Bill & Melinda Gates Foundation

Long-Acting Contraceptives for Low and Middle Income Countries

Dennis Lee, Senior Program Officer – Integrated Development, Global Health

BILL & MELINDA GATES foundation

CRS LA Workshop 2022
Jul 11, 2022

OUR HISTORY

1994

Bill Gates Sr. starts a small philanthropic foundation at his son's request.

1997

Bill and Melinda read an article about rotavirus and are inspired to act.

2000

The Bill & Melinda Gates Foundation is created, with a focus on health, education, and libraries.

2006

Warren Buffett pledges Berkshire Hathaway stock valued at $31 billion.

2008

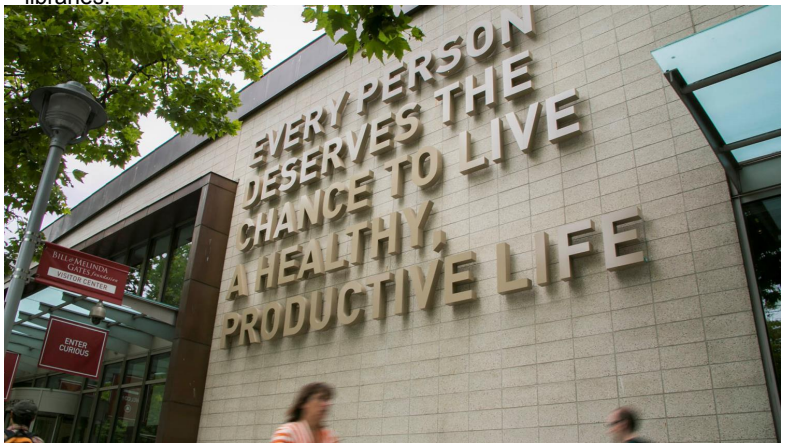
Bill joins Melinda full-time at the foundation.

2011

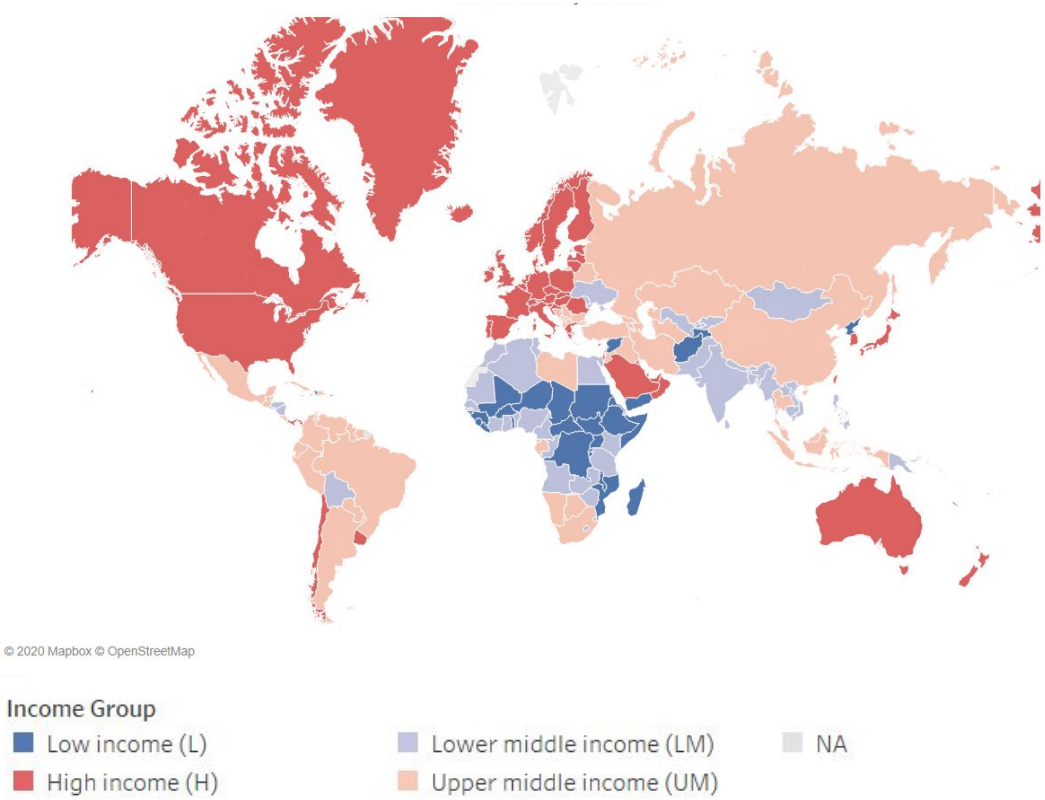
The foundation moves to its new permanent home in Seattle.

2020

Mark Suzman becomes our new CEO.



THE WORLD BY INCOME



The World Bank classifies economies for analytical purposes into four income groups: **low, lower-middle, upper-middle, and high income.**

For this purpose, it uses gross national income (GNI) per capita data in U.S. dollars.

