3rd LONG-ACTING INJECTABLES AND IMPLANTABLES CONFERENCE

6 - 7 FEB 2020
LA JOLLA

The Alexandria at Torrey Pines
La Jolla, California

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*

Agenda

Global health and long-acting formulations		
	Arrival of participants and start of cocktail	
	Open meeting	*Charles Flexner - LEAP*
	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*

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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 

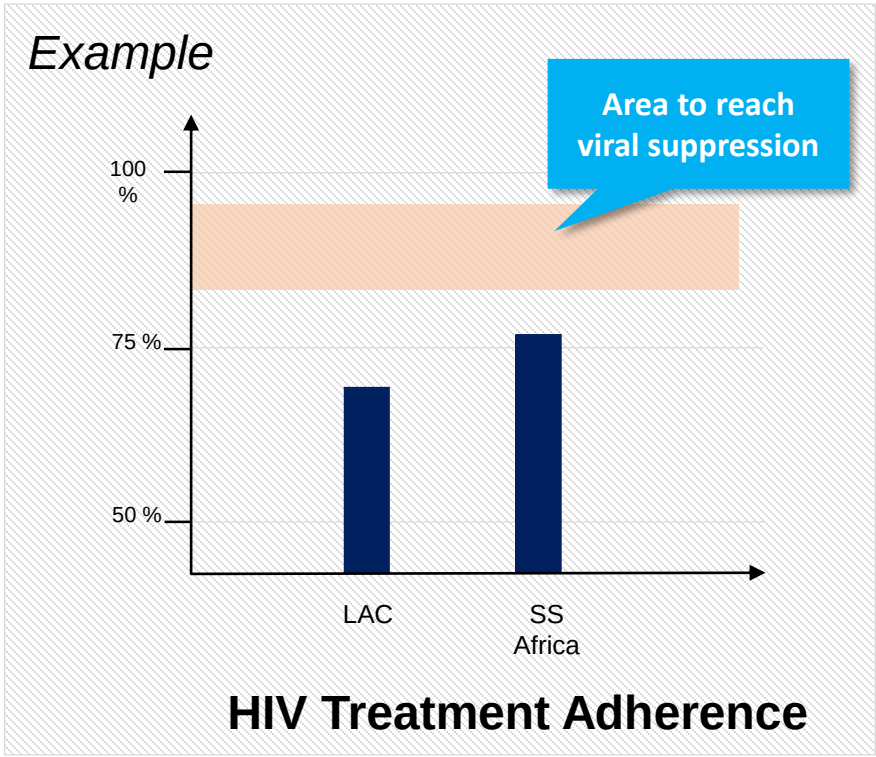
anti HIV drugs

The Challenge: difficulties to comply with treatment and prevention

Low adherence across diseases

Very low levels for some populations

Common root causes



The challenge: Impact of poor adherence and retention

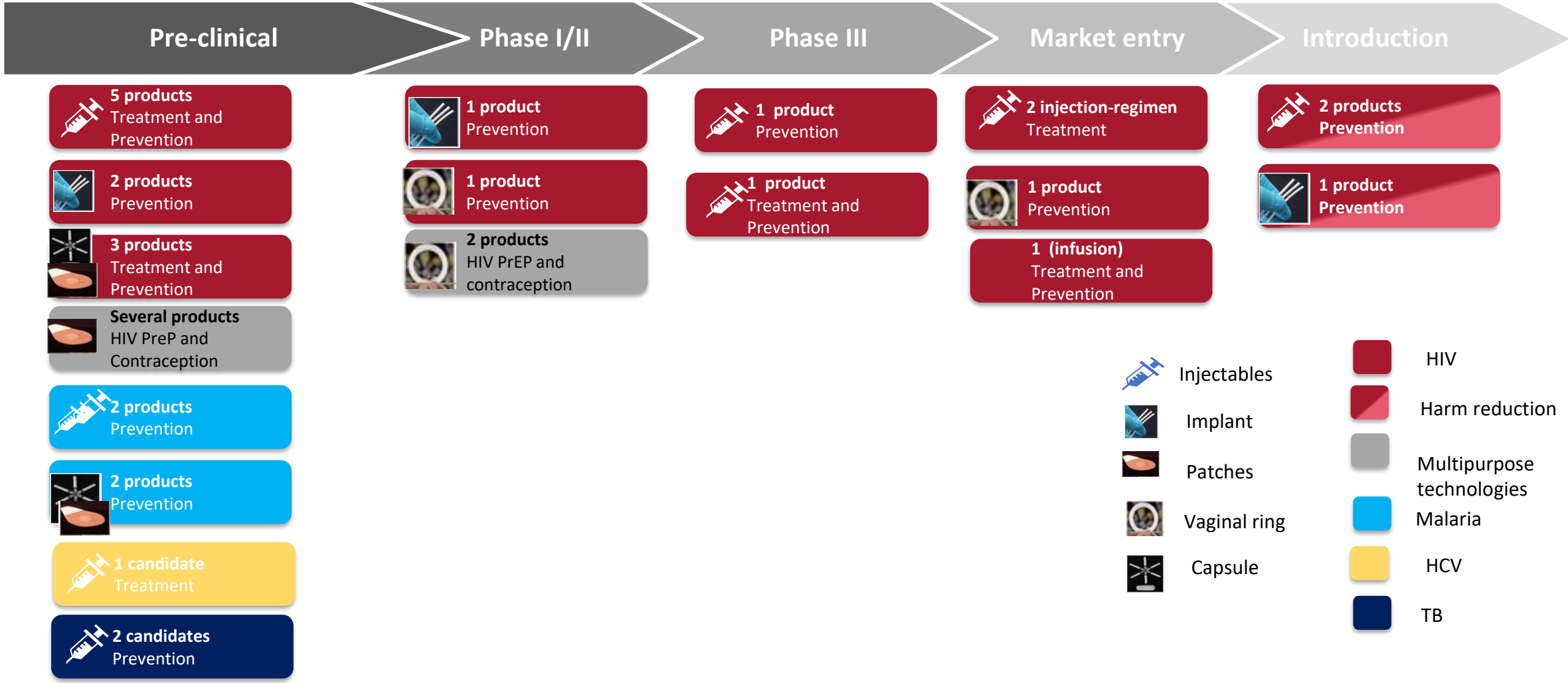
	New infections	Deaths
HIV	1.7 million	770 000
TB	10 million	1 600 000
MAL	228 million	405 000
HCV	1.8 million	399 000

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.

BILL & MELINDA GATES foundation

FAMILY PLANNING

THE CHALLENGE

