

Bringing innovation to the front line for impact:

**Long-acting technologies for the prevention
and treatment of major infectious diseases**

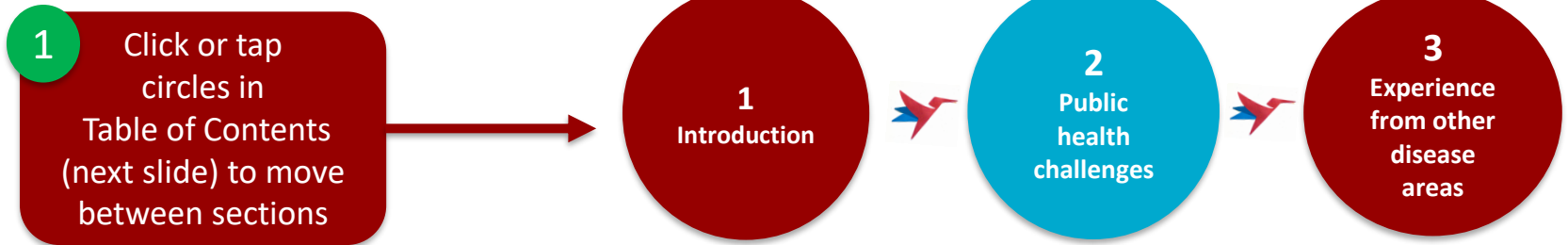
COMPENDIUM OF TECHNICAL AND MARKET INFORMATION

November 2018

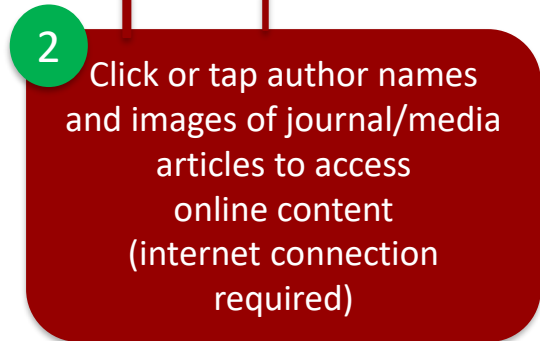
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How to use this compendium



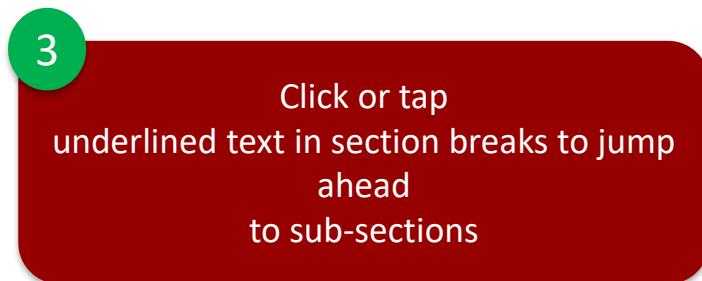
(Cohen et al, 2011)



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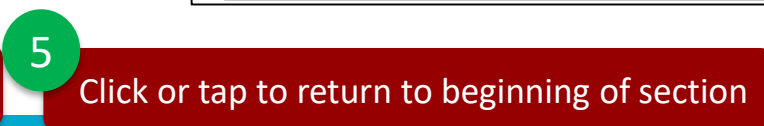
Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients

Jennifer Williams¹, Harlan R Sayles², Jane L Meza², Patrick Sayre³, Uriel Sandkovsky¹, Howard E Gendelman^{1,4}, Charles Flexner³, and Susan Swindells^{1,*}

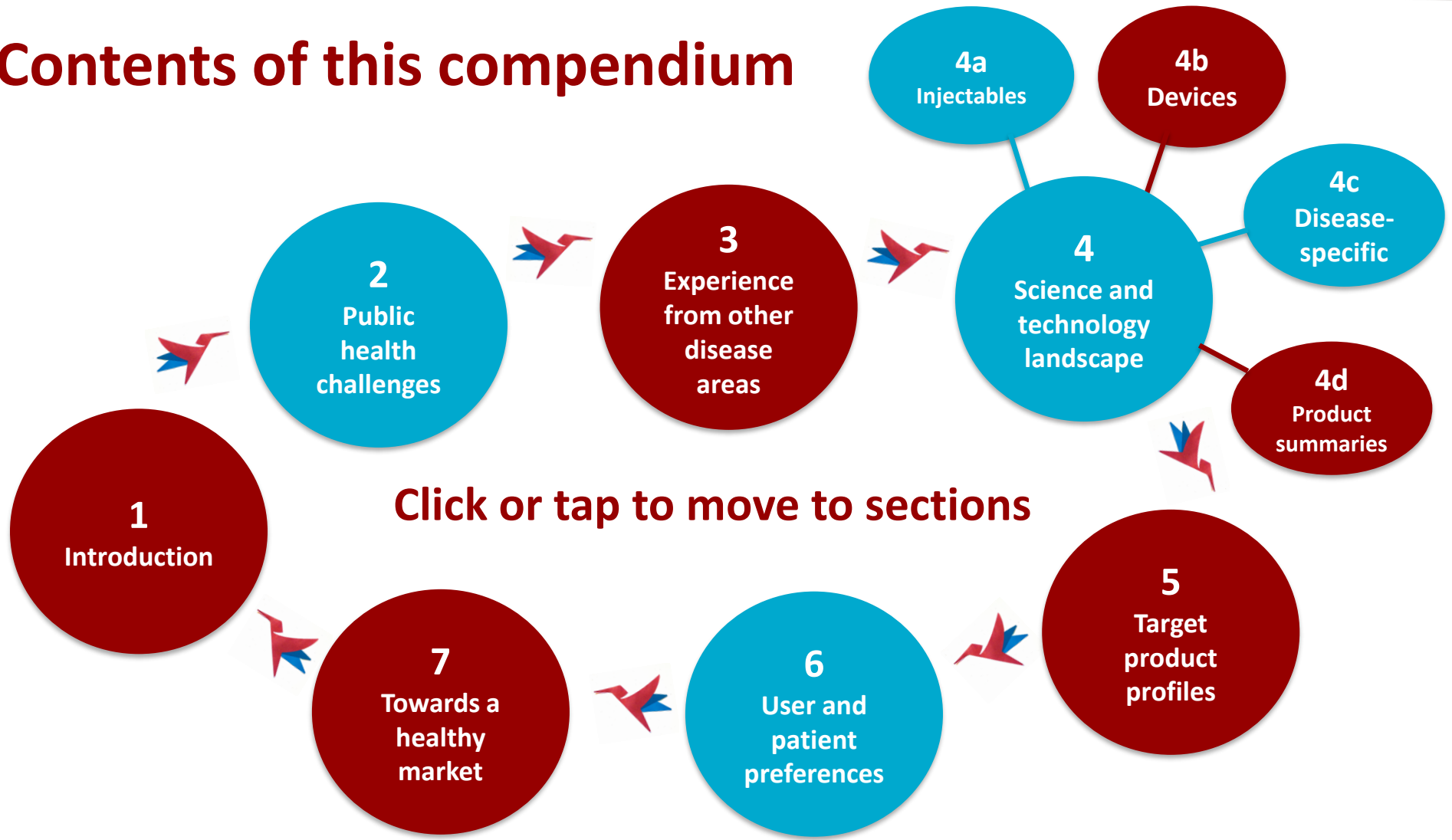


Part 4: Science and technology landscape

- Part 4a: Nano-formulation processes for LA injectable medicines**
- Part 4b: Pipeline of innovative devices for drug delivery**
- Part 4c: Pipeline of LA drugs by disease area**



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- Project Reference Group
- Theory of change for potential Unitaid investment
- Major stakeholders in the development of long-acting drugs and delivery systems/devices for LMICs



Overview: A potential new era in medicine

- Scientific and technological advances herald a **potential new era** in delivery of medicines: moving from daily oral medication to weekly, monthly and less frequent long-acting (LA) formulations could accelerate efforts to control/end major global epidemics by improving patient adherence, containing resistance and reducing costs.
- Diverse LA products have been **successfully introduced** into the market in high-income countries
 - *Paliperidone palmitate* was approved in 2015 for use in **schizophrenia** as an intramuscular injection every three months, and has already had a significant impact on the mental health care system and patient adherence.
 - In 2016 and 2017, the FDA approved extended-release forms of *buprenorphine* as a six-monthly implant and subcutaneous injection for **opioid substitution therapy**.
 - Long-acting approaches also exist in numerous other areas, including for **chronic asthma** (injectable *mepolizumab*).
- In low/middle-income countries (LMICs), LA delivery methods have drastically changed the **hormonal contraception space**, e.g. injectables that last several months and implants and intra-uterine devices that last for five years or longer
- While not yet approved for prevention or treatment of HIV and co-infections, TB or malaria, LA products are in various stages of development, with HIV the most advanced.



Long-acting: A new era in medicine?

HEALTH CARE > Posted May 17 | Updated May 17

INCREASE FONT SIZE 

FDA approves long-acting drug to prevent migraines

Aimovig, taken in a monthly shot, is the first in a new class of migraine drugs to win approval. It will cost \$6,900 a year, without insurance.

New \$1,600 a month heroin-fighting medicine a 'game changer'

POSTED 10:26 PM, JULY 24, 2018, BY CHRIS HAYES, UPDATED AT 03:02PM, JULY 24, 2018

Tezepelumab, a First-in-Class Injectable Asthma Drug, Shows Promise in Trial

New AstraZeneca, Amgen drug reduces exacerbations by up to 71%

Tezepelumab (AstraZeneca/Amgen), a new kind of injectable biotech treatment for severe asthma, may help a much broader range of patients than existing medicines, findings from a mid-stage clinical trial show.

RESEARCH ARTICLE | APPLIED SCIENCES AND ENGINEERING

3D printing of a wearable personalized oral delivery device: A first-in-human study

Kun Liang[†], Simone Carmone, Davide Brambilla[†] and Jean-Christophe Leroux[†]

Aequus Announces Expansion of Market Opportunity for its Long Acting Anti-Nausea Transdermal Patch

Published: July 19, 2018 8:45 a.m. ET



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Extended-Release Injection for Schizophrenia Receives FDA Approval

JULY 30, 2018

Cecilia Pessoa Gingerich

@CeciliaKPG

Top Stocks Set to Disrupt the Diabetes Market

Revolutionary new drugs and medical devices could make these companies smart additions to your portfolio



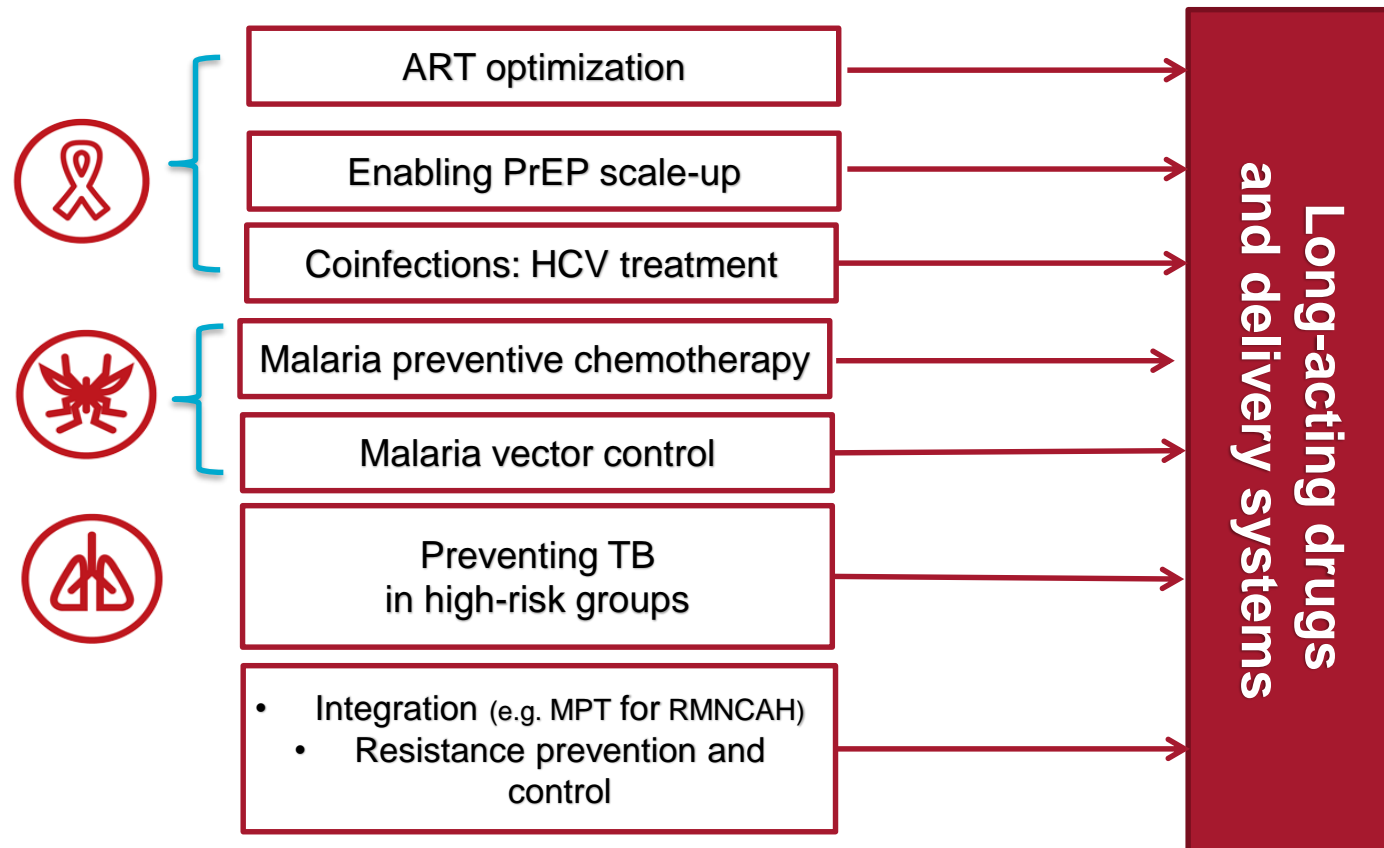
Why is Unitaid exploring long-acting technologies for the prevention and treatment of HIV, TB, malaria and HCV?

Unitaid is working with partners to explore potential interventions to ensure that innovation in long-acting (LA) technologies for infectious diseases meets the needs of LMICs and that time lag for scale-up is minimized

- Emerging pipeline of game-changing long-acting injectables and other drug delivery systems (patches, implants, oral delivery) in high-income markets and experience with LA contraception in LMICs
- Potential for impact in major diseases in LMICs (to improve adherence, clinical outcomes and eventually costs)
- Need to think ahead to prepare for a healthy market in LMICs, ensuring affordability and adaptability to their needs



Fit within Unitaid strategy and current Areas for Intervention



Preliminary analysis of the landscape shows potential for LA approaches across different areas

Scope of project and working definition of “long-acting”

- This project covers prevention and treatment of diseases currently within Unitaid mandate – HIV and related co-infections/co-morbidities (HCV), TB and malaria
- The project **does not** include vaccines
- Monoclonal antibodies delivered by IV-infusion that are currently in various stages of clinical research are noted
- For the purposes of this project, **“long-acting” is defined** according to the method of administration and dosing frequency:

Administration method	Oral	Injectable	Implant or other device
Dosing frequency	Once weekly (or less frequent)	Once monthly (or less frequent)	Once every 6 months (or less frequent)



Purpose of this compendium

- To identify and elaborate upon the **public health challenges** of current treatment and prevention medications in HIV and coinfections, TB, and malaria
- To provide analysis of the potential **broad impact of long-acting technologies** to improve treatment and/or prevention programs, ensure adherence, decrease cost per individual and contain resistance
- To provide an **overview of the science and clinical development of long-acting technologies** in the relevant disease areas, exploring the three dimensions of long-acting solutions: **the medicines, processes for formulating them and the range of potential delivery methods**
- To provide an overview of the **range of stakeholders** currently engaged in the development of relevant long-acting technologies
- To provide a basis for discussion on the **market dynamics** across the three dimensions as they relate to demand, market viability and potential challenges and opportunities to expand access in LMICs
- To guide Unitaid and partners to identify **gaps in and potential areas for increased engagement in long-acting technologies**, with a view to potentially accelerating access and impact in LMICs.



How was this compendium developed?

Methods

- 50+ key informant interviews, including academia, industry, funders, international organizations, implementers and community
- Literature review
- Explore 5 dimensions of Unitaid market analysis framework
- Peer review by reference group

Limitations

- Initial, broad scoping exercise of a rapidly evolving field
- Key informants were a snapshot of all those engaged in LA development
- Limited market information available



Project Reference Group

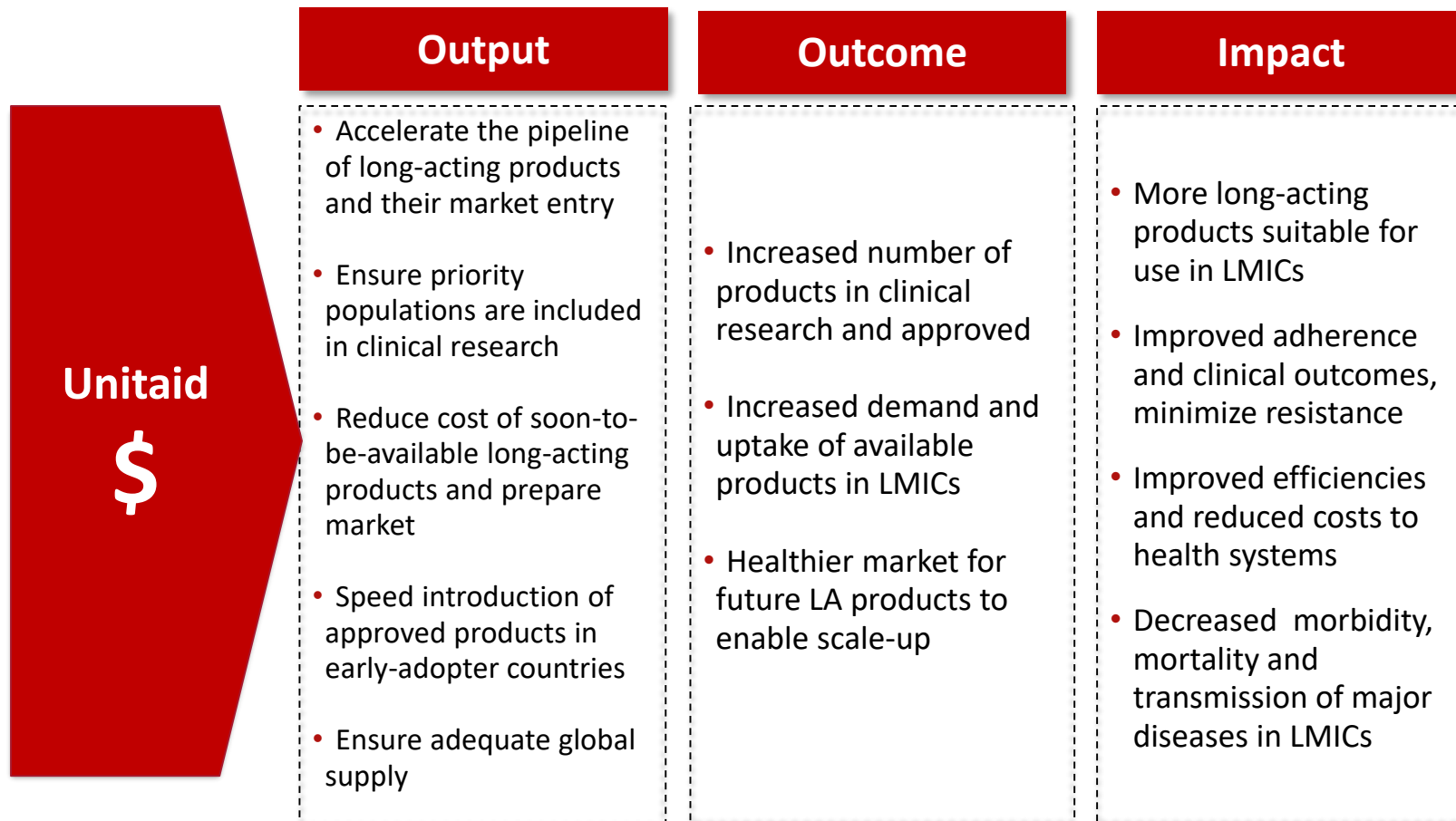
- Meg Doherty, WHO HIV/Hepatitis Department
- Rachel Baggaley, WHO HIV/Hepatitis Department
- Charles Flexner, LEAP Consortium, Johns Hopkins University
- Irene Mukui, Kenya National AIDS Program
- Wame Mosime, International Treatment Preparedness Coalition
- Peter Godfrey-Faussett, UNAIDS
- Mitchell Warren, AVAC and Prevention Market Manager

The project reference group helped to guide the development of the compendium and the overall project, including the consultation process.



Unitaid theory of change for LA technologies

Potential public health and market impact by addressing market shortcomings



Long-acting technologies for LMICs: Major stakeholders

Technical agencies and partnerships

Funding agencies

Industry/developers/academia



National Institutes of Health



HIV Prevention Market Manager



Long-Acting/Extended Release Antiretroviral Resource Program



Advocacy groups



... and more





Part 2: Public health challenges

- Global progress, challenges and ambitious goals in the response to HIV, TB, malaria and HCV
- The challenges of adherence and retention in treatment and prevention for HIV, TB, and malaria
- Drug resistance is a concern across the disease areas
- Other challenges in responding to the diseases





Global progress, challenges and ambitious goals in the response to HIV, TB, malaria and HCV

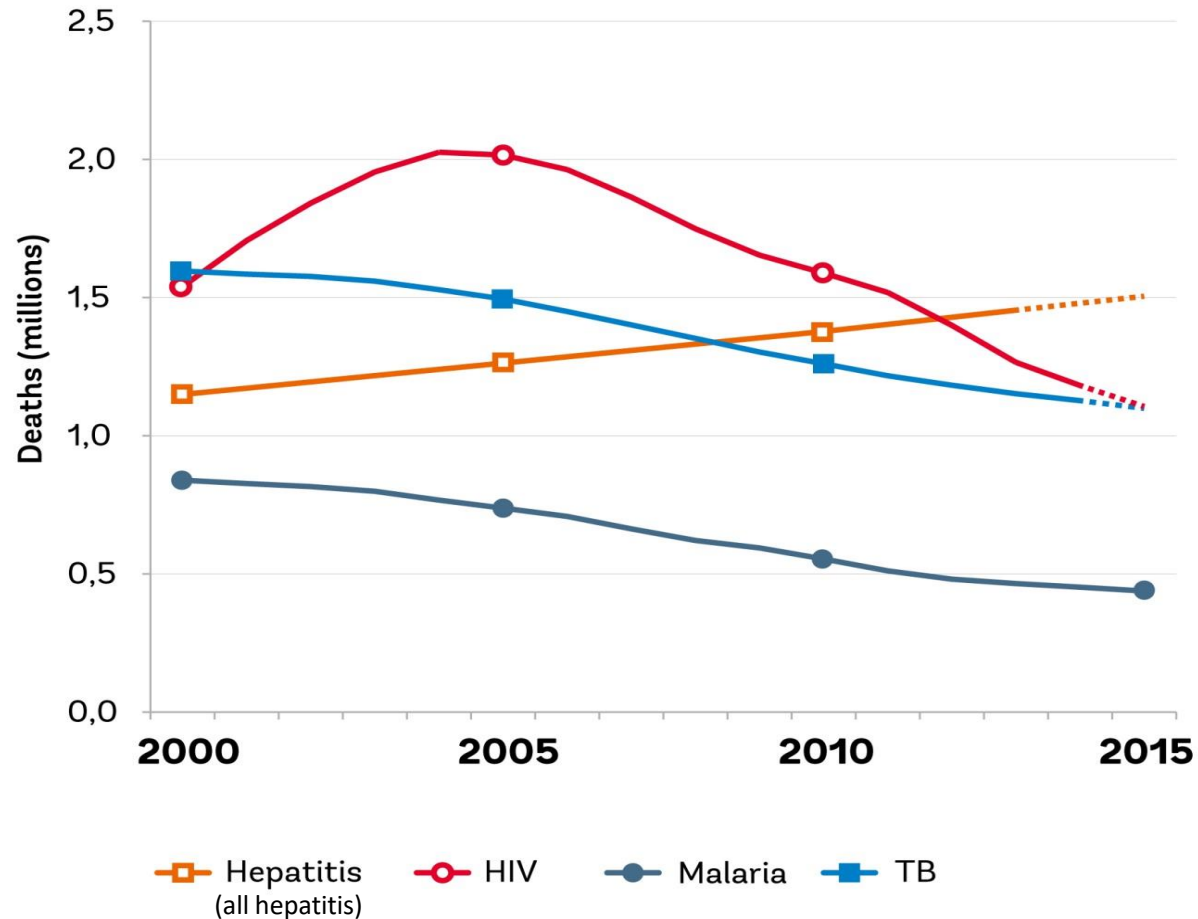


Significant progress has been made in scaling up responses to major infectious diseases in the last 20 years

- **HIV:** Global scale up of ART to 21.7 million people has helped to reduce deaths from AIDS-related causes by almost half from a peak of 1.9 million in 2005 to 940,000 in 2017, while efforts to strengthen prevention and treatment programmes have reduced new HIV infections by 16 per cent since 2010, to 1.8 million ([UNAIDS, 2018](#)).
- **TB:** the global mortality rate fell by 37 per cent between 2000 and 2016 and millions of people are being diagnosed and successfully treated every year. Among people living with HIV, TB-related deaths fell by a third between 2005 and 2015 ([WHO, 2017](#)).
- **Malaria:** Millions of deaths due to malaria have been averted in endemic countries since 2000 through scale-up of prevention and treatment, and more countries are now accelerating their efforts to achieve malaria elimination ([WHO, 2017](#)).
- **Hepatitis C** remains a major global public health challenge, but several pioneering countries have shown how testing and treatment can be rapidly scaled-up through a combination of political leadership and reductions in the prices of essential medicines and diagnostics. Direct-acting antivirals provide an 8-12 week cure for HCV, but only a fraction of those in need have access to diagnosis and treatment ([WHO, 2017](#)).