These are often referred in an abbreviated format, for example:

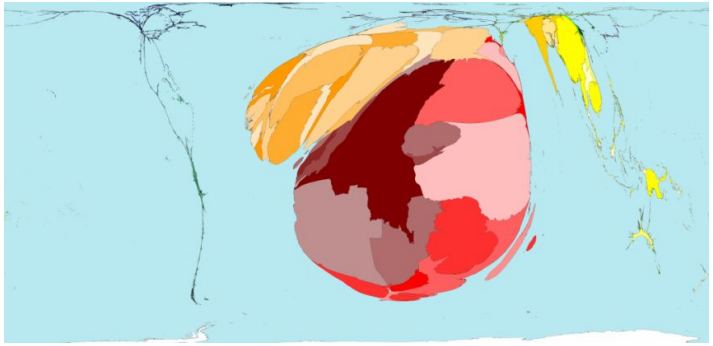
HIC = High income countries

LMIC = Low- and lower-middle- income countries

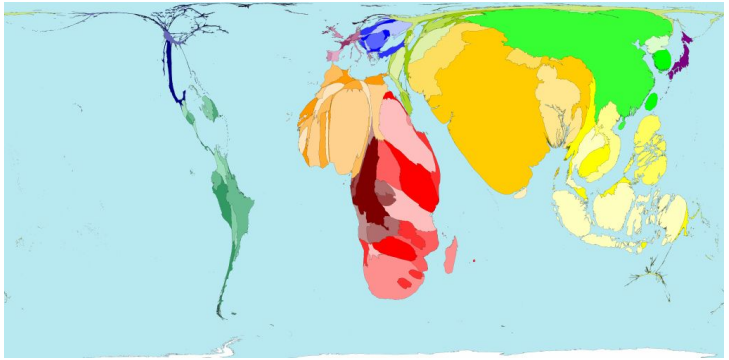
https://datatopics.worldbank.org/world-

MISMATCH BETWEEN DISEASE BURDEN AND AVAILABLE MEDICAL CARE

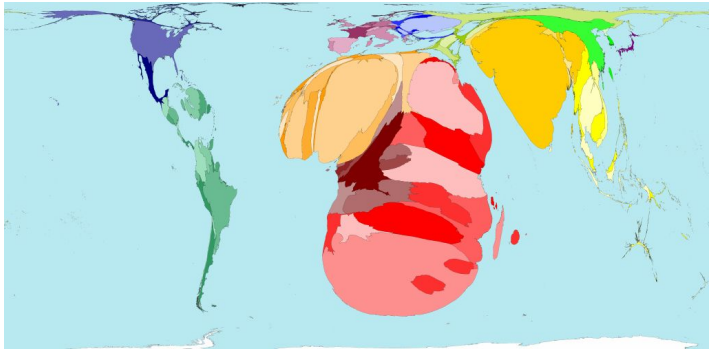
Malaria deaths



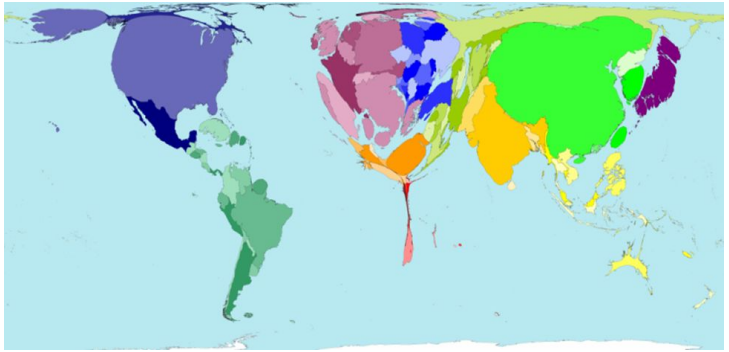
TB cases



HIV prevalence



Physicians



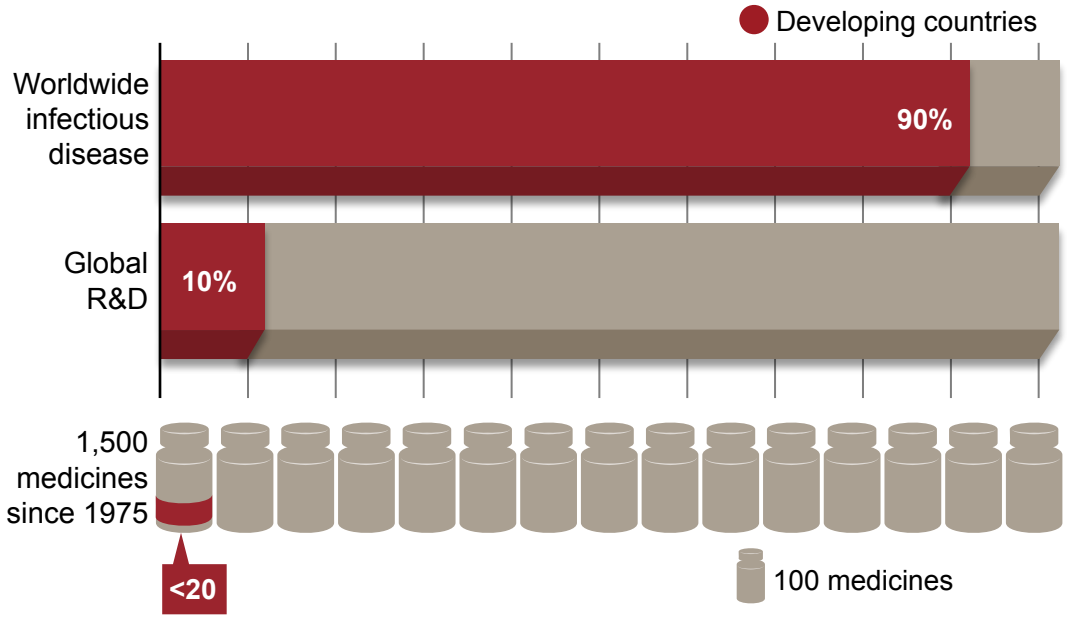
Source: http://www.worldmapper.org/

THE CHALLENGE

90% of the world's infectious disease burden is in developing countries.

10% of global R&D addresses developing countries' needs.

Fewer than 20 of the 1,500 medicines licensed since 1975 have been for diseases that primarily affect developing countries.



WHAT WE DO

The foundation has four missions that help us achieve our vision of a world where every person has the opportunity to live a healthy, productive life:

Ensure more children and young people survive and thrive

Empower the poorest, especially women and girls,
to transform their lives

Combat infectious diseases that particularly affect the poorest

Inspire people to take action to change the world

HOW WE DO WHAT WE DO

Grantees and partners are at the center of our work

Together, we take risks, push for new solutions and harness the power of science and technology

This work requires support from governments, the private sector, communities, nonprofits, and individuals

OUR GLOBAL REACH AND PRESENCE

1,763
employees worldwide

$5.8B
grant payments

2136
active grantees

134
Countries

BILL & MELINDA GATES foundation

FAMILY PLANNING

CREATING NEW OPTIONS FOR CONTRACEPTIVES

THE CHALLENGE

- 220 million+ women in developing countries lack access to modern contraceptives leading to an estimated 80 million women with an unintended pregnancy

THE OPPORTUNITY

- Reduction in unintended pregnancy by 70% (50M annually)
- Maternal deaths would drop by 67% (200,000 fewer deaths)
- New born deaths would drop by 77% (2.3M 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

CHALLENGES IN PRODUCT DEVELOPMENT

Important to understand as product developers

Shortage of healthcare providers

- Not just physicians – nurses also in scare supply.
