Disclosures

• Honoraria received for advisory boards and lectures from AbbVie, BMS, Gilead, Merck, Viiv, Janssen, Teva

• Educational grants for [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org), [www.hep-druginteractions.org](http://www.hep-druginteractions.org), and [www.cancer-druginteractions.org](http://www.cancer-druginteractions.org) from AbbVie, BMS, Gilead, Janssen, Merck, Viiv, Astellas, AstraZeneca, Boehringer Ingelheim, BMS, Ipsen, Janssen, Pfizer, Roche, Sanofi
### Defining Long Acting ARVs by Administration Route.

- Prerequisite for an LA ARV – less frequent dosing than once daily

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Parenteral (i.m; s.c)</th>
<th>Implant/Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Frequency</td>
<td>≥ 1 week</td>
<td>≥ 1 month</td>
<td>≥ 6 months</td>
</tr>
</tbody>
</table>

- Choice
- Convenience
- Simplify Adherence
- Reduce API* administered

*API = Active Pharmaceutical Ingredient

Importance of Drug Exposure and Potency for LA.

- Achieving the required plasma exposure dependent on the formulation of the API, absorption, clearance and potency.

Achieving Long Acting: Technologies for Drug Delivery

- Long-acting injection
- Microneedle drug patch
- Subdermal implant
- Oral Nanomedicine
- Wearable infusion pump
- Vaginal ring

Characteristics of Successful Long Acting Agents.

- Most developed from oral formulations:
  - Low oral dose
  - Medium to long half lives
  - Therapeutic concentrations must be low

- Different strategies to improve these characteristics – nanoformulations; delivery devices; prodrugs.

<table>
<thead>
<tr>
<th></th>
<th>Daily oral dose</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td>2.5-10 mg</td>
<td>17 h</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>150 µg</td>
<td>26 h</td>
</tr>
<tr>
<td>Cabotegravir</td>
<td>30 mg</td>
<td>14 h</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>25 mg</td>
<td>50 h</td>
</tr>
</tbody>
</table>
2. Long Acting Oral.
Islatravir (MK-8591): Long-Acting NRTTI

- MK-8591: nucleoside reverse transcriptase translocation inhibitor (NRTTI) in phase II study
- Preclinical data: potent activity against WT & multidrug resistance HIV-1[1]
- Long half-life may allow weekly or longer dosing intervals[2]
- In vitro data demonstrate that, when given at 0.25 mg daily or 10 mg weekly, the IQ is higher than other NRTIs[3]


Slide credit: clinicaloptions.com
3. Long Acting Injectables.
**ATLAS Study: Randomized, Multicenter, International, Open-Label, Noninferiority Study in Adults with Virologic Suppression**

**Screening Phase**

- N=705
- PI-, NNRTI-, or INSTI-based regimen with 2 NRTI backbone*

**Maintenance Phase**

- 1:1 Randomization
- Oral CAB + RPV n=308
- CAB LA (400 mg) + RPV LA (600 mg)‡
- IM monthly n=303
- Day 1 Baseline Week 4 ‡ 5 8 24 40 41 48 52

**PRO assessments**

**Extension Phase‡**

- Extension Phase or transition to the ATLAS-2M study

---

*Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study; ‡Optional switch to CAB + RPV LA at Week 52 for those on CAR; ††Participants who withdraw/complete IM CAB + RPV LA must complete 52 weeks of follow-up; ‡‡Participants received an initial loading dose of CAB (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onwards, participants received CAB (400 mg) + RPV LA (600 mg) injections every 4 weeks.

ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside RTI; PI, protease inhibitor; PRO, patient-reported outcome; RPV, rilpivirine; VL, viral load.


10th IAS Conference on HIV Science; July 21–24, 2019; Mexico City, Mexico
FLAIR Study: Randomized, Multicenter, International, Open-Label, Noninferiority Study in ART- Naïve Adults

Murray M et al IAS 2019
Pooled analysis ATLAS and FLAIR week 48
Noninferiority achieved for primary and secondary endpoints

Virologic outcomes

Adjusted treatment difference (95% CI)*

Primary Endpoint:
LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

Key Secondary Endpoint:
LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

Overton E IAS MOPEB257 Mexico City July 21-24 2019
ATLAS LA Participants Preferred CAB + RPV LA to Daily Oral Therapy

"For the past 44 weeks you have received Long Acting injectable HIV medication every month. Today we would like you to compare your experience on the Long Acting injections with the oral medication you received prior to entering the study. Which therapy do you prefer?"