HIV, TB and malaria deaths declining, hepatitis deaths increasing



But.. substantial disease burden and treatment gaps remain

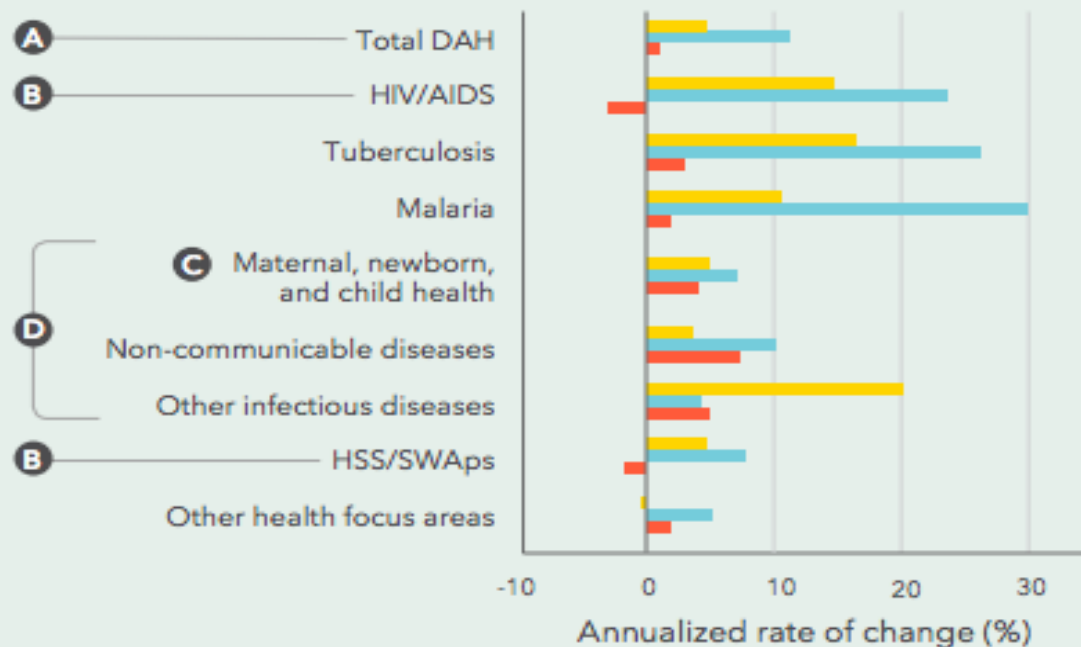
	New infections/cases	Deaths	Number receiving treatment	Total needing treatment	Treatment gap
HIV	1.8 million (Target 500,000 by 2030)	940 000 (95-95-95 by 2030)	21.7 million	36.9 million	15.2 million (Coverage 59%)
MAL	216 million	445 000	<ul style="list-style-type: none"> In 18 household surveys in sub-Saharan Africa, the median proportion of children under 5 years of age for whom care was sought and who received <i>any</i> antimalarial drug was 41% 46% of people at risk of malaria in sub-Saharan Africa are not protected by ITNs 		
TB	10.4 million MD-RTB: 400 000	1.7 million	6.3 million cases detected and notified		4 million+ per year not detected/reported MD-RTB: 1/5 treatment
HCV	1.75 million in 2015	399 000 in 2015	1.76 million in 2016	71 million	~62 million (Coverage 13%)



Funding for infectious diseases in LMICs is static or declining

DEVELOPMENT ASSISTANCE FOR HEALTH (DAH)

Rate of change in DAH by health focus area, 1990-2017



HSS = Health systems strengthening
SWApS = Sector-wide approaches

● 1990-2000
● 2000-2010
● 2010-2017

In 2017, total DAH was **\$37.4 billion**

For most health focus areas, the largest annualized percent change was between 2000 and 2010

From 2010 to 2017:

Nearly all health focus areas saw reductions in the growth rate, relative to 2000-2010.

- A** Total DAH growth from 2000 to 2010 was 11.2% annually, while growth from 2010 to 2017 was only 1.0%, a more than 90% reduction.
- B** HIV/AIDS declined 3% annually; Health systems strengthening/SWApS declined 2% annually.
- C** Maternal, newborn, and child health saw the greatest absolute change – a \$2.8 billion increase.
- D** Non-communicable diseases, other infectious diseases, and maternal, newborn, and child health had the largest annualized percent change in DAH from 2010 to 2017 at 7%, 5%, and 4%, respectively.

[Institute for Health Metrics and Evaluation \(IHME\), University of Washington, 2017.](#)



Development assistance for HIV at lowest levels since 2010



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Press release

[\(UNAIDS, 2017\)](#)

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PRESS CENTRE

PRESS RELEASE

Kaiser/UNAIDS study finds donor government funding for HIV declined by 7% in 2016, falling to lowest level since 2010

Donor government funding to support HIV efforts in low- and middle-income countries decreased by US\$511 million from US\$7.5 billion in 2015 to US\$7 billion in 2016, finds [a new report](#) from the Kaiser Family Foundation and the Joint United Nations Programme on HIV/AIDS (UNAIDS). This marks the second successive year of declines, and is the lowest level since 2010.

The decrease stems from actual cuts in funding (accounting for an approximate net 50% of the decline), exchange rate fluctuations (20%), and the timing of U.S. contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria (30%), due to U.S. law that limits its funding to one-third of total contributions to the Global Fund.

In 2016, bilateral funding decreased by slightly more than US\$100 million, falling for nine of 14 donors profiled (seven of which declined in currency of origin). Multilateral contributions fell by US\$400 million. As noted above, some of this was due to U.S. legislative limitations on Global Fund contributions. However, some was due to donor decisions to front-load their funding early in the 2014-2016 Global Fund pledge period.



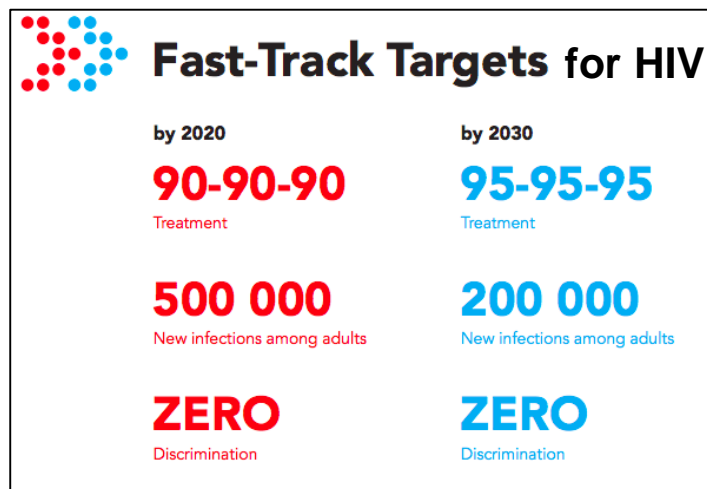
Ambitious targets to achieve SDG 3

- Progress between 2000 and 2015 emboldened the international community to make ambitious commitments to **ending the epidemics of HIV, TB and malaria** by 2030 and to further scale-up responses to viral hepatitis and other communicable diseases
- But in all four disease areas, **the current pace of scale-up is too slow to achieve SDG 3 and related disease-specific targets**

Global Malaria Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS, 2016–2021

TARGET AREA	BASELINE 2015	2020 TARGETS	2030 TARGETS
Impact targets			
Incidence: New cases of chronic viral hepatitis B and C infections	Between 6 and 10 million infections are reduced to 0.9 million infections by 2030 (95% decline in hepatitis B virus infections, 80% decline in hepatitis C virus infections)	30% reduction (equivalent to 1% prevalence of HBsAg ⁹ among children)	90% reduction (equivalent to 0.1% prevalence of HBsAg among children) ¹⁰
Mortality: Viral hepatitis B and C deaths	1.4 million deaths reduced to less than 500 000 by 2030 (65% for both viral hepatitis B and C)	10% reduction	65% reduction



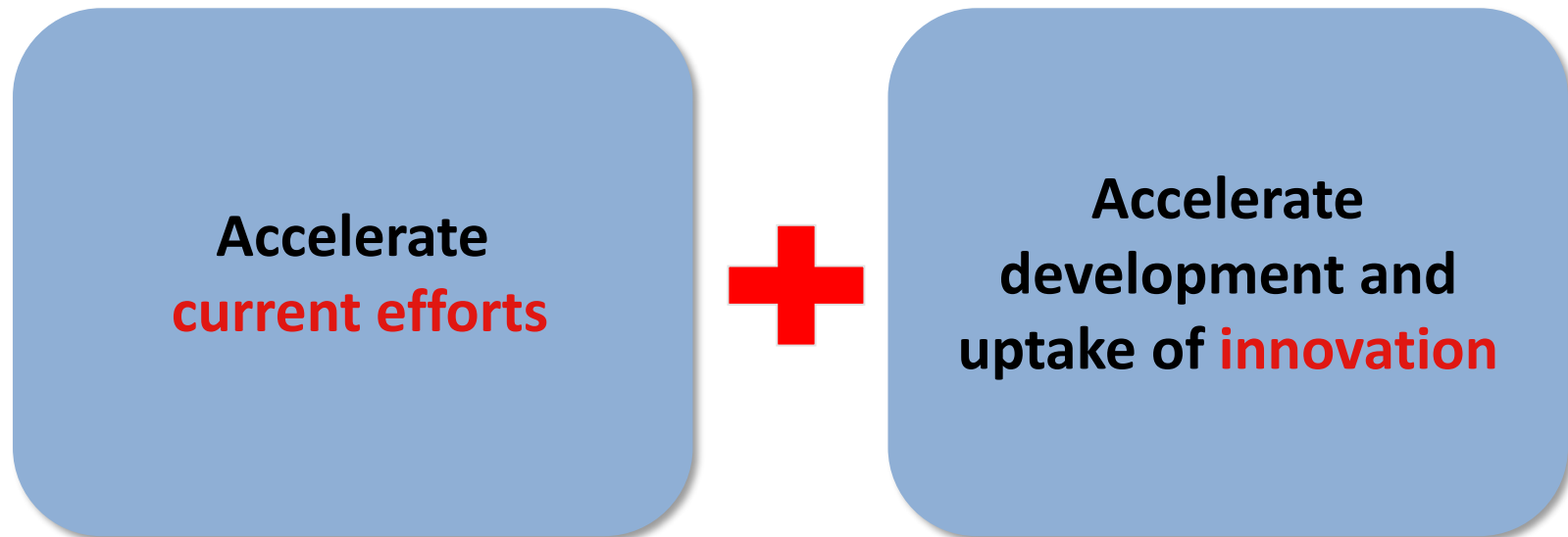
END THE GLOBAL TB EPIDEMIC

	MILESTONES		TARGETS	
	2020	2025	SDG* 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

* The United Nations Sustainable Development Goals (SDGs) include ending the TB epidemic by 2030 under Goal 3



Innovative approaches and commodities are needed to achieve global goals





The challenges of adherence to treatment and prevention for HIV, TB and malaria



Overview: Adherence and retention

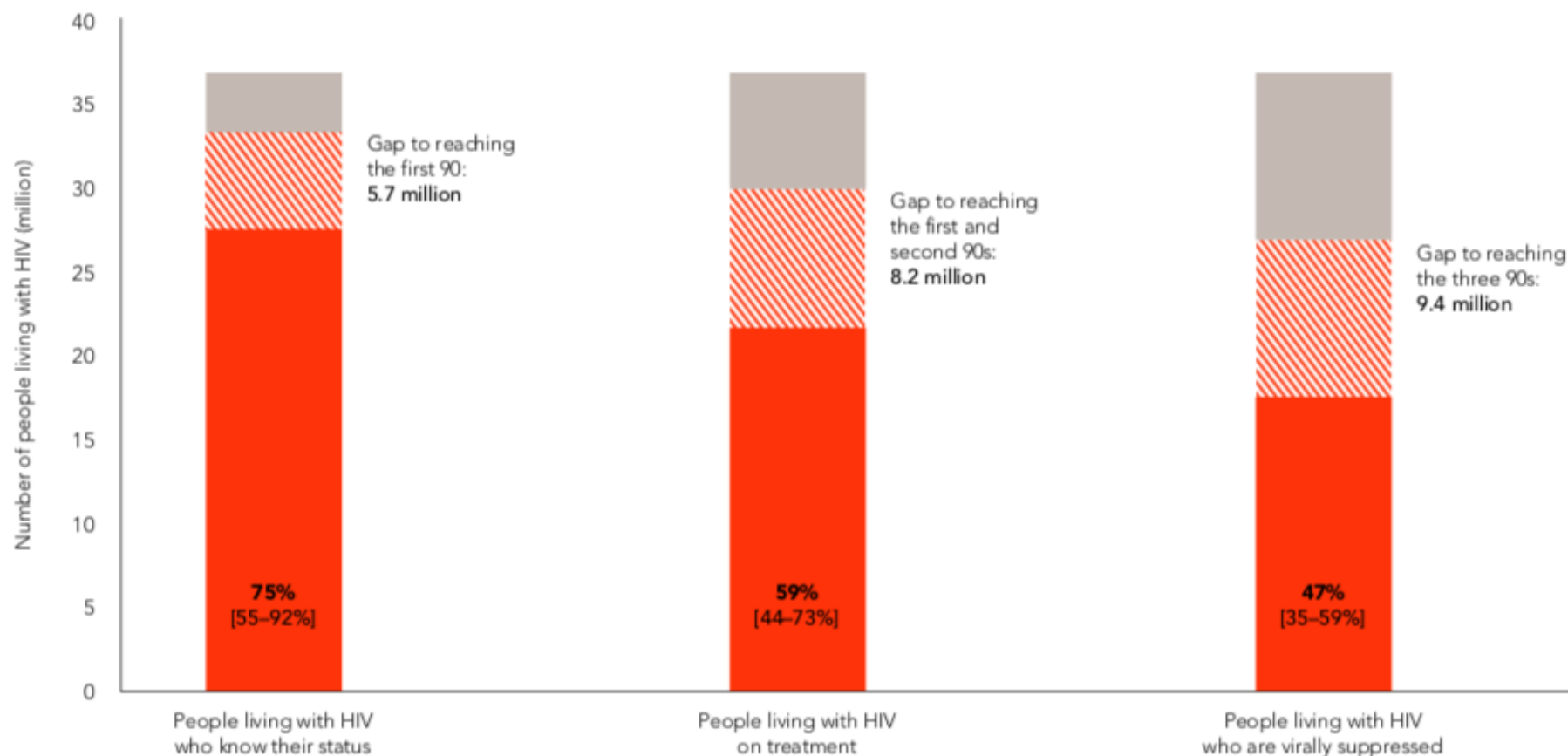
- WHO defines adherence as “the extent to which a person’s behaviour – taking medication, following a diet, or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” ([WHO, 2003](#)).
- In addition to incomplete or intermittent uptake of prescribed medications, in chronic daily treatments such as HIV ART, treatment interruptions (defined as stopping treatment for more than a week or up to 6 months) are now responsible for at least a third of cases of advance HIV disease ([MSF, 2017](#)).
- Across acute and chronic diseases, reducing dosage frequency from multiple daily dosing to once-daily dosing improves adherence to therapies among patients; improving adherence may result in subsequent decreases in health care costs ([Coleman et al, 2012](#); [Srivistava et al, 2013](#)).
- Current tools and strategies to support and monitor adherence have only a mixed record of success.



Fewer than half of all people with HIV currently achieve viral suppression

HIV testing and treatment cascade, global, 2017

Source: [Miles to Go, UNAIDS, 2018](#)



HIV: Adherence to treatment and prevention (1)

- Ensuring optimal adherence to lifelong ART and daily PrEP for HIV prevention is essential to meeting global targets (including “the third 90” on HIV viral suppression) and to minimizing the emergence of drug resistance. Adherence data below are highly context-specific.
- Adherence to daily oral antiretroviral therapy (ART) is closely linked to suppression of HIV viral load in plasma ([Paterson et al, 2000](#); [Arnsten et al, 2001](#)) which leads to immune reconstitution and decreases onward HIV transmission ([Cohen et al, 2011](#)).
- An adherence rate of 95% has been commonly used as the threshold necessary for viral suppression ([Paterson et al, 2000](#)). More recent analysis suggests that adherence levels as low as 80% to 90% may be adequate for viral suppression in patients taking newer antiretroviral drugs ([Bezabhe et al, 2016](#))
- Adherence levels reported globally and regionally vary considerably by context, e.g.
 - 70% in Latin America and the Caribbean ([de Mattos Costa et al, 2017](#))
 - 55% North America, 77% sub-Saharan Africa ([Mills et al, 2006](#))
- Adherence to HIV treatment can be a particular challenge for some populations in some settings, including adolescents living with HIV ([Kim et al, 2014](#); [Kim et al, 2017](#)), for women during pregnancy and in the postpartum period ([Haas et al, 2016](#); [Nachega et al, 2016](#)), and among prisoners ([Uthman et al, 2016](#)) and people who inject drugs ([Spire et al, 2007](#)). However, some health providers may defer initiation of ART among key populations on the basis of inappropriately assumed poor adherence ([Ferro et al, 2017](#)).
- These and other analyses suggest that levels of adherence to HIV treatment necessary to achieve viral suppression are frequently below the optimal threshold for viral suppression in many settings, highlighting the importance of efforts to further optimize adherence to ART.



HIV: Adherence to treatment and prevention (2)

- Among the most common reasons for lack of adherence to HIV treatment are forgetting, being away from home, and a change in daily routine. Depression, alcohol and substance abuse, secrecy/stigma, feeling sick, and health service-related barriers (e.g. distance to clinic, stockouts) are also reported.
- Pill burden and adverse events are less frequently reported with the advent of fixed-dose combinations and more tolerable ART regimens ([Shubber et al, 2016](#)).
- The most implemented interventions to support adherence to ART are peer counselling, adherence clubs and text messaging. Other interventions (digital technologies, decentralized and differentiated models of care) could potentially have greater impact if brought to scale ([Haberer et al, 2017](#)).
- Multiple adherence interventions have shown superiority over single interventions, suggesting additive effects. The estimated effects of interventions may be modest and wane over time ([Kanters et al, 2016](#)).
- For **HIV pre-exposure prophylaxis (PrEP)**, efficacy in six early clinical trials (before 2013) ranged from 0-75%, largely due to differences in adherence. Participants in more recent trials, open-label extensions and pilot projects show higher levels of adherence; potential explanations include known PrEP efficacy and increased motivations to take PrEP. To date, relatively few interventions to support PrEP adherence have been implemented and evaluated. Promising approaches include enhanced counselling, drug level feedback, text messages and smartphone apps. Event-driven PrEP (i.e. less than daily dosing) may involve additional benefits and challenges for adherence. Women and adolescents may also face particular challenges adhering to PrEP ([Haberer JE, 2016](#)).



Adherence to opioid substitution therapy: Link to HIV/HCV transmission and adherence to ART

- Treatment of drug dependence, in particular opioid substitution therapy (OST) for people dependent on opioids, helps to reduce the risk of HIV transmission and supports adherence to HIV treatment ([WHO, 2018](#)).
- There are an estimated 15 million people who inject drugs (PWID) globally ([Degenhardt et al, 2017](#))
- PWID are a key population for both HIV and HCV. The risk of acquiring HIV for PWID is 22 times higher than for those who do not inject drugs ([UNAIDS, 2018](#)). Key populations and their partners accounted for 47% of all new HIV infections globally in 2017 and more than 95% of new HIV infections in Eastern Europe and Central Asia. Nearly one third of new HIV infections in this region are among PWID ([UNAIDS, 2018](#)).
- Around 2.3 million people are co-infected with HIV and HCV, and half of them inject drugs ([WHO, 2017](#)).
- HIV and HCV prevention interventions include need and syringe programs (NSP), opioid substitution therapy (OST), HIV testing, HIV treatment and condom use.
- A meta-analysis of studies found that OST was associated with a 54% reduction in risk in HIV infection among PWID ([MacArthur et al, 2012](#)). The expected impact of providing OST and NSP at 60% coverage is a reduction in HCV prevalence of 20% ([Csete et al, 2016](#)).
- Coverage of harm reduction interventions is low: in 2018, only 86/144 countries and 44/177 countries reported that NSP and OST programs, respectively, were operational ([UNAIDS, 2018](#)).
- HIV-positive PWID are at greater risk for non-adherence to ART ([Spire et al, 2007](#)). Providing OST for people who are HIV-positive increases initiation of and adherence to ART and improves treatment outcomes ([Lawrinson et al, 2008](#), [Kamarulzaman et al, 2015](#)).
- Opioid agonists (e.g. naltrexone) and antagonists (e.g. methadone, buprenorphine) for opioid dependence may be effective in combination with other interventions, such as PrEP. ([Ujei et al, 2017](#)).



TB: Adherence to treatment and prevention

Active TB:

- Low adherence to daily TB treatment contributes to prolonged infectiousness, drug resistance, relapse and death ([Volmink et al, 2007](#); [Shargie et al, 2007](#)).
- Major factors associated with non-adherence to daily oral TB treatment (both DOT and self-administered) over the 6-8 month course of treatment include health service factors (e.g. distance to clinic, drug stock outs, rigid clinic routines and unsupportive health provider behaviour), social context (e.g. family and peer support, poverty and financial burden of care) and patient knowledge and attitudes, including poor understanding of treatment, belief in curability of TB and not feeling ill enough to take treatment ([Munro et al, 2007](#)).

Latent TB:

- TB is a leading cause of death among people with HIV, and HIV significantly increases a person's risk of progressing from latent to active TB infection ([WHO](#)).
- The global burden of LTBI is enormous: 1.7 billion people in 2014 ([Houben et al, 2016](#)). 10% of people with HIV and LTBI progress to active TB every year.
- Analyses of preventive treatment of latent TB infection (LTBI) show wide disparities in the rates of completion of treatment globally, ranging from 4% to 100% across different population groups ([Sandgren et al, 2016](#)). Completion rates range from 46% to 95% in the general population, 38% to 89% in people who inject drugs, 55% to 95% in people with HIV, 4% to 48% in inmates, and 7% to 83% among immigrants.
- A shorter course of treatment tended to be associated with improved adherence.
- Completion rates of LTBI treatment may be slightly higher in groups with higher risk of progression to active TB than in the groups with higher risk of TB infection.

HIV/TB co-infection:

- ART can have a significant impact on HIV and TB-related morbidity and mortality in co-infected people, but concomitant treatment is complicated by factors such as overlapping drug toxicities, drug-drug interactions, possible paradoxical reactions and increased pill burden ([Gebremarian et al, 2010](#)). Co-infected people may therefore be at increased risk for non-adherence to both regimens.
- Patient beliefs about the increased severity of concomitant diseases and drug tolerability, adverse events, timing or sequencing of the two regimens, poverty and lack of social support are among the factors contributing to non-adherence (ibid). Provision of food and minimal financial support may be associated with increased adherence (ibid).



Malaria: Adherence to treatment and prevention

Malaria treatment:

- Suboptimal adherence to daily malaria treatment is associated with treatment failure, severe disease, death and the emergence of drug resistance ([Bruxvoort et al, 2014](#); [Siddiqui et al, 2015](#)).
- 2014 meta-analyses of adherence to ACTs showed a wide range of adherence rates between countries and settings, ranging from <50% to 100% ([Banek et al, 2014](#); [Bruxvoort et al, 2014](#)). A 2015 meta-analysis showed adult ACT adherence rates of 76% in the public sector and 45% in the retail sector.
- Adolescents and children tend to be less adherent. Poor adherence is widely reported in children under 5 years, who bear the highest burden of morbidity and mortality.
- Factors associated with poor adherence include lower socio-economic status, poor knowledge of regimen, low education levels, and severity of malaria at presentation. Poor adherence is mainly associated with the last two doses at the end of the 3-day course (feeling of being cured before completing treatment). Adherence lower in low malaria transmission areas ([Yakasai et al, 2015](#)).

Malaria prevention:

- Chemoprophylaxis regimens for travellers to malaria endemic regions vary from weekly or daily oral regimens that must be taken prior to travel and 1-4 weeks after travel.
- Adherence rates to the full course of medicine including continuation after travel are reported in the ranges of 60-75% ([Abraham et al, 1999](#)) and 60%-90% ([Landman et al, 2016](#)).
- Common factors in non-adherence include forgetting and experience or fear of adverse events.



Improving and measuring ART adherence

- Inherent drug improvement to increase tolerability
 - Single regimen ART
 - Fewer side effects
- Improved delivery method
 - Long acting intramuscular injectables
 - Oral ART pharmacy refills for longer periods
- Monitored adherence support
 - Objective technological measures (EAMs, RNA & drug levels)
 - Subjective personal measures (self-report, caregiver report, SMS)
 - Person-centred approaches using both/either of above

Concern – if adherence to daily oral ART is difficult to monitor, what lessons can be learned to improve adherence to less frequent IM injectables?

[See additional slides on adherence to ART by Andrew Hill](#)



Technological tools to measure drug adherence

SMS & Instant messaging



EAMs (MEMS-cap)



Real-time wireless EAMs



Drug levels (plasma or hair)



HIV RNA testing



Digital medicine systems



Barriers to success, e.g.

Self-report bias, no airtime

Pocket dosing, curiosity openings

Mobile network loss, battery life

Dose masking (delayed testing)

Cost & equipment requirements

Failure of one/more tech components

And soon...?

TIME

A New Pill With a Digital Tracker Can Tell Your Doctor If You Swall...