- Healthcare provider may have a couple of years training beyond college – or even high school

Weak supply chains

- Stock outs frequent
- Puts premium on FDC's, prefilled injection devices – with all the above characteristics

Transportation – last mile may be literally on the back of a donkey or motorcycle

- Requires rugged products; premium on lightweight compact formats

Healthcare facilities may be hard to access

- May be days walk away for rural patients
- Overburdened facilities / long waits for urban patients
- Very high barriers for the most vulnerable who must work every day

Additional infrastructure that supports a well functioning healthcare system may be absent as well

- Cold chain – sporadic or absent outside the best hospitals in the largest cities; requires stability at ambient temperatures for 3-5 years under most extreme climates on the planet
- Even electricity may be lacking or sporadic – so procedures that require equipment beyond a microscope may be out of reach

Often need different product formats to compensate for deficiencies in healthcare systems and infrastructure – but must also be affordable and cost effective

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 ~ $1 / 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
- 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
- Inflexible interval is a barrier for spacing children

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

IDEV CONTRACEPTIVE PORTFOLIO

Multiple options (COCs, POPs)

Depo-Provera

Sayana Press

Implanon/ Nexplanon

Jadelle/Levoplant

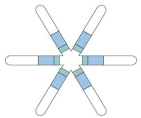
LNG-IUS

Copper IUD

Tubal ligation

Daily Oral | Monthly Oral | 1 – 3 Month Injectables | 6 Month Injectables and MAPs | 18-24 Month Bioerodible Implants | 3 and 5 Year Implants | 3-10 Year IUDs | 10+ Year Controllable | Permanent

Innovations BOW



Lyndra
Long-acting oral

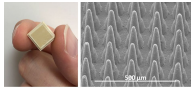
SI BOW

DMPA-6 suspension (Teva)

LNG/ENG

- **Prodrug (Evestra)**
- **BEPO hydrogel (MedinCell)**
- **Silica gel (DelSiTech)**
- **PLGA microparticles (SIPPR)**

Microarray patches (5 grants)



Innovations BOW

LNG/ENG implants

- **PLGA (SIBPT)**
- **Cholesterol pellet (pH Sciences)**
- **Bioerodible implant (Inflammasome)**
- **Polymeric implant (Innocore)**

