs (Implants)
Nanoformulations may or may not be long acting formulations
Past Live Webinars

The webinar will be archived and available for educational purposes. For physicians who did not participate in the live activity, CME credits will be available for viewing the archived webinar, but the webinar slides are not available for download. ABIM MOC points and Pharmacy and Nursing credits will not be available for viewing the archived webinar.

Past Live Webinars

“Flexner’s Fabulous Formulations!” A Review of Long-Acting Antiretrovirals and Other New Investigational Drugs for HIV Infection **DUPLICATE**
The potential value of nanomedicine and novel oral dosage forms in the treatment of HIV

James J Hobson¹, Andrew Owen² & Steve P Rannard*¹
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²Department of Molecular & Clinical Pharmacology, University of Liverpool, Pembroke Place, Liverpool, L69 3GF, UK
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“there is a considerable scope for the improvement of current oral regimens and the reformulation of existing ARVs using nanotechnology and nanomedical approaches”

First draft submitted: 28 May 2018; Accepted for publication: 4 June 2018; Published online: 6 September 2018
Oral Nanoformulation: 
*Delivery of poorly water soluble drugs in aqueous system*

Dispersal of drugs into water may have explicit benefits for paediatric formulation without the need for organic solvents.

**Paediatric Kaletra**

Each 1 ml of Kaletra oral solution contains 80 mg of lopinavir co-formulated with 20 mg of ritonavir.

Excipients with known effect: Each 1 ml contains 356.3 mg of alcohol (42.4% v/v), 152.7 mg of propylene glycol (15.3% w/v)

*Courtesy of Professor A Owen*
Drugs included in initial studies:
- Dolutegravir,
- Cabotegravir,
- Rilpivirine
Overview

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Long Acting: definition

- Drug with a prolonged effect because of a formulation resulting in the slow release of the active principle or the continued absorption of small amounts of the dosage of the drug over an extended time.
Long Acting (non-oral) – What’s the attraction?

- Infrequent dosing
- Lower overall drug dose
- Prevents poor adherence
- Use in patients with pill fatigue (possibly temporarily?)
- Potential of directly observed therapy
- Target tissues?
- Better protects health privacy and treatment-related stigma
Long Acting im: Cabotegravir and Rilpivirine

- CAB Oral 30 mg ($t_{1/2}$, ~40 hours)
- CAB LA nano 200 mg/mL ($t_{1/2}$, ~20-40 days)
- RPV Oral 25 mg ($t_{1/2}$, ~50 hours)
- RPV LA nano 300 mg/mL ($t_{1/2}$, ~30-90 days)

• Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1
• im 2-drug CAB + RPV maintained VL < 50 in LATTE 2*
LATTE-2 Study: Phase 2b
Switch to Cabotegravir LA + Rilpivirine LA IM

- **Objective**
  - Primary: % HIV RNA < 50 c/mL at W32 of maintenance phase: selection of dosing schedule for phase III studies (confirmation of dose on W48 analysis) ; safety

- **Design**

  Induction (oral)
  - CAB 30 mg QD + ABC/3TC (N = 309)

  Randomisation
  - 2 : 2 : 1

  Maintenance
  - (if HIV RNA < 50 c/mL at W4 and Day 1)
  - CAB 600 mg IM + RPV 900 mg IM Q8W * (N = 115)
  - CAB 400 mg IM + RPV 600 mg IM Q4W ** (N = 115)
  - CAB 30 mg QD + ABC/3TC QD (oral) (N = 56)

  Induction phase: HIV RNA < 50 c/mL (ITT-E) after 20 weeks = 91.3 % ; discontinuation in 18/309 patients, including 6 for adverse event and 2 for lack of efficacy

**Margolis DA. Lancet. 2017 Sep 23;390(10101):1499-1510.**
LATTE-2 Study: Phase 2b Switch to Cabotegravir LA + Rilpivirine LA IM

HIV RNA < 50 c/mL at W48 and W96 (snapshot analysis, ITT-ME)

- Non inferiority of the 2 IM regimens vs oral CAB, at W48 and W96
- Lower performance of Q4W (vs Q8W) at W96 due to more discontinuations for AE (9 vs 1)
- Protocol-defined virologic failure: 1 in oral arm (no resistance), 2 in Q8W arm (emergence of resistance at failure: K103N, E138G, K238T (NNRTI) and Q148R (INSTI) in 1, R269R/G in 1

LATTE-2 Study: Switch to Cabotegravir LA + Rilpivirine LA IM

Patient reported-outcomes – week 96

LATTE-2 Subject 551 - W48 PDVF vs. Q8W Dosing: Plasma Concentrations

PDVF: <1.0 log_{10} c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 log_{10} c/mL increase from nadir HIV-1 RNA value ≥200 c/mL

Cr, trough concentration; PA-IC90, protein binding–adjusted 90% inhibitory concentration; Q8W, every 8 weeks; SD, standard deviation.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen

**ATLAS study meets primary endpoint, showing similar efficacy of a once-a-month, investigational, injectable two-drug regimen of cabotegravir and rilpivirine compared to a standard of care, daily, oral three-drug regimen**

**Full results from the study will be presented at an upcoming scientific meeting**

**London, 15 August 2018** - ViiV Healthcare today announced positive headline results from its global, phase III ATLAS study of a long-acting, injectable two-drug regimen (2DR) for the treatment of HIV. ATLAS (Antiretroviral Therapy as Long-Acting Suppression) was designed to establish if HIV-1-infected adult participants who had maintained viral suppression for at least six months, on a daily oral regimen comprised of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent, maintained similar rates of viral suppression upon switching to the investigational, two-drug, long-acting, injectable regimen of cabotegravir and rilpivirine, compared with continuing the three-drug oral regimen.