HEALTH • MEDICINE

A New Pill With a Digital Tracker Can Tell Your Doctor If You Swallow It





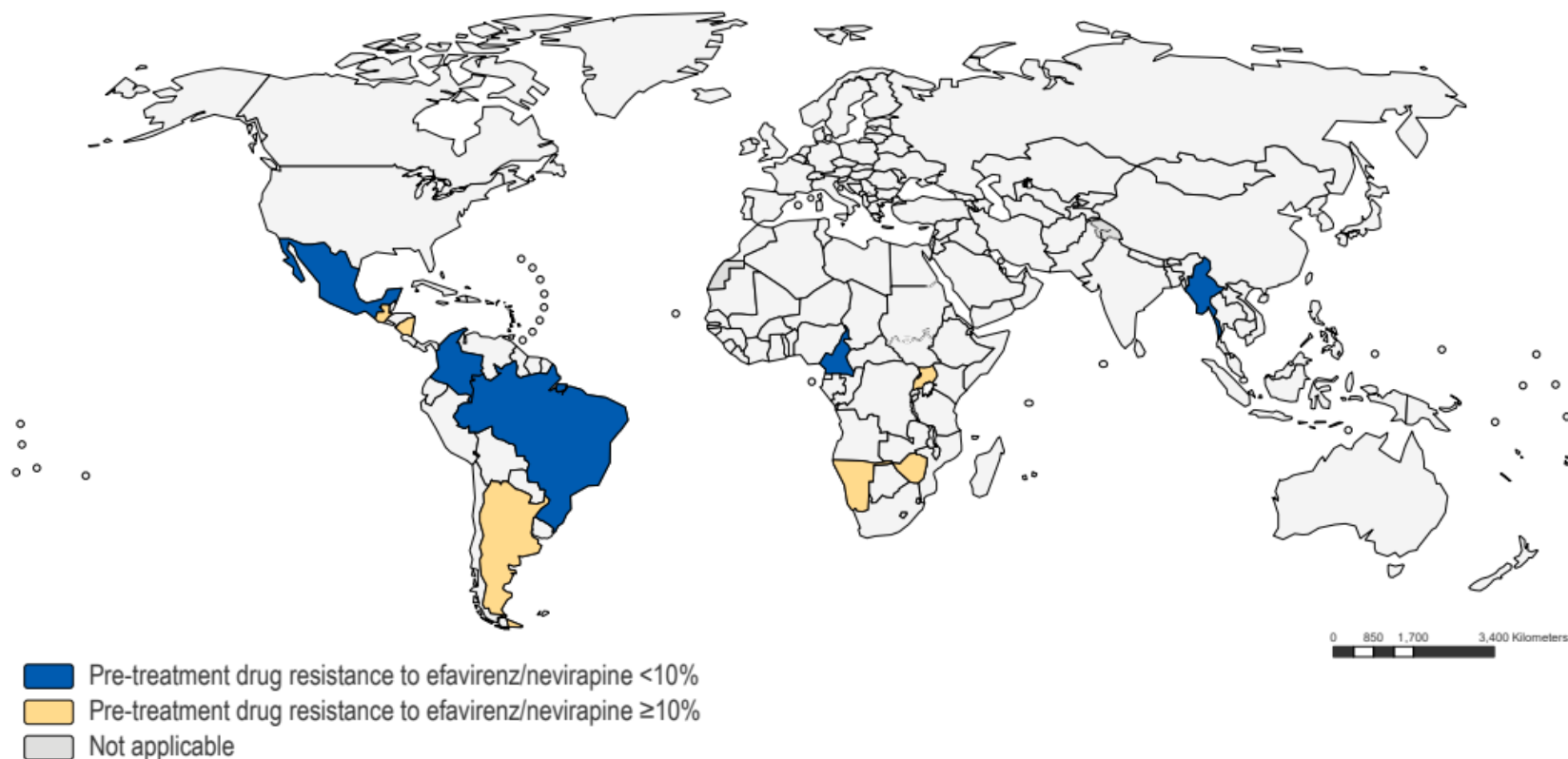
Drug resistance is a concern across the disease areas

Resistance is associated with sub-optimal adherence, sub-optimal regimens, poor prescribing and poor drug quality



HIV drug resistance [\(WHO, 2017\)](#)

NNRTI pretreatment HIV drug resistance in 11 countries reporting national survey data to WHO, 2014-2016



Four countries (Cameroon, Guatemala, Vietnam and Zambia) have reported prevalence of **acquired** NNRTI resistance ranging from 4.3% to 16.7% among people on ART for 12–24 months, and from 4.2% to 28.3% among those on treatment for longer durations (36–48+ months).

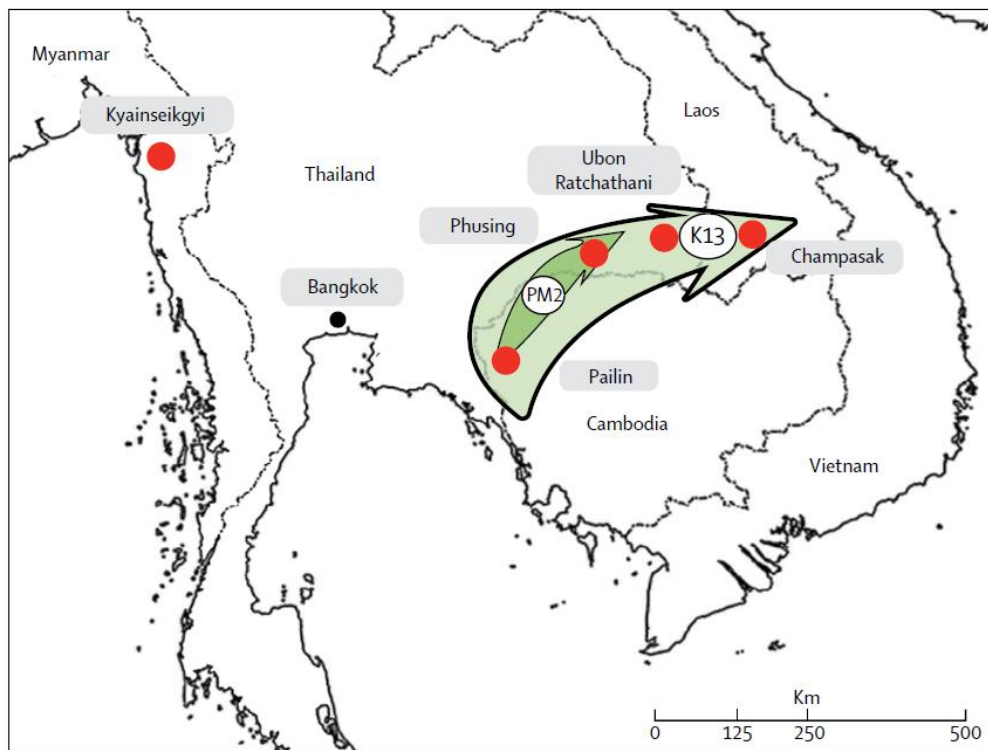


Malaria: Artemisinin- and piperazine-resistance in the Greater Mekong sub-region

The Greater Mekong sub-region has long been the epicentre of antimalarial drug resistance. *P. falciparum* resistance to artemisinin is present in Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. There is increased focus on malaria elimination in these countries.

Key drivers of antimalarial drug resistance are:

- Unusual genetic structure of malaria parasites in regions known for antimalarial drug resistance
- Counterfeit or substandard treatments
- Unregulated or poorly administered antimalarial drug use
- Artemisinin drug use without a complementary combination treatment, such as lumefantrine (WHO, 2017)

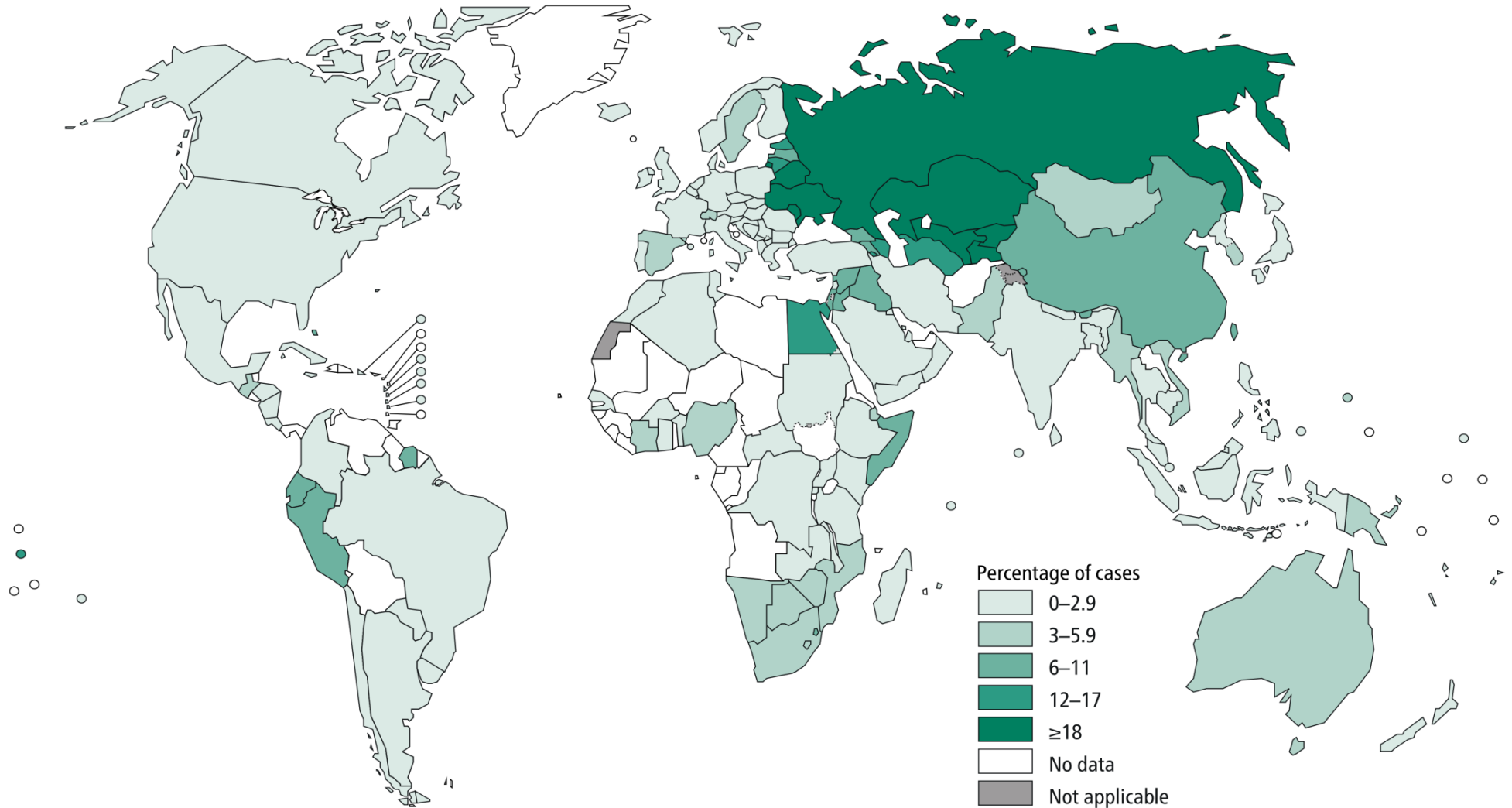


Parasites remain responsive to mefloquine and/or artemether-lumefantrine + amodiaquine

Imwong, M., *et al.*, (2017) *Lancet Infectious Diseases* 17: 491-497
 Amaratunga C, *et al.*, (2016) *Lancet Infect Dis.* 16:357-65



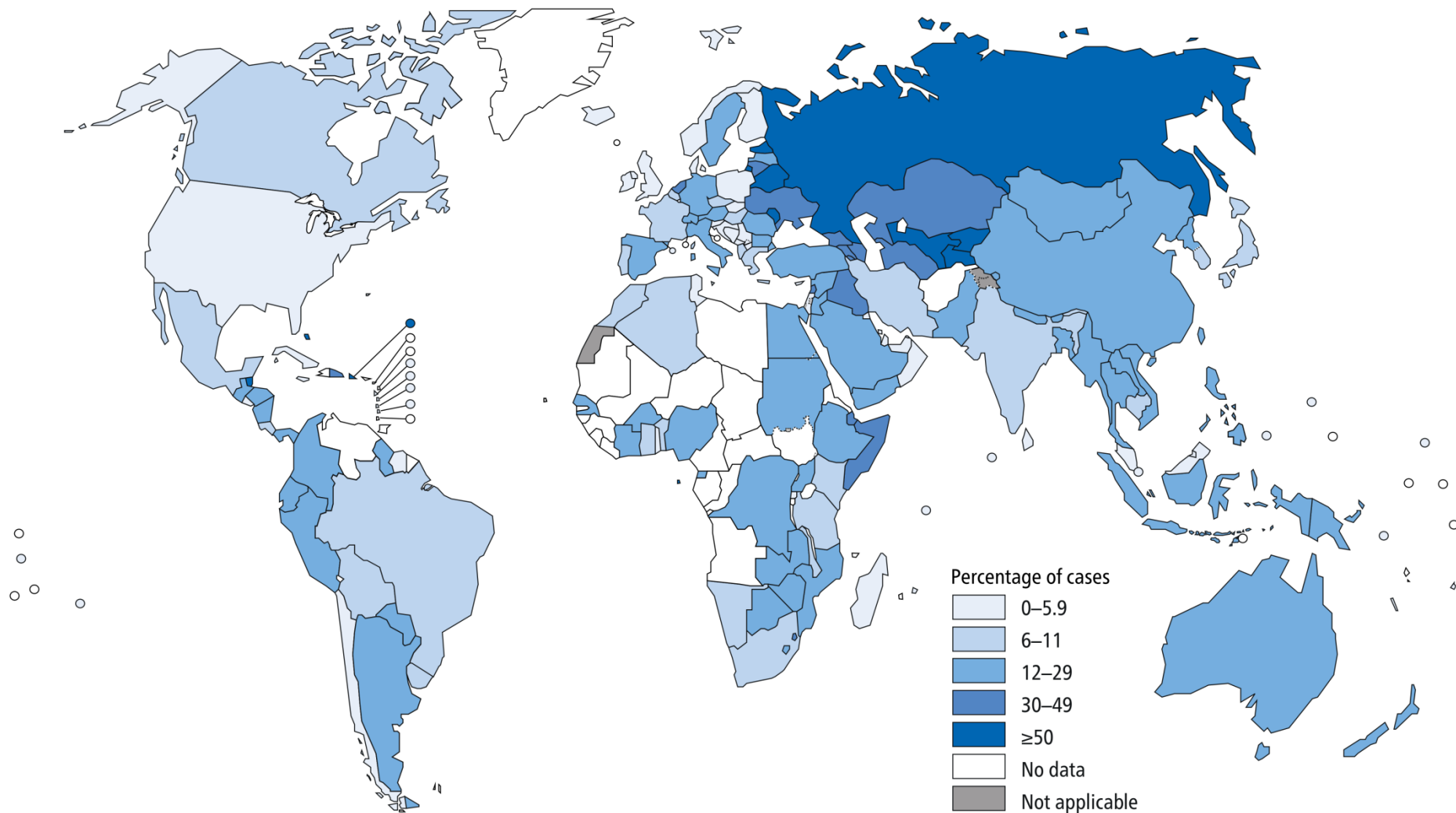
TB: Proportion of MDR/RR-TB in new tuberculosis cases



2017 report. Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before 2002 are not shown



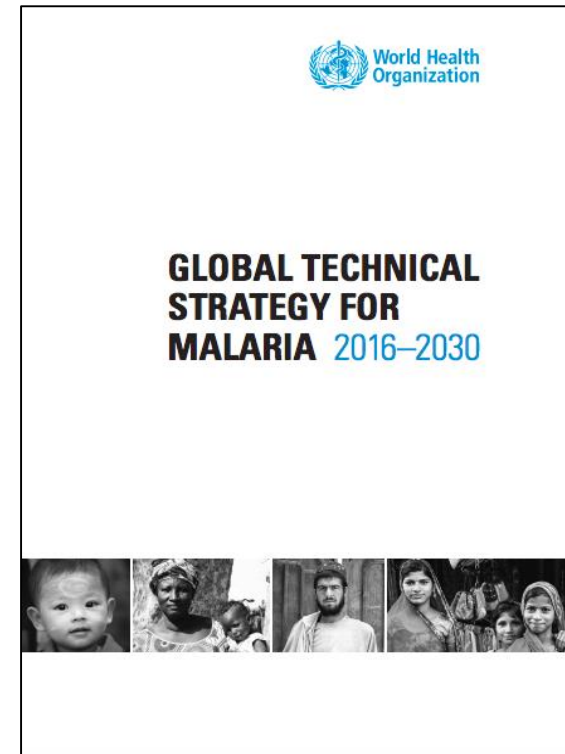
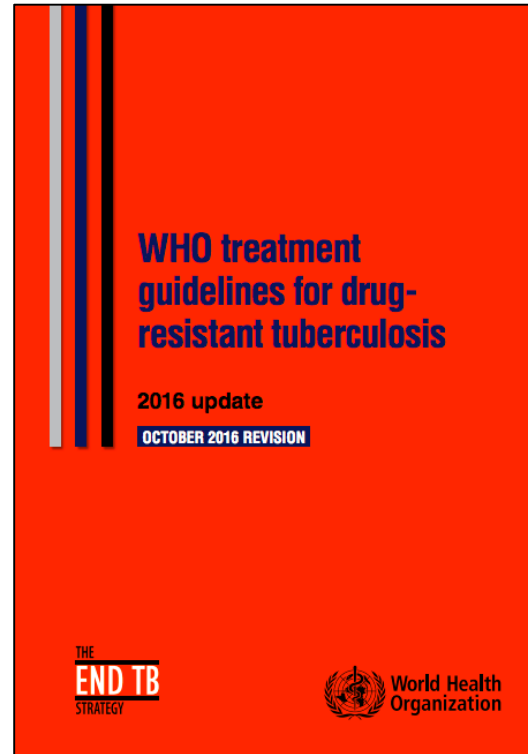
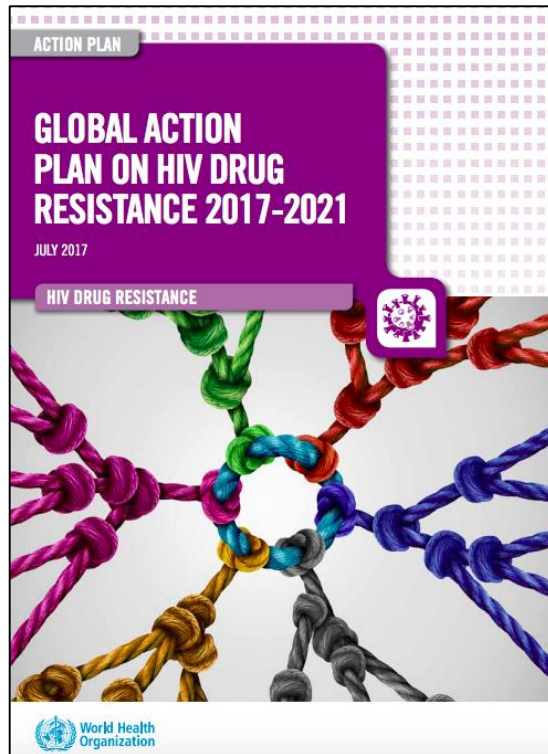
TB: Proportion of MDR/RR-TB in previously treated cases



2017 report. Figures are based on the most recent year for which data have been reported, which vary among countries. Data reported before 2002 are not shown. The high percentages of previously treated TB cases with MDR-TB in Bahamas, Belize, French Polynesia, Puerto Rico and Sao Tomé and Príncipe refer to only a small number of notified cases (range: 1–8 notified previously treated TB cases).



Efforts to optimize patient adherence and retention are key elements of global drug resistance strategies and guidelines





Other challenges in the global response to the diseases



Other challenges in the global response to HIV, TB, malaria and HCV (not exhaustive)

- Lack of highly-efficacious vaccine for HIV, TB, malaria or HCV on the horizon; lack of a cure for HIV
- Other health (e.g. NCDs) and development priorities for donors and countries in the SDG era; need to optimize synergies across disease-specific, health systems and structural interventions
- Stigma/discrimination, including those associated with daily pill uptake/use for prevention or treatment
- Growing burden on health and procurement and supply systems with increased numbers of people on treatment and prevention
- Poor drug quality, especially for malaria and TB medicines



Part 3: Experience from other disease areas: LA products and impact



- **Schizophrenia**
- **Osteoporosis**
- **Hormonal contraception**



Long-acting injectable anti-psychotics improve adherence to treatment and patient outcomes for schizophrenia

- The majority of patients with schizophrenia relapse after 5 years; poor adherence to daily oral medication is the most common cause.
- The discontinuation rate for oral antipsychotics is 26% to 44%; up to a third of patients are at least partially non-adherent.
- Non-adherence is associated with increased relapse, hospitalization and suicide.
- Long-acting injectable treatment is associated with lower rates of relapse, discontinuation and hospitalization versus oral anti-psychotics, and increased cost-effectiveness, functionality, quality of life and patient satisfaction; LA may have neuro-protective effects when used as early treatment.
- Improved quality of life with less frequent injections (2-weekly v 3 monthly).
- Barriers to the use of long-acting injectables include provider beliefs about efficacy and misperceptions about patient preference, adherence and tolerability; patient fear of injection pain and tolerability ([Kaplan et al, 2013](#))

Patient Preference and Adherence

 Open Access Full Text Article

Dovepress
open access to scientific and medical research

REVIEW

Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia

This article was published in the following Dove Press journal:
Patient Preference and Adherence
12 November 2013
[Number of times this article has been viewed](#)

Abstract: Schizophrenia is a debilitating chronic disease that requires lifelong medical care and supervision. Even with treatment, the majority of patients relapse within 5 years, and suicide may occur in up to 10% of patients. Poor adherence to oral antipsychotics is the most common cause of relapse. The discontinuation rate for oral antipsychotics in schizophrenia ranges from 26% to 44%, and as many as two-thirds of patients are at least partially non-adherent, resulting in increased risk of hospitalization. A very helpful approach to improve adherence in schizophrenia is the use of long-acting injectable (LAI) antipsychotics, although only a minority of patients receive these. Reasons for underutilization may include negative attitudes, perceptions, and beliefs of both patients and health care professionals. Research shows, however, significant improvements in adherence with LAIs compared with oral drugs, and this is accompanied by lower rates of discontinuation, relapse, and hospitalization. In addition, LAIs are associated with better functioning, quality of life, and patient satisfaction. A need exists to encourage broader LAI use, especially among patients with a history of nonadherence with oral antipsychotics. This paper reviews the impact of nonadherence with antipsychotic drug therapy overall, as well as specific outcomes of the schizophrenia patient, and highlights

Gabriel Kaplan^{1,2}
Julio Casoy³
Jacqueline Zummo³

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Long-acting injectables for osteoporosis treatment

- Adherence to oral bisphosphonates for the treatment of osteoporosis is low and at least one-third of patients do not take them as prescribed.
- Rates of adherence to oral tablets decrease over time.
- Patients overwhelmingly prefer a once-yearly injectable product (IV zoledronic acid).
- Once-yearly injectable treatment improves adherence and drug persistence and may be especially suitable for people who do not tolerate or adhere to oral drugs (e.g. people with cognitive dysfunction, polypharmacy, physical limitations).

[Ther Adv Musculoskelet Dis](#). 2013 Aug; 5(4): 182–198.

doi: [10.1177/1759720X13485829](https://doi.org/10.1177/1759720X13485829)

PMCID: PMC3728980

PMID: [23904863](https://pubmed.ncbi.nlm.nih.gov/23904863/)

Clinical experience with intravenous zoledronic acid in the treatment of male osteoporosis: evidence and opinions

[Ieva Ruza](#), [Sasan Mirfakhraee](#), [Eric Orwoll](#), and [Ugis Gruntmanis](#)[✉]

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Review

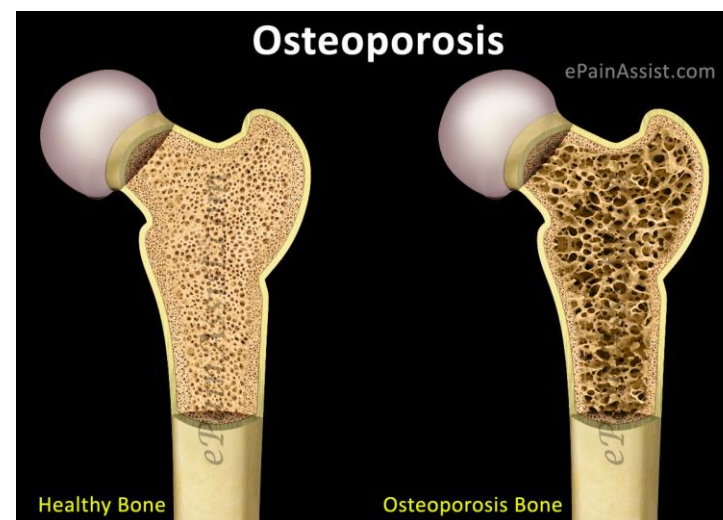
Adherence and preference of intravenous zoledronic acid for osteoporosis versus other bisphosphonates

[Maria José Fobelo Lozano](#)¹, [Susana Sánchez-Fidalgo](#)^{1, 2}

[Author affiliations](#) +

Abstract

Objective To evaluate adherence as well as patient preference and satisfaction of once-yearly intravenous zoledronic acid versus other bisphosphonates treatments.