- 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 AND CHALLENGES IN SUB-SAHARAN AFRICA

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

Injectable Depot

Non-degradable Implant

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

Sayana Press (3-month DMPA injectable in Uniject)

Jadelle (5-year LNG implant)

Implanon (3-year ENG implant)

Monthly oral

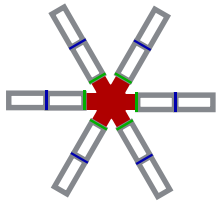
3-month injectable

6 month injectables

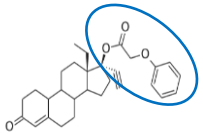
3 and 5 year implants

10+ year controllable

permanent



Lyndra
Long-acting delivery



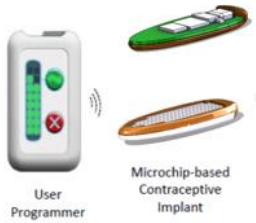
FHI360 / SIPPR
PLGA microparticles

Evestra
Pro-drugs

MedinCell
In Situ Forming Depot

DelSiTech
Silica hydrogel

Dissolvable Microneedles



MicroCHIPS
Programmable implant

Non-Surgical Permanent Contraception

BMGF LONG-ACTING ARV IMPLANTS AND INJECTABLES

Collaborations with drug delivery technology companies and research institutes

Intarcia

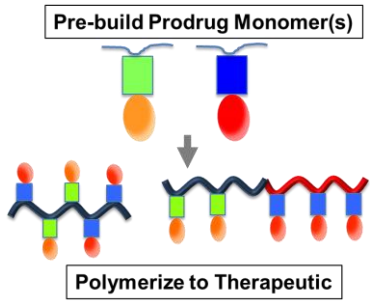
Non-erodible, zero-order release implant

