SATELLITE DINNER
INNOVATION AND GLOBAL HEALTH:
Thursday, February 6, 2020
6:30 PM – 8:30 PM

Organized in conjunction with LAII 2020 by
• MedinCell • Medicines Patent Pool • Drug Delivery Experts • Bill & Melinda Gates Foundation • Unitaid
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<th>Agenda</th>
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<td><strong>Global health and long-acting formulations</strong></td>
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<td>Arrival of participants and start of cocktail</td>
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<td>Open meeting</td>
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| Setting the scene | Carmen Pérez Casas - Unitaid  
                     Dennis Lee - BMGF |
| **Practical application for long-acting technologies in LMICs – Case studies and discussion** |
| Project 1: Academia perspective | Andrew Owen - University of Liverpool |
| Project 2: Academia perspective | Rodney Ho - University of Washington |
| Project 3: Industry perspective | Stephanie Barrett - Merck |
| Project 4: Industry perspective | Christophe Roberge - MedinCell |
| Breaking down barriers to access | Esteban Burrone - Medicines Patent Pool |
| Moderated discussion: How to address challenges? How to boost the pipeline to address LMICs needs? |
| Wrap up and close | Charles Flexner - LEAP |
SETTING THE SCENE:
GLOBAL HEALTH AND
LONG-ACTING FORMULATIONS

Charles Flexner - LEAP
Carmen Pérez Casas - Unitaid
Dennis Lee – Bill & Melinda Gates Foundation
The case for long-acting prevention and treatment in infectious diseases
Today, 24.5 million individuals worldwide receive anti HIV drugs.
The Challenge: difficulties to comply with treatment and prevention

- Low adherence across diseases
- Very low levels for some populations
- Common root causes

**Example**

Area to reach viral suppression

HIV Treatment Adherence
The challenge: Impact of poor adherence and retention

<table>
<thead>
<tr>
<th>Morbidity &amp; Mortality</th>
<th>Transmission</th>
<th>Wasted resources</th>
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<tbody>
<tr>
<td>HIV</td>
<td>1.7 million</td>
<td>770 000</td>
</tr>
<tr>
<td>TB</td>
<td>10 million</td>
<td>1 600 000</td>
</tr>
<tr>
<td>MAL</td>
<td>228 million</td>
<td>405 000</td>
</tr>
<tr>
<td>HCV</td>
<td>1.8 million</td>
<td>399 000</td>
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The opportunity: drug delivery technology can make important contributions to Global Health and Universal Health Coverage

- Improving adherence by decreasing frequency or simplifying dosing.
- Addressing stigma.
- Increasing effectiveness.
- Alleviating burden on health care providers and fragile systems.
- Simplifying Mass Drug Administration.

Final products must be **cost-effective and affordable to be used at scale in LMICs**
The opportunity: examples in major infectious diseases ... and beyond.

Reinforced efforts needed to address gaps and access.
FAMILY PLANNING
214 million+ women in developing countries have an unmet need for modern contraceptives leading to an estimated 74 million women with an unintended pregnancy per year.

THE OPPORTUNITY

- Reduction in unintended pregnancy by 52M (70%) annually
- Maternal deaths would drop by 150,000 annually
- New born deaths would drop by ~ 2M annually
- When women have the ability to time and space their pregnancies, it unlocks a virtuous cycle of prosperity for families and entire communities

“Family planning and access to contraception—including information, supplies, and services—is an issue that I am passionate about, and it has become one of my personal priorities at the foundation. I believe it’s one of the most urgent issues of our time.”

—Melinda Gates
## Contraceptive Use in Sub-Saharan Africa

- More than 1/3 of contraceptive users in SSA choose injectable depots
  - Durations range from 1-3 months
  - Cost is ~ $0.80/dose
- Non-degradable implants are also widely used
  - Durations range from 3-5 years

## Delivery Challenges for Current Injectable Depots

- **Most common reason for unplanned pregnancy for users of injectable depots is missed dosing**
- Need to access clinic 4-12 times a year, at the right schedule
- Shipping costs and stock-outs of drug and/or supplies
- Need for healthcare worker training

## Delivery Challenges for 3-5 year Implants

- Need for healthcare worker training for implant and removal
- **Requires surgical removal at end of delivery duration**

## Cost Remains a Barrier to Access

- Procurement budgets are fixed and do not cover needs of all women who desire access to modern contraceptives
Sayana press: gold standard for long-acting self-injectable contraceptive

Sayana Press
(medroxyprogesterone acetate)

- 3-Months subQ suspension formulation in a prefilled, single-dose, non-reusable Uniject™ injection system
- Enables administration by any level of provider, as well the user
- Eliminates need for injection supplies
- Opens access to remote areas or areas with limited supply of trained providers
- < $0.80 / dose
Moving forward
BMGF Long-Acting Contraceptive Portfolio

