Long-acting Antiviral Agents for HIV Treatment

David Back
University of Liverpool
January 2015

11th Residential Course on Clinical Pharmacology of Antiretrovirals Torino
• cART trials routinely demonstrate regimen efficacy of 90% or higher.

• Orally administered ARVs used in PrEP reduce the risk of HIV-1 infection by ~90%.

• Yet…….is daily oral therapy the only or best way for all patients?
Long-acting formulations

• Have been used to improve adherence and prevent missed doses/tx fatigue in several therapeutic areas:

• Contraception: (Depo Provera; i.m every 12 weeks)
• Schizophrenia: 6 long-acting antipsychotics available (e.g. risperidone, olanzapine; i.m every 2-4 weeks)
• Hypogonadism: (testosterone undecanoate; i.m every 2-4 weeks)
Nomenclature

- Long Acting
- Controlled release
- Sustained release
- Extended release
- Timed release
- Prolonged release

Proposed dosing intervals of $\geq 1$ week, $\geq 1$ month or $\geq 6$ months, for oral, injectable or implantable strategies, respectively.
- Availability of drug from the depot
- Variability in plasma exposure – possibly higher than after oral administration
What are the possible risks and benefits of LA ARVs?
Long acting - benefits

- Sustained release results in longer half life
- Oral dosing by-passed; bioavailability ~100%

- Potentially therapy and prevention
- Lower total dose nanoformulations
- Reduced frequency of dosing
- Use in subject with pill fatigue
- Protection from poor adherence
Long Acting - Limitations

- What drugs can be combined?
- Injection volume?
- What to do about missed doses
- Long term low drug levels at end of dosing interval
- Management of adverse events – non-reversible
  - Need for oral lead-in
- How much long term safety and efficacy data required?
• Main focus on prevention but interest also in treatment
• 2 drugs in clinical trials (PK and PK-PD):
  • Rilpivirine
  • Cabotegravir
Pre-exposure prophylaxis (PrEp): Ideal agent

- Safe
- Penetrates target tissue & protects against HIV
- Demonstrates long-lasting activity with convenient dosing
- High genetic barrier to resistance
- No or few DDIs
- Affordable and easy to implement
Rilpivirine long-acting injectable

- Oral formulation of NNRTI approved for treatment
  - Allows for accelerated prevention product development

- Novel dosage form technology for long-acting injectable
Rilpivirine long-acting injectable: SSAT 040 Phase I trial

• **Study design**
  – HIV-negative volunteers, between 18–50 years, low risk for HIV
  ▪ Single IM dose
    – 20 women per arm at 300 mg, 600 mg or 1200 mg (n=60)
    – 6 men at 600 mg

• **Primary objectives**
  – Plasma PK through day 84 post dose
  – PK in genital tract and rectal fluids/tissues
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 Urvi M. Parikh,¹ Kristen A. Hamanishi,¹ Laura Else,² David Back,² Marta Boffito,³ Akil Jackson,³,4 and John W. Mellors¹
<table>
<thead>
<tr>
<th>Time After TMC278LA Injection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RPV Concentration, ng/mL</th>
<th>Resistance Mutation Detected&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CD4&lt;sup&gt;+&lt;/sup&gt; T-Cell Count, Cells/μL (% of WBCs)</th>
<th>K101E Frequency, % Frequency of K101E&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>57 d</td>
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<tr>
<td>115&lt;sup&gt;e&lt;/sup&gt; d</td>
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<td>644 925</td>
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<td>275 d</td>
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<td>309 d</td>
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A Phase 1 Open Label Safety, Acceptability, Pharmacokinetic, and Pharmacodynamic Study of Intramuscular TMC278 LA (the MWRI-01 Study)
### MWRI-01 Single Dose Cohorts

**Study Progress**

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<tr>
<th>Screen</th>
<th>Baseline</th>
<th>+1</th>
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<th>+3</th>
<th>+4</th>
<th>+5</th>
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<td>Arm 1A♀</td>
<td>1200mg</td>
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<tr>
<td>Arm 2A♀</td>
<td>600mg</td>
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</table>

**Female & Male Arms to run in parallel independently**

| Arm 1B♂  | 1200mg |    |    |    |    |    |    |
| Arm 2B♂  | 600mg  |    |    |    |    |    |    |
Plasma Pharmacokinetics (females)

1200 mg (n=12) 600 mg (n=12)
Plasma Pharmacokinetics (females)

1200 mg (n=12)

600 mg (n=12)
Genital & Rectal Fluid PK (females)

1200 mg (n=12)

600 mg (n=12)
Tissue PK (females)

1200 mg (n=12)

600 mg (n=12)
Rectal Tissue Pharmacodynamics

Dose Effect $P = 0.0009$
Visit Effect $P < 0.0001$
Dose*Visit Interaction $P = 0.2131$
**Vaginal Tissue Pharmacodynamics**

![Graph showing Vaginal Tissue Pharmacodynamics](image)

- **Dose Effect** $P = 0.4804$
- **Visit Effect** $P = 0.1197$
- **Dose*Visit Interaction** $P = 0.0575$
Rectal Tissue

$P < 0.0001$

$Log_{10}[RT]\text{ng/mL}$

$Log_{10}[p24]\text{pg/mg}$

$P < 0.0001$

$Log_{10}[RF]\text{ng/mL}$

$Log_{10}[Plasma]\text{ng/mL}$

$P = 0.1369$

$600\text{mg Single Dose}$

$1200\text{mg Single Dose}$
CABOTEGRAVIR

- Analogue to Dolutegravir (DTG)
- Similar preclinical profile to DTG
- PrEP: consideration for both mono use or combination with Rilpivirine

- High genetic barrier
- Low DDI potential
LA Cabotegravir Single Injection Provides Detectable Drug in Plasma for 48 Weeks!