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

DelSiTech

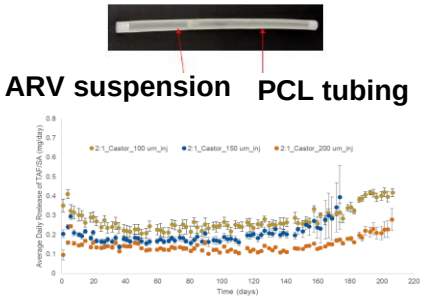
Injectable erodible silica gel matrix

Stayton (UW)



Injectable "drugamers" with tunable linker chemistry

RTI International



Erodible, zero-order release implant

Unitaid : Accelerating impact of long-acting formulations in LMICs

medicines patent pool

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

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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

Longevity

UNIVERSITY OF LIVERPOOL

Target product overview

Indication	Drug	Comment
Malaria chemoprophylaxis	Atovaquone	Only if evidence supports it, or in combination.
Latent TB prevention	Rifapentine	In combination with isoniazid prodrug.
	Novel isoniazid prodrug	In combination with rifapentine.
	Bedaquiline and/or delamanid	Only if data to support use in TB prevention emerges.
HCV cure	Glecaprevir	In combination with pibrentasvir.
	Pibrentasvir	In combination with glecaprevir.

JOHNS HOPKINS MEDICINE

University of Nebraska Medical Center

CLINTON HEALTH ACCESS INITIATIVE

medicines patent pool

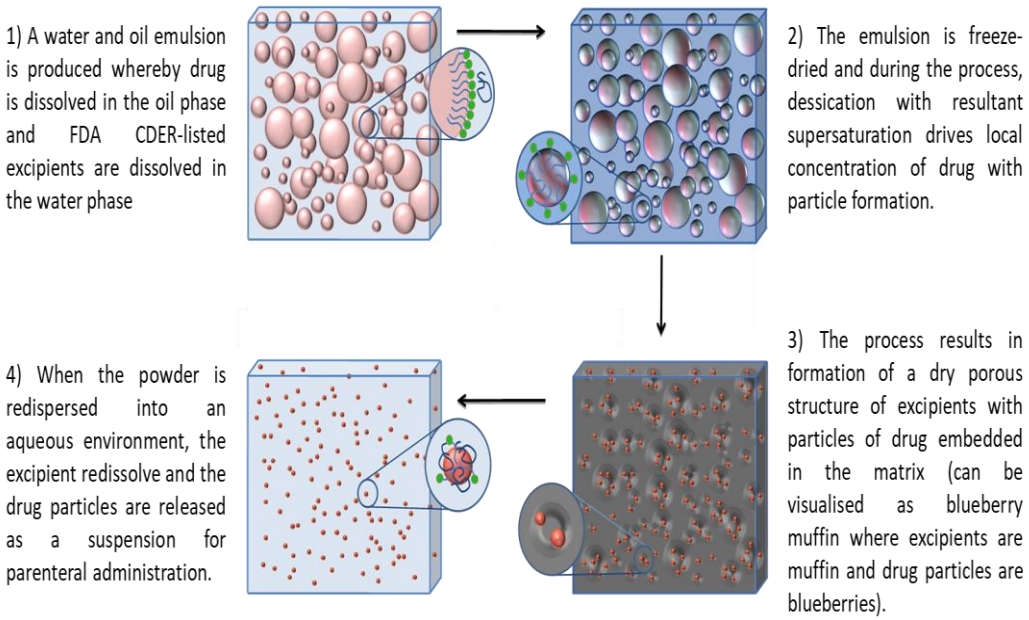
TAG Treatment Action Group

Tandem Nano Ltd

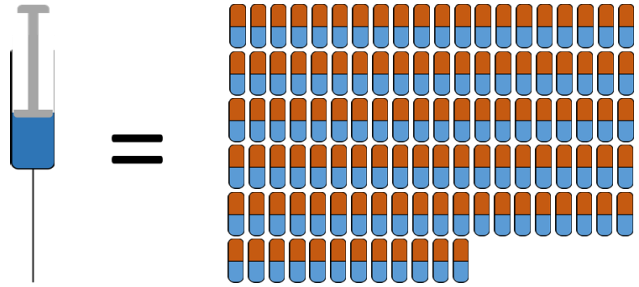
Longevity

UNIVERSITY OF LIVERPOOL

Emulsion-Templated Freeze Drying (ETFD)