Commercial products
Investments

Monthly oral

3-month injectable

Sayan Press (3-month DMPA injectable in Uniject)

6 month injectables

3 and 5 year implants

Jadelle (5-year LNG implant)

10+ year controllable

Implanon (3-year ENG implant)

Permanent

Lyndra
Long-acting delivery

FHI360 / SIPPR PLGA microparticles

Evestra Pro-drugs

MedinCell In Situ Forming Depot

DelSiTech Silica hydrogel

Dissolvable Microneedles

MicroCHIPS Programmable implant

Non-Surgical Permanent Contraception
Collaborations with drug delivery technology companies and research institutes

- Once-yearly (or less frequent) implant
- Once- or twice-yearly injectables or bioerodible implants

Intarcia

- Osmotic Mini-Pump for SubQ Implantation
- Device Design and Release Mechanism
- Zero-Order Release Profile

Non-erodible, zero-order release implant

DelSiTech

- Injectable erodible silica gel matrix

Stayton (UW)

- Pre-build Prodrug Monomer(s)
- Polymerize to Therapeutic
- Injectable “drugamers” with tunable linker chemistry

RTI International

- ARV suspension
- PCL tubing
- Erodible, zero-order release implant
Unitaid: Accelerating impact of long-acting formulations in LMICs

NEW PROJECTS: Unitaid is investing nearly US$ 40 million to develop long-acting medicines that could transform the way the world prevents & treats #HIV, #TB #HepC and #malaria.
@UW @LivUni @UNLincoln @CHAI_health @JohnsHopkins

@MedsPatentPool http://ow.ly/e6ve30qdAjO

Access to products in the market or emerging from pipeline: interventions under consideration
Thank you

Unitaid
Carmen Pérez Casas

BMGF
Dennis Lee
PRACTICAL APPLICATION FOR LONG-ACTING TECHNOLOGIES IN LMICS: CASE STUDIES

Andrew Owen - University of Liverpool
Rodney Ho - University of Washington
Stephanie Barrett - Merck
Christophe Roberge - MedinCell
Esteban Burrone - Medicines Patent Pool
Project LONGEVITY: Long-acting injectables for malaria chemoprophylaxis, TB prevention and HCV therapy

Andrew Owen, Ph.D, FRSB, FBPhS, FLSW
University of Liverpool
### Target product overview

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<tr>
<th>Indication</th>
<th>Drug</th>
<th>Comment</th>
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<tr>
<td>Malaria chemoprophylaxis</td>
<td>Atovaquone</td>
<td>Only if evidence supports it, or in combination.</td>
</tr>
<tr>
<td>Latent TB prevention</td>
<td>Rifapentine</td>
<td>In combination with isoniazid prodrug.</td>
</tr>
<tr>
<td></td>
<td>Novel isoniazid prodrug</td>
<td>In combination with rifapentine.</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline and/or delamanid</td>
<td>Only if data to support use in TB prevention emerges.</td>
</tr>
<tr>
<td>HCV cure</td>
<td>Glecaprevir</td>
<td>In combination with pibrentasvir.</td>
</tr>
<tr>
<td></td>
<td>Pibrentasvir</td>
<td>In combination with glecaprevir.</td>
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Emulsion-Templated Freeze Drying (ETFD)

- Novel particle engineering technology to process poorly water soluble compounds.
- Simple manufacturing process able to generate highly drug-loaded powders and liquid formulations containing high drug mass for parenteral delivery.
Cost and commercial strategy

• Detailed market intelligence will determine commercial viability and sustainability.

• MPP and CHAI will leverage existing expertise in market projections, license management, pricing and COGs.

• LMICs demand projections will account for:
  • epidemiological/treatment data
  • availability of national/donor programmes and private market
  • likely market dynamics in replacing existing options (or competing)
  • understanding existing in-country capacity for implementation
  • understanding of cultural variations in local preferences

• Pricing and COGs activities will require in depth understanding of the scaled-up manufacturing process and the current prices of existing treatments.

• This information will be harnessed to develop and effect a robust strategy for scale-up.
GLAD Project: TLD-3 drug-LAI product for longer lasting HIV therapy

TLC-ART-Targeted, Long-acting Combinational Anti-Retroviral Therapeutic Program

Rodney JY Ho, Ph.D, FAAAS, FAAPS
University of Washington
GLOBAL LONG-ACTING DRUG COMBINATION DEVELOPMENT (GLAD)

Aim: To transform short-acting TLD oral dosage form to long-acting injectable TLD intended for HIV treatment in low and middle-income countries

• Sustained HIV suppression required multiple HIV drugs;
  o Emerging LA products in development (LAI-CAB; LAI-RPV) are single agent dosage form (produce different PK);

• DcNP technology enable transformation of 3 existing and potent TLD oral drug combination that are short-acting into long-acting, LAI-TLD
Drug Combination Nanoparticle Platform (DcNP) in 3-major steps