Long-acting hormonal contraception

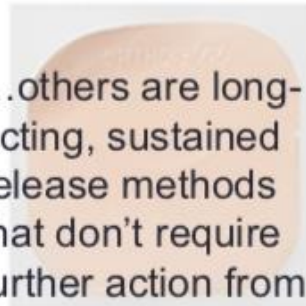
Hormonal contraceptives come in many shapes, doses and formulations



...some are short-acting and require regular action from the user



...others are long-acting, sustained release methods that don't require further action from the user



Experience with LA hormonal contraception

- LA hormonal contraception has been available since 1960 (3-monthly injection of medroxy-progesterone acetate) and is now available as an intra-muscular or subcutaneous injection, sub-dermal implant or intra-uterine system. The products have different characteristics and different effects on menstrual cycles and bleeding patterns. Hormonal contraceptives have been used by at least 500 million women alive today. Choice in delivery methods is important for different women in different cultural and social contexts.
- Two **injectable** products are currently marketed
 - 1) Depot-medroxy-progesterone acetate: DMPA (Depo Provera™) administered as an intramuscular injection every 3 months (DPMA-IM). There are mixed data on the impact of DMPA-IM on HIV susceptibility in women - this is now being studied in a large, randomized controlled trial (ECHO). More recently DPMA was formulated as a sub-cutaneous injection (DPMA-SC or Sayana Press™) that can be given by a community health worker or self-administered.
 - 2) Norethisterone enantate (Noristerat™ or NET-EN), administered every 2 months
 - Over 40 million women worldwide use injectable contraception and nearly half (47%) of modern contraception users in sub-Saharan Africa rely on injectable contraceptives to prevent pregnancy. Discontinuation rates of injectable contraceptives in sub-Saharan Africa are high, contributing to growing popularity of longer-acting implants. Efforts are underway to develop longer-acting IM formulations (e.g. levonorgestrel butanoate).
- The first sub-cutaneous contraceptive **implant** was developed in the 1970s (progestin megestrol acetate); after it was associated with breast tumours in beagles, development then turned to the use of levonorgestrel (LNG)
 - Two types of implants have been developed: “rods” and “capsules”
 - Norplant 1 developed by the Population Council was the first SQ implant in widespread use (6 capsules, 5 year duration) – discontinued and substituted with Norplant 2 (Janelle™ – 2 rods, 5-year duration); Levoplant/Sinoplant 2-rod implant is nearly identical but contains more drug (5-year duration)
 - Implanon™, Nexplanon™ and Implanon NXT™ are similar products with 3-year duration
 - Two sub-cutaneous implant products use progestin nesterone, with duration of 6 months-2 years
- Intrauterine systems** were first developed in the 1970s (Progastasert™, discontinued due to failure rates)
 - LNG-releasing systems (LNG-IUS) are now the most common e.g. Mirena™ (5-7 year duration)



Examples of long-acting reversible contraception (LARC)

		
<p>LNG-IUS</p> <ul style="list-style-type: none"> • 99% effective • 20 mcg LNG*/day • Up to 5 (7?) years 	<p>Copper T IUD</p> <ul style="list-style-type: none"> • 99% effective • Copper ions • Up to 12 years 	<p>Subdermal Implant</p> <ul style="list-style-type: none"> • 99% effective • 60 mcg ENG**/day • Up to 3 years



PRESS RELEASES

FDA Approves the First One-Year Contraceptive Fully under a Woman's Control

10 August 2018

SHARE: [t](#) [f](#) [in](#)

The Population Council, a global nonprofit research organization, announced it has received U.S. Food and Drug Administration (FDA) approval for Annovera™ (segesterone acetate and ethinyl estradiol vaginal system), the first and only contraceptive that provides an entire year of protection against unintended pregnancy while fully under a woman's control. The approval marks an important step toward expanding contraceptive options for women.



Photo credit: Population Council / Hallie Easley



LARC: pros and cons

- Pros
 - Safe for nearly all women
 - Lowest systemic dose of all available options
 - Highly effective (99% +)
 - 'Forgettable' contraception
 - Ease of use, convenient
 - Eliminates adherence issues (perfect use=actual use)
 - Immediately reversible
 - The highest satisfaction rates among all contraceptive users
 - 86% of IUD users are 'highly' or 'very' satisfied
- Cons
 - Must be placed and removed by a clinician
 - Small procedural risks



Fortney JA, et al. *J Reprod Med.* 1999;44:269-274; Belhadj H, et al. *Contraception.* 1986;34:261-267; Skjeldestad F, et al. *Adv Contracept.* 1988;4:179-184; Arumugam K, et al. *Med Sci Res.* 1991;19:183; Peterson HB, et al. *Am J Obstet Gynecol.* 1996;174:1161-1168; Forrest JD. *Obstet Gynecol Surv.* 1996;51:S30-S34.



Long-acting contraception is popular and highly effective



JOURNAL OF WOMEN'S HEALTH

Mary Ann Liebert, Inc. publishers

Journals

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Alerts

J Womens Health (Larchmt). 2015 May 1; 24(5): 349–353.
doi: [10.1089/jwh.2015.5191](https://doi.org/10.1089/jwh.2015.5191)

PMCID: PMC4441000
PMID: [25825986](https://pubmed.ncbi.nlm.nih.gov/25825986/)

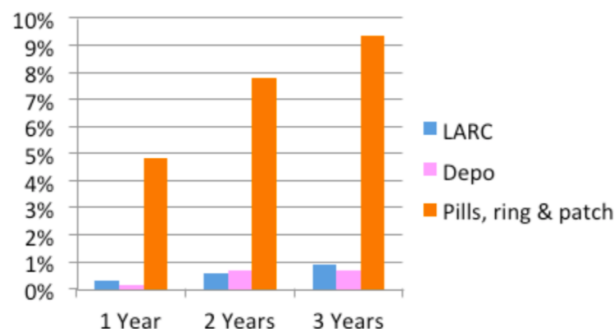
Preventing Unintended Pregnancy: The Contraceptive CHOICE Project in Review

Natalia E. Birgisson, BS, Qiuhong Zhao, MS, Gina M. Secura, PhD, MPH, Tessa Madden, MD, MPH, and Jeffrey F. Peipert, MD, PhD[✉]

[Author information](#) ▶ [Copyright and License information](#) ▶ [Disclaimer](#)

- **USA:** Given a choice between long-acting and other forms of contraception, 72% of women in the CHOICE study chose a long-acting method (injection or IUD).
- Long-acting methods of contraception were associated with greater continuation, much higher efficacy, fewer teenage pregnancies and fewer repeat abortions.

Unintended Pregnancy by Contraceptive Method



HR_{adj} = 22.3 (95% CI 14.0, 35.4) TWENTY-FOLD DIFFERENCE!

Winner, et al. NEJM 2012

Published in final edited form as:

Popul Dev Rev. 2017 May ; 43(Suppl Suppl 1): 166–191. doi:10.1111/padr.12051.

Contraceptive Practice in Sub-Saharan Africa

Amy O. Tsui¹, Win Brown², and Qingfeng Li¹

¹Johns Hopkins University

²Bill & Melinda Gates Foundation

Abstract

Forty eight of the African continent's 54 sovereign states are located in the Sub-Saharan Africa (SSA) region, with the government of each defining and shaping its own health services and delivery systems. This paper reviews the trends and patterns of contraceptive practice in the region. Using survey data available from the Demographic and Health Surveys and Performance Monitoring and Accountability 2020, the study finds modern contraceptive practice to be on the rise overall but with much geographic variation. The contraceptive methods most frequently used are injectables and, more recently, implants. Higher levels of use are observed among unmarried sexually active than married females. Although use is rising, contraceptive discontinuation rates are also high. Recent program initiatives discussed include expanding long-acting contraceptive options, promoting and delivering contraceptive methods in the postpartum period, and relying on community health workers for contraceptive outreach and service delivery. SSA's family planning situation remains challenged by weak health systems which must address competing priorities to manage disease prevention as well as primary health care. Increasing investments in family planning delivery in many SSA countries, however, augur for continued rapid uptake of modern contraception, possibly matching if not outpacing the record of other regions.



Sub-dermal, injectable, hormonal contraception (DMPA-SC): Provision by community health workers and self-administration

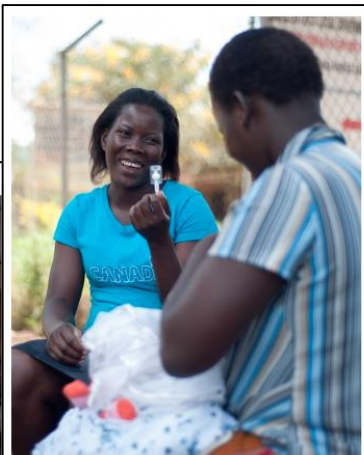
Selected resources on
this slide from



June 18, 2018

Training for DMPA-SC, the all-in-one injectable contraceptive

Several thousands of health workers around the world have been trained to safely provide DMPA-SC injections in clinics, community locations, and villages, and even to support women to self-inject.



June 18, 2018

Practical guidance for DMPA-SC introduction and scale-up

Family planning leaders can draw from an established base of evidence to integrate DMPA-SC in efforts to address unmet need and increase access to contraception through a range of delivery channels.



June 18, 2018

Self-injection best practices: designing family planning programs that work

Research in Uganda and elsewhere has shown that women are able to self-administer DMPA-SC safely and effectively, that they like doing so, and that self-injection helps support women to continue using injectable contraception.

[Lancet Glob Health. 2018 May;6\(5\):e568-e578. doi: 10.1016/S2214-109X\(18\)30061-5. Epub 2018 Mar 8.](https://doi.org/10.1016/S2214-109X(18)30061-5)

Effect of self-administration versus provider-administered injection of subcutaneous depot medroxyprogesterone acetate on continuation rates in Malawi: a randomised controlled trial.

Burke HM¹, Chen M², Buluzi M³, Fuchs R², Wewill S², Venkatasubramanian L², Dal Santo L², Ngwira B³.

Conclusion: Women who self-injected DMPA-SC had significantly higher rates of continuation than those receiving provider-injected DMPA-SC. Community-based provision of injectable contraception for [self-injection](#) in low-resource settings seems to be safe and feasible. Self-administration of DMPA-SC should be made widely available.

Self-Injection Feasibility and Acceptability

Research results from Senegal and Uganda

Injectable contraceptives are the most commonly used method of family planning in Senegal and Uganda. A new injectable contraceptive, subcutaneous DMPA (DMPA-SC, brand name Sayana[®] Press) has the power to expand access and options: DMPA-SC is easy to use, allowing for less specialized health care workers to administer the contraceptive. New research from [Senegal](#) and [Uganda](#) also suggests self-administration of DMPA-SC is both feasible and acceptable.



What women say about self-injection

Self-injection is very easy to do

- Senegal: 64% (first injection), 66% (second injection), 72% (third injection)
- Uganda: 61% (first injection), 92% (second injection)

Would like to continue self-injecting in the future

- Senegal: 93%
- Uganda: 98%

Very likely to recommend to others

- Senegal: 73%
- Uganda: 88%

Able to store DMPA-SC securely

- Senegal: 97%
- Uganda: 98%

Where women store the device

- Senegal: Armoire/dresser (74%)
- Uganda: Handbag (61%)

Experiences with disposal of the device

- Stored spent devices in an impermeable container until safely discarded (Senegal 49%; Uganda 71%)
- Disposed in a pit latrine, as per instructions (Senegal 49%; Uganda 94%)



Background resources on the evolution of LA hormonal contraception

Long-acting hormonal contraception

Women's Health, 2015

Today, a new category of fertility-regulating agents has been created: long-acting, reversible hormonal contraceptives; they minimize compliance, while maximize effectiveness. They comprise subdermal implants and intrauterine devices. Other long-acting agents exist, such as Depo Provera and Noristerat. Use of Depo Provera and Noristerat carries great effectiveness, good clinical safety and usefulness in developing countries. They cause no significant increase in breast cancer risk, but they may carry an increased risk of HIV. Subcutaneous delivery systems have two common features: prolongation of effect is obtained by a drug reservoir and for most of their duration of action they provide a continuous, sustained release of the active hormone. Finally, the intrauterine system Mirena represents both a very effective contraceptive and a specific treatment for menorrhagia.

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& Ivo Brosens³

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Review article

Towards the development of a longer-acting injectable contraceptive: past research and current trends

Vera Halpern, Randy M. Stalter*, Derek H. Owen, Laneta J. Dorflinger,
Anja Lendvay, Kate H. Rademacher

FHI 360, 359 Blackwell Street, Suite 200, Durham, NC 27701, USA

Received 7 January 2015; revised 10 February 2015; accepted 25 February 2015



Part 4: Science and technology landscape



Part 4a: Nano-formulation processes for LA injectable medicines

Part 4b: Pipeline of innovative devices/systems for drug delivery

Part 4c: Pipeline of LA drugs by disease area

- Pipeline overview (all drugs and diseases)
- HIV prevention and treatment
- Malaria chemoprophylaxis and vector control
- Treatment for latent TB infection
- Hepatitis C treatment
- HIV & HCV prevention through opioid substitution therapy

Part 4d: Product summaries for LA drugs in Phase 2-3 trials and approved LA drugs





Part 4a: Nano-formulation processes for LA injectable medicines



Nano-formulation basics

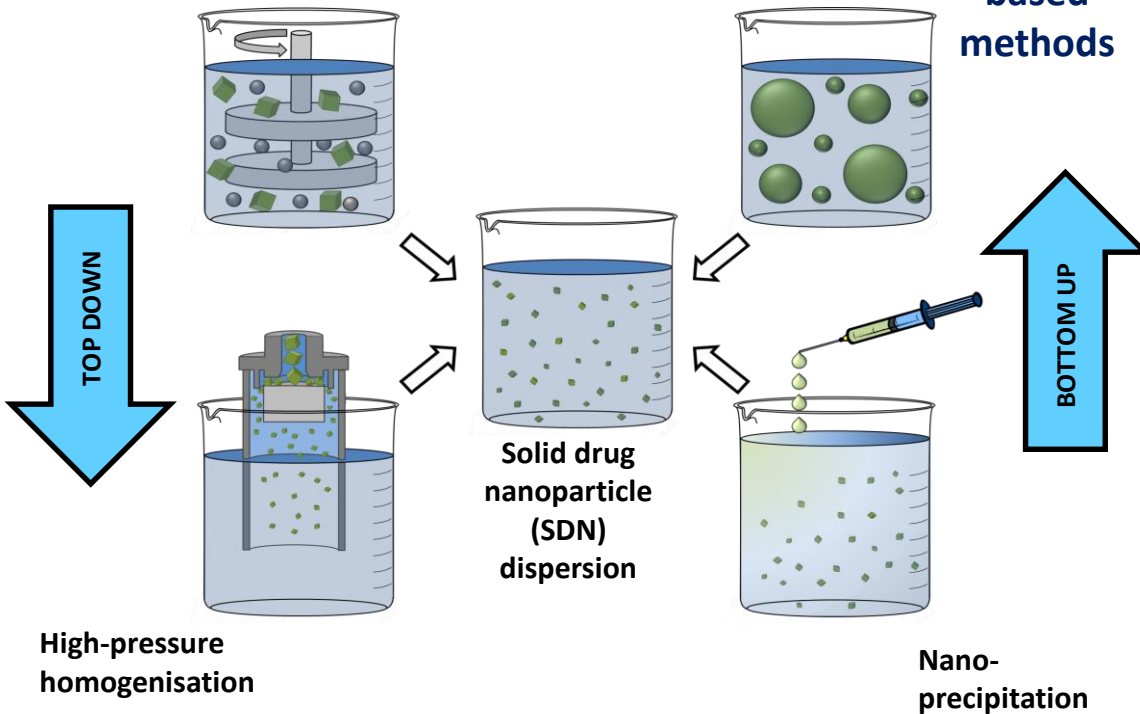
- LA injectable products can be developed using nano-technology
- Formulation of nano-particles has already been used for numerous approved medicines (both oral and injectables)
 - **Oral nano-formulations** offer potential for increased drug bioavailability and dose reduction = cost-savings (but the products are usually still daily oral pills)
 - **Injectable LA nano-formulations** may be manufactured using two main methods:
 - 1) nano-milling and 2) precipitation of solutions (e.g. emulsion-based methods utilizing freeze-drying or spray-drying – see next slide)
- The suitability of a drug for nano-formulation is dependent on a number of critical properties including potency, pharmacokinetics and physiochemistry
 - Volume of the depot is the critical factor
- All injectable drug products require sterile manufacturing
- The regulatory pathway may be simpler when applied to reformulation of existing drugs (e.g. FDA 505(b)(2) process may be accessible)



Processes for manufacturing nanoparticles

(also called solid drug nanoparticles or SDNs, nanocrystals, nanodispersions, nanosuspensions)

Nanomilling



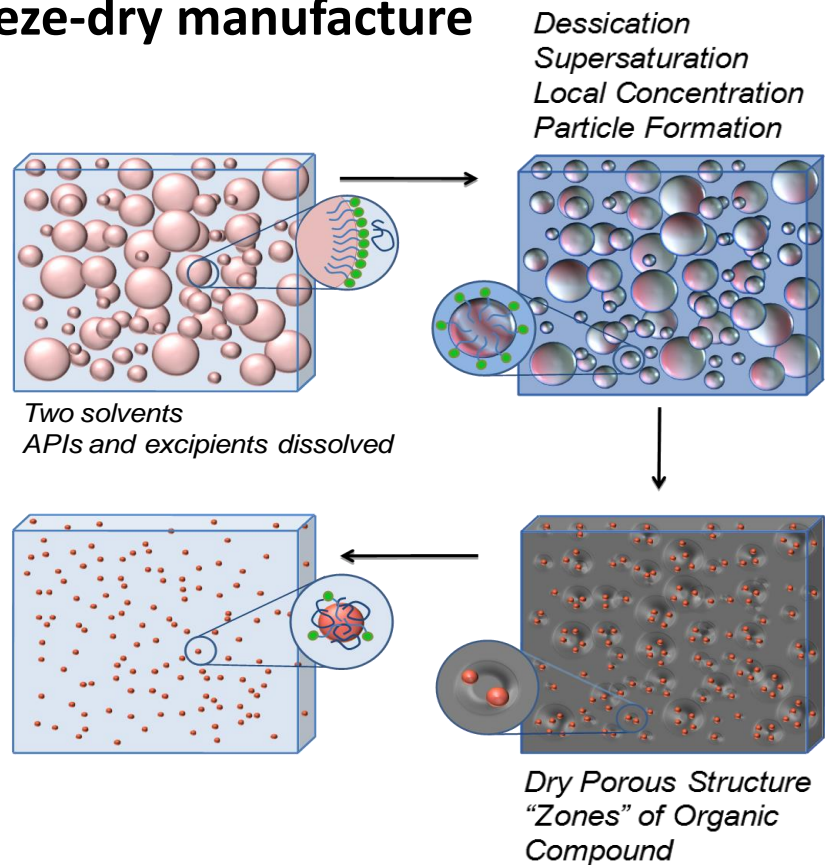
Oral products

Long-acting injectables

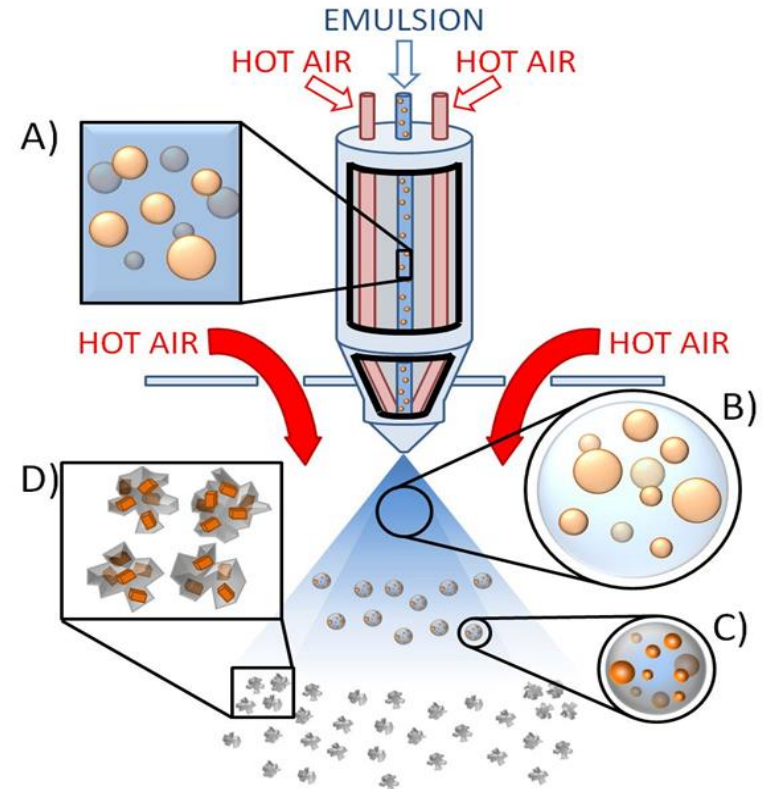


Processes for manufacturing nanoparticles: Emulsion methods

Freeze-dry manufacture



Spray-dry manufacture



Examples of FDA-approved nanocarrier oral and injectable medicines



Breast
Cancer



Fungal
Infection



Macular
Degeneration



Breast
Cancer



Ovarian
Cancer



Menopausal
Symptoms



Anaesthetic



Febrile
Neutropenia



Hepatitis C



Fungal
Infection



Multiple
Sclerosis



Kaposi's
Sarcoma



Kidney
Disease



Hepatitis A
Vaccine



Lipid
Disorders



Acromegaly



Leukemia



Hepatitis C



Fungal
Infection



Meningitis



Enzyme
Replacement



Menopausal
Symptoms

Injectable

Oral

Dermal

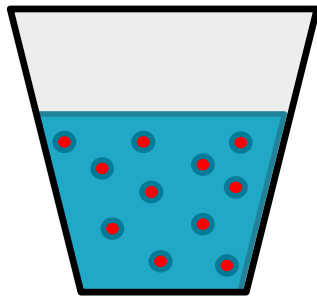
Drops



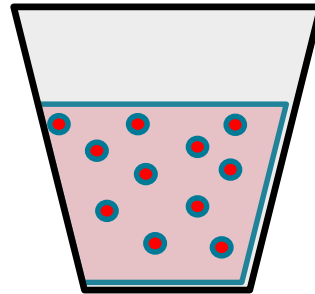
Why aren't all agents formulated as nano-formulations?

Technology compatibility requires low aqueous solubility drugs to form nano-suspension

- **Pro-drug approaches** have been applied to decrease solubility for LA injectable approaches

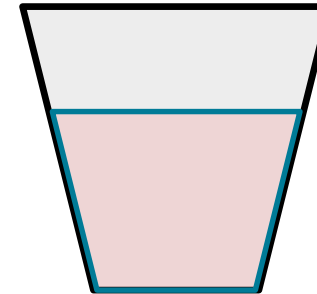


**Insoluble drug
nanoparticle
suspension
(suitable for
LA injectable)**



**Soluble drug
nanoparticle
suspension**

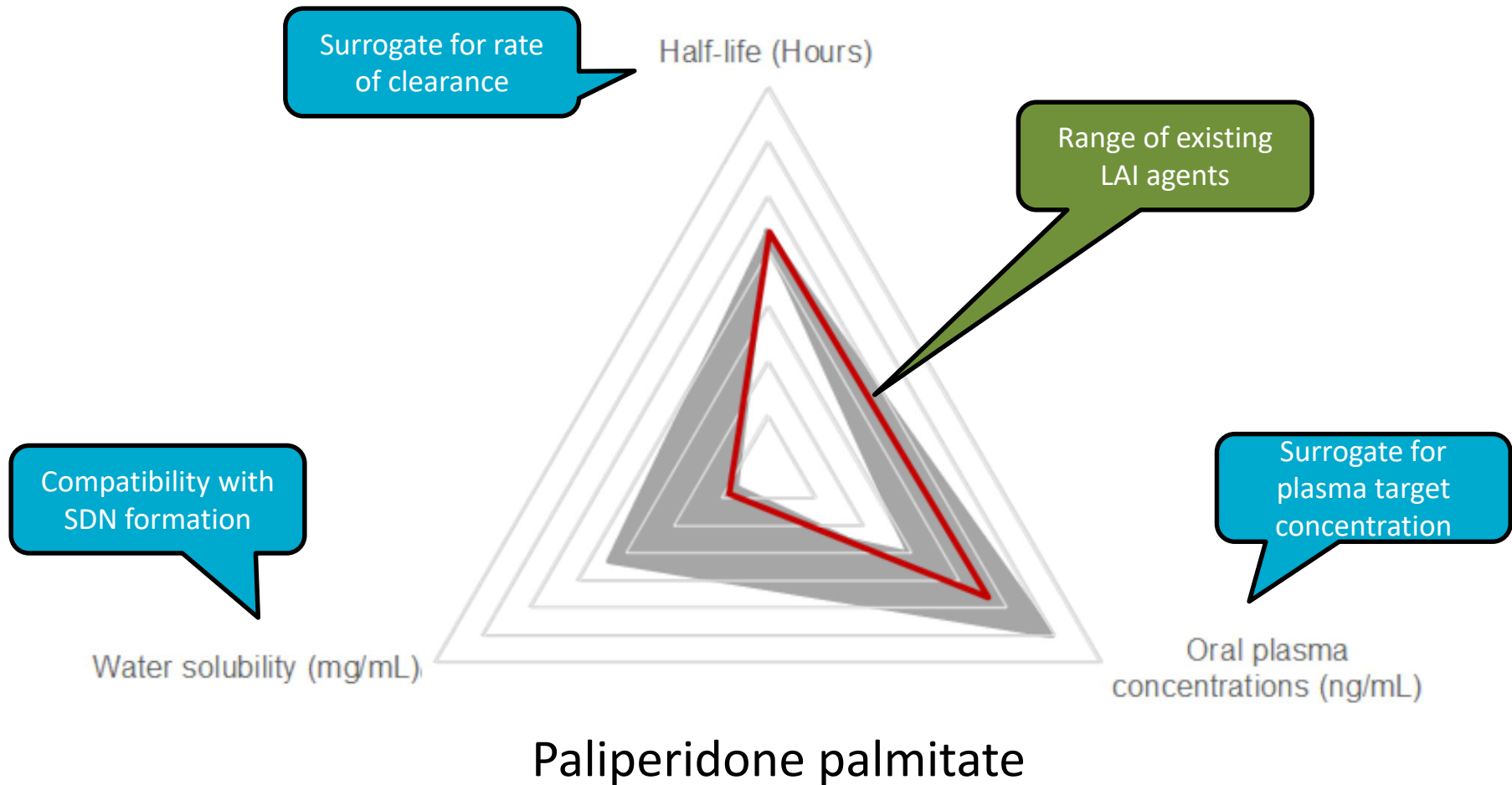
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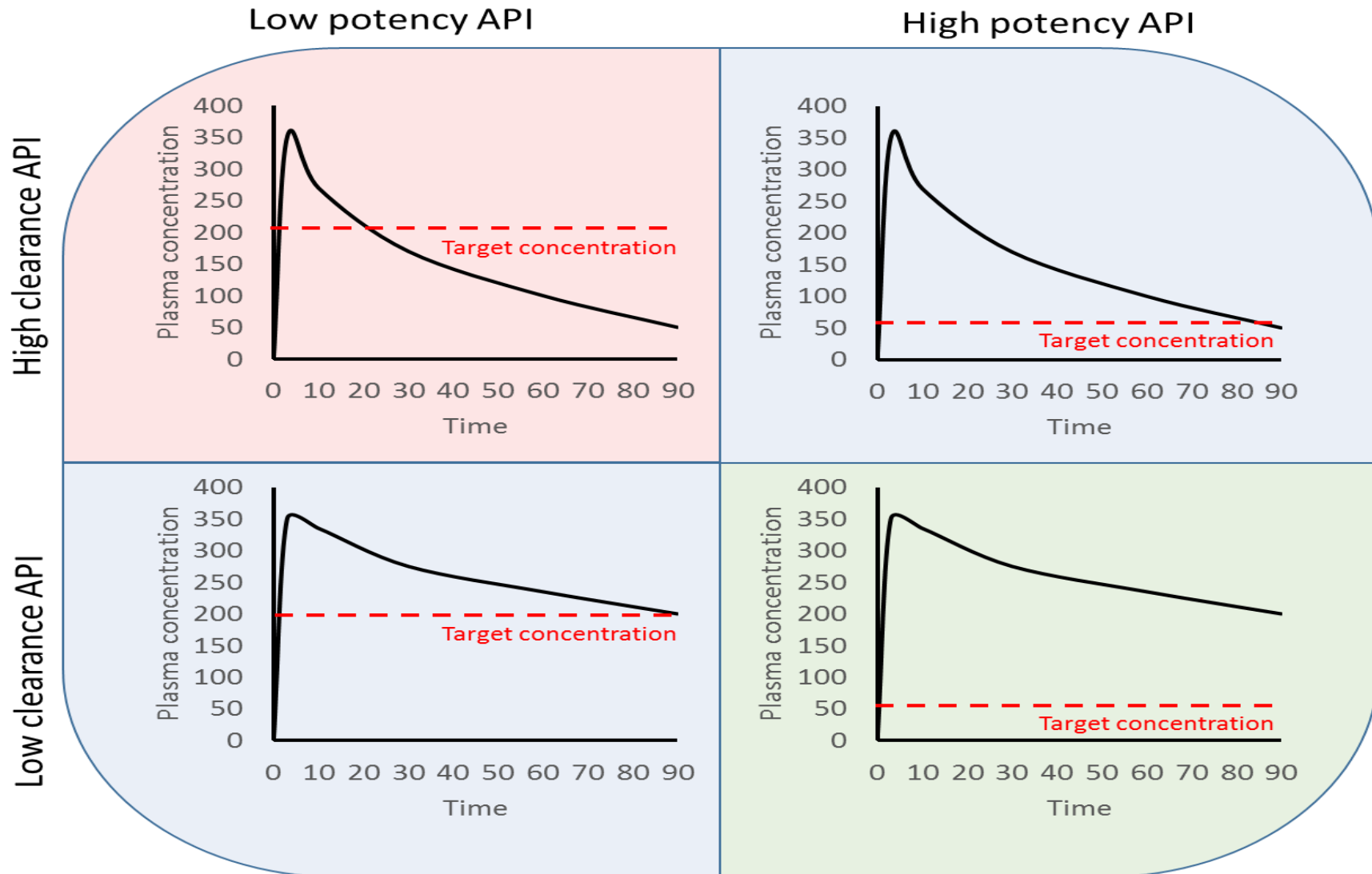
**Soluble drug
solution
(unsuitable for
current
nanomilled
formulations)**