Preferences of Responding Participants*

97%; 266/273

3%; 7/273

CAB + RPV LA

CAR

*Out of the ITT-E population, 273/308 (88%) had a recorded response to the preference question at Week 48; 266/308 (86%) preferred monthly injection; 7/308 (2%) preferred daily oral.

CAB, cabotegravir; CAR, current antiretroviral; ITT, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

ViiV Healthcare reports positive phase III study results of investigational, long-acting, injectable HIV-treatment regimen administered every two months.

ATLAS-2M study met its primary endpoint, showing similar efficacy of cabotegravir and rilpivirine administered every eight weeks compared to four-week administration.

- 1045 virally suppressed patients given LA CAB + RPV every 8 weeks versus LA CAB + RPV every 4 weeks.
- Non-inferiority assessed by comparison of plasma HIV-RNA $\geq 50$ c/ml at week 48.
## Long Acting Injectables Work: What do we need to know?

### Pharmacology

- 2 monthly use?  
- What about discarding the oral lead in?  
- How to cover the tail; for how long?  
- What about missed doses?  
- Can injection volume be reduced?  
- What happens to drug levels with TB drugs?  
- Imputation of DDIs from oral CAB  
- What happens to drug levels in renal or hepatic impairment?  
- What about adolescents, pregnant women?
Long Acting Injectables Work: What do we need to know?

Pharmacology

- What about discarding the oral lead in?
- How to cover the tail; for how long?
- What about missed doses?
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- 2 monthly use?
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Upcoming/ongoing CAB/RPV studies for HIV treatment

### CAB + RPV
- **Children/Adolescents: MOCHA 12–18** (n=150)
- **Poor Adherers ACTG 5359** (n=350)
  - VL >200 at entry
  - No RPV or INSTI mutations
  - Phase 1: 24 weeks SOC (incentivised)
  - Then open label switch CAB/RPV 48 wks
  - 52 week tail if discontinue
- **LATTE 1 rollover POLAR** (n~100)
- **Implementation study (US): CUSTOMIZE**
  - N=135
  - one year single arm study

### CAB
- **ACTG 5357** CAB LA + bNab VRC01LS
  - (n=75)
  - Single arm study
  - Endpoint is to maintain viral suppression

Adapted from Orkin C IAS 2019
Long-Acting Formulations for PrEP?

- Cabotegravir currently in Phase III for PrEP
- Hope is that LA dosing strategy will improve PrEP adherence, currently a challenge for the TDF/FTC approach
Other Long-Acting Formulations: Dolutegravir

Ultra-long-acting removable drug delivery system for HIV treatment and prevention

Martina Kovarova¹, S. Rahima Benhabbour², Ivana Massud³, Rae Ann Spagnuolo¹, Brianna Skinner⁴, Caroline E. Baker¹, Craig Sykes⁵, Katie R. Mollan⁶, Angela D. M. Kashuba⁵, J. Gerardo García-Lerma³, Russell J. Mumper² & J. Victor Garcia³

- Single dose subcutaneously
- Within 48 h forms a solid ‘globule’
- Delivers dolutegravir for up to 9 months in pre-clinical models.
- Rapid elimination after removal
- Potential application in pre-exposure prophylaxis.

Other Long-Acting Formulations; GS-6207 (Capsid Inhibitor)

GS-6207, A potent and selective first-in-class long-acting HIV-1 capsid inhibitor.

Yant SR, et al. CROI 2019 P480

Figure 1. GS-6207 has a Multi-Stage Mechanism of Action

Properties ideal for a low-dose, long-acting injectable

- Picomolar antiviral potency (>10 times more potent than current ARVs)
- Low predicted clearance.
- Low aqueous solubility.
- Shows sustained exposure in pre-clinical species

Yant SR et al CROI 2019 & IAS 2019; Sager J et al CROI 2019
Other Long-Acting Formulations; GS-6207 (Capsid Inhibitor)

Safety and PK of subcutaneous GS-6207, A novel HIV-1 capsid inhibitor.
Sager J, et al. CROI 2019 O141