Novel systems

- **Mark Saltzman (Yale U)**
- **Molly Stevens (ICL)**
- **Gio Traverso (BWH)**

Innovations BOW

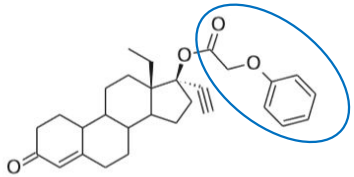
Dare LARC1
Implant

Commercial products
BMGF Investments

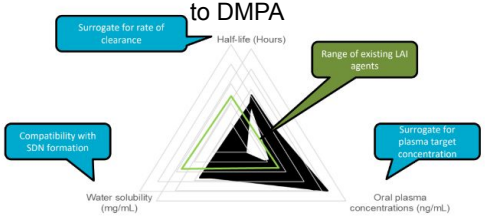
LONG-ACTING **6-MONTH INJECTABLES**

Evestra

LNG pro-drug suspension formulation



Duration of anti-ovulatory activity superior to DMPA

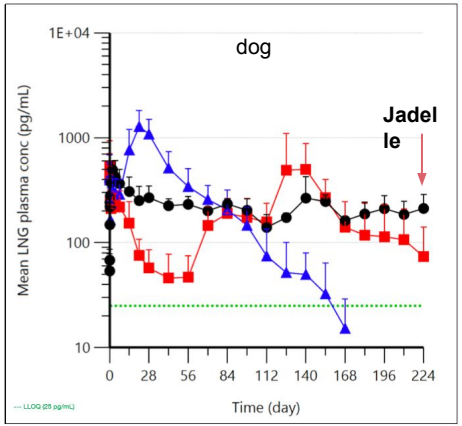


Example: Data for *paliperidone palmitate*

Andrew Owen

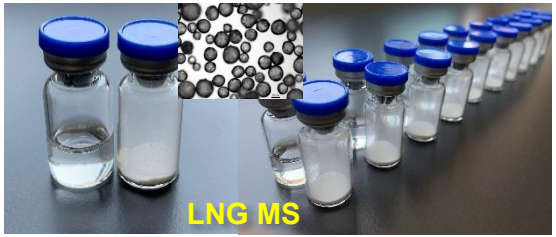
Medincell

- LNG or ENG
- In situ forming gel
- PLA-PEG/organic solvent



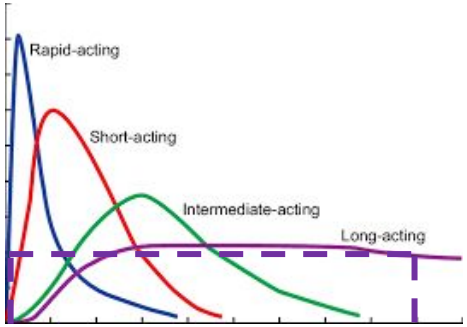
FHI360 / Shanghai Institute of Planned Parenthood Research (SIPPR)

- LNG
- PLGA microparticle

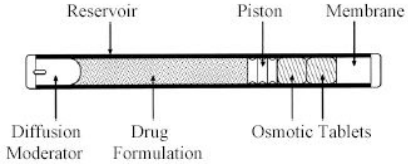


monthly oral | 3-month injectable | **6-month injectable** | 1-2 year biodegradable | 3 and 5 year implants | Very long-acting controllable

LONG-ACTING 1-2 YEAR **BIORESORBABLE** IMPLANTS



Implanon



Viadur

Intarcia

A Challenging Target Product Profile

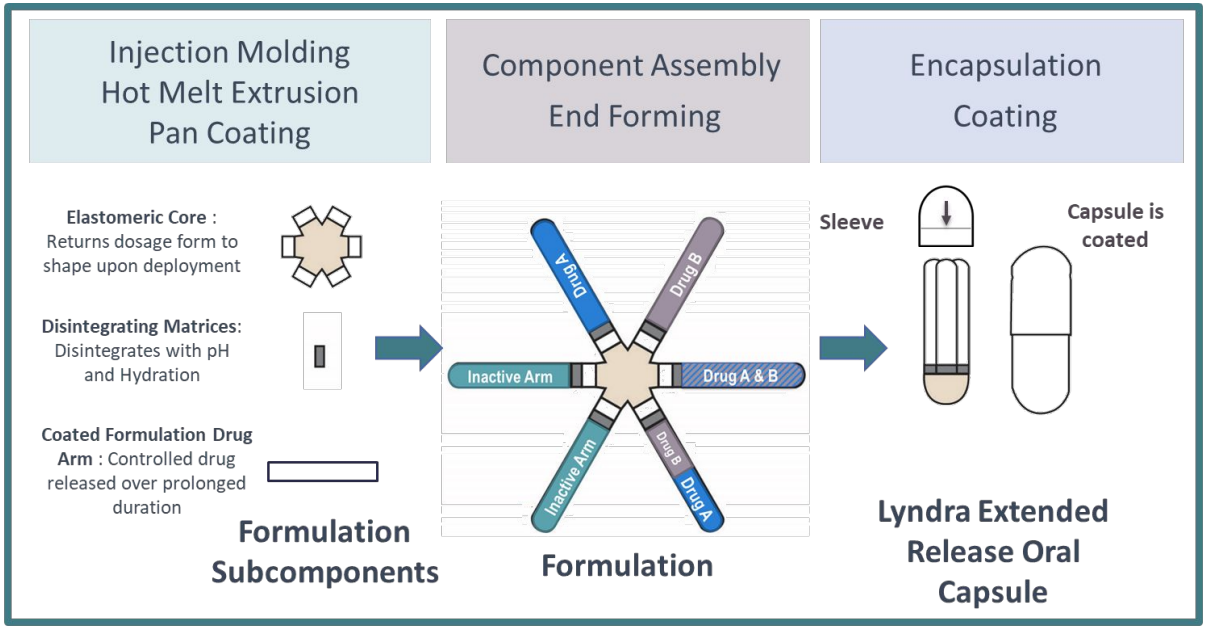
- Minimal or “ideal” burst
- Zero order release
- Minimal tail (return to fertility, safety)
- Removable if needed (structural integrity)