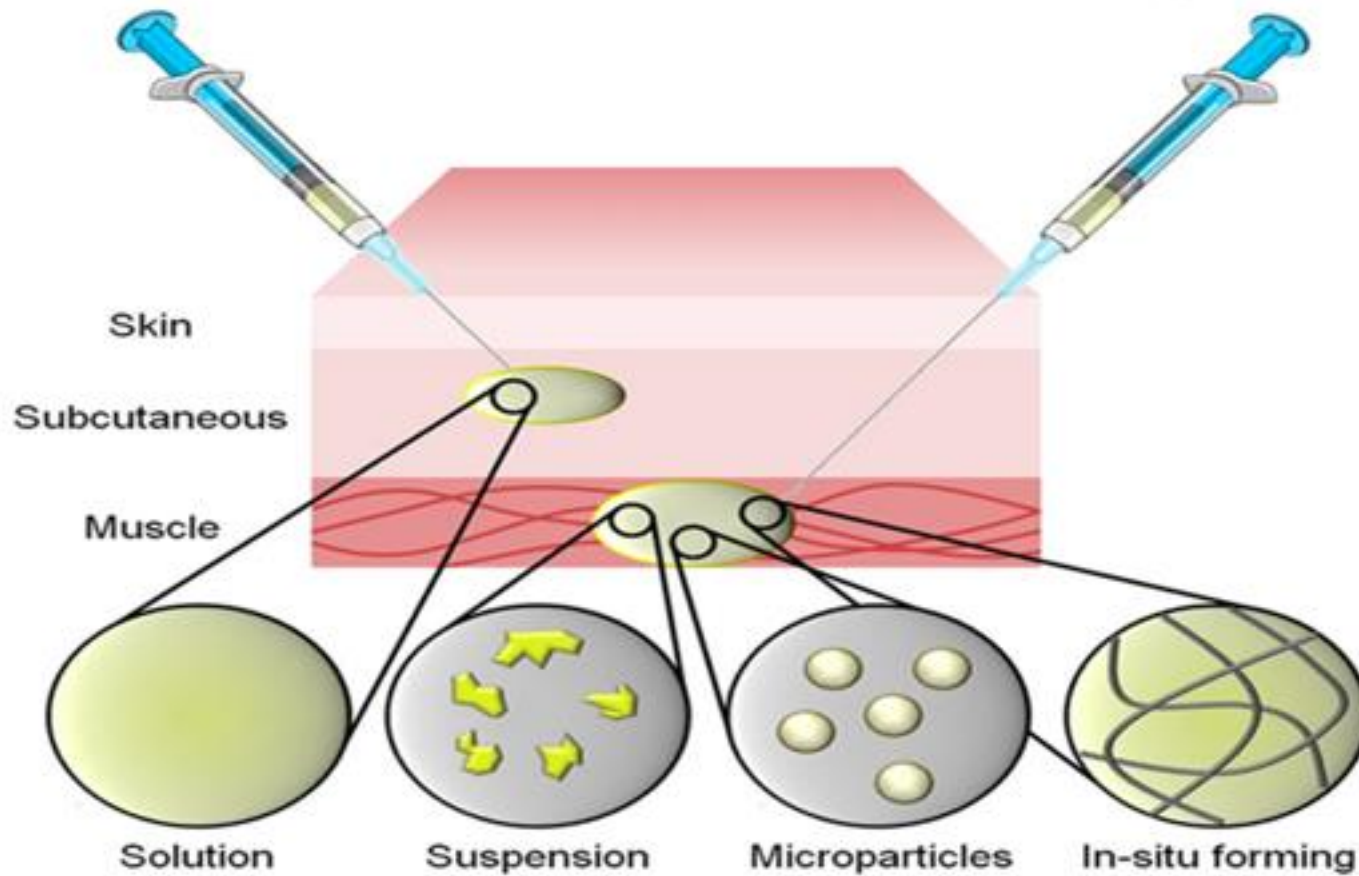
Key physiochemical and pharmacokinetic characteristics of LA injectables: Factors in choice of agent for current LA candidates (technology specific)



High drug potency underpins the LA approach



LA injectables: Potential exists across indications to achieve long-acting delivery



LA injectables: Scenarios for administration



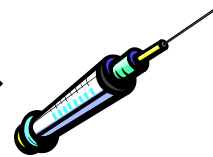
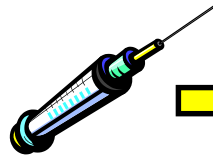
Dose oral to steady state

- Rule out safety concerns (e.g. hypersensitivity)
- Ensure “target” exposures are met

Approach used in current Ph 2b/3 trials of LA injectable ARVs



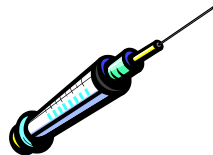
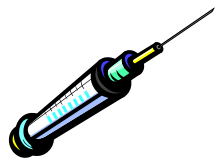
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Dose oral

Overlap oral and injection dosing

- Strategy depends on ability to achieve “target” exposures



Initial (loading) injection dose

Subsequent (maintenance) injection dose

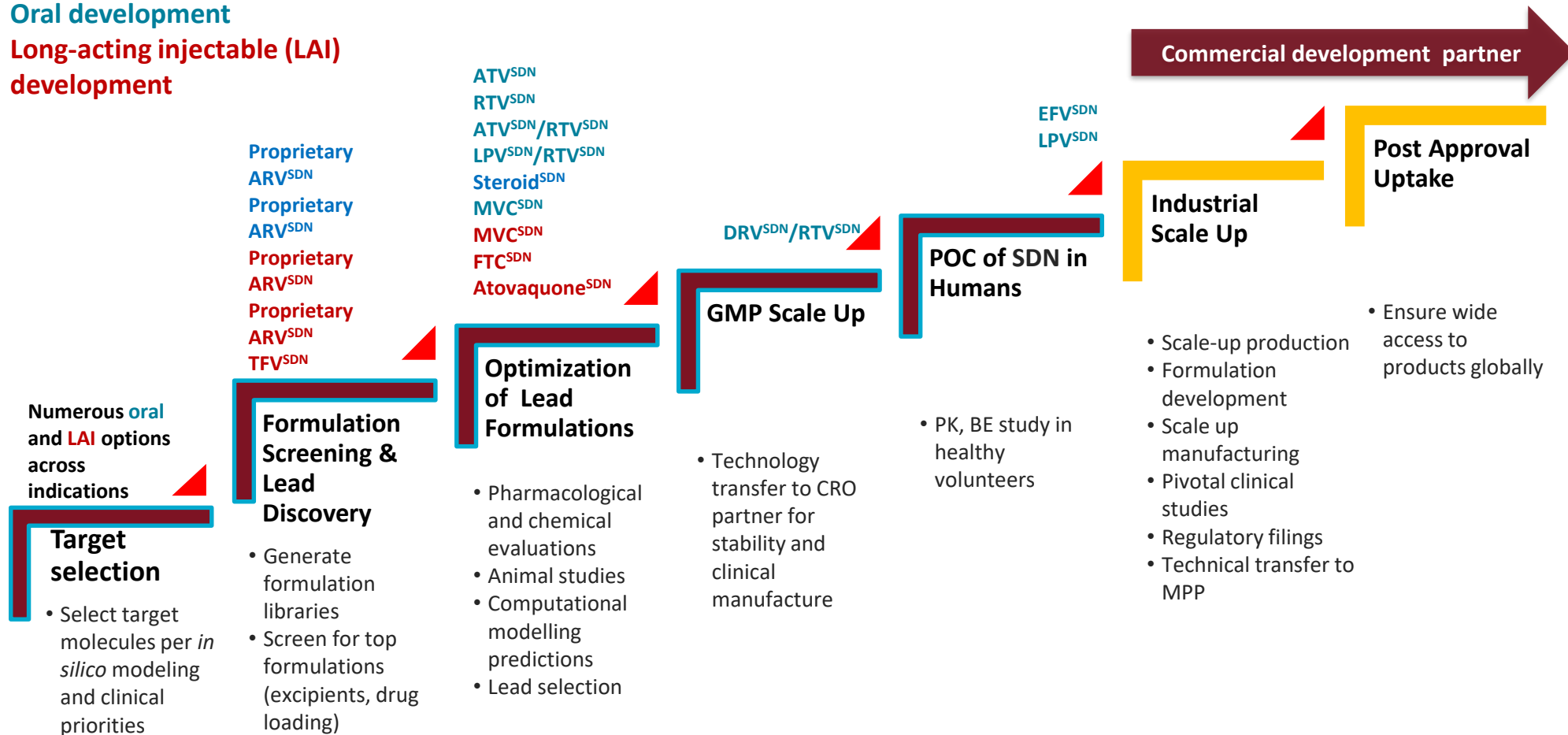
- Can be used in absence of oral lead-in and may be ideal if adequate exposures are achieved with initial (loading) dose



Current status of SDN development for oral and injectable LA drugs (University of Liverpool)

Oral development

Long-acting injectable (LAI) development



Background technical paper: Long-Acting Injectable Nano-particle Technologies

Barrett Rabinow, Ph.D.

- **Historical development**
 - Insoluble drug candidates
 - Modified pharmacokinetics
 - Technical decision criteria for selection of techniques
- **Manufacturing processes**
 - Surfactant stabilized crystalline drug core
 - Homogenization
 - Microprecipitation
 - Wet milling
 - Polymeric microspheres
 - Emulsion-templated freeze-dried solid drug nanoparticles
- **Quality by design considerations**
- **Commercialized products**
- **Risk-based decision criteria for selection of technique**

[Background paper](#)
[Long-Acting Injectable](#)
[Nano-particle Technologies](#)
[Barrett Rabinow \(2018\)](#)

[Companion slides](#)
[Long-Acting Injectable Nano-](#)
[particle Technologies](#)
[Barrett Rabinow \(2018\)](#)





Part 4b: Pipeline of innovative drug delivery devices/systems

- Overview of current pipeline
- Rings
- Long-acting oral approaches
- Implants
- Patches



Overview: Current pipeline for innovative drug delivery approaches*

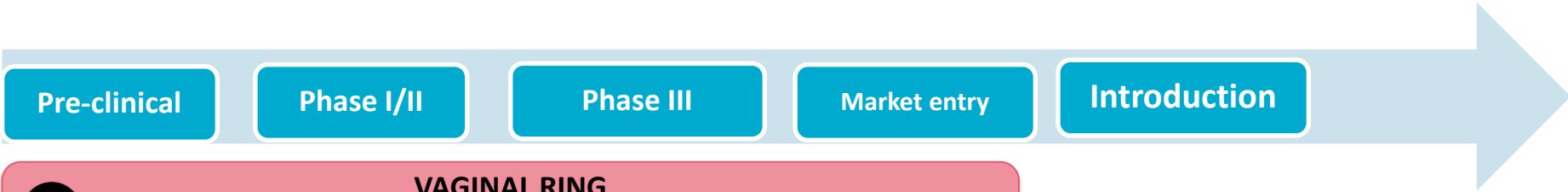
Name	Manufacturer/partners	Type/use
Vaginal ring	International Partnership for Microbicides (with DVP) Several others in development	HIV prevention and multipurpose prevention tool
Patch	PATH/Queens University for micro-array needle patch Several others in development	HIV prevention & treatment; malaria; others?
Implants	Several types in development by multiple groups Implantable pump being developed by Intarcia**	HIV treatment or prevention
LA capsule	Lyndra/BMGF, NIH Merck?	HIV treatment or prevention, malaria

*Most of these devices are in pre-clinical development, except for the DPV ring which has completed Phase 3 trials and has been submitted for EMA opinion.

**Development of the Intarcia implantable pump is more advanced for use in the treatment of Type 2 diabetes than for its use in HIV prevention



Current status of delivery systems/devices in pipeline (1): Rings



VAGINAL RING
DPV for PreP – 30 days
IPM

VAGINAL RING
TDF
PrEP - 90 days
CONRAD

VAGINAL RING
TDF + Levonorgestrel
90 days
CONRAD

VAGINAL RING
DPV + Levonorgestrel
IPM – 90 days

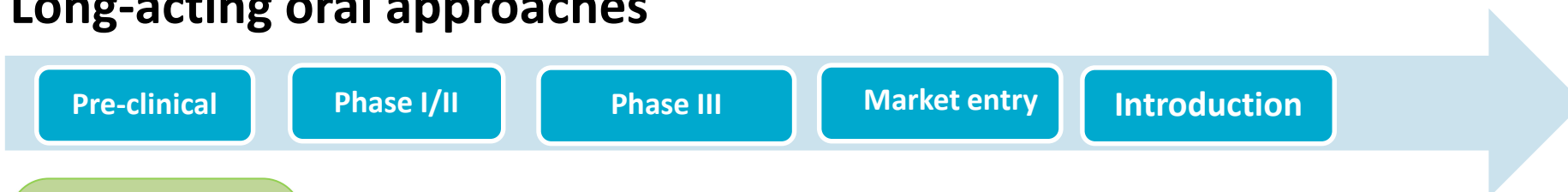


HIV

MPT



Current status of delivery systems/devices in pipeline (2): Long-acting oral approaches



Extended release gastric resident system
Malaria vector control using Ivermectin
14 days
Lyndra/BMGF

Extended release gastric resident system
HIV treatment or prevention – DTG, RPV or CAB
7+ days
Lyndra/ BMGF/ NIH

Possible LA oral
HIV treatment or prevention using MK-8591 (EFdA)
Merck

Extended release gastric residence system (“Lyndra” ingestible capsule)

- Initially developed by R. Langer’s group at MIT
- 2015: BMGF grant on malaria (Ivermectin)
- 2017: BMGF supporting initial application in HIV
- TAF excluded. Animal studies with DTG, CAB and RVP (BMGF, NIH)
- April 2018: Joint venture with Global Drug Commercialization Center (Chengdu, China) for future commercialization in the Chinese market

MAL

HIV

4
Science4b
Devices

Lyndra capsule for HIV prevention or treatment

New drug capsule may allow weekly HIV treatment

Replacing daily pills with a weekly regimen could help patients stick to their dosing schedule

Date: January 9, 2018


Source: Massachusetts Institute of Technology

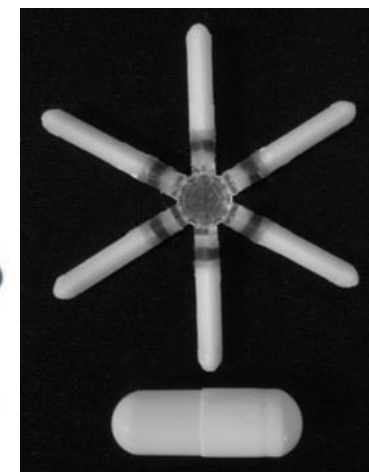
Summary: Researchers have developed a capsule that can deliver a week's worth of HIV drugs in a single dose. This advance could make it much easier for patients to adhere to the strict schedule of dosing required for the drug cocktails used to fight the virus, the researchers say.

Article | [OPEN](#) | Published: 09 January 2018

Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy

Ameya R. Kirtane, Omar Abouzid, Daniel Minahan, Taylor Bensel, Alison L. Hill, Christian Selinger, Anna Bershteyn, Morgan Craig, Shirley S. Mo, Hormoz Mazdiyasi, Cody Cleveland, Jaimie Rogner, Young-Ah Lucy Lee, Lucas Booth, Farhad Javid, Sarah J. Wu, Tyler Grant, Andrew M. Bellinger, Boris Nikolic, Alison Hayward, Lowell Wood, Philip A. Eckhoff, Martin A. Nowak, Robert Langer  & Giovanni Traverso 

Nature Communications 9, Article number: 2 (2018) | [Download Citation](#) 



[For more information on this technology, see slides shared by Lyndra \(September 2018\)](#)

- The capsule “unfolds” and releases drug(s) in the stomach. Capsule arms can be loaded with up to 6 different drug formulations.
- In a pig model, the capsule delivered therapeutic levels of DTG, CAB and RVP (tested separately) for one week. TAF was excluded due to chemical instability/unsuitability with this approach
- Modelling of use of the approach for HIV PrEP estimated 20% increase in efficacy compared to daily PrEP and 200,000 HIV infections averted (3.4% cumulative reduction) over 20 years
- Increased coverage of PrEP from 30% to 60% as a result of the weekly regimen would increase the estimated number of new infections averted to between 700,000 and 900,000.



Lyndra capsule for oral malaria vector control

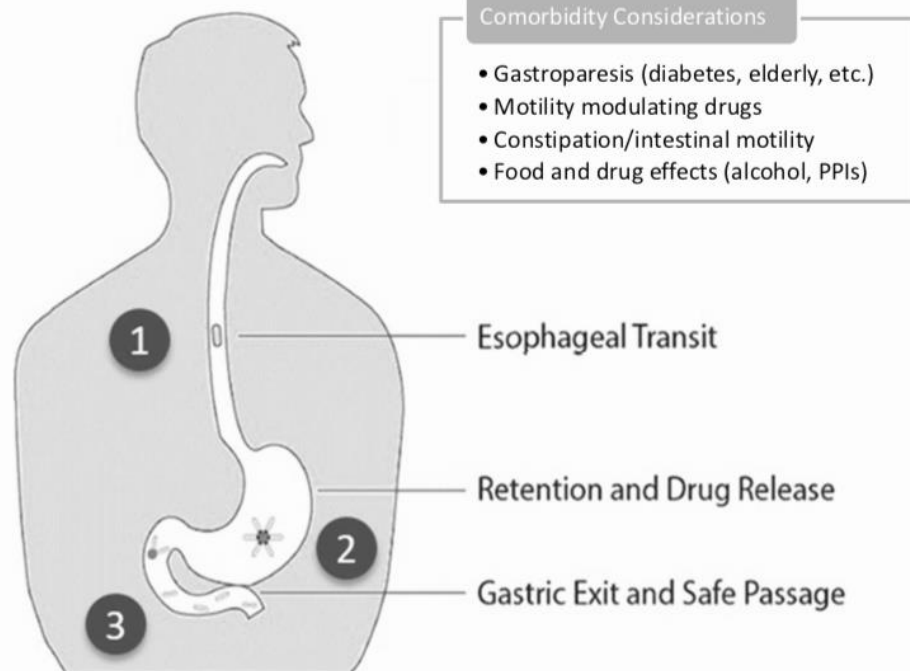
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

DRUG DELIVERY

Oral, ultra-long-lasting drug delivery: Application toward malaria elimination goals

Andrew M. Bellinger,^{1,2,3*} Mousa Jafari,^{1*} Tyler M. Grant,^{1,3*} Shiyi Zhang,^{1,*†} Hannah C. Slater,⁴ Edward A. Wenger,⁵ Stacy Mo,¹ Young-Ah Lucy Lee,¹ Hormoz Mazdiyasi,¹ Lawrence Kogan,¹ Ross Barman,¹ Cody Cleveland,^{1,6} Lucas Booth,¹ Taylor Bensel,¹ Daniel Minahan,¹ Haley M. Hurowitz,¹ Tammy Tai,¹ Johanna Daily,⁷ Boris Nikolic,⁸ Lowell Wood,⁵ Philip A. Eckhoff,⁵ Robert Langer,^{1,9,10‡} Giovanni Traverso^{1,6,11‡}

Efforts at elimination of scourges, such as malaria, are limited by the logistic challenges of reaching large rural populations and ensuring patient adherence to adequate pharmacologic treatment. We have developed an oral, ultra-long-acting capsule that dissolves in the stomach and deploys a star-shaped dosage form that releases drug while assuming a geometry that prevents passage through the pylorus yet allows passage of food, enabling prolonged gastric residence. This gastric-resident, drug delivery dosage form releases small-molecule drugs for days to weeks and potentially longer. Upon dissolution of the macrostructure, the components can safely pass through the gastrointestinal tract. Clinical, radiographic, and endoscopic evaluation of a swine large-animal model that received these dosage forms showed no evidence of gastrointestinal obstruction or mucosal injury. We generated long-acting formulations for controlled release of ivermectin, a drug that targets malaria-transmitting mosquitoes, in the gastric environment and incorporated these into our dosage form, which then delivered a sustained therapeutic dose of ivermectin for up to 14 days in our swine model. Further, by using mathematical models of malaria transmission that incorporate the lethal effect of ivermectin against malaria-transmitting mosquitoes, we demonstrated that this system will boost the efficacy of mass drug administration toward malaria elimination goals. Encapsulated, gastric-resident dosage forms for ultra-long-acting drug delivery have the potential to revolutionize treatment options for malaria and other diseases that affect large populations around the globe for which treatment adherence is essential for efficacy.



Oral, Slow-Release Ivermectin: Biting Back at Malaria Vectors

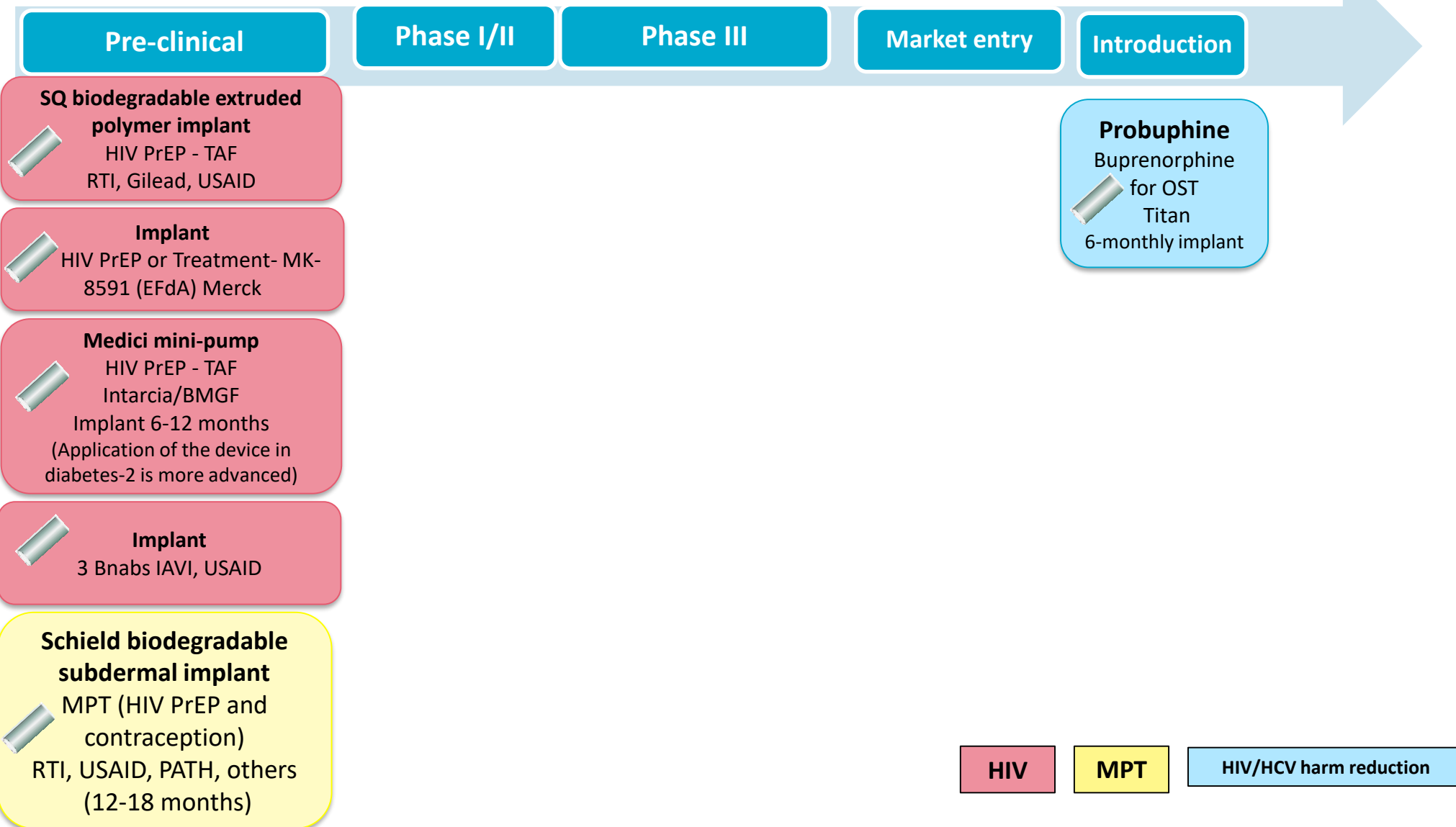
Carlos J. Chaccour and N. Regina Rabinovich

Bellinger and colleagues offer an elegant twist for a promising new tool against malaria. This formulation is designed to release ivermectin, a mosquito-killing drug for 10 days after a single oral dose. This could reduce the vector population and serve as a complementary tool for malaria elimination.