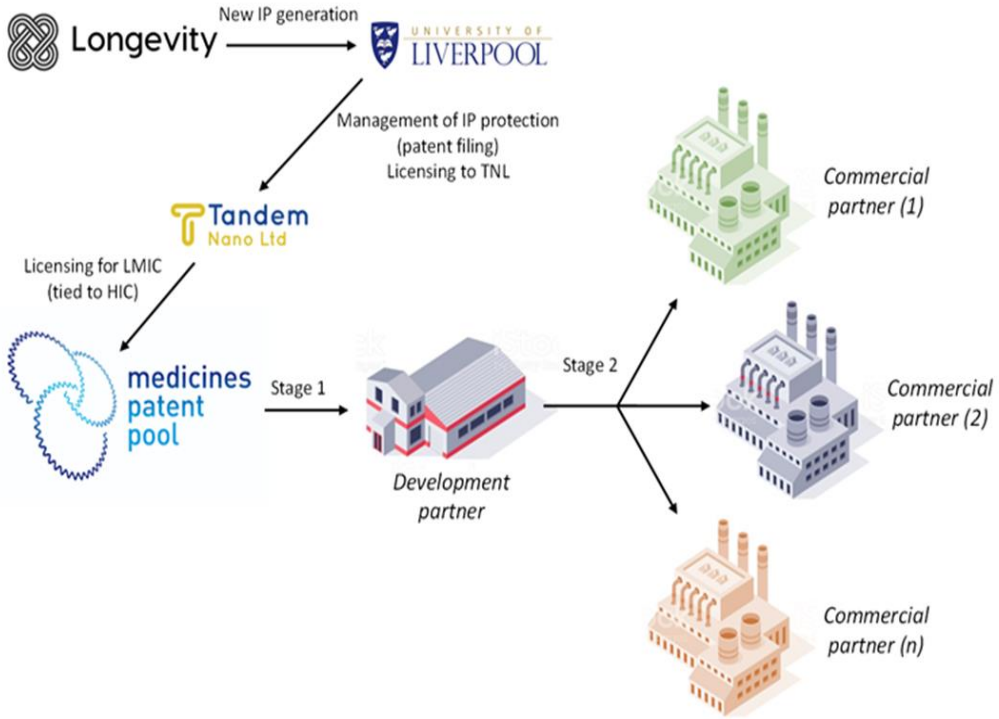


- Novel particle engineering technology to process poorly water soluble compounds.
- Simple manufacturing process able to generate highly drug-loaded powders and liquid formulations containing high drug mass for parenteral delivery.



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)

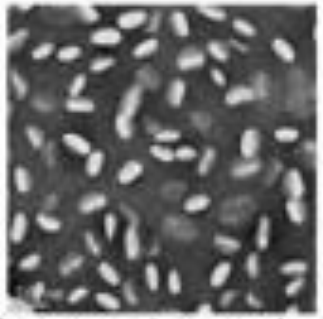
Aim: To transform short-acting TLD oral dosage form to long-acting injectable TLD intended for HIV treatment in low and middle-income countries

- Sustained HIV suppression required multiple HIV drugs;
  - 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

TLC-ART 101
suspension in vial



Electron-micrograph of
DcNP in suspension

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.