Spreen WR et al Curr Opin HIV AIDS 2013
Pharmacokinetics, Safety, and Tolerability With Repeat Doses of GSK1265744 and Rilpivirine (TMC278) Long-Acting Nanosuspensions in Healthy Adults

William Sreen, PharmD,* Peter Williams, PhD,† David Margolis, MD,* Susan L. Ford, PharmD,* Herta Crauwels, PhD,† Yu Lou, MS,* Elizabeth Gould, BS,* Marita Stevens, MD,† and Stephen Piscitelli, PharmD*
EDITORIAL

Welcome to the preexposure prophylaxis revolution

Jared Baeten\textsuperscript{a,b,c} and Sheena McCormack\textsuperscript{d}

......new PrEP delivery approaches, particularly long-acting injectable agents, may not only bring tremendous promise but also face potentially significant pitfalls that will be evaluated in ongoing work (Landovitz, pp. 122–128).
Prevention Trials

HPTN 077

A Phase IIa Safety, Tolerability and Acceptability Study of an Investigational Injectable HIV Integrase Inhibitor, GSK1265744, for PrEP in HIV Uninfected Men and Women

- 176 HIV uninfected men & women over 2 years
- 800 im injections every 3 months

HPTN 076

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre Exposure Prophylaxis (PrEP)

- 132 HIV uninfected women over 100 weeks
- 1200 mg injections every 2 months
Treatment
Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial

David A Margolis, Cynthia C Brinson, Graham H R Smith, Jerome de Vente, Debbie P Hogins, Joseph J Eron, Sandy K Griffith, Marty H St Clair, Marita C Stevens, Peter E Williams, Susan L Ford, Britt S Standl, Melinda M Bomer, Krischan J Hudson, Kimberly Y Smith, William R Spreen, for the LATTE Study Team

<table>
<thead>
<tr>
<th>Oral Induction Phase</th>
<th>Oral Maintenance Phase</th>
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<tbody>
<tr>
<td>HIV ART-naive</td>
<td>CAB 10 mg + RPV 25 mg</td>
</tr>
<tr>
<td>HIV-1 RNA ≥1000 c/mL</td>
<td></td>
</tr>
<tr>
<td>CD4 ≥200 cells/mm³</td>
<td>CAB 10 mg + 2 NRTIs*</td>
</tr>
<tr>
<td>1:1:1:1 Randomization</td>
<td>CAB 30 mg + 2 NRTIs</td>
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<tr>
<td>Stratified by VL</td>
<td>CAB 60 mg + 2 NRTIs</td>
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<tr>
<td>and NRTI</td>
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*ABC/3TC or TDF/FTC
Following Week 96, subjects on the CAB arms trans are withdrawn from the study at Week 96.

Figure 2: Proportion of patients with HIV-1 RNA concentration of less than 50 copies per mL by visit in the intention-to-treat exposed population. Error bars indicate 95% CI.
ViiV Healthcare announces positive headline results from a study of two drug injectable regimen for HIV maintenance therapy

- LATTE-2: Phase IIb study
- Pts – Induction phase with cabotegravir + 2 NRTIs

- LA Cabotegravir and Rilpivirine were comparable in maintaining viral suppression to 32 weeks as a 3-drug regimen of Cabotegravir + 2NRTIs.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Viral Suppression</th>
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<tbody>
<tr>
<td>Cabotegravir + 2NRTIs</td>
<td>91% &lt; 50 cps</td>
</tr>
<tr>
<td>Cabotegravir + Rilpivirine Q8W</td>
<td>95% &lt; 50 cps</td>
</tr>
<tr>
<td>Cabotegravir + Rilpivirine Q4W</td>
<td>94% &lt; 50 cps</td>
</tr>
</tbody>
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Viiv Press Release – Nov 3rd 2015
Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients

Aim: To gauge patient interest in receiving long-acting injectable nanoformulated antiretroviral therapy. Methods: Four hundred adult HIV-infected patients currently prescribed antiretroviral therapy were surveyed. χ² tests were used for comparisons of interest across groups. Results: Respondents were 68% male and 53% African–American, with a mean age of 47 years. Overall, 73% of patients indicated that they would definitely or probably try injectable nanoformulated antiretroviral therapy; 61% with weekly dosing; 72% every 2 weekly; and 84% monthly. In total, 48% indicated that they were very concerned about the possible side effects and 35% were very concerned about needle use. Conclusion: The majority of respondents indicated that they definitely or probably would try parenteral nanoformulated antiretroviral therapy.