[Trends in Parasitology, March 2017, Vol. 33, No. 3](#)



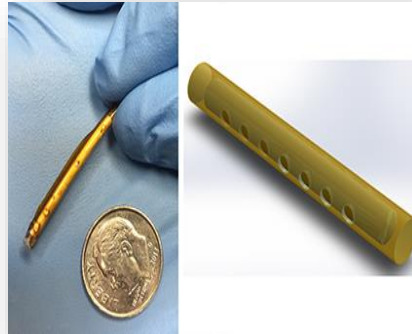
Current status of delivery systems/devices in pipeline (3): Implants



Several groups are exploring implant technology for LMICs



IRTI
INTERNATIONAL



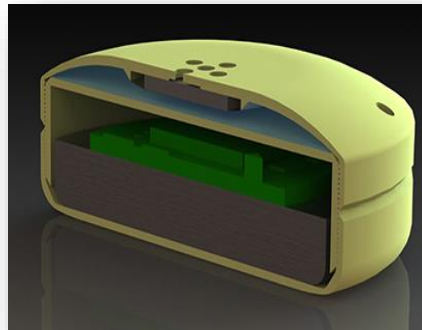
OAK CREST
INSTITUTE
OF
SCIENCE
CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



Intarcia
Therapeutics, Inc.



Northwestern
University



HOUSTON
Methodist
LEADING MEDICINE



Courtesy of AVAC

4
Science

4b
Devices

Unitaid

Examples of implantable devices for LA HIV PrEP

Pharm Res. 2016 Jul;33(7):1649-56. doi: 10.1007/s11095-016-1904-6. Epub 2016 Mar 14.

A Tunable, Biodegradable, Thin-Film Polymer Device as a Long-Acting Implant Delivering Tenofovir Alafenamide Fumarate for HIV Pre-exposure Prophylaxis.

Schlesinger E¹, Johengen D², Luecke E³, Rothrock G⁴, McGowan J⁵, van der Straten A^{3,6}, Desai T^{7,8}.

Conference Dates and Location:
March 4–7, 2018 | Boston, Massachusetts

Abstract Number:
486

PHARMACOKINETICS OF TENOFOVIR ALAFENAMIDE BY SUBCUTANEOUS IMPLANT FOR HIV PrEP

Author(s):

Greg Gatto¹, Natalie Girouard¹, Rhonda M. Brand², Leah Johnson¹, Mark A. Marzinke³, Sudie Rowshan¹, Jarret C. Engstrom², Ian McGowan², Zach Demkovich⁴, Ellen Luecke⁴, Ariane van der Straten⁴

¹RTI International, Research Triangle Park, NC, USA; ²University of Pittsburgh, Pittsburgh, PA, USA; ³Johns Hopkins Hospital, Baltimore, MD, USA; ⁴RTI International, San Francisco, CA, USA

Abstract Body:

We evaluated the pharmacokinetics of tenofovir alafenamide (TAF), an antiretroviral prodrug with high potency and potential for HIV Pre-exposure prophylaxis (PrEP), released from polycaprolactone (PCL) implants at the midway point of a 3-month study in rabbits.

1

The Thin Film Polymer Device (TFPD)

- User-independent, biodegradable, subcutaneous implant capable of achieving sustained release of PrEP drugs with zero-order release kinetics
- Compatible with existing trocar applicators.
- Target TFPD geometries range from 2-2.5mm diameter x 40mm length.

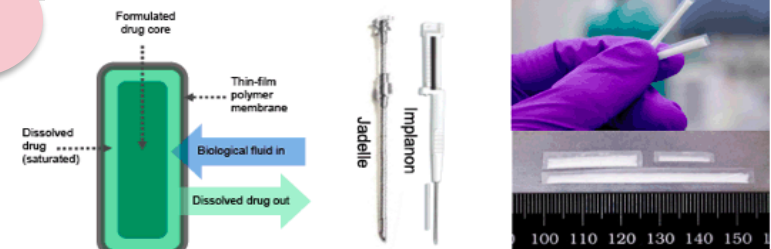


Figure 1. Schematic of release mechanism (left), examples of existing trocar products for subcutaneous implantation (middle), actual prototype TFPD implants with millimeter scale for reference (right).

Bill and Melinda Gates back an implant that could prevent HIV

The mini pump could be key to eradicating a scourge in Africa.

2

THE MEDICI DRUG DELIVERY SYSTEM™

medici
drug delivery system™

Intarcia's investigational technology platform, the Medici Drug Delivery System™, is a proprietary subcutaneous delivery system comprised of three unique technologies:

- A stabilization technology that allows for proteins, peptides, antibody fragments, and other highly potent small molecules to be stabilized at or above human body temperatures for up to three years or more
- A matchstick-sized osmotic mini-pump that is placed just under the dermal layer of skin to deliver a continuous and consistent flow of medication
- A placement technology including proprietary tools designed to provide an optimal user experience

How it Works

The Medici Drug Delivery System is designed to enable placement by a trained healthcare professional in an in-office procedure. Once in place under the skin, water from the extracellular fluid enters the pump device at one end – by diffusing through a semi-permeable membrane directly into an osmotic engine – that expands to drive a piston at a controlled rate. This allows the drug within the pump to be released in a continuous fashion at the other end of the device. Each osmotic mini-pump is designed to deliver an appropriate volume of drug over different dosing intervals.

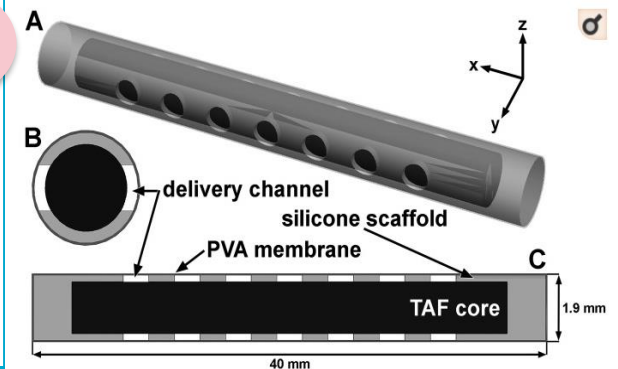
Antimicrob Agents Chemother. 2015 Jul;59(7):3913-9. doi: 10.1128/AAC.00656-15. Epub 2015 Apr 20.

Pharmacokinetics of long-acting tenofovir alafenamide (GS-7340) subdermal implant for HIV prophylaxis.

Gunawardana M¹, Remedios-Chan M², Miller CS¹, Fanter R¹, Yang F¹, Marzinke MA³, Hendrix CW⁴, Beliveau M⁵, Moss JA¹, Smith TJ⁶, Baum MM⁷.

Author information

3



4
Science

4b
Devices

Unitaid



Potential use of MK-8591 in implantable device for LA HIV treatment and/or prevention

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

Stephanie E. Barrett, Ryan S. Teller, Seth P. Forster, Li Li, Megan A. Mackey, Daniel Skomski, Zhen Yang, Kerry L. Fillgrove, Gregory J. Doto, Sandra L. Wood, Jose Lebron, Jay A. Grobler, Rosa I. Sanchez, Zhen Liu, Bing Lu, Tao Niu, Li Sun, Marian E. Gindy

DOI: 10.1128/AAC.01058-18

- MK-8591 is a highly potent nucleoside reverse transcriptase translocation inhibitor (NRTTI) drug candidate in clinical development as part of a regimen for HIV treatment, with potential utility as a single agent for PrEP.
- A current Phase 2b trial, **DRIVE2SIMPLIFY**, is evaluating the safety, tolerability, PK and efficacy of once-daily oral MK-8591 administered with doravirine and lamivudine, ending by 2020.
- A single administration of the subcutaneous implant in rodents and non-human primates achieved clinically relevant drug exposure for greater than 6 months.
- The high potency of the compound may lend itself to a range of long-acting approaches, including implants and an LA oral formulation.



TREATMENT ▶

Could this Long-Lasting PrEP Pill Change Everything?



Researchers from New York's Aaron Diamond AIDS Research Center presented a new long-lasting PrEP pill at the 25th Conference on Retroviruses and Opportunistic Infections (CROI).

By Benjamin M. Adams
MARCH 14 2018 7:47 AM EDT

BIO SHARES  

The drug being called MK-8591 or EFdA is an exceptionally long-lasting and potent HIV drug being developed by researchers for Merck & Co. Inc. — And it just might become the weekly pre-exposure prophylaxis (PrEP) pill you've been waiting for.



Example of implantable 6-month LA buprenorphine for opioid substitution therapy (OST)



US FDA-approved, 2016



See <https://probuphine.com/about-probuphine/>



Current status of delivery systems/devices (4): Patches

Pre-clinical

Phase I/II

Phase III

Market entry

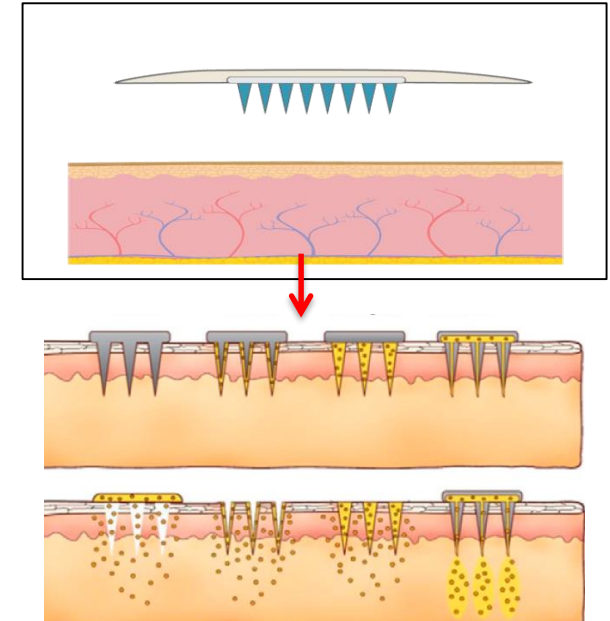
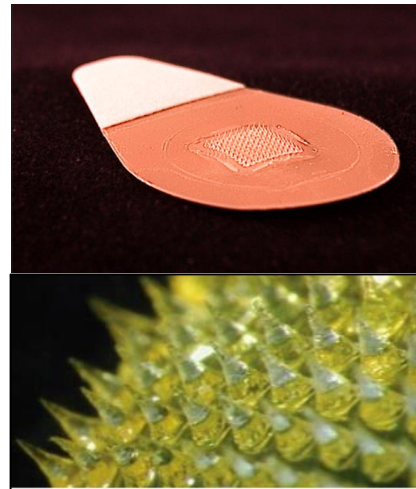
Introduction

Microarray patches with multiple potential drugs

e.g.

Cabotegravir (USAID, PATH)

Primaquine (PATH, BMGF)



Drug Discov Today, 2018 May;23(5):1026-1033. doi: 10.1016/j.drudis.2017.10.013. Epub 2017 Oct 23.

Microarray patches: potentially useful delivery systems for long-acting nanosuspensions.

Donnelly RF¹, Larrañeta E².

⊕ Author information

Abstract

Long-acting drug nanosuspension formulations are coming to the fore as controlled release strategies for several medical conditions and as a preventative measure against HIV infection. However, such delivery systems must, by necessity, be given by hypodermic injection, typically into muscle. This poses problems for patients who are needle-phobic, given that injections have to be administered on a weekly or monthly basis. Needle-stick injuries, inappropriate reuse of needles, and poor disposal practices are major challenges in developing countries. Dissolving microneedles (MNs) are capable of delivering high drug doses, if suitably designed and formulated, and are also capable of delivering nanoparticles (NPs) into viable skin. Given that such microneedles are minimally invasive and self-disabling, the potential for major enhancement in patient care and compliance exists. In this review, we explore the key considerations in the development of these combination drug delivery systems.

PMID: 29074440 DOI: [10.1016/j.drudis.2017.10.013](https://doi.org/10.1016/j.drudis.2017.10.013)



Examples of micro-array needle patches (2)

Novel drug delivery system has game-changing potential to reduce rates of HIV infection

December 1, 2017 by PATH

PATH
10::▲0+//2□0

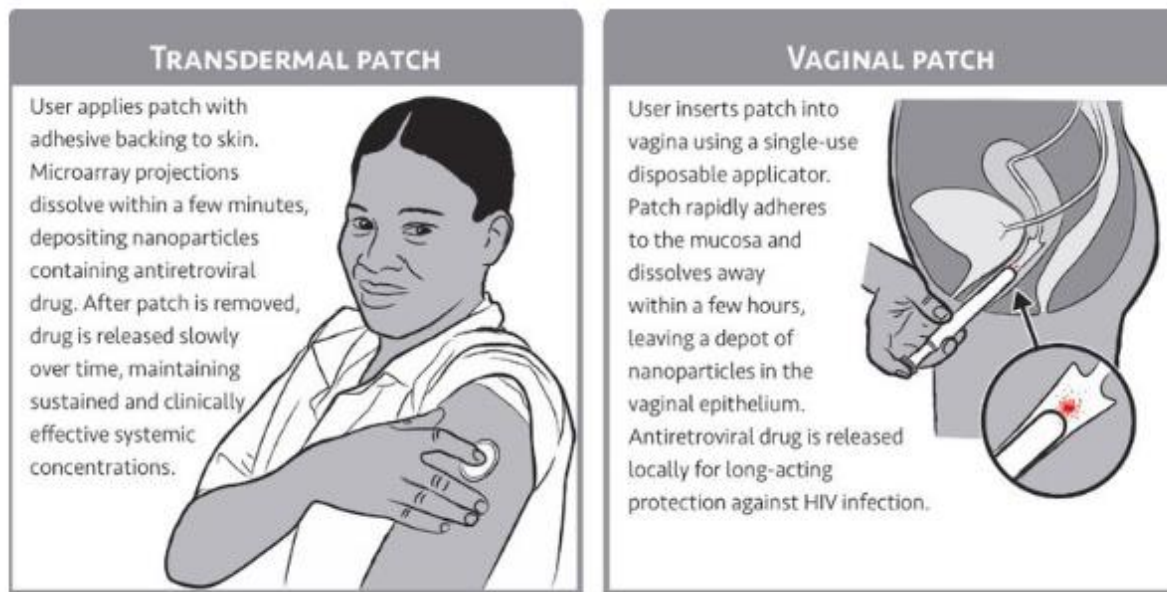
HIV/AIDS

Devices

An international collaboration announces preclinical development of a microarray patch delivery system for HIV pre-exposure prophylaxis

Media contact: Kate Davidson | media@path.org

Seattle, WA, December 1, 2017—The United States Agency for International Development (USAID), through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), awarded PATH a three-year, \$9.4 million grant to advance a needle-free microarray patch for delivery of HIV pre-exposure prophylaxis (PrEP). Microarray patches are a discreet, easy-to-use technology that contains an array of tiny projections that painlessly penetrate the top layer of skin to deliver a drug.



VACCINE AND PHARMACEUTICAL TECHNOLOGIES

PATH

VAGINAL APPLICATOR DEVELOPMENT FOR DELIVERY OF MICROARRAY PATCHES CONTAINING RILPIVIRINE FOR HIV PRE-EXPOSURE PROPHYLAXIS

B. Creelman¹, B. Blair¹, C. Jarrahian¹, R. Donnelly², G. Austin¹, Y. Moyo¹, A. Rein-Weston¹, E. Saxon¹, D. Zehrung¹

¹PATH (www.path.org), ²Queen's University (www.qub.ac.uk)



4
Science

4b
Devices

Unitaid













Part 4c: Disease-specific LA drug pipeline

- Overview across diseases
- HIV
- Malaria
- TB
- HCV
- Multi-purpose prevention technology
- HIV/HCV harm reduction




Disease-specific LA pipeline: overview for HIV




-  **ELSULFAVIRINE**
PrEP and Tx, Viriom
-  **TDF/3TC/LPV/RTV**
*Tx, Univ WA,NIH
-  **GS-9131**
Tx, Gilead
-  **GS 6207 (GS-CA1)**
PrEP and Tx, Gilead
-  **DTG removable SC**
PreP and Tx
U North Carolina
-  **TAF - PrEP**
Gilead, RTI, USAID
Intarcia, BMGF
-  **3 Bnabs**
IAVI, USAID
-  **PrEP and Tx**
Lyndra, BMGF/NIH
-  **MK-8591 (EFdA)**
PrEP and Tx, Merck
-  **RILPIVIRINE PrEP**
Path/USAID
(possible vaginal)

 **TDF**
PrEP, CONRAD




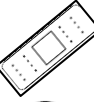


 **CABOTEGRAVIR**
PrEP, ViiV

 **RILPIVIRINE & CABOTEGRAVIR**
Tx, Janssen & ViiV

 **VRC01 (McAb)**
PrEP and Tx, NIAID

 **DAPIVIRINE**
PrEP, IPM

Technology

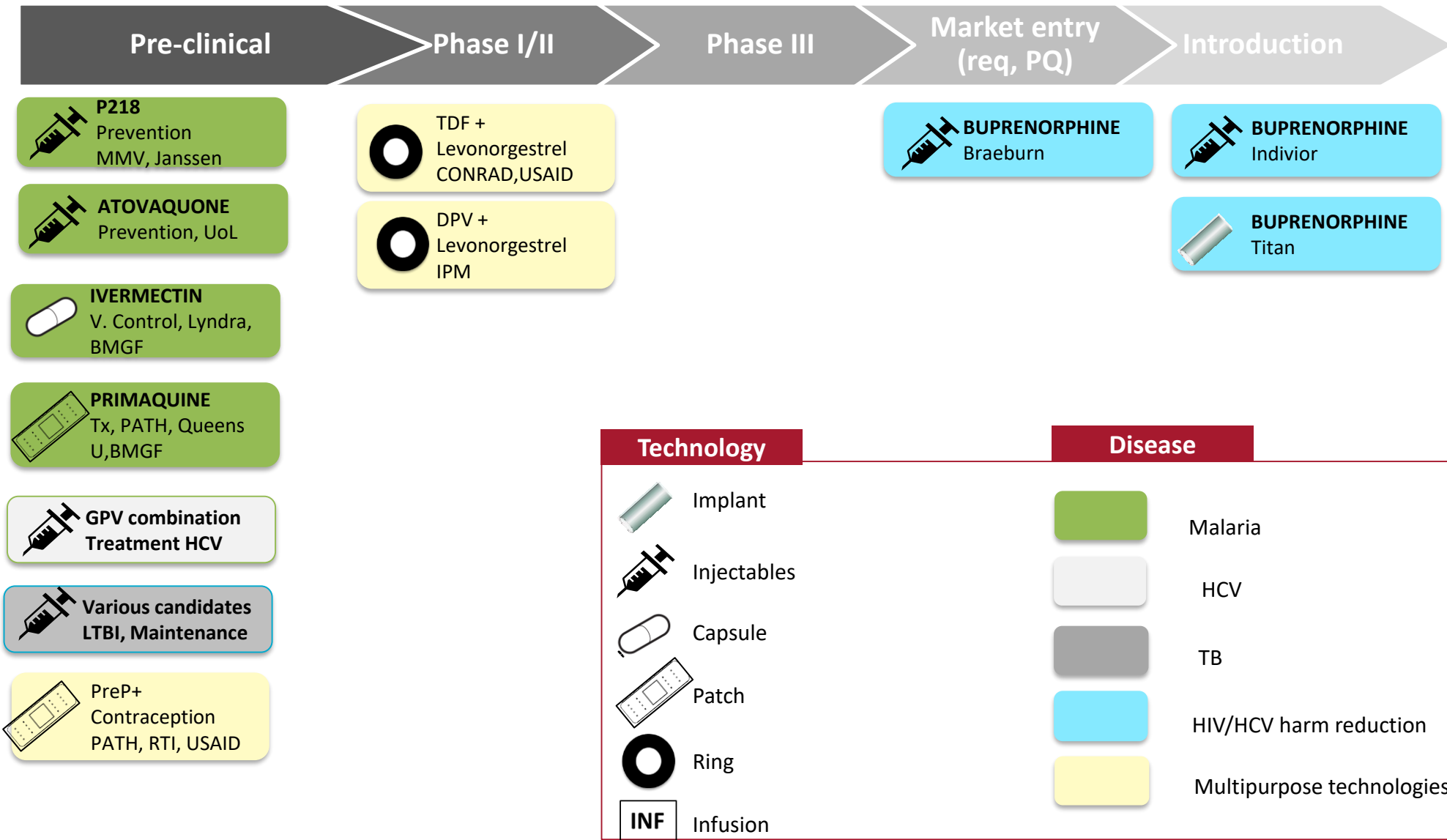
-  Implant
-  Injectables
-  Capsule
-  Patch
-  Ring
-  Infusion

Disease

HIV



Disease-specific LA pipeline: overview for other indications



Presentation of LA pipeline in the following slides



New chemical entities (NCEs)



Repurposing existing oral drugs for use as LA

(Potential access to expedited regulatory approval e.g. FDA 501(2)(b))



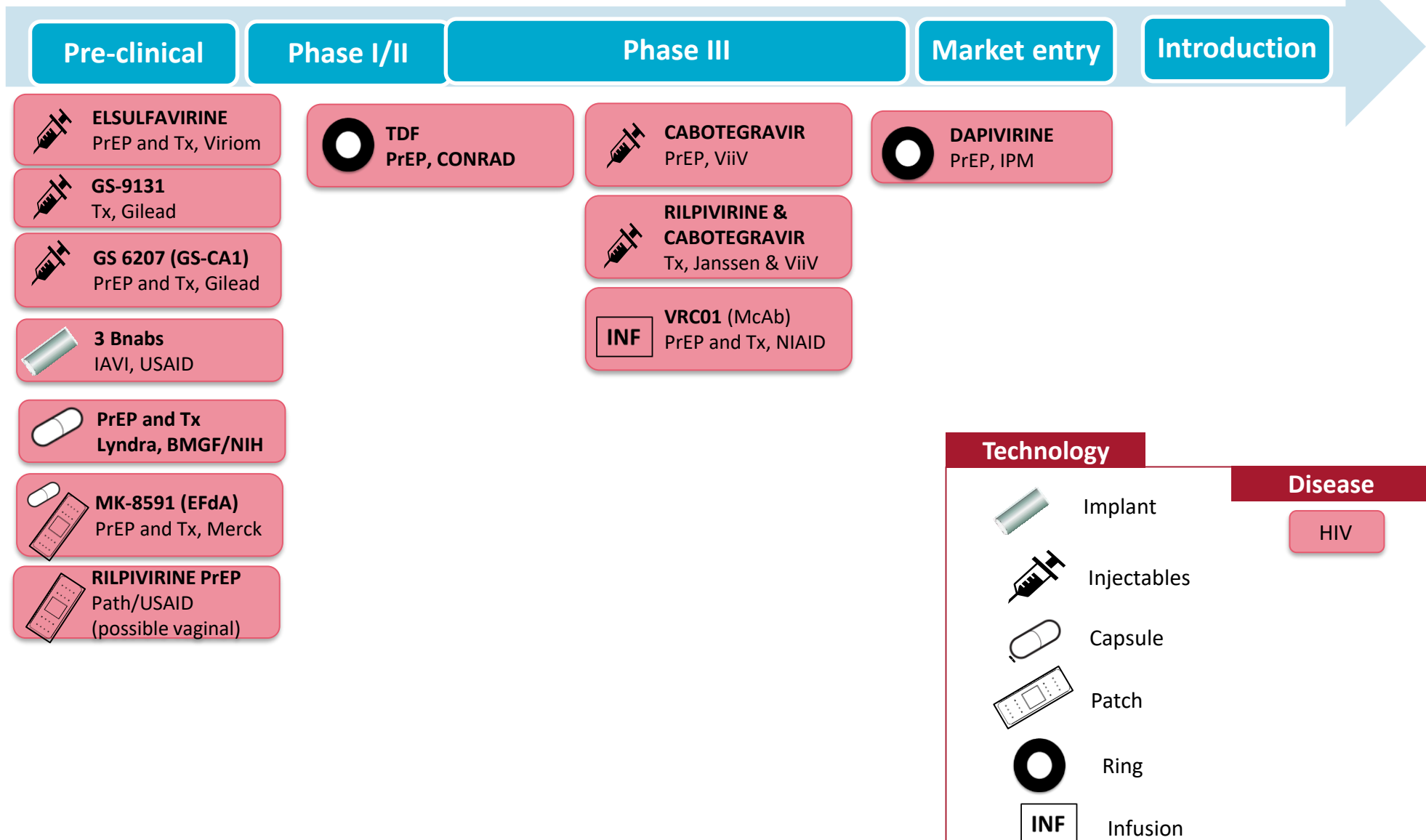
Long-acting medicinal products by disease area.