- First-in-human phase I study[1]
  - Single SC dose in 32 healthy volunteers
  - PK support > 12-wk dosing interval

<table>
<thead>
<tr>
<th>Dose</th>
<th>IQ at Wk 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>4.7</td>
</tr>
<tr>
<td>300</td>
<td>4.1</td>
</tr>
<tr>
<td>100</td>
<td>1.3</td>
</tr>
<tr>
<td>30</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Safety and antiviral activity over 10 days following a single dose of subcutaneous GS-6207, first in class, long acting HIV capsid inhibitor in people living with HIV.
Daar E et al. IAS 2019

- Phase Ib GS-US-200-4072, recruiting:[2]
  - HIV-1 RNA 10,000 to 400,000 c/mL and CD4+ cell count > 200 cells/mm³
  - ART-naive and –experienced but naive to CAI and INSTI, with no ART in 12 weeks prior to screening

4. Implants and other.
Other Long-Acting Formulations: Islatravir (ISL; MK-8591)

- ISL – nucleoside RT translocation inhibitor
- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator
- Initial trial uses prototype implant

Simulated Human PK Profiles

Projected human Islatravir plasma concentration (μM)

0 20 40 60 80 100 120
0.00001 0.0001 0.001 0.01 0.1
Time (Days)

Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

- Long intracellular half life

Implantable Devices: Advantages and Disadvantages

**Advantages:**
- Removable at end of treatment and for adverse effects
- Potentially provide therapy for years with a single implant
- Potentially improved pharmacokinetics

**Disadvantages:**
- Minor procedure required for insertion (and removal)
- Palpation will not determine the duration of use.
- Potentially complicated regulatory environment.

Flexner C, Curr Opin HIV AIDS 2018; Scarsi K, 2019; 9th International Workshop on HIV & Women
Other Long-Acting Formulations; Microneedle Patches

- Patch size comparable to a nicotine patch (25 cm²)
- Needles are made up of nanoparticle drug + dissolvable polymer
- USAID supported collaboration for CAB-LA for PrEP:
  - Queen’s University, PATH, ViiV Healthcare, the Population Council and LTS Lohmann Therapie-Systeme AG

https://daro.qub.ac.uk/hiv-microneedles-patch
5. Are interactions likely to be an issue with Long Acting Drugs?
There are Important DDIs with Long Acting Contraceptives.

1. Contraception


Double dose levonorgestrel implant does not fully overcome interaction with efavirenz.

Scarsi KK, et al. CROI 2019 O51

3/20 women had unintended pregnancy in EFV Group

There are Important DDIs with Long Acting Contraceptives.

Potential concern for timing of DMPA injection among women treated for HIV and TB. (ACTG 5338)
Mngqibisa, et al. CROI 2019 O78

- MPA levels were lower in women on EFV and RIF compared with women with HIV not on these drugs
- 12% of women had low MPA levels which is concerning and might indicate early contraceptive failure and thus an increase in the risk of ovulation in women co-infected with HIV and TB
- Shortening the DMPA dosing interval for women with TB and HIV, most likely to every 8-10 weeks, seems prudent
LA Cabotegravir/Rilpivirine and Rifampicin

Hormonal contraceptives do not alter cabotegravir PK in HIV uninfected women. HPTN 077
Blair C, et al. CROI 2019 P473

- PBPK models qualified against observed data for oral formulation

CAB, cabotegravir; RIF, rifampicin; PBPK, physiologically based pharmacokinetic.
Potential for DDI: Release from Injection site

Potential Interaction affecting drug release:
- Inhibition of nanoparticle phagocytosis by macrophages
- Inhibition of angiogenesis

# Potential Interactions with Other LA Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islatravir (MK-8591)</td>
<td>Few interactions anticipated</td>
</tr>
<tr>
<td>GS-6207</td>
<td>New drug class - need data</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Interactions with strong inducers likely to be important</td>
</tr>
</tbody>
</table>
Key Message

• Exciting developments with injectable/implants and other LA formulations.
• There will be implementation challenges
• By skipping the GI/hepatic first pass, DDIs will likely be fewer than when the drug is given orally (for many if not all compounds). Modelling important to predict DDIs in virtual patients
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  • Charles Flexner

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• University of Nebraska Medical Center
  • Kim Scarsi