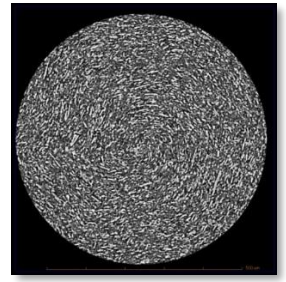
Extended-Duration Islatravir (ISL)-Eluting Implant as a Candidate for HIV Treatment and Prevention

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®

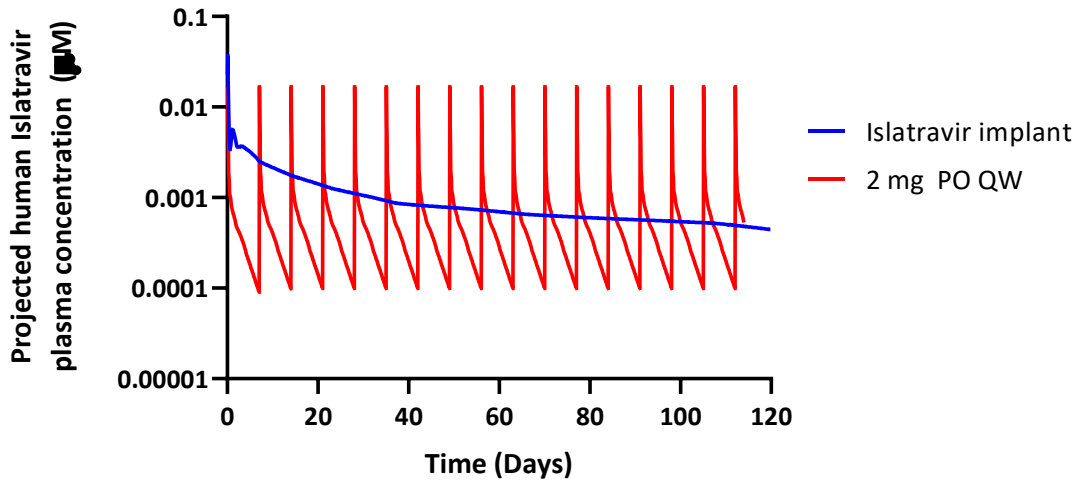
- Uses same polymer
- Uses Nexplanon® applicator