Overview of pipeline for HIV treatment and prevention

Product	Manufacturer	Type
New chemical entities		
Cabotegravir	ViiV	Integrase inhibitor
MK-8591 (EFdA)	Merck	Nucleoside reverse transcriptase translocation inhibitor
GS-9131	Gilead	Nucleoside reverse transcriptase inhibitor
GS 6207 (GS-CA1)	Gilead	Capsid protein inhibitor
VRC01	NIAID	Monoclonal antibody
Repurposed oral drugs		
Rilpivirine	Janssen	Non-nucleoside reverse transcriptase inhibitor
Tenofovir alafenamide	Gilead/RTI	Nucleoside reverse transcriptase inhibitor – subdermal implant
Tenofovir disoproxil fumarate	Gilead	Nucleoside reverse transcriptase inhibitor – vaginal ring
Elsulfavirine	Viriom	Non-nucleoside reverse transcriptase inhibitor
Dapivirine	IPM	Non-nucleoside reverse transcriptase inhibitor – vaginal ring



HIV LA pipeline (1): New chemical entities



HIV treatment: Injectable ARVs (Phase 2b results)

Novel 2-drug combination CAB/RVP in separate IM injections

LATTE-2, Margolis et al, 2017

Articles



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

Dawid A Margolis, Juan González-García, Hans-Jürgen Stellbrink, Joseph J Eron, Yazdan Yazdgerani, Daniel Podzamczak, Thomas Lutz, Jonathan B Angel, Gary J Richmond, Benaventura Clotet, Felix Gutierrez, Louis Sloan*, Marty Se Clair, Miranda Murray, Susan L Ford, Joseph Mus, Pascal Patel, Herta Crausek, Sandy K Griffith, Kenneth C Sutton, David Davey, Kimberly Y Smith, Peter F Williams, William R Spence

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-naïve 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. Randomisation was computer-generated with stratification by HIV-1 RNA (<50 copies per mL, yes or no) during the first 12 weeks of the induction period. The primary endpoints were the proportion of patients with viral suppression at week 96 (as defined by the US Food and Drug Administration snapshot algorithm), protocol-defined virological failures, and safety events through 96 weeks. All randomly assigned patients who received at least one dose of study drug during the maintenance period were included in the primary efficacy and safety analyses. The primary analysis used a Bayesian approach to evaluate the hypothesis that the proportion with viral suppression for each long-acting regimen is not worse than the oral regimen proportion by more than 10% (denoted comparable) according to a prespecified decision rule (ie, posterior probability for comparability >90%). Difference in proportions and associated 95% CIs were supportive to the primary analysis. The trial is registered at ClinicalTrials.gov, number NCT02120352.

Findings Among 309 enrolled patients, 286 were randomly assigned to the maintenance period (115 to each of the 4-week and 8-week groups and 56 to the oral treatment group). This study is currently ongoing. At 32 weeks following randomisation, both long-acting regimens met primary criteria for comparability in viral suppression relative to the oral comparator group. Viral suppression was maintained at 32 weeks in 51 (91%) of 56 patients in the oral treatment group, 108 (94%) of 115 patients in the 4-week group (difference 2–8% [95% CI –5–8 to 11–5] as oral treatment), and 109 (95%) of 115 patients in the 8-week group (difference 3–7% [–4–8 to 12–2] as oral treatment). At week 96, viral suppression was maintained in 47 (84%) of 56 patients receiving oral treatment, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of 115 patients in the 8-week group. Three patients (1%) experienced protocol-defined virological failure (two in the 8-week group; one in the oral treatment group). Injection-site reactions were mild (3648 [84%] of 4360 injections) or moderate (673 [15%] of 4360 injections) in intensity and rarely resulted in discontinuation (two [<1%] of 230 patients); injection-site pain was reported most frequently. Serious adverse events during maintenance were reported in 22 (10%) of 230 patients in the intramuscular groups (4-week and 8-week groups) and seven (13%) of 56 patients in the oral treatment group; none were drug related.

Interpretation The two-drug combination of all-injectable, long-acting cabotegravir plus rilpivirine every 4 weeks or every 8 weeks was as effective as daily three-drug oral therapy at maintaining HIV-1 viral suppression through 96 weeks and was well accepted and tolerated.

Funding ViiV Healthcare and Janssen R&D.

Introduction

An estimated 36.7 million individuals were living with HIV worldwide at the end of 2015.¹ Advances in highly active antiretroviral therapies (ARTs) have improved

treatment efficacy for patients with HIV, enhancing patient survival and quality of life.^{2,3} However, adherence to medication remains an important challenge; poor compliance can result in treatment failure and the

Published Online: July 24, 2017
[http://dx.doi.org/10.1016/S0140-6736\(17\)31917-7](http://dx.doi.org/10.1016/S0140-6736(17)31917-7)
 See Online/Commentary
[http://dx.doi.org/10.1016/S0140-6736\(17\)31917-7](http://dx.doi.org/10.1016/S0140-6736(17)31917-7)
 ViiV Healthcare, Research Triangle Park, NC, USA
 (D A Margolis MD, M Se Clair BS, J Mus MD, Pascal Patel PharmD, S K Griffith PharmD, K C Sutton MD, K Y Smith MD, W R Spence PharmD) Hospital Universitario La Paz/IBIMA, Madrid, Spain
 (J González-García MD); ICH, Hertenberg, Hertenberg, Germany
 (Prof J J Stellbrink MD); University of North Carolina, Chapel Hill, NC, USA
 (Prof J Eron MD); Hôpital Bichat-Claude Bernard, Paris, France
 (Prof Y Yazdgerani MD); Hospital Universitario de Bellvitge, Hospitalet, Barcelona, Spain
 (D Podzamczak PhD); Infektiologikum, Frankfurt, Germany (T Lutz MD); The Ottawa Hospital, Ottawa, ON, Canada (J B Angel MD); Brown General Medical Center, Fort Lauderdale, FL, USA (G J Richmond MD); Hospital Germans Trias i Pujol, UAB, SPW, UCC, Badalona, Catalonia, Spain (H Clotet MD); Hospital General de Elche & Universidad Miguel Hernández, Alicante, Spain
 (Prof F Gutierrez MD); North Texas Infectious Disease Consultants, Dallas, TX, USA
 (Prof L Sloan MD); ViiV Healthcare, London, UK
 (Murray MD); Janssen Global R&D, Research Triangle Park, NC, USA
 (S L Ford PharmD); Janssen Research and Development, Beerse, Belgium
 (H Crausek PhD), P Williams PhD and Janssen R&D, Mississauga, ON, Canada (D Spence PharmD)

- Cabotegravir is a novel commercial entity (NCE – new ARV drug); rilpivirine is FDA-approved as a daily oral pill
- Results reported from Phase 2b open-label trial (LATTE-2)
- All patients initially received QD oral CAB/abacavir/3TC for 20 weeks; a sub-set was retained as comparator arm
- Two regimens in other two arms: 1) IM CAB 400mg + RVP 600mg in two 2ml injections at 4-weekly intervals 2) IM CAB 600mg + RVP 900mg in two 3 ml injections at 8-weekly intervals
- At week 96, viral suppression was maintained in 47 (84%) of 56 patients on daily oral treatment, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of patients in the 8-week group
- Mild-moderate injection site reactions and pain reported, with few discontinuations due to adverse events
- The two-drug combination of injectable LA CAB and RVP every 4 or 8 weeks was as effective as daily oral 3-drug therapy at 96 weeks
- CAB/RVP LA is now in Phase 3 trials (ATLAS, FLAIR, ATLAS-2M, results are expected 2019)
- CAB LA alone for PrEP now in Phase 3 trials (results are expected 2021-22)
- Note: No data on CAB for pediatrics, adolescents, pregnancy or breast-feeding



HIV treatment : 48-week Phase 3 results of monthly CAB/RVP injectables in ART-experienced patients (ATLAS), August 2018

ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen

ATLAS study meets primary endpoint, showing similar efficacy of a once-a-month, investigational, injectable two-drug regimen of cabotegravir and rilpivirine compared to a standard of care, daily, oral three-drug regimen

Full results from the study will be presented at an upcoming scientific meeting

London, 15 August 2018 - ViiV Healthcare today announced positive headline results from its global, phase III ATLAS study of a long-acting, injectable two-drug regimen (2DR) for the treatment of HIV. ATLAS (Antiretroviral Therapy as Long-Acting Suppression) was designed to establish if HIV-1-infected adult participants who had maintained viral suppression for at least six months, on a daily oral regimen comprised of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent, maintained similar rates of viral suppression upon switching to the investigational, two-drug, long-acting, injectable regimen of cabotegravir and rilpivirine, compared with continuing the three-drug oral regimen.

The study showed long-acting cabotegravir and rilpivirine, injected once a month, had similar efficacy to a standard of care, daily, oral three-drug regimen at Week 48. The injectable treatment regimen met the primary endpoint for non-inferiority (the proportion of participants with plasma HIV-1 RNA ≥ 50 copies per milliliter [c/mL] using the FDA Snapshot algorithm at Week 48). Overall safety, virologic response and drug resistance results for the injectable regimen were consistent with results from the phase II LATTE and LATTE-2 studies.^{[1][2]}



HIV prevention: Injectable LA CAB (Phase 2a results)

ECLAIR study, Markowitz et al, 2017

- ECLAIR compared 800mg LA CAB for HIV PrEP given 3-monthly v placebo; 4-week oral lead-in. Participants mainly MSM
- CAB safe and well-tolerated; frequency of Grade 2+ adverse events higher in CAB group (80%) compared to placebo group (48%); most common AE was injection site pain with a mean duration of 5.4 days
- Most (75%) were more satisfied with injection-based treatment than with oral regimen one week after the third injection
- Absorption rate of CAB faster than expected, indicating potential need to dose 2-monthly rather than 3-monthly

Ongoing Phase 3 studies

- HPTN 083 among cisgender men and transgender women in 43 sites (Argentina, Brazil, South Africa, Peru, Thailand, USA, Vietnam);
- HPTN 084 among women in 20 sites in Sub-Saharan Africa; results for both studies expected in 2022 or earlier

[Lancet HIV](#). 2017 Aug;4(8):e331-e340. doi: 10.1016/S2352-3018(17)30068-1. Epub 2017 May 22.

Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial.

Markowitz M¹, Frank I², Grant RM³, Mayer KH⁴, Elion R⁵, Goldstein D⁵, Fisher C⁶, Sobieszczyk ME⁷, Gallant JE⁸, Van Tieu H⁹, Weinberg W¹⁰, Margolis DA¹¹, Hudson KJ¹¹, Stancil BS¹², Ford SL¹², Patel P¹¹, Gould E¹³, Rinehart AR¹¹, Smith KY¹¹, Spreen WR¹¹.



“Ultra-long-acting” injectable, removable system using dolutegravir for HIV prevention (Kovarova et al, University of North Carolina)

Article | [OPEN](#) | Published: 08 October 2018

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

Martina Kovarova , S. Rahima Benhabbour, Ivana Massud, Rae Ann Spagnuolo, Brianna Skinner, Caroline E. Baker, Craig Sykes, Katie R. Mollan, Angela D. M. Kashuba, J. Gerardo García-Lerma, Russell J. Mumper & J. Victor Garcia 

Nature Communications 9, Article number: 4156 (2018) | [Download Citation](#) ↓

Abstract

Non-adherence to medication is an important health care problem, especially in the treatment of chronic conditions. Injectable long-acting (LA) formulations of antiretrovirals (ARVs) represent a viable alternative to improve adherence to HIV/AIDS treatment and prevention. However, the LA-ARV formulations currently in clinical trials cannot be removed after administration even if adverse events occur. Here we show an ultra-LA removable system that delivers drug for up to 9 months and can be safely removed to stop drug delivery. We use two pre-clinical models for HIV transmission and treatment, non-human primates (NHP) and humanized BLT (bone marrow/liver/thymus) mice and show a single dose of subcutaneously administered ultra-LA dolutegravir effectively delivers the drug in both models and show suppression of viremia and protection from multiple high-dose vaginal HIV challenges in BLT mice. This approach represents a potentially effective strategy for the ultra-LA drug delivery with multiple possible therapeutic applications.

- Single-dose “ultra-long-acting” subcutaneous injection delivered DTG for up to 9 months in non-human primate and humanized murine models
- Polymer excipients solidify to form an “implant” under the skin that slowly releases drug
- Sustained DTG concentrations in plasma and efficient penetration of tissue in female reproductive tract
- The deposit is biodegradable, and can also be surgically removed with a small incision
- “Offer the flexibility to include multiple drugs and the future potential to be reloadable *in situ*”



HIV treatment or prevention: Monoclonal antibodies

- Monoclonal (broadly neutralizing) antibodies are being studied for treatment and prevention of HIV
- Two harmonized Phase 2b HIV prevention trials of VRC01 (HPTN 081/HVTN 703 and HPTN 085/HVTN 704, also known as the Antibody Mediated Prevention or AMP trials) are currently underway.
- One trial is a cohort of men who have sex with men and transgender women in North and South America and Europe and the other is of heterosexual women in sub-Saharan Africa (total 47 sites in 11 countries).
- The trials are examining the safety and tolerability of VRC01 and optimal dosing based on intravenous infusions every 8 weeks, and whether there is a signal that this product reduces risk of HIV infection.
- Phase I trials of three other monoclonal antibodies are currently in developmental stages.

[Curr Opin HIV AIDS](#), 2018 Jul;13(4):366-373. doi: 10.1097/COH.0000000000000475.

Broadly neutralizing antibodies for treatment and prevention of HIV-1 infection.

Cohen YZ¹, Caskey M.

Ⓜ Author information

Abstract

PURPOSE OF REVIEW: Several anti-HIV-1 broadly neutralizing antibodies (bnAbs) with exceptional breadth and potency that target different HIV-1 envelope epitopes have been identified. bnAbs are an attractive new strategy for HIV-1 prevention and therapy, and potentially, for long-term remission or cure. Here, we discuss findings from early clinical studies that have evaluated these novel bnAbs.

RECENT FINDINGS: Phase 1 studies of bnAbs targeting two distinct HIV-1 envelope epitopes have demonstrated their favorable safety and pharmacokinetic profile. Single bnAb infusions led to significant, but transient, decline in viremia with selection of escape variants. A single bnAb also delayed viral rebound in ART-treated participants who discontinued ART. Importantly, in-vivo efficacy was related to antibody potency and to the level of preexisting resistance. Studies in animal models showed that bnAbs can clear HIV-infected cells and modulate host immune responses. These findings suggest that bnAbs may target the latent HIV reservoir in humans and could contribute to long-term remission of HIV-1 infection.

SUMMARY: bnAbs may offer advantages over traditional ART for both the prevention and treatment of HIV-1 infection. In addition, bnAbs may target the latent viral reservoir. bnAb combinations and bnAbs engineered for prolonged half-life and increased potency are currently undergoing clinical evaluation.

PMID: 29697469 DOI: 10.1097/COH.0000000000000475

[Adv Exp Med Biol](#), 2018;1075:53-72. doi: 10.1007/978-981-13-0484-2_3.

HIV Broadly Neutralizing Antibodies: VRC01 and Beyond.

Wu X¹.

Ⓜ Author information

Abstract

Developing an effective prophylaxis HIV-1 vaccine is likely to require the elicitation of broadly neutralizing antibodies (bnAbs). As the HIV-1 envelope (Env) glycoprotein - the sole target of bnAbs - has evolved multiple mechanisms to evade antibody neutralization, the processes for bnAb generation are highly selective and time-consuming. Benefiting from antibody isolation technologies of single B cell culturing and direct single B cell sorting and cloning, a new generation of monoclonal bnAbs has been isolated since 2009, exhibiting remarkable breadths and potencies, thus breaking through a nearly 20-year-long limit of four monoclonal bnAbs with moderate breadth and potency. The discovery of a long list of monoclonal bnAbs has provided in-depth understanding of the sites of vulnerability on the HIV-1 Env and the complexity of human B cell immunology to generate such responses, thus presenting both guidance and challenges to move the Env immunogen design effort forward.



See also

PERSPECTIVE | THERAPEUTICS

Broadly neutralizing antibodies to prevent HIV-1

Myron S. Cohen¹, Lawrence Corey²

+ See all authors and affiliations

Science 06 Oct 2017;
Vol. 358, Issue 6359, pp. 46-47
DOI: 10.1126/science.aap8131

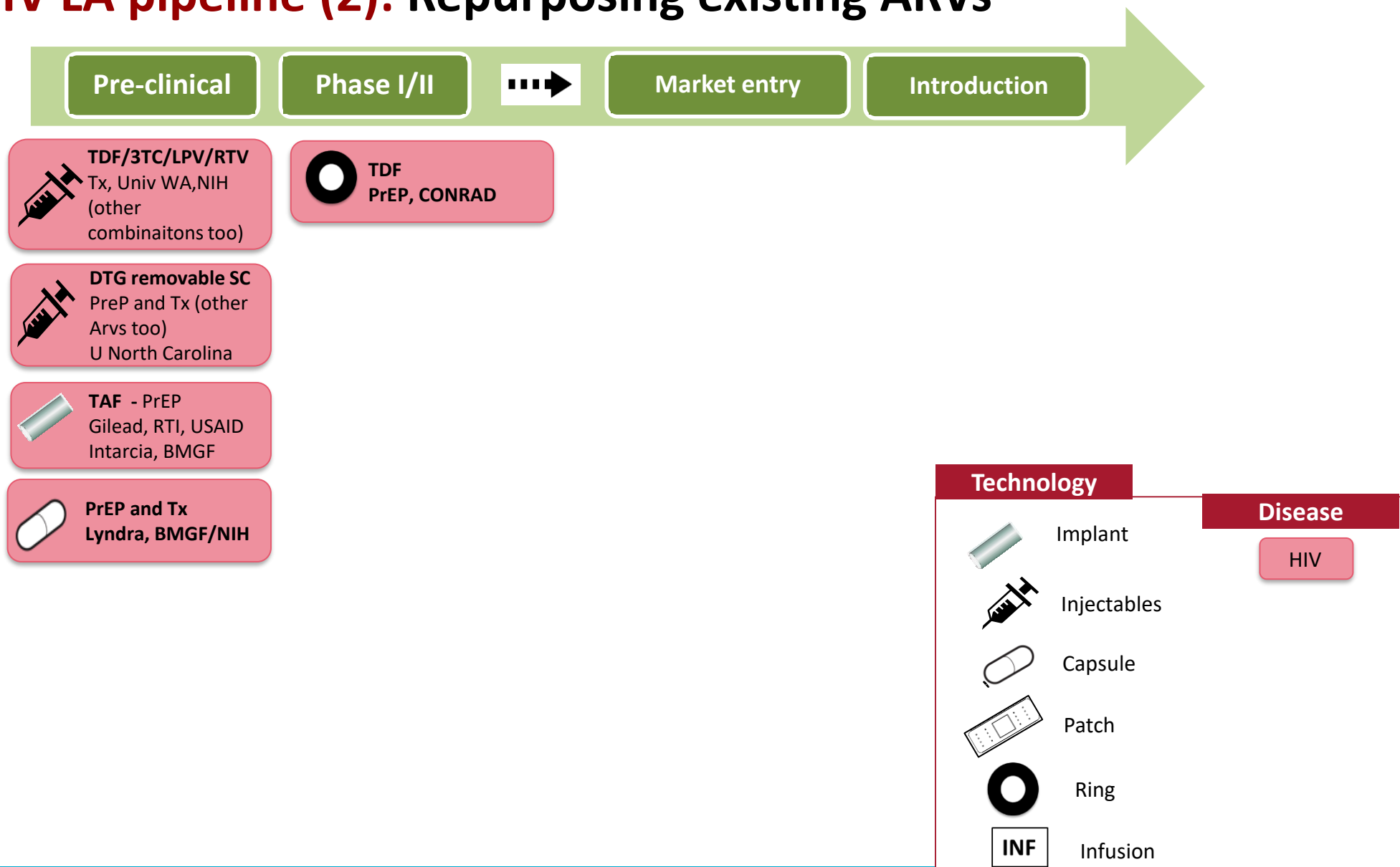


HIV-1 Broadly neutralizing antibodies: Clinical status, November 2018

HIV-1 bNAb	Non LS	LS	IP holder	Potential commercial interest	Phase 1 safety, PK
VRC01	X	X	NIAID	Sanofi (1/3 of SAR441236)	X
VRC07-523		X	NIAID	early stage interest	X
10E8V		X	NIAID	Sanofi (1/3 of SAR441236)	ongoing
N6		X	NIAID	GSK	ongoing
CAP256		X	NIAID, CAPRISA	-	planned for Q2 2019
PGT121	X	X	IAVI	Gilead variant for Rx	X (non LS)
PGDM1400	X	X	IAVI	-	X (non-LS)
3BNC117	X	X	Rockefeller	-	X / ongoing (LS)
10-1074	X	X	Rockefeller	-	X / ongoing (LS)
10E8V2.0/iMab	X		NIAID, ADARC	TaiMed	TBD
SAR441236		X	Sanofi	Sanofi	planned for Q1 2019



HIV LA pipeline (2): Repurposing existing ARVs



Repurposing existing oral ARVs: Sub-cutaneous LA injectable drug combination dosage forms targeted to cells for HIV treatment

(Ho R., Collier A. et al, TLC-ART Program, University of Washington)

Long-acting combination anti-HIV drug suspension enhances and sustains higher drug levels in lymph node cells than in blood cells and plasma

John C. Kraft^a, Lisa A. McConnachie^a, Josefin Koehn^a, Loren Kinman^a, Carol Collins^a, Danny D. Shen^a, Ann C. Collier^{b,c} and Rodney J.Y. Ho^{a,c,d}

Objective: The aim of the present study was to determine whether a combination of anti-HIV drugs – tenofovir (TFV), lopinavir (LPV) and ritonavir (RTV) – in a lipid-stabilized nanosuspension (called TLC-ART101) could enhance and sustain intracellular drug levels and exposures in lymph node and blood cells above those in plasma.

Design: Four macaques were given a single dose of TLC-ART101 subcutaneously. Drug concentrations in plasma and mononuclear cells of the blood (PBMCs) and lymph nodes (LNMCs) were analysed using a validated combination LC-MS/MS assay.

Results: For the two active drugs (TFV, LPV), plasma and PBMC intracellular drug levels persisted for over 2 weeks; PBMC drug exposures were three- to four-fold higher than those in plasma. Apparent terminal half-lives ($t_{1/2}$) of TFV and LPV were 65.3 and 476.9 h in plasma, and 169.1 and 151.2 h in PBMCs. At 24 and 192 h, TFV and LPV drug levels in LNMCs were up to 79-fold higher than those in PBMCs. Analysis of PBMC intracellular TFV and its active metabolite TFV-diphosphate (TFV-DP) indicated that intracellular exposures of total TFV and TFV-DP were markedly higher and persisted longer than in humans and macaques dosed with oral TFV prodrugs, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).

Conclusions: A simple, scalable three-drug combination, lipid-stabilized nanosuspension exhibited persistent drug levels in cells of lymph nodes and the blood (HIV host cells) and in plasma. With appropriate dose adjustment, TLC-ART101 may be a useful HIV treatment with a potential to impact residual virus in lymph nodes.

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AIDS 2017, **31**:765–770

Keywords: drug combination nanoparticles, enhanced and persistent drug exposure, HIV treatment, intracellular HIV drug exposures, long-acting, lopinavir, lymphatic drug insufficiency, lymphatic targeting, targeted drug delivery, tenofovir

- Combined TDF, LPV/ritonavir nano-suspension (2 active drugs)
- Single-dose SQ injection in 4 macaques
- Plasma and PBMC intracellular concentrations of the 2 active drugs persisted for more than 2 weeks, with 3-4 fold higher PBMC exposures than in plasma

AIDS, in press, no link to article

Extended cell and plasma drug levels after one dose of a three-in-one nanosuspension containing lopinavir, efavirenz, and tenofovir in nonhuman primates

Josefin Koehn^a, Jennifer F. Iwamoto^a, John C. Kraft^a, Lisa A. McConnachie^a, Ann C. Collier^{b,c} and Rodney J.Y. Ho^{a,c,d}

- Combined TDF, LPV, EFV nano-suspension (3 active drugs)
- Single-dose SQ injection in 2 macaques
- Plasma and PBMC concentrations for all 3 drugs persisted for two weeks, targeted to PBMC and LNMC with 57-228 fold higher concentrations in lymph node cells
- Targeted to LNMC and PBMC-with higher lymph node cell concentrations than PBMC

See also

Mechanism-based pharmacokinetic (MBPK) models describe the complex plasma kinetics of three antiretrovirals delivered by a long-acting anti-HIV drug combination nanoparticle formulation

John C. Kraft^a, Lisa A. McConnachie^a, Josefin Koehn^a, Loren Kinman^a, Jianguo Sun^{a,1}, Ann C. Collier^{b,c}, Carol Collins^a, Danny D. Shen^a, Rodney J.Y. Ho^{a,c,d,*}

Journal of Pharmaceutical Sciences 107 (2018) 1787-1790



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journal homepage: www.jpjpharmsci.org

Rapid Communication

Long-Acting Profile of 4 Drugs in 1 Anti-HIV Nanosuspension in Nonhuman Primates for 5 Weeks After a Single Subcutaneous Injection

Check for updates

Lisa A. McConnachie¹, Loren M. Kinman¹, Josefin Koehn¹, John C. Kraft¹, Sarah Lane¹, Wonsok Lee¹, Ann C. Collier^{2,3}, Rodney J.Y. Ho^{1,3,4,*}

¹ Department of Pharmaceutics, University of Washington, Seattle, Washington 98195

² Department of Medicine, University of Washington, Seattle, Washington 98195

³ Center for AIDS Research, University of Washington, Seattle, Washington 98195

⁴ Department of Biomedical Engineering, University of Washington, Seattle, Washington 98195

- Combined TDF, LPV/ritonavir, 3TC nano-suspension (3 active drugs)
- Single-dose SQ injection in 4 macaques
- Plasma and PBMC levels of the 3 active drugs were sustained for 5 weeks
- PBMC exposures to the 3 active drugs were 12-42 fold higher than in plasma



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Review of LA injectable candidates HIV treatment and prevention (September 2018)

Background paper prepared by Andrew Hill for WHO HIV Department

[Background paper](#)
[Review of Long-acting Injectable HIV Treatment and Prevention Candidates](#)
 (September 2018)
[Andrew Hill](#)

[Companion slides](#)
[Review of Long-acting Injectable HIV Treatment and Prevention Candidates](#)
 (August 2018)
[Andrew Hill](#)

Review of Long-Acting Injectable Candidates for HIV Treatment and Prevention

September 2018

Executive Summary

Despite the wide range of available fixed-dose regimens, adherence to daily lifelong ART is still a challenge for many patients. Long-acting (LA) injectable antiretroviral candidates as an alternative to oral daily therapy are currently being evaluated for the treatment and prevention of HIV infection. Other non-injectables such as implants, patches, vaginal rings are also currently under development. While LA formulations could help overcome adherence issues, multiple barriers and concerns must be addressed overcome before they can be widely accepted for use (Table 1). Many drug candidates for HIV treatment and prevention are still in the early stages of development (Table 2 and 3). Considering the process of drug development, from preclinical testing to final regulatory approval, we can only expect more injectable LA drugs to enter to market around mid-2020s.

