Future Perspectives for Delivery of Antiretroviral Drugs

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University of Liverpool
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. Long Acting ARVs (Oral)
3. Long Acting ARVs (im)
4. Long Acting ARVs (implants)
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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
- **2018ff**: New Delivery Systems

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

<table>
<thead>
<tr>
<th>Recently Approved</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI (CCR5, CD4)</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ibalizumab (<em>Mab</em>)</td>
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<td>Albuvirtide (<em>China</em>)</td>
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<td></td>
<td>Bictegravir</td>
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<table>
<thead>
<tr>
<th>Phase 3</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI (CCR5, CD4)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Doravirine</td>
<td></td>
<td>Fostemsavir PRO140 UB421</td>
<td>Cabotegravir</td>
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<table>
<thead>
<tr>
<th>Phase 2</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI (CCR5, CD4)</th>
<th>II</th>
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<tbody>
<tr>
<td>Apricitabine</td>
<td></td>
<td>BILR 355</td>
<td>Elsulfavirine</td>
<td>Cenicriviroc PF-232798</td>
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<tr>
<td>Festinavir</td>
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<tr>
<td>Dexelvucitabine</td>
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<thead>
<tr>
<th>Phase 1/2</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI (CCR5, CD4)</th>
<th>II</th>
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</thead>
<tbody>
<tr>
<td>MK-8591</td>
<td></td>
<td>Elsulfavirine</td>
<td>TMC 310911</td>
<td>VRCO1 UB-421</td>
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<td>GS9131</td>
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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)
2-Drug Regimens (2DR)

Why 2DR?

- Less API Cost?
- Potential preservation of future treatment options
- Reduce impact of long-term exposure to multiple ARVs
- Less potential for AEs?
- Fewer drugs - Potential to reduce DDIs Important with Aging patients and Comorbidities
- Establish new treatment paradigms and evolve SoC.

Why take 3 (or 4) drugs, when 2 can do?

AE, adverse event; ARV, antiretroviral; DDI, drug-drug interaction; HCP, healthcare professional; SoC, standard of care; 2DR, two-drug regimen.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRV/r + 3TC</th>
<th>LPV/r + 3TC</th>
<th>DTG + 3TC</th>
<th>DTG/RPV</th>
<th>CAB + RPV</th>
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<tbody>
<tr>
<td>Half lives; Balance &amp; Forgiveness</td>
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<tr>
<td>Tissue Penetration</td>
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<td>DDI profile</td>
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<td>Use in Pregnancy</td>
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<td>Use in Renal Impairment</td>
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<tr>
<td>Use in Chronic HBV</td>
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<td>Initial therapy; High VLs?</td>
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<td>Past tx failures?</td>
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Overview

1. The changing face of treatment.
2. Long Acting ARVs (Oral)
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Nanotechnologies being explored in Drug Delivery

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

- **“Bottom-Up”**
  - Precipitation of solutions

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

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

- Lipid-based carriers
- Polymer-based carriers
- Inorganic carriers
- Biological
Nanotechnology can reduce drug costs

Nanoformulations of Lopinavir and Efavirenz allow a 50% reduction in daily dose and the potential for cost savings of ~ $250m in API per year.

Owen A et al CROI 2017 Abs 39

Figure from Mol Pharm 2015; 12: 3556.
PK of Efavirenz & Lopinavir Nano-formulations in Healthy Volunteers

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Drug: 50mg NANO-efavirenz</td>
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<tr>
<td></td>
<td>Drug: 400mg NANO-Lopinavir</td>
</tr>
<tr>
<td></td>
<td>Drug: 200mg NANO-Lopinavir</td>
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<tr>
<td></td>
<td>Drug: 100mg Ritonavir</td>
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<tr>
<td></td>
<td>Drug: 300mg NANO-Efavirenz</td>
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<tr>
<td></td>
<td>Drug: 600mg Sustiva</td>
</tr>
<tr>
<td></td>
<td>Drug: 200mg NANO-Efavirenz</td>
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<tr>
<td></td>
<td>Drug: Kaletra® (lopinavir 400mg/ritonavir 100mg)</td>
</tr>
<tr>
<td></td>
<td>Drug: +/- 200mg NANO-Lopinavir</td>
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<tr>
<td></td>
<td>Drug: +/- 200mg ritonavir NORVIR</td>
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<tr>
<td></td>
<td>Drug: 400mg Sustiva</td>
</tr>
</tbody>
</table>
Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy

Nature Comms 2018; Jan 9th
Overview

1. The changing face of treatment.

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4. Long Acting ARVs (implants)
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
Treatment and prevention of HIV infection with long-acting antiretrovirals

Rilpivirine long-acting for the prevention and treatment of HIV infection

Pharmacokinetics of a Long-Acting Nanoformulated Dolutegravir Prodrug in Rhesus Macaques
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*

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Dr David A Margolis, MD [MD], Juan Gonzalez-Garcia, MD, Prof Hans-Jürgen Stebbink, MD, Prof Joseph J Eron, MD, Prof Yazdan Yazdanpanah, MD, Daniel Podzamczer, PhD, Thomas Lutz, MD, Jonathan B Angel, MD, Gary J Richmond, MD, Bonaventura Clotet, MD, Prof Felix Gutierrez, MD, Prof Louis Sloan, MD¹, Marty St Clair, BS, Miranda Murray, PhD, Susan L Ford, PharmD, Joseph Mrus, MD, Parul Patel, PharmD, Herta Cruweils, PhD, Sandy K Griffith, Pharm D, Kenneth C Sutton, MA, David Dorey, MMath, Kimberly Y Smith, MD, Peter E Williams, PhD, William R Spreen, Pharm D

¹ Prof Louis Sloan died in June, 2017

Published: 24 July 2017

CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; $t_{1/2}$, half-life.

LATTE-2 Study: 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**
- ARV naive > 18 years
- HIV RNA ≥ 1 000 c/mL
- CD4 > 200/mm³
- HBs Ag negative
- ALT < 5 UNL
- Creatinine clearance > 50 mL/min

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

- **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)

* CAB IM, loading dose 800 mg at D1 and 600 mg at W4
** CAB IM, loading dose 800 mg at D1

Q8W: injection every 8 weeks ; Q4W: injection every 4 weeks

LATTE-2 Study: 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
(HIV Treatment satisfaction questionnaire, status version)

- IM CAB LA + RPV LA
  - Q4W (N = 100)
    - Very satisfied: 76%
    - Very dissatisfied: 3%
  - Q8W (N = 108)
    - Very satisfied: 85%
    - Very dissatisfied: <1%
  - Oral CAB + ABC/3TC (N = 46)
    - Very satisfied: 76%
    - Very dissatisfied: 2%

- IM CAB LA + RPV LA
  - Q4W (N = 100)
    - Very satisfied: 88%
    - Very dissatisfied: 1%
  - Q8W (N = 108)
    - Very satisfied: 89%
    - Very dissatisfied: <1%
  - Oral CAB + ABC/3TC (N = 46)
    - Very satisfied: 43%
    - Very dissatisfied: 2%

CAB & RPV Pharmacokinetics

- Both Q4W and Q8W steady state exposures approximate once-daily oral dosing

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

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
LATTE-2 Subject 551 - W48 PDVF vs. Q8W Dosing: Plasma Concentrations

PDVF: <1.0 log₁₀ 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 log₁₀ 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.
Selection of Rilpivirine-Resistant HIV-1 in a Seroconverter From the SSAT 040 Trial Who Received the 300-mg Dose of Long-Acting Rilpivirine (TMC278LA)

Kerri J. Penrose,1 Urvir M. Parikh,1 Kristen A. Hamanishi,1 Laura Else,2 David Back,2 Maria Boffito,3 Akil Jackson,3,4 and John W. Mellors1

Penrose K et al. JID 2016; 213: 1013-1017
RPV was found in plasma and genital tract fluids > 18 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
DDIs with Long Acting?