Nexplanon®



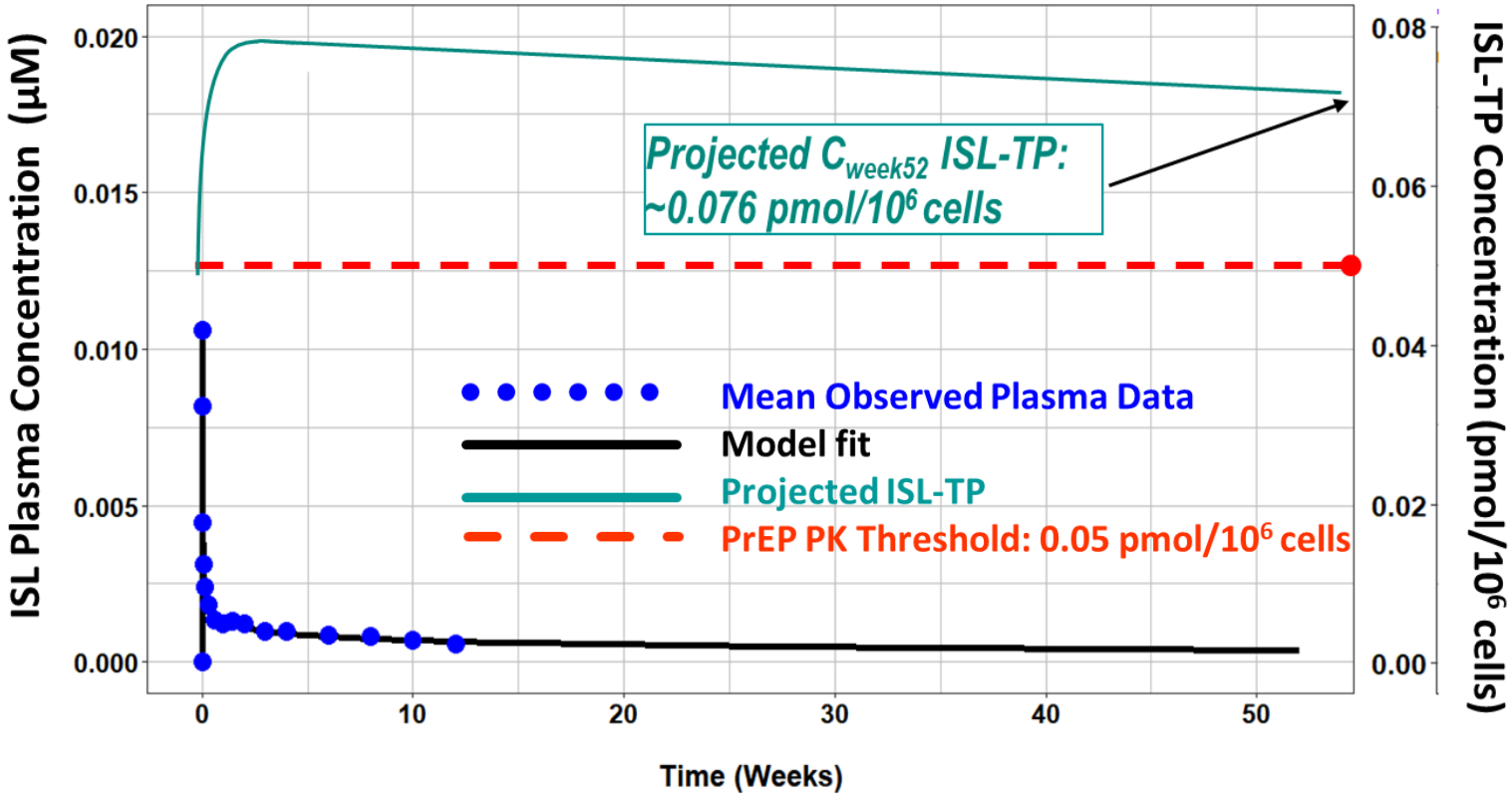
XRCT of ISL implant

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

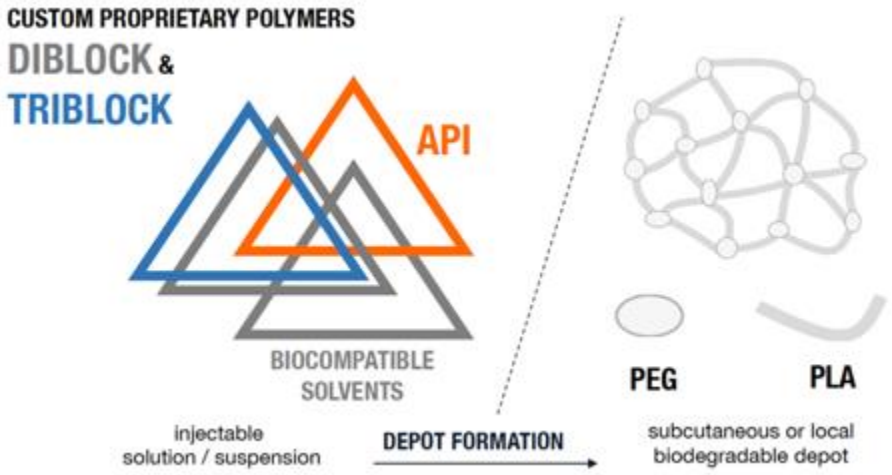
MedinCell

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

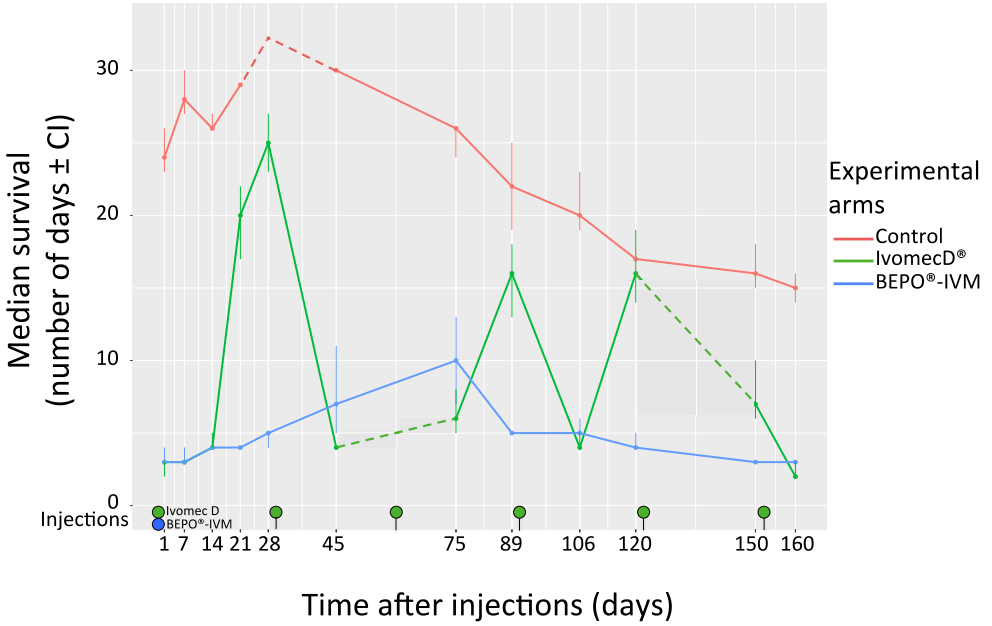
- Clinically advanced injectable in-situ forming depot technology using a combination of two bioresorbable copolymers and a solvent as excipients.
- Drug release can be tuned from days to months.
- Simple manufacturing process.
- Injectable using standard syringes and needles.



