This webinar will begin shortly. All participants are currently muted.

Live Webinar – 2 May 2018
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Welcome

Dr. Bethany Young Holt (IMPT)
Objectives

 Employ long-acting delivery methods to develop MPTs that are consistent with the needs of HIV prevention

 Define and develop drug substances consistent with the technical requirements of long-acting MPTs
Agenda

- Introduction
- Panel presentations
- Q&A
- Closing remarks
MPTs combine protection against:
• Unintended pregnancy
• HIV
• Other STIs
MPTs in the R&D Pipeline

- Vaginal rings
- Innovative vaginal delivery products
- Injectables and implant technologies
- Other novel technologies and platforms
Initiative for MPTs

- Science
- Women's Voices and access
- Advocacy & Market Development
- Funder Collaboration
- Product launch and introduction
Expert Presenters

Dr. Charles Flexner  
(Johns Hopkins University)

Dr. Arnab Chatterjee  
(California Institute for Biomedical Research)
Employing long-acting delivery methods to develop an MPT that are consistent with the needs of HIV prevention

Dr. Charles Flexner  
(Johns Hopkins University)
Employing long-acting delivery methods to develop MPTs that are consistent with the needs of HIV prevention

Charles Flexner, MD
Johns Hopkins University
How close are we to having approved long acting treatments for HIV?
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


Summary

Background Cabotegravir and rilpivirine are antiretroviral drugs in development as long-acting injectable formulations. The LATTE-2 study evaluated long-acting cabotegravir plus rilpivirine for maintenance of HIV-1 viral suppression through 96 weeks.

Methods In this randomised, phase 2b, open-label study, treatment-naive adults infected with HIV-1 initially received oral cabotegravir 30 mg plus abacavir–lamivudine 600–300 mg once daily. The objective of this study was to select an intramuscular dosing regimen based on a comparison of the antiviral activity, tolerability, and safety of the two intramuscular dosing regimens relative to oral cabotegravir plus abacavir–lamivudine. After a 20-week induction period on oral cabotegravir plus abacavir–lamivudine, patients with viral suppression (plasma HIV-1 RNA <50 copies per mL) were randomly assigned (2:2:1) to intramuscular long-acting cabotegravir plus rilpivirine at 4-week intervals (long-acting cabotegravir 400 mg plus rilpivirine 600 mg; two 2 mL injections) or 8-week intervals (long-acting cabotegravir 600 mg plus rilpivirine 900 mg; two 3 mL injections) or continued oral cabotegravir plus abacavir–lamivudine.
Figure 2: Proportion of patients with HIV-1 RNA concentration less than 50 copies per mL (FDA snapshot algorithm) by visit in the maintenance-exposed population and snapshot outcomes at week 96.

Error bars show 95% CIs, derived using the normal approximation. FDA = US Food and Drug Administration. LA = long-acting.

<table>
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<th>Study visit</th>
<th>Oral cabotegravir plus abacavir-lamivudine induction (maintenance-exposed population)</th>
<th>Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)</th>
<th>Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)</th>
<th>Oral cabotegravir plus abacavir-lamivudine (n=56)</th>
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<tr>
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<td>Virological response</td>
<td>100 (87%)</td>
<td>108 (94%)</td>
<td>47 (84%)</td>
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<td>Virological non-response</td>
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<td>1 (2%)</td>
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<td>8 (14%)</td>
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<td>1 (&lt;1%)</td>
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<td>0</td>
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</tbody>
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Margolis et al., Lancet 2017; 390: 1499-1510
Cabotegravir Nanosuspension – What is it?

- Drug nanocrystal suspended in liquid = nanosuspension
- Nano-dimensions vastly increase drug dissolution rate
- Allows high drug loading compared to matrix approaches
  - Examples of approved product = paliperidone palmitate (Xeplion®, Invega®, Sustenna®)

LA/ER Cabotegravir Single Injection Provides Detectable Drug in Plasma for 48 Weeks!

Mean Plasma GSK1265744 Concentration-Time Profiles following Single Dose LAP Injections in Healthy Subjects (Cohorts 1-7)
Long Acting ARV Injections

- Potential advantages
  - Well known drug delivery technology
  - Can be inexpensive to formulate
  - Readily applicable to a number of small molecule APIs
  - Could be combined with existing contraceptive injections like DMPA

- Potential disadvantages
  - Not reversible in case of AE’s
  - PK may be variable and dependent on injection site
  - Not easy to co-formulate into a single injection for MPTs
  - Injection volumes may be large
  - Current formulations require an oral lead-in for tolerability
Novel LA/ER technologies: What’s in the pipeline for HIV prevention?
Novel LA/ER technologies: Vaginal rings
Long Acting Vaginal Rings

- Potential advantages
  - Topical drug delivery
  - Easily inserted and removed
  - Already approved for contraception (NuvaRing®)
  - Clinical proof of concept for PrEP (dapivirine)
  - Can be paired in a single device with a contraceptive hormone