Media contacts

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OR call +44 7557 290 420

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OR call +1 919 614 6521
Long Acting Injectables: Some Key Issues

- Which drugs can be combined?
- Injection volume for im?
- What to do about missed doses
- Long term low drug levels at end of dosing interval
- Management of adverse events since non reversible
  - Need for oral lead-in
- How much long term safety and efficacy data required?
- DDIs different?
Evidence of a Long PK Tail of Rilpivirine after im Dosing

- RPV was found in plasma and genital tract fluids 12-24 months after SD of LA RPV
- Characterizing the extended PK profile is critical to inform management of the PK tail to avoid the potential for antiretroviral resistance

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Time since Injection (days)</th>
<th>Rilpivirine concentration* (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>450</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>480</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>490</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>4.7</td>
</tr>
<tr>
<td>6</td>
<td>580</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>590</td>
<td>2.9</td>
</tr>
<tr>
<td>8</td>
<td>700</td>
<td>0.3</td>
</tr>
<tr>
<td>9</td>
<td>830</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Note: Target concentration for antiviral activity is 12.2 ng/ml

McGowan I et al; HIVR4P October 2016
DDIs with Long Acting Cabotegravir and Rilpivirine?

Results

![Graph showing Cabotegravir concentrations](#)

**Cabotegravir single oral dose**

- CAB Alone
- CAB + 600 mg RIF

**Cabotegravir (400 mg) monthly maintenance dose**

- CAB Alone
- CAB + 600 mg RIF

Courtesy of Professor S Khoo
# Yearly intake of ARV by regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Daily Dose (mg)</th>
<th>Yearly dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-Drug Regimens:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r + FTC/TDF</td>
<td>800/100 + 200/300</td>
<td>511.0</td>
</tr>
<tr>
<td>RAL + F/TAF</td>
<td>800 + 200/10</td>
<td>368.7</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>50/600/300</td>
<td>346.8</td>
</tr>
<tr>
<td><strong>2-Drug Regimens:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>50 + 300</td>
<td>127.8</td>
</tr>
<tr>
<td>DTG + RPV</td>
<td>50 + 25</td>
<td>27.4</td>
</tr>
<tr>
<td>CAB_{im} + RPV_{im}</td>
<td>400 + 600 every 8wks</td>
<td>6.0</td>
</tr>
</tbody>
</table>
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**FIGURE 1.** Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad\(^a\) and DRC, June 2011 to November 2015

<table>
<thead>
<tr>
<th>Method</th>
<th>Chad</th>
<th>Democratic Republic of the Congo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCPs</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Injectables</td>
<td>29%</td>
<td>8%</td>
</tr>
<tr>
<td>IUDs</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Implants</td>
<td>53%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Abbreviations: DRC, Democratic Republic of the Congo; IUDs, intrauterine devices; OCPs, oral contraceptive pills; TL, tubal ligation.

\(^a\) None of the family planning users in Chad chose no-scalpel vasectomy.
Long Acting Implants

- Potential advantages over injectables
  - Removable
  - More consistent drug release
  - Could remain in place for years.

- Potential disadvantages over injectables
  - Specialised device required for insertion
  - Removal?
  - Generic marketplace?

Schlesinger E et al Pharm Res 2016; 33: 1649-1656; Gunawardana M et al; AAC; 2015; 59: 3913-3919
MK-8591 (EFdA): A Potent Long Acting Agent

Nucleoside Reverse Transcription Translocation Inhibitor (NRTTI)
- Immediate chain termination via blockage of translocation
- Delayed chain termination incorporation and altered viral DNA structure.

Potent antiviral activity based on preclinical and early clinical data.

Long half-life in early clinical studies
- MK-8591-TP half-life of ~ 120 h in healthy adults

MK-8591 (EFdA): A Novel Nucleoside with a Unique Mechanism of Action

- 10 mg oral SD in HIV+ pts gives 1.6log drop in VL at day 7-10 (> than SD TAF).

Single doses as low as 0.5 mg of the novel NRTTI MK-8591 suppress HIV for at least 7 days
R P Matthews

IAS 2017: TUPDB0202LB

Grobler J et al CROI 2016
Extended Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

Stephanie E. Barrett, Ryan S. Teiler, Seth P. Forster, Li Li, Megan A. Mackey, Daniel Skomski, Zhen Yang, Kerry L. Fillgrove, Gregory J. Doto, Sandra L. Wood, Jose Lebron, Jay A. Grobler, Rosa I. Sanchez, Zhen Liu, Bing Lu, Tao Niu, Li Sun, Marian E. Gindy

- Plasma MK-8591 concentrations (a) and PBMC MK-8591-TP concentrations (b) in non-human primates with subcutaneous implants.
Microneedles or Microarray Patches (MAPs)

Hydrogel skin patch worn continuously for sustained, transdermal delivery of rilpivirine (free active pharmaceutical ingredient). Target dosage frequency: patch would be reapplied once every week.
Conclusions

• Effective dose and release rates of cabotegravir and rilpivirine formulations have been identified using PBPK models.

• Appropriately-formulated high-loading MAPs about 30 cm$^2$ could be effectively used for the monthly administration of cabotegravir and weekly administration of rilpivirine, improving patient compliance through this minimally-invasive route.
Other Infectious Diseases suitable for LA Formulations

- Tuberculosis
- Hepatitis C
- Hepatitis B
- Malaria
- Ebola
Acknowledgements

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  • Saye Khoo
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