- Products can be developed as ready-to-use.
- Ongoing BEPO® programs to address LMICs needs in contraception and HIV PreP funded by **BMGF**

Drug Product BEPO®- IVM

- **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.



- ***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.

Breaking down barriers to access

Esteban Burrone

Medicines Patent Pool

medicines patent pool

2013

FDA

2014

2015

2016

World Health Organization

2017

FDA

TL

> 83%

2018

2019

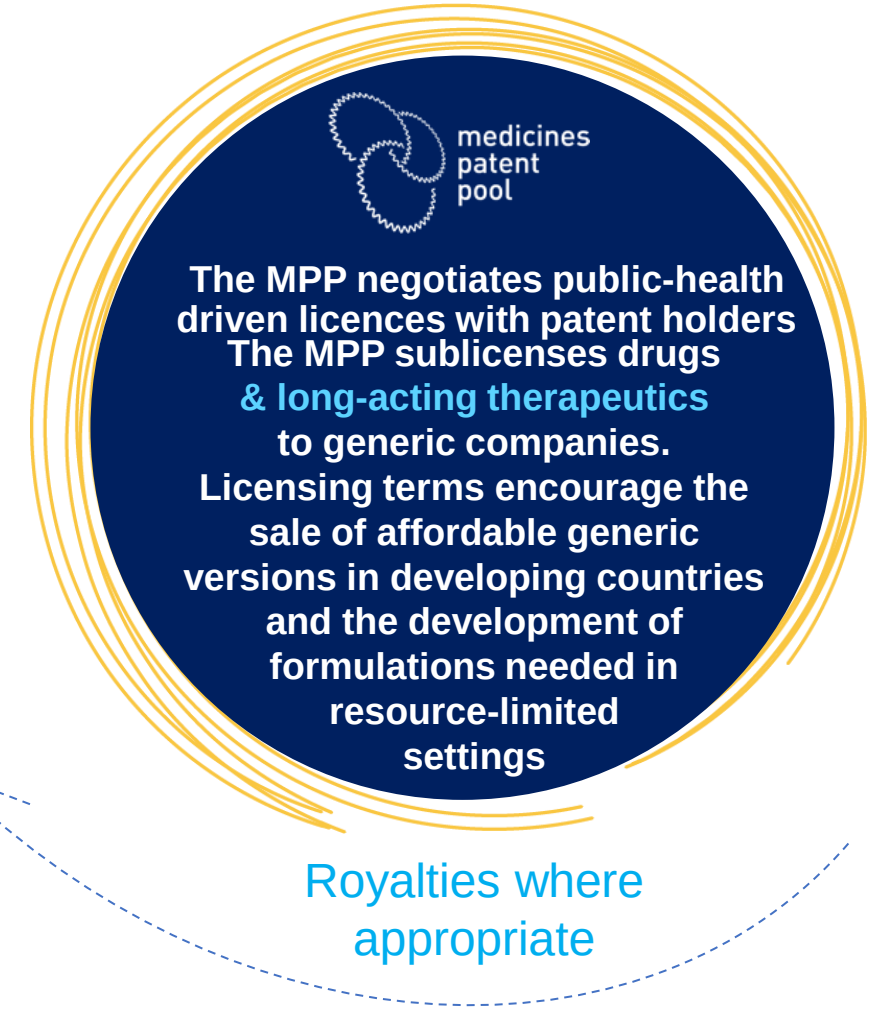
5.9 million people are estimated to be on TLD