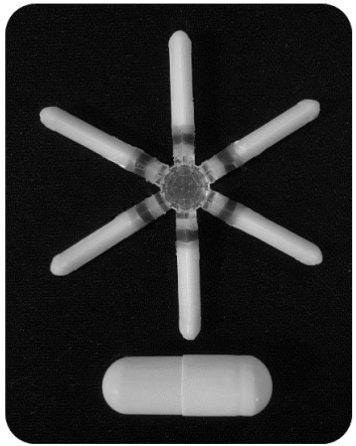
Also interest in combination drug implant (MPT)

- Contraception & HIV Prevention

LONG-ACTING **ORAL** DELIVERY TECHNOLOGY

Partnerships to develop novel drug delivery technology with potential for multiple applications in Global Health





Overall Closed Length for Size 00 EL Capsule

Modularity of Dosage Form Allows for Delivery of a Combination of Molecules

Source: Lyndra Therapeutics, Inc.

LYNDRA: PHARMACOKINETICS

Pre-clinical

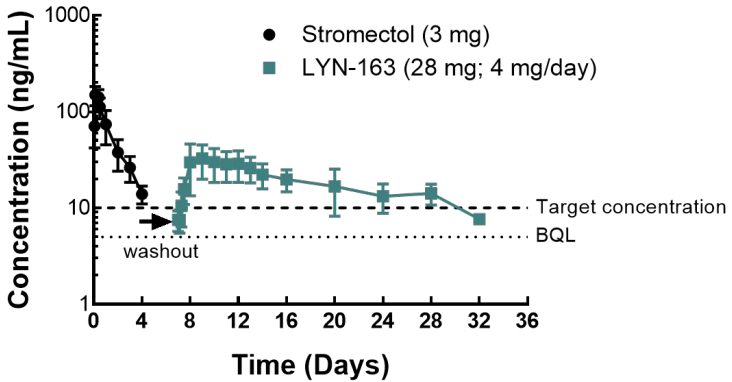
ivermectin for onchoceriasis and malaria vector control

Clinical

once-weekly oral dosing of a short-acting drug

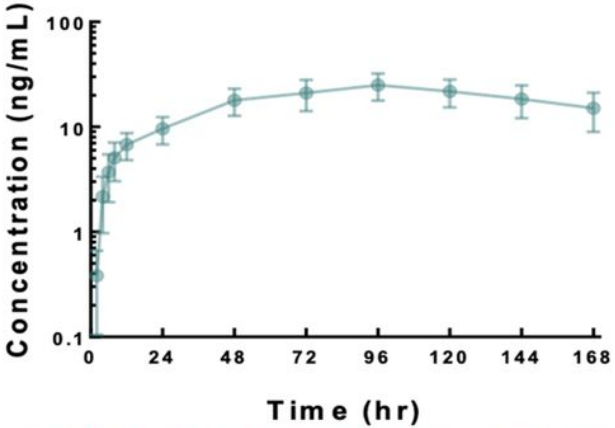
Single Dose PK of Ivermectin Clinical Lead Formulation in Preclinical Studies

n=6 dogs in a cross-over design with a 2-day washout between Stromectol and LYN-163 dosing



- Plasma concentration > 10 ng/mL for 20 days (Day 1 – Day 21)
- Gastric retention for >12 days

Predictable Pharmacokinetics with ~90% Bioavailability & No Burst Release of Drug

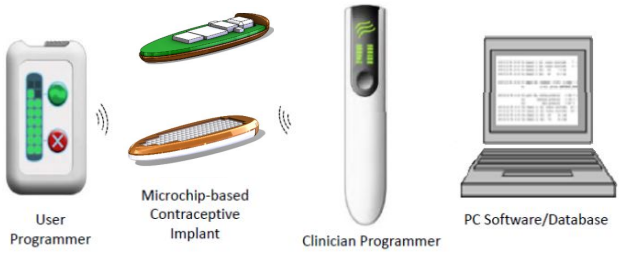


mean ± SD PK data for plasma memantine in 8 Subjects in Phase 1 study

Source: Lyndra Therapeutics, Inc.