DcNP formulation process of TLC-ART 101 (LPV, RTV, TFV) is matured

- 3-Step Process – well controlled and defined SOPs
  1. Spray Drying APIs solubilized in ethanol to produce DcNP powder (Pass/No pass)
  2. Suspension Production and Particle Size Reduction
     - API concentrations that meet product specification
     - Particle size 50-70 nm in suspension that meet injectable product quality
     - Stability at 4°C (2 year) and 25°C (1 year) in single dose vials
  3. Fill and Finish
     - Sterility, osmolarity, pH, quality
ART Long-acting

• Advantages:
  • First-pass and higher cellular over plasma drug concentration (targeting);
  • Potentially synchronizing intracellular levels of 3 drugs in HIV host cells.

• Characteristics that make it appealing for products aimed at LMICs
  • A single injectable 3-in-one dosage form, stable in suspension without the need of cold chain, simple scaling allowing technology transfer to LMICs;
  • Availability and wide-access of the APIs (TLD), selected by WHO as preferred regimen and being scaled-up in LMICs;
  • Potential for low target price.
The Use of Long-acting Implants for HIV Prevention & Treatment

Stephanie E. Barrett, Ph.D
Merck & Co., Inc.
Extended-Duration Islatravir (ISL)-Eluting Implant as a Candidate for HIV Treatment and Prevention

**Aim:** Develop long-acting implants of ISL as new HIV treatment and prevention interventions that aim to improve adherence by reducing the complexity of regimens, the frequency of the dosages, and allow for more forgiving options with regards to missed doses.

**ISL Implant Design Similar to Nexplanon®**
- Uses same polymer
- Uses Nexplanon® applicator

**Projected human Islatravir plasma concentration (mM)**

**Simulated Human PK Profiles**

Matthews *et al.* IAS 2019
62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months

- 62 mg implant had concentrations above PK threshold at 12 weeks
  - Projected to be well above threshold at 12 months and likely for several months beyond
  - **Supports potential of the ISL implant as a once-yearly PrEP option**

Matthews et al. IAS 2019
LONG-ACTING INJECTABLE IVERMECTIN USING BEPO® TECHNOLOGY AS A POTENTIAL NEW VECTOR CONTROL TOOL TO COMBAT MALARIA TRANSMISSION

Christophe Roberge
MedinCell
Drug Product BEPO®- IVM

Aim: Development of an injectable long-acting formulation of ivermectin as a complementary vector control method to reduce Malaria transmission in LMICs

- Injectable 3-month acting formulation of ivermectin for subcutaneous use.
- The sustained mosquitocidal efficacy of ivermectin is expected to result into a significant epidemiological impact in countries/areas where malaria is endemic.
BEPO® Technology

- Clinically advanced injectable in-situ forming depot technology using a combination of two bioresorbable copolymers and a solvent as excipients.
- Drug release can be tuned from days to months.
- Simple manufacturing process.
- Injectable using standard syringes and needles.
- Products can be developed as ready-to-use.
- Ongoing BEPO® programs to address LMICs needs in contraception and HIV PreP funded by BMGF
Characteristics that make BEPO®-IVM appealing for LMICs

- A single injection will cover the period at higher risk of transmission (rainy season).
- Particularly appealing if one considers Mass Drug Administration of ivermectin for Malaria transmission reduction without the necessity of repeated oral dosing
- Bioresorbable drug delivery technology => Will not necessitate implant removal
- Straightforward manufacturing allowing production cost to align with LMICs requirements
- Can be developed as a ready-to-use dosage form
- Wider benefit with a likely impact on Neglected Tropical Diseases (NTDs) where ivermectin tablet is used.

Preliminary data from a funded program « ANIVERMATE » with IRS/CIRDES/IRSS and University of Liebig have already shown sustained efficacy over several months following a single SC injection of a BEPO®-IVM prototype formulation in cattle.

- Graph represents median survival of *Anopheles coluzzii* mosquitoes after being fed during direct skin feeding assays at several time points after injection of the treatments.

Drugs Product BEPO®-IVM
Breaking down barriers to access

Esteban Burrone
Medicines Patent Pool
CASE STUDY ON HIV MEDICINE DOLUTEGRAVIR (TLD)

5.9 million people are estimated to be on TLD

> 83%
The MPP negotiates public-health driven licences with patent holders. The MPP sublicenses drugs & long-acting therapeutics to generic companies. Licensing terms encourage the sale of affordable generic versions in developing countries and the development of formulations needed in resource-limited settings. Royalties where appropriate.
MODERATED DISCUSSION:
HOW TO ADDRESS CHALLENGES?
HOW TO BOOST THE PIPELINE TO ADDRESS LMICs NEEDS?

Charles Flexner - LEAP