- Potential disadvantages
  - Easily removed!
  - Adherence dependent
  - Co-formulation: may be difficult to achieve desired drug release properties for both drugs
Novel LA/ER technologies: Implants
Long Acting ARV Implants

- Potential advantages over injectables
  - Removable
  - More consistent and predictable drug release
  - PK not dependent on injection site
  - May remain in place for years (inert, non-degradable subcutaneous versions)

- Potential disadvantages over injectables
  - Specialized device required for insertion
  - Minor surgical procedure to remove
  - Regulated as both a drug and a device
  - Difficulty moving to a generic marketplace
LA ARV Implants – Tenofovir Alafenamide

See also CROI 2017 Abstract 420

FIG 1 Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the y-z (B) and x-y planes (C).
FIG 3 Subdermal implantation of TAF LA prototype device in beagle dogs maintains sustained drug levels with low systemic exposure to TAF and TFV with concomitant, efficient PBMC loading with TFV-DP. Pharmacokinetic profiles of plasma TAF (closed circles) and TFV (open circles) and PBMC TFV-DP (closed diamonds). Each data point represents the means ± standard deviations from four beagle dogs, and dotted lines correspond to the median concentrations for each analyte over the 40-day study. Note that TFV-DP levels were measured only after day 20.
MK-8591 (EFdA) Implant Formulations
Release Effective Drug Levels for >180 days

- >180-day extended release from solid state formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

- Grobler JA et al. CROI, 2/22-2/25, 2016, Boston, MA
Etonogestrel and levonorgestrel serum concentrations for 3 years following a single implant

- Makarainen et al., *Fertility & Sterility* 1998; 69: 716
LA/ER Drugs: Broadly-neutralizing monoclonal antibodies
HIV-1 Spike Protein, Showing Sites Targeted by Broadly Neutralizing Monoclonal Antibodies.

The inset shows the virus with its surface spikes. The left panel shows target sites of monoclonal antibodies in clinical development. The right panel illustrates the binding of four different broadly neutralizing antibodies.
PK profile of VRC01-LS

Fig 2. Measurement of antibody serum concentration (µg/mL). (A) Serum VRC01LS concentrations (colored plots) are shown from first measurement through week 24 after a single administration. The infusion dose and route are as specified in the legend. All values are the mean of duplicate samples run in different wells within the same plate. Previously published VRC01 concentrations based on historical data (black plots) after administration at weeks 0 and 4 are shown for comparison. (B) Geometric mean serum VRC01LS concentrations per group over time. The dotted line at 10 µg/mL on each graph is shown as a reference value. IV, intravenous; SC, subcutaneous.

https://doi.org/10.1371/journal.pmed.1002493.g002
Broadly-neutralizing monoclonal antibodies

- Potential advantages
  - Humanized, well-tolerated
  - "Extendification" possible
    - LA version of VRC01 in clinical development
  - May induce beneficial host cell-mediated immunity
    - ADCC responses
  - Use in prevention applications, PrEP

- Potential disadvantages
  - Expensive
  - Intravenous route of administration
  - Pre-existing resistance commonplace
  - Select for resistance viruses
Novel LA/ER technologies: Oral dosing?
Fig. 1 Concept of oral long acting antiretrovirals. a The design of the gastric resident dosage forms. The dosage form consists of an elastomeric core (grey) and six drug loaded arms (multi-coloured). b The cross section of the arm. The outer sleeve of the arms is made of a rigid structural polymer which provides the arm its mechanical strength. This sleeve is then filled with a drug-polymer matrix which releases the drug at a desired rate. c The manufacturing scheme of the dosage form. The expected performance of the dosage form in vivo is shown in d. The dosage form is loaded with three different polymers (blue, red and yellow) which release the drug at different rates. Selection of appropriate polymers may result in almost constant and sustained plasma drug concentrations. It should be noted that d is a schematic representing an ideal system, and is not experimentally obtained data.
Fig. 4 Plasma pharmacokinetics of immediate release and sustained release antiretrovirals. The concentration time profiles of (a) DTG immediate release (b), DTG sustained release (c), RPV immediate release (d), RPV sustained release (e), CAB immediate release and (f) CAB sustained release are shown. Each dosage form was tested in three animals, and plasma samples from each animal were processed three times. Data was first averaged within each animal (shown by the grey lines) and then between animals in each treatment group (shown by the black line). * indicates $p < 0.05$, two sample t test comparing sustained release formulations and immediate release formulations at matching time points.
Gastric resident “starfish”

- Potential advantages over parenteral formulations
  - Convenient, self-administered
  - Multiple ARV’s in a single device
  - Spontaneous degradation for GI elimination
  - Removable (by endoscopy)

- Potential disadvantages over parenteral formulations
  - Published device is very large for oral administration
  - Dosing interval limitation of 1-2 weeks (?)
  - GI tolerability in humans unknown
  - Possibility of gastrointestinal ulceration and obstruction
  - Unknown food and antacid effects
Who We Are

Funded by an R24 grant from the National Institutes of Health, the mission of LEAP is 3-fold:

1. To support scientific innovation through investigator access to broad-based scientific expertise including the pharmaceutical industry.
2. To develop a communications and data hub to support investigators in this field.
3. To provide a Modeling and Simulation Core Service that helps investigators identify the most promising approaches to the development of new products.