LONG-ACTING **REVERSIBLE CONTRACEPTION** (DARE)

- 10 or more years of reversible birth control with a single implantable device
- Implant placed under the skin by a trained provider,and can be wirelessly activated or deactivated by the user without requiring removal
- Reduce need for women to access medical services; Decrease burden on health care providers for routine visits
- Allows women to control their contraception (on or off) without need to remove the device

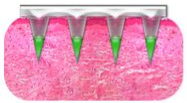


monthly oral → 3-month injectable → 6-month injectable → 18-24 month biodegradable → 3 and 5 year implants → **Very long-acting controllable**

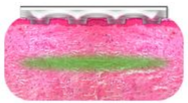
MICROARRAY PATCH: LONG-ACTING **DISSOLVABLE MICRONEEDLES**

Opportunity

- Non-invasive, pain-free parenteral administration of long-acting drug formulation
- Self-administration



Microneedle patch is applied to skin



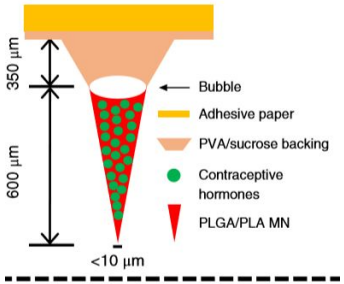
Microneedles dissolve and release their cargo

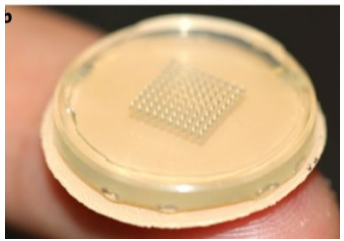
Sharps-free backing is removed and discarded

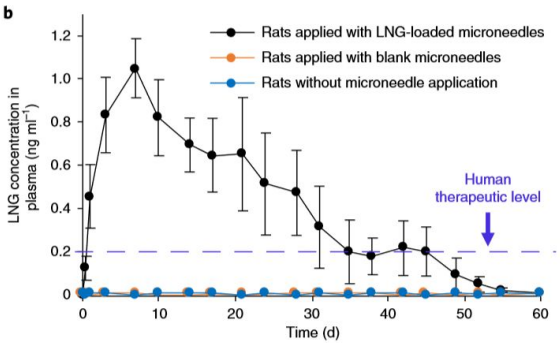
Challenges

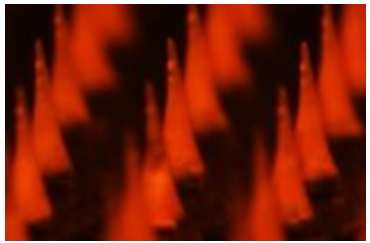
- Technical feasibility
  - **drug loading for 6 months duration**
  - Microneedle detachment
  - reproducibility
- Manufacturing
- Design (user-needs and preferences, applicator, patch size)

- Long-term technology investment
  - first product will likely be vaccine









Prausnitz, Nat. Biomed. Eng. 2019
USAID

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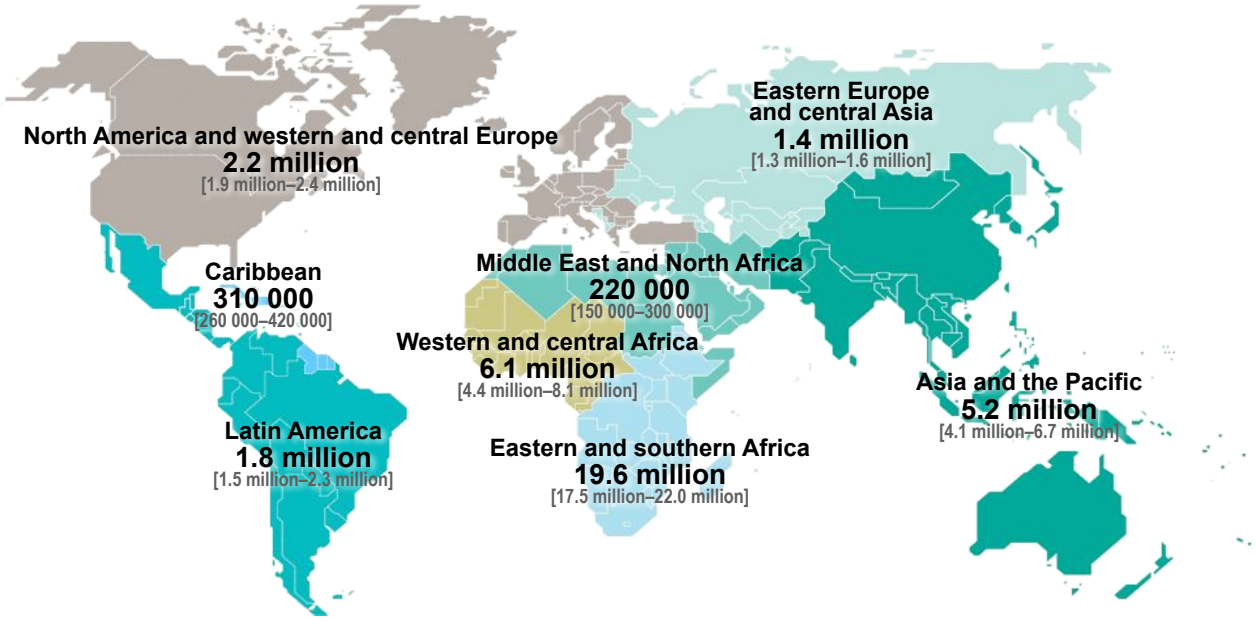
ACCELERATING THE DECLINE OF THE HIV BURDEN IN SUB-SAHARAN AFRICA