In Silico Drug Interaction of Long-acting Rilpivirine and Cabotegravir With Rifampin

Rajith KR Rajoli1, Paul Curley1, David Back1, Charles Flexner2, Andrew Owen1, Marco Siccardi1
1. Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK
2. Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, MD, USA

Results

- Cabotegravir single oral dose
- Cabotegravir (400 mg) monthly maintenance dose

Comparisons:
- CAB Alone vs. CAB + 600 mg RIF
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?
# 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>EVG/c/FTC/TAF</td>
<td>150/150/200/10</td>
<td>186.2</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&lt;sub&gt;oral&lt;/sub&gt; + RPV&lt;sub&gt;oral&lt;/sub&gt;</td>
<td>30 + 25</td>
<td>20.1</td>
</tr>
<tr>
<td>CAB&lt;sub&gt;im&lt;/sub&gt; + RPV&lt;sub&gt;im&lt;/sub&gt;</td>
<td>400 + 600 every 8wks</td>
<td>6.0</td>
</tr>
</tbody>
</table>

17 kg

300g

50 years of tx
Overview

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4. Long Acting ARVs (implants)
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>Country</th>
<th>OCPs</th>
<th>Injectables</th>
<th>IUDs</th>
<th>Implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chad</td>
<td>4%</td>
<td>29%</td>
<td>14%</td>
<td>53%</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>10%</td>
<td>8%</td>
<td>30%</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.

Rattan J Global Health Sci Prac 2016: 4 Suppl 2: S5-S20
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?
- Regulated as both a drug and device.
- Generic marketplace?

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

Nucleoside Reverse Transcription Translocation Inhibitor (NRTTI)

- 4’-Ethynyl-2-fluoro-2’-deoxyadenosine (EFdA)
- Immediate chain termination via blockage of translocation
- Delayed chain termination incorporation and altered viral DNA structure.

Potent antiviral activity based on preclinical data.

Long half-life in preclinical and early clinical studies

- MK-8591-TP half-life of ~50 h in Macaque
- MK-8591-TP half-life of ~120 h in healthy adults
MK-8591 (EFdA): A Novel Nucleoside with a Unique Mechanism of Action

- IC EFdA-TP half life = 103h
- 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
MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days

- >180 day extended release from solid formulations after single **injection** in rat.
- Extended release from **implant** in NHP

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. Ginody

- 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 cm² could be effectively used for the monthly administration of cabotegravir and weekly administration of rilpivirine, improving patient compliance through this minimally-invasive route.
Transforming HIV treatment with nanoformulations

OPTIMIZE – a global partnership to accelerate access to simpler, safer and more affordable HIV treatment – is investing in bringing nanoformulated antiretroviral therapy from the laboratory to the market to improve HIV treatment for patients and programs.

Current reality

The UNAIDS 90-90-90 targets and WHO's "Treat all" guidelines demand a rapid expansion of access to ART. In 2015, around 46% of all people living with HIV had access to treatment.

Harnessing the power of science, technology, innovation and partnerships can help close the gap between those who are living with HIV, and those who need treatment.

Traditional process

This process will get nanofomulated ARVs to patients as quickly as possible.

Powered by OPTIMIZE, a global partnership unifying distinct voices to achieve a common goal: accelerating access to simpler, safer and more affordable HIV treatment.

For further information or to request technical assistance from OPTIMIZE, please contact Joanne (Jo) Sharp, UoL Program Manager, at momeej2@liverpool.ac.uk or +44 151-794 5553.

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Other Infectious Diseases suitable for LA Formulations

- Tuberculosis
- Hepatitis C
- Hepatitis B
- Malaria
- Ebola
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  – Saye Khoo
  – Sara Gibbons
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  – Laura Else

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  – Ian McGowan

• University of Basle
  – Catia Marzolini

• Chelsea & Westminster Hospital, London
  – Marta Boffito