The MPP model applied to long-acting therapeutics?

PATENT **HOLDER**

PATENT **HOLDER**

PATENT **HOLDER**



GENERIC MANUFACTURER

GENERIC MANUFACTURER

PEOPLE LIVING IN LOW- AND MIDDLE-INCOME COUNTRIES

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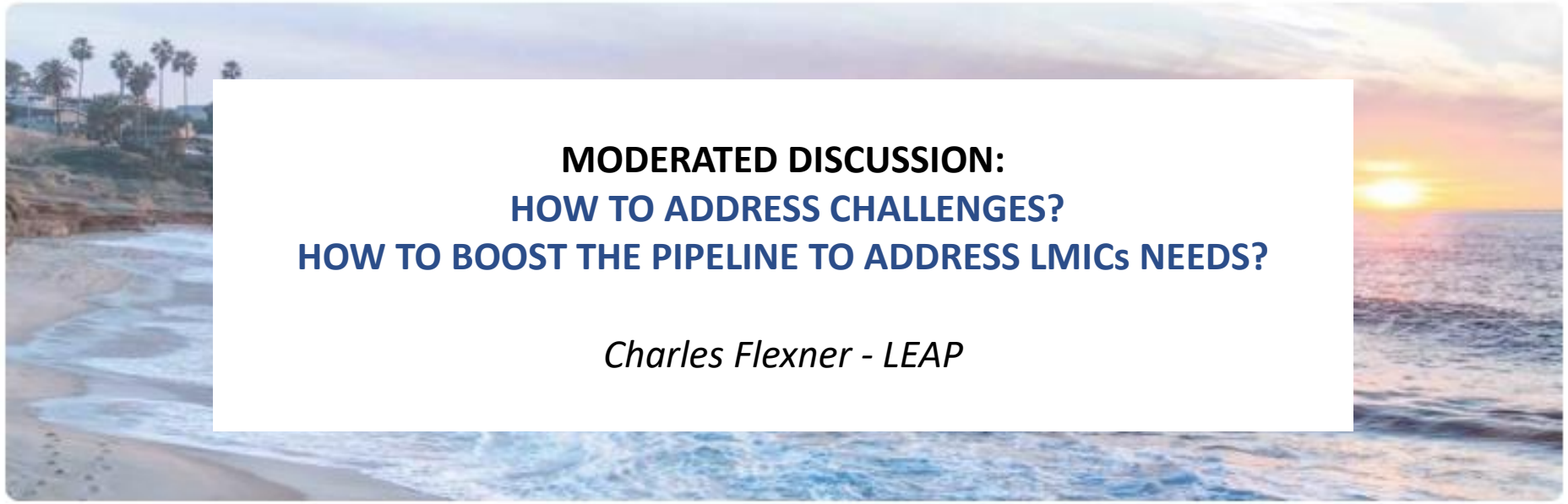

MODERATED DISCUSSION:

HOW TO ADDRESS CHALLENGES?
HOW TO BOOST THE PIPELINE TO ADDRESS LMICs NEEDS?

Charles Flexner - LEAP