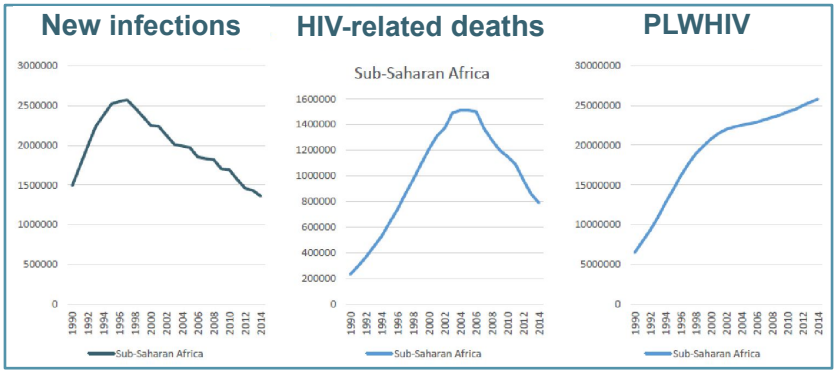
Adults and children estimated to be living with HIV 2017



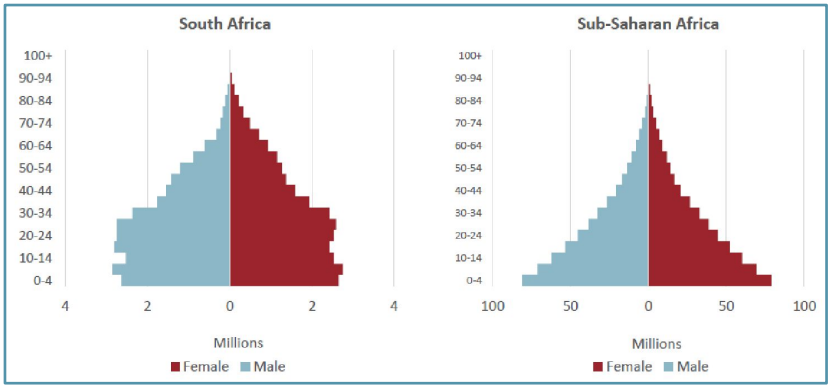
Total: 36.9 million [31.1 million–43.9 million]

HIV PROGRESS AND CHALLENGES

Advances in HIV treatment



Population demographics



- Advances in HIV treatment have led to substantial declines in the numbers of new infections and AIDS-related deaths
- However, the rate of HIV acquisition remains high in certain high prevalence areas, especially among young women
- Increased ***focus on prevention*** needed to ensure that recent gains are not reversed and to continue the progress in reducing the HIV burden

People living with HIV

DRUG DELIVERY TECHNOLOGY CAN MAKE IMPORTANT CONTRIBUTIONS TO GLOBAL HEALTH

"Drugs don't work in patients who don't take them"

- **Improve adherence by decreasing frequency or simplifying dosing**
- **Increase patient access**
- **Alleviate burden on health care providers**
- **Simplify supply chain**

Counsel uninfected individuals to strictly adhere to the recommended TRUVADA dosing schedule. The **effectiveness** of TRUVADA in reducing the risk of acquiring HIV-1 **is strongly correlated with adherence** as demonstrated by measurable drug levels in clinical trials

The products must also be both *cost effective* and *affordable* within Global Health budget constraints

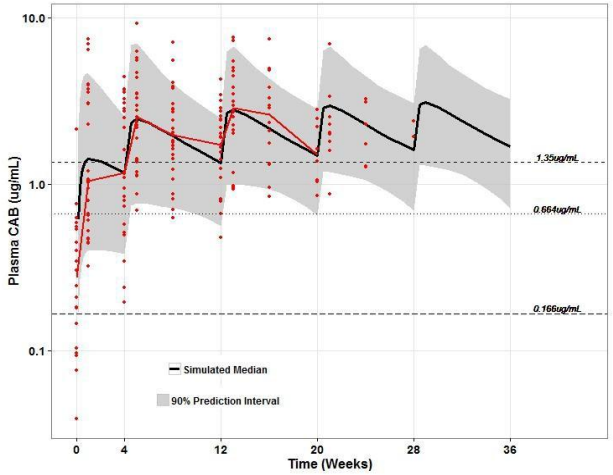
Source: C. Everett Koop, MD

CABOTEGRAVIR: LONG-ACTING IM HIV PROPHYLACTIC

Leveraging commercial drug development efforts by Big Pharma to address Global Health needs

- Developed by Viiv for HIV treatment in combination with rilpivirine (Janssen) - Cabenuva FDA approved Jan 2021
- Clinical PK data suggest that long-acting IM injectable nano-suspension may provide protection for at least 8 weeks
- Collaboration with Viiv and other funders to evaluate cabotegravir IM injectable for the prevention of HIV infection
- ***Interim analysis from HPTN 084 study shows long-acting injectable cabotegravir administered every two months is 89% more effective than daily pills in preventing HIV acquisition in women***
- ***Findings follow data from HPTN 083, a partner HIV prevention study in men who have sex with men and transgender women, which also demonstrated long-acting injectable cabotegravir was superior to daily oral pills for PrEP***

Multiple dose administration of cabotegravir IM injections in healthy adults

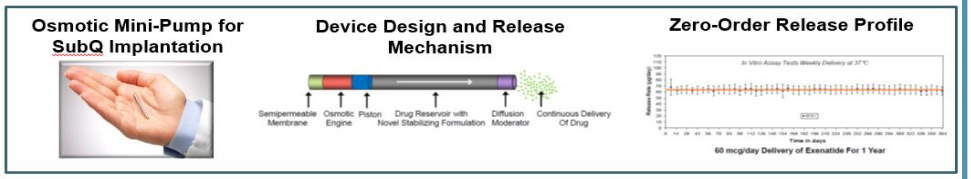


Source: Spreen, Williams, et al. J Acquir Immune Defic Syndr 2014; 67: 487-492.