Review of Long-Acting Injectable HIV Treatment and Prevention Candidates

August 2018



Selected articles on LA HIV treatment and prevention

Journal List > [Glob Health Sci Pract](#) > v.5(2); 2017 Jun 27 > PMC5487081



[Glob Health Sci Pract](#). 2017 Jun 27; 5(2): 182–187.

Published online 2017 Jun 27. doi: [10.9745/GHSP-D-17-00206](#)

PMCID: PMC5487081

PMID: [28655797](#)

Long-Acting HIV Treatment and Prevention: Closer to the Threshold

[Matthew Barnhart](#)^a

[Author information](#) ▶ [Copyright and License information](#) ▶ [Disclaimer](#)

GHSP

[Drug Delivery and Translational Research](#)

December 2017, Volume 7, [Issue 6](#), pp 805–816 | [Cite as](#)

Long acting systemic HIV pre-exposure prophylaxis: an examination of the field

Authors

[Authors and affiliations](#)

William R. Lykins, Ellen Luecke, Daniel Johengen, Ariane van der Straten, Tejal A. Desai

Perspective

Monoclonal Antibodies for Emerging Infectious Diseases — Borrowing from History

Hilary D. Marston, M.D., M.P.H., Catharine I. Paules, M.D., and Anthony S. Fauci, M.D.

Article	Figures/Media	Metrics
		April 19, 2018 N Engl J Med 2018; 378:1469-1472 DOI: 10.1056/NEJMp1802256

5 References

Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy☆



Andrew Owen^a, Steve Rannard^b

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^b Department of Chemistry, Crown Street, University of Liverpool, L69 3BX, UK

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ABSTRACT

Advances in solid drug nanoparticle technologies have resulted in a number of long-acting (LA) formulations with the potential for once monthly or longer administration. Such formulations offer great utility for chronic diseases, particularly when a lack of medication compliance may be detrimental to treatment response. Two such formulations are in clinical development for HIV but the concept of LA delivery has its origins in indications such as schizophrenia and contraception. Many terms have been utilised to describe the LA approach and

[Expert Rev Clin Pharmacol](#). 2018 May;11(5):507-517. doi: [10.1080/17512433.2018.1453805](#). Epub 2018 Mar 29.

Treatment and prevention of HIV infection with long-acting antiretrovirals.

[Benítez-Gutiérrez L](#)^{1,2}, [Soriano V](#)³, [Requena S](#)², [Arias A](#)¹, [Barreiro P](#)³, [de Mendoza C](#)².

Author information

Abstract

Current antiretroviral therapy allows to achieve and sustain maximal suppression of HIV replication in most treated patients. As result, the life expectancy of HIV-infected persons has improved dramatically and is nowadays similar to that of the HIV-negative population. However, oral antiretrovirals have to be taken daily and indefinitely to avoid resumption of HIV replication and selection of drug resistance. Unfortunately, drug adherence is often suboptimal and tends to decline over time. Areas covered: New drugs, formulations and delivery systems are being developed for extended-release of antiretrovirals. At this time, intramuscular cabotegravir and rilpivirine, dapivirine vaginal rings and tenofovir alafenamide subdermal implants are the products in more advanced stages of clinical development. Their pharmacokinetics/dynamics and safety/efficacy are reviewed. Expert commentary: In the absence of eradication therapy for individuals with HIV infection and protective vaccines for persons at risk, long-term antiretroviral therapy is the best approach for preventing disease progression in patients and halting transmissions, either as result of 'treatment as prevention' for HIV carriers or 'pre-exposure prophylaxis' for uninfected individuals at risk. In all these scenarios, the advent of long-acting antiretrovirals will expand options for overcoming the challenge of suboptimal drug adherence and reduce the burden of HIV infection.

KEYWORDS: HIV; Long-acting; MK-8591; antiretrovirals; cabotegravir; dapivirine; drug adherence; drug resistance; extended-release; maintenance therapy; pre-exposure prophylaxis; rilpivirine; subdermal implants; tenofovir alafenamide; vaginal rings

PMID: 29595351 DOI: [10.1080/17512433.2018.1453805](#)

[Curr Opin HIV AIDS](#). Author manuscript; available in PMC 2016 Jul 1.

Published in final edited form as:

[Curr Opin HIV AIDS](#). 2015 Jul; 10(4): 290–295.

doi: [10.1097/COH.000000000000159](#)

PMCID: PMC4620059

NIHMSID: NIHMS730827

PMID: [26049956](#)

Planning ahead for implementation of long acting HIV prevention: challenges and opportunities

[Kathrine Meyers](#), DrPH, MPP and [Sarit A. Golub](#), PhD, MPH



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AVAC: Online resources on R&D for HIV prevention

HIV Prevention Research Timeline



This graphic shows the status of selected biomedical HIV prevention clinical trials from 2017 through 2020.

Global Trial Map

Click to view our [map of HIV prevention trials](#).



HIV Prevention Research & Development Database

The **HIV Prevention Research & Development Database (PxRD)** was developed to be a comprehensive source of information on biomedical HIV prevention clinical trials that are planned, ongoing or completed. The database allows users to view clinical trials around the world, gaining an understanding of the many developments currently being made in the field of HIV prevention research. The database:

- Provides **Summary Tables** of HIV prevention clinical trials
- Enables investigators, funders and advocates to view a **Global Map of Ongoing HIV Prevention Trials**
- Allows users to **Search** for prevention trials through various criteria

Search

Prevention Option

- Antibody Related Research
- HIV Vaccine
- Combination Prevention
- Condoms, Male and Female
- Cure

Products

- 1% tenofovir gel
- 10-1074
- 3BNC117
- AAV
- Ad26

Country

- Afghanistan
- Albania
- Algeria

Population

- Injecting drug users
- HIV negative
- HIV positive
- Serodiscordant



Long-Acting/Extended Release Antiretroviral Resource Program (LEAP)

LEAP (based at Johns Hopkins University) is funded by the NIH:

- To support scientific innovation related to the development of LA/ER antiretroviral drugs and TB drugs through investigator access to broad-based scientific expertise, including the pharmaceutical industry.
- To develop a communications and data hub to support investigators in this field, and
- To provide a Modeling and Simulation Core Service that helps investigators identify the most promising approaches to the development of new products.



www.leapresources.org

Long-Acting/Extended Release Antiretroviral Resource Program



LA medicinal products by disease area

Overview of long-acting drug pipeline for malaria


Product	Developer	Type
New chemical entity		
P 218	Janssen (MMV)	Treatment or chemoprophylaxis
Repurposed oral drugs		
Ivermectin	Lyndra (BMGF)	Endectocide
Atovaquone	University of Liverpool, others	Chemoprophylaxis
Primaquine	PATH, Queens U (BMGF)	Treatment




Malaria LA pipeline: New and repurposed products




P218
 Chemo-prophylaxis
 Janssen
 Injectable





ATOVAQUONE
 Chemo-prophylaxis
 U of Liverpool
 Injectable



IVERMECTIN
 Endectocide
 vector control
 Lyndra BMGF EGRS
 capsule



PRIMAQUINE
 Malaria treatment
 Microarray patch
 PATH, Queens U, BMGF




Malaria chemoprophylaxis: P218 injectable



MMV
Medicines for Malaria Venture

Developing antimalarials

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[Home](#) > [Newsroom](#) > [News](#) > MMV brings new partner Janssen Pharmaceuticals on board

MMV brings new partner Janssen Pharmaceuticals on board

Partnership to develop vital long-acting antimalarials for treatment and prevention

19 Jan 2017

MMV has formed a new collaboration with Janssen Pharmaceuticals, Inc. (Janssen) and Johnson & Johnson Global Public Health to help develop better medicines to treat and protect vulnerable populations, such as children and pregnant women, from malaria.

The partnership will focus on the development of new medicines suitable for reduced-dosing regimens. Simpler regimens facilitate adherence to treatments and ensure they remain effective. One of the ways to do this is to formulate the medicine in such a way that it releases slowly into the body. This enables it to be active over a longer period of time. Janssen is an expert in long-acting injectable formulation technology while MMV is an expert in malaria drug development. Through the partnership, this expertise will be combined for the good of people at risk of malaria.

The MMV/Janssen team will begin investigations with P218 – a compound with the potential to provide protection against malaria discovered through an MMV partnership with BIOTEC Thailand, Monash University and the London School of Hygiene and Tropical Medicine.



Photo: Thomas Rückle/MMV



Malaria chemoprophylaxis: atovaquone injectable (1)

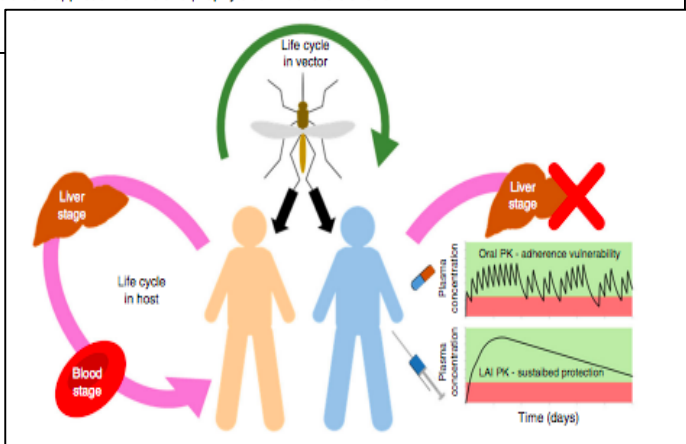
ARTICLE

DOI: 10.1038/s41467-017-02603-z OPEN

Long-acting injectable atovaquone nanomedicines for malaria prophylaxis

Rahul P. Bakshi^{1,2}, Lee M. Tatham³, Alison C. Savage⁴, Abhai K. Tripathi^{2,5}, Godfree Mlambo^{2,5}, Matthew M. Ippolito^{1,2,6}, Elizabeth Nenortas^{1,2}, Steve P. Rannard⁴, Andrew Owen³ & Theresa A. Shapiro^{1,2,5}

Chemoprophylaxis is currently the best available prevention from malaria, but its efficacy is compromised by non-adherence to medication. Here we develop a long-acting injectable formulation of atovaquone solid drug nanoparticles that confers long-lived prophylaxis against *Plasmodium berghei* ANKA malaria in C57BL/6 mice. Protection is obtained at plasma concentrations above 200 ng ml⁻¹ and is causal, attributable to drug activity against liver stage parasites. Parasites that appear after subtherapeutic doses remain atovaquone-sensitive. Pharmacokinetic-pharmacodynamic analysis indicates protection can translate to humans at clinically achievable and safe drug concentrations, potentially offering protection for at least 1 month after a single administration. These findings support the use of long-acting injectable formulations as a new approach for malaria prophylaxis in travellers and for malaria control in the field.



Utility of long-acting antimalarial prophylaxis Pharmacokinetic exposure to atovaquone monotherapy via oral administration blocks liver and erythrocytic stages of the parasite life cycle within the host (causal and suppressive activity, respectively). However, there is a vulnerability of oral dosing to non-adherence. The current work reports the preclinical development of an intramuscular long-acting nanomedicine, which provides sustained protection to parasite exposure in a preclinical model, expected to provide at least 1-month protection in humans.

Injectable antimalarials revisited: discovery and development of new agents to protect against malaria

Fiona Macintyre, Hanu Ramachandruni, Anna Thomas, Jeremy N. Burrows, Jörg J. Möhrle, Rob Hooft van Huijsduijnen, ... Timothy N.C Wells*, Wiweka Kaszubska

*wellst@mmv.org

Medicines for Malaria Venture, Route de Pré Bois 20, 1215 Geneva, Switzerland

Different use cases for LA malaria chemoprophylaxis include

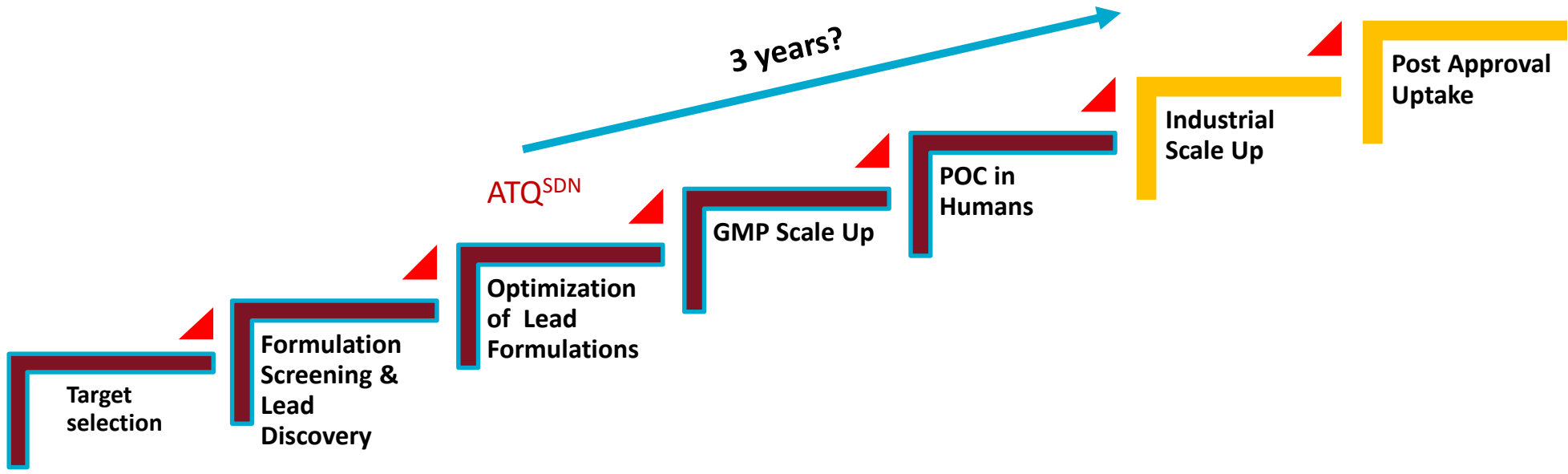
- people travelling from non-malarial to endemic regions (e.g. internal migrants)
- addressing malaria outbreaks among non-immune groups in malaria-free areas (including where Ebola outbreaks occur), and
- protecting vulnerable populations (especially children <5 years) in endemic areas (seasonal malaria chemoprevention, SMC).

[McIntyre, F et al, 2018](#)
[Injectable antimalarials revisited: Discovery and development of new agents to protect against malaria](#)



Malaria chemoprophylaxis: atovaquone injectable (2)

Potential route for nano-technology application



Malaria vector control: Oral long-acting ivermectin capsule

[Malar J.](#) 2017; 16: 161.

Published online 2017 Apr 24. doi: [10.1186/s12936-017-1801-4](https://doi.org/10.1186/s12936-017-1801-4)

PMCID: PMC5402169

PMID: [28434401](https://pubmed.ncbi.nlm.nih.gov/28434401/)

Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety

[Carlos Chaccour](#)^{1,2,3} [Felix Hammann](#)⁴ and [N. Regina Rabinovich](#)^{1,5}

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An oral ultra long-acting ivermectin for malaria elimination

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NIHMSID: NIHMS840836

PMID: [27856796](https://pubmed.ncbi.nlm.nih.gov/27856796/)

Oral, ultra-long-lasting drug delivery: Application toward malaria elimination goals

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Abstract

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Efforts at elimination of scourges, such as malaria, are limited by the logistic challenges of reaching large rural populations and ensuring patient adherence to adequate pharmacologic treatment. We have developed an oral, ultra-long-acting capsule that dissolves in the stomach and deploys a star-shaped dosage form that releases drug while assuming a geometry that prevents passage through the pylorus yet allows passage of food, enabling prolonged gastric residence. This gastric-resident, drug delivery dosage form releases small-molecule drugs for days to weeks and potentially longer. Upon dissolution of the macrostructure, the components can safely pass through the gastrointestinal tract. Clinical, radiographic, and endoscopic evaluation of a swine large-animal model that received these dosage forms showed no evidence of gastrointestinal obstruction or mucosal injury. We generated long-acting formulations for controlled release of ivermectin, a drug that targets malaria-transmitting mosquitoes, in the gastric environment and incorporated these into our dosage form, which then delivered a sustained therapeutic dose of ivermectin for up to 14 days in our swine model. Further, by using mathematical models of malaria transmission that incorporate the lethal effect of ivermectin against malaria-transmitting mosquitoes, we demonstrated that this system will boost the efficacy of mass drug administration toward malaria elimination goals. Encapsulated, gastric-resident dosage forms for ultra-long-acting drug delivery have the potential to revolutionize treatment options for malaria and other diseases that affect large populations around the globe for which treatment adherence is essential for efficacy.

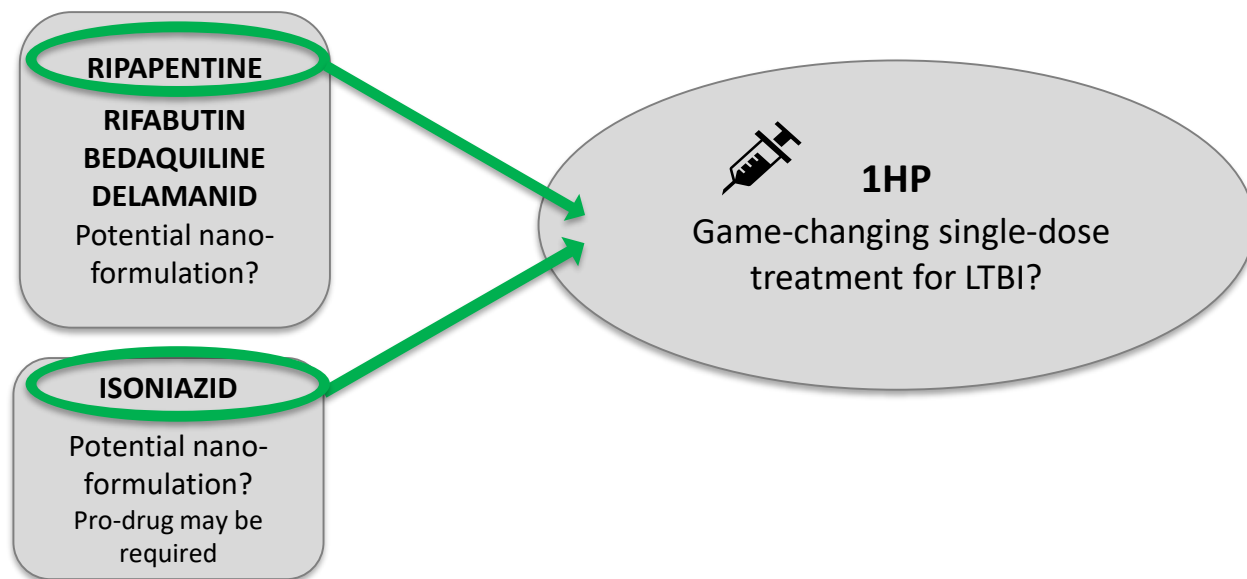
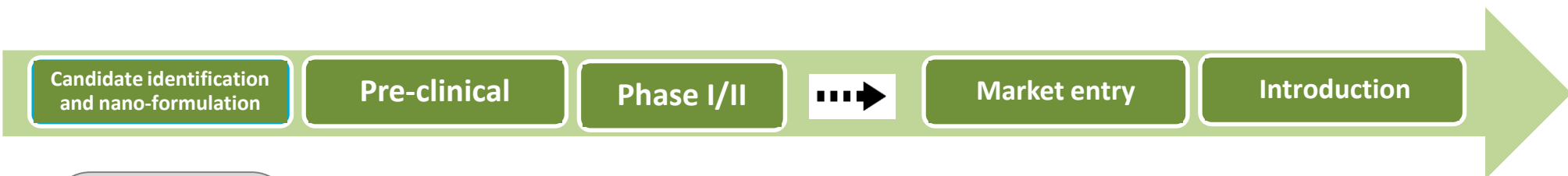
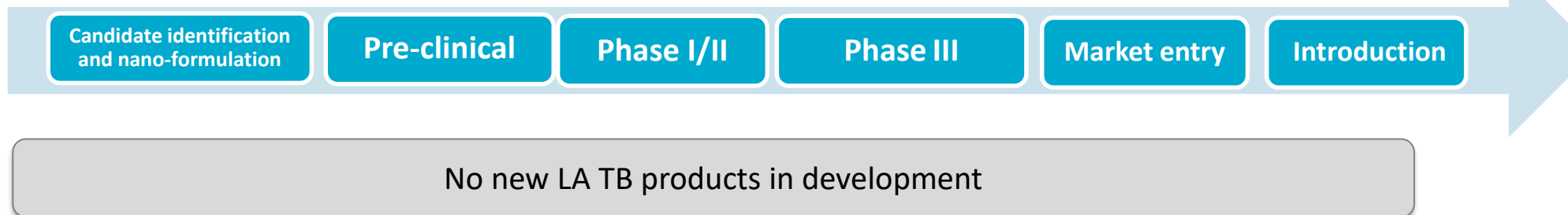


4
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TB LA pipeline: Potential to repurpose oral products?



TB: Suitability of drugs for LA formulation

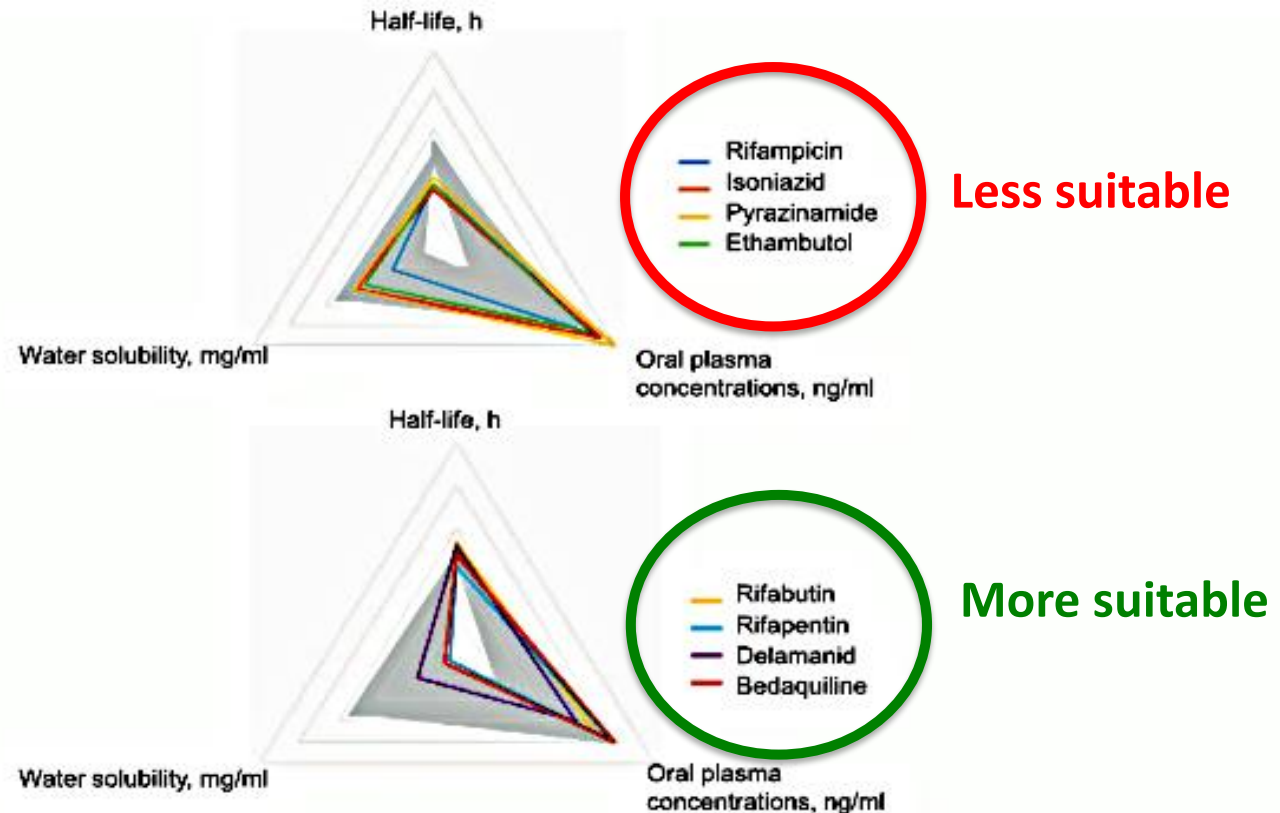