Original submitted 24 May 2012; Revised submitted 2 November 2012; Published online 23 April 2013
### Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV

Rajith K. R. Rajoli · David J. Back ·
Steve Rannard · Caren L. Free Meyers ·
Charles Flexner · Andrew Owen · Marco Siccardi

DOI 10.1007/s40262-014-0227-1

<table>
<thead>
<tr>
<th>Drug</th>
<th>IM Dose (mg)</th>
<th>Release rate (h⁻¹)</th>
<th>Weekly/Monthly</th>
<th>AUC (µg.h/ml) (Mean ± SD)</th>
<th>C\textsubscript{max} (ng/ml) (Mean ± SD)</th>
<th>C\textsubscript{trough} (ng/ml) (Mean ± SD)</th>
<th>Cut-off limit (ng/ml)</th>
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<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
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<tr>
<td>Emtricitabine</td>
<td>1500</td>
<td>0.0015</td>
<td>Monthly</td>
<td>43.1 ± 15.4</td>
<td>94.2 ± 32.5</td>
<td>51.2 ± 41.3</td>
<td>50.2 (IC\textsubscript{90})</td>
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<tr>
<td></td>
<td>375</td>
<td>0.01</td>
<td>Weekly</td>
<td>20.5 ± 8.9</td>
<td>199.4 ± 76.1</td>
<td>55.6 ± 26.4</td>
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<tr>
<td>Tenofovir</td>
<td>1,300</td>
<td>0.002</td>
<td>Monthly</td>
<td>52.2 ± 15.4</td>
<td>99.2 ± 28.6</td>
<td>43.8 ± 17.2</td>
<td>18 (IC\textsubscript{90})</td>
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<tr>
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<td>200</td>
<td>0.008</td>
<td>Weekly</td>
<td>16.6 ± 7.1</td>
<td>155.6 ± 58.5</td>
<td>49.1 ± 23.0</td>
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<tr>
<td><strong>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
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<td>Efavirenz</td>
<td>800</td>
<td>0.007</td>
<td>Monthly</td>
<td>333.9 ± 99.3</td>
<td>850.4 ± 194.6</td>
<td>140.0 ± 50.8</td>
<td>126 (PBIC\textsubscript{95})</td>
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<td>200</td>
<td>0.015</td>
<td>Weekly</td>
<td>73.2 ± 22.1</td>
<td>546.5 ± 139.5</td>
<td>273.3 ± 81.8</td>
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<td>Etravirine</td>
<td>700</td>
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<td>Weekly</td>
<td>43.4 ± 12.3</td>
<td>359.3 ± 80.7</td>
<td>126.1 ± 60.7</td>
<td>116 (PBIC\textsubscript{95})</td>
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<tr>
<td>Rilpivirine*</td>
<td>250</td>
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<td>Monthly</td>
<td>32.9 ± 14.7</td>
<td>75.4 ± 30.1</td>
<td>22.6 ± 8.2</td>
<td>20.3 (PBIC\textsubscript{95})</td>
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<td>60</td>
<td>0.015</td>
<td>Weekly</td>
<td>10.8 ± 4.8</td>
<td>97.4 ± 33.3</td>
<td>26.1 ± 18.7</td>
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<td><strong>Integrase Inhibitors (IIs)</strong></td>
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<td>Dolutegravir</td>
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<td>Monthly</td>
<td>95.6 ± 8.5</td>
<td>212.1 ± 18.1</td>
<td>65.7 ± 7.1</td>
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<td>24.2 ± 2.8</td>
<td>169.5 ± 18.1</td>
<td>101.7 ± 14.8</td>
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<tr>
<td>Raltegravir</td>
<td>800</td>
<td>0.002</td>
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<td>26.1 ± 5.2</td>
<td>66.9 ± 13.1</td>
<td>15.7 ± 2.8</td>
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<td>8.23 ± 1.47</td>
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<td>30.1 ± 5.4</td>
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<td><strong>Protease Inhibitors (PIs)</strong></td>
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<td>Atazanavir</td>
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<td>334.3 ± 70.7</td>
<td>114.8 ± 25.4</td>
<td>60 (PBIC\textsubscript{95})</td>
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Who We Are

The mission of LEAP is 3-fold; 1) support scientific innovation through investigator access to broad-based scientific expertise including the pharmaceutical industry, 2) develop a communications and data hub to support investigators in this field, and 3) provide a Modeling and Simulation Core Service to address development questions of highest priority to investigators.

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Funding Opportunities

Through this site, you'll find the latest funding opportunities for research and clinical work.
Long acting - Summary

- The emergence of Long Acting ARVs is exciting

- LA is of great interest to the HIV community

- Particular use in special/vulnerable populations with poor adherence or difficult to treat

- Administration at least monthly but preferably longer

- Need to understand mechanisms of entry from depot into systemic circulation and reasons for variability.
Acknowledgments

Andrew Owen
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Ian McGowan
Manuel Battegay
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Marta Boffito
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Washington DC, USA • 8 - 10 June 2016

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