Funding Opportunities

Finding funds for research can be a challenge. The following resources are provided to help guide your
Defining and developing drug substances consistent with the technical requirements of long-acting MPTs

Dr. Arnab Chatterjee
(California Institute for Biomedical Research - Calibr)
Outline of key messages

- Introduction to Calibr/TSRI
- Key elements for selecting compounds that are good candidates multipurpose prevention technologies selection
  - Formulation compatibility matching
  - Mechanism of action considerations including target tissue/cell considerations
- Key research gaps and priorities for
  - Addressing potency/clearance properties
  - New chemical matter versus drug repurposing
Calibr – non-profit drug discovery

- Founded in 2012 as a 501c3 non-profit by Peter G. Schultz, based on successful model he established at GNF/Novartis
- Expanded into 70,000+ sq. ft. facility in La Jolla, CA
- $260+M in total funding commitments (Gates Foundation, JDRF, Wellcome Trust, CIRM, Merck, Pfizer, BMS and others)
- High-throughput screening and protein/cellular engineering discovery capabilities
- Medicinal chemistry and pharmacology preclinical development in-house resources
- Significant preclinical and clinical drug discovery and development expertise – currently three small molecules in clinical trials
- Portfolio of 40+ projects at various phases of preclinical discovery, including 8 programs entering the clinic over the next 12-18 months
- Collaborations with foundations and institutions throughout the world including BMGF, JDRF, Wellcome Trust, CIRM, etc.
- Formed a subsidiary relationship with TSRI in 2016, creating a new model for integrated drug discovery
New model for a “bench-to-patient” non-profit research institute that joins:

- The creativity, talent and investment in basic biomedical research at TSRI
- The expertise, focus and infrastructure of translational research at Calibr

... to accelerate the development and lower the cost of new medicines for unmet needs

- Capitalize on the translational engine that Calibr has built by ensuring a sustainable influx of innovative research from TSRI to seed the drug discovery pipeline
- Combine the strengths of two proven organizations rather than building from scratch
- Realize substantial licensing revenues from pharma/biotech partners to reinvest in research and development – an ‘evergreen’ model for biomedical research and translational medicine
Intra-muscular (IM) Approach

- Keeping drug levels above minimal chemoprophylactic concentrations (MCC of $C_{eff}$) is essential.
- Oral “run-in” might be required before long acting formulation can reach above MCC.
Oil/Water partitioning

- High loading concentrations, melting point and particle size can effect dissolution
Prodrugs can improve PK properties

- Typically prodrugs are used to improve permeability across (gut lumen, blood-brain barrier, cancer target cells, etc)

- In HIV, prodrugs such as phosphonamidites like tenofovir alafenamide (TAF) improve target cell levels and improve clearance by reducing clearance from target PBMCs

- Taking oral drugs to be used as parenteral formulation is not easy (similar to work in biologics, vaccines, etc)
**HIV prophylaxis: tenofovir alafenamide (TAF)**

TAF is a potent antiviral which possesses a unique attribute to bio-accumulate within PBMCs as the negatively charged triphosphate and release less of TFV which has known toxicities. This makes TAF superior to TDF.
Unpublished case study: Atovaquone (kAAC207) for malaria chemoprophylaxis

- Changing a prodrug to solely improve formulation loading and release rate compared to parent oral drug (graph below)
- Drug stability in formulated material is important research gap to close given product needs for multipurpose prevention products

Exposure of Atovaquone Following IM Delivery of kAAC207 (suspension), mCBK068 (oil solution) and mCBE161 (suspension) in Rat (13 weeks)

Exposure of Atovaquone Following IM Delivery of kAAC207 (suspension), mCBK068 (oil solution) and mCBE161 (suspension) in Rat (4 weeks)
Future considerations

- Do we stick to oral drugs or should we place greater importance on novel candidate?
  - Often oral drug lead optimization leaves many good candidates for IM depots compounds on the table with low aqueous solubility and good clearance/potency properties that are ideal for MPT

- Chemical modifications (prodrugs, etc) allow for new approaches to come to bear

- Drug and formulation compatibility for multiple agents will be essential going forward
Q&A

Reminder: Please use the chat box or the raise-hand feature to provide questions or comments.

All participants will be unmuted during this time. When not speaking, press *6 to mute and *7 to unmute.
Join the MPT movement
Thank you!

This project is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of Cooperative Agreement #AID-OAA-A-16-00045. The contents are the responsibility of the IMPT, CAMI Health, PHI, and its partners and do not necessarily reflect the views of USAID or the U.S. Government. The Initiative for Multipurpose Prevention Technologies (IMPT) is a project of CAMI Health, an organization dedicated women’s reproductive health and empowerment, housed at the Public Health Institute (PHI).