DEVELOPMENT OF LONG-ACTING ARV IMPLANTS AND INJECTABLES

Collaborations with drug delivery technology companies and research institutes

Intarcia



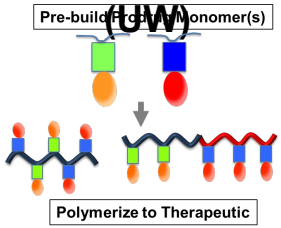
Non-erodible, zero-order release implant

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

DelSiTec

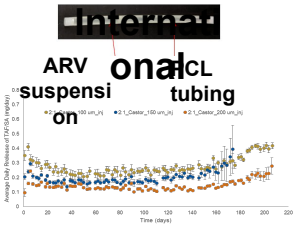
Injectable erodible silica gel matrix

Stayton (UW)



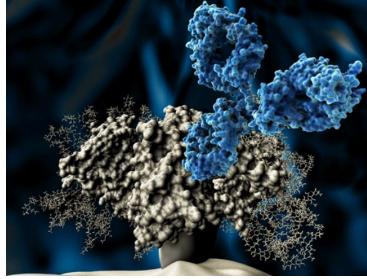
Injectable "drugamers" with tunable linker chemistry

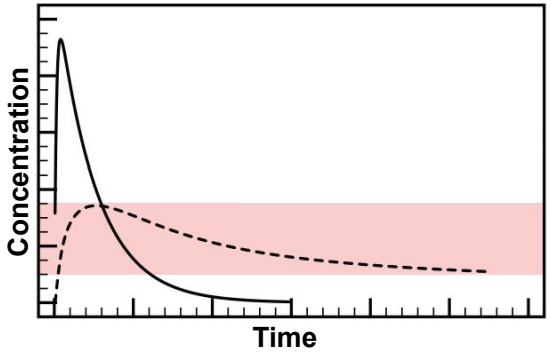
RTI

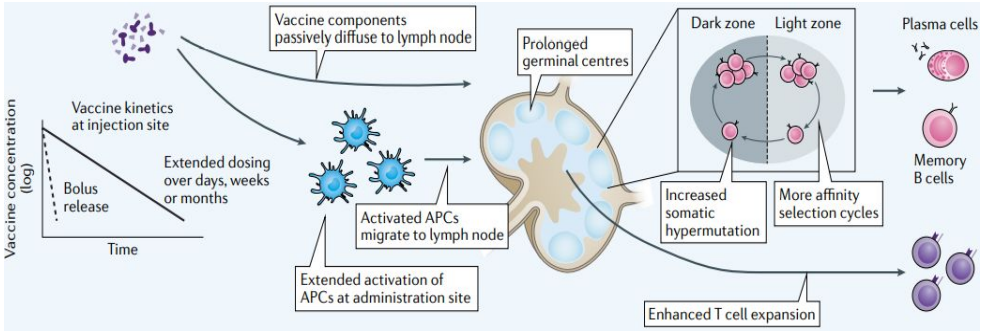


Erodible, zero-order release implant

LONG-ACTING BIOLOGICS DELIVERY







Broadly neutralizing antibodies (bnAbs) for HIV

- Long-acting formulations to decrease the burden of repeat administration
- 6-12 months duration
- High doses (e.g. 20% loading)
- Combination bnAb treatments

Multiple cycles of somatic hypermutation and affinity selection yields a high degree of antibody affinity maturation required for potent and broadly neutralizing antibody responses

Appel, Nature Review Material s, 2021

- Proof of concept in animal studies with repeated injections or osmotic pumps
- 2-4 week sustained release vaccines
- Low dose
  - Antigen: protein subunit or mRNA
  - Adjuvant: small molecule or nanoparticle (e.g. Matrix M)

SUMMARY: LONG-ACTING TECHNOLOGIES

- Innovative drug delivery technologies have the potential to increase patient access, alleviate burdens on healthcare systems, and improve health outcomes in Global Health settings
- We believe that the application areas will expand as additional long-acting systems and technologies are developed and more products demonstrate impact in the hands of patients and healthcare workers
- Global Health interventions may require different attributes to meet the needs of patients, healthcare systems and supply chains in LMIC settings as well as being cost-effective and affordable for procurers

IF YOU WANT TO GO FAST,
GO ALONE.
IF YOU WANT TO GO FAR,
GO TOGETHER.

— African proverb


WE ENVISION A
WORLD WHERE
EVERY
PERSON
HAS THE OPPORTUNITY
TO LIVE A HEALTHY,
PRODUCTIVE LIFE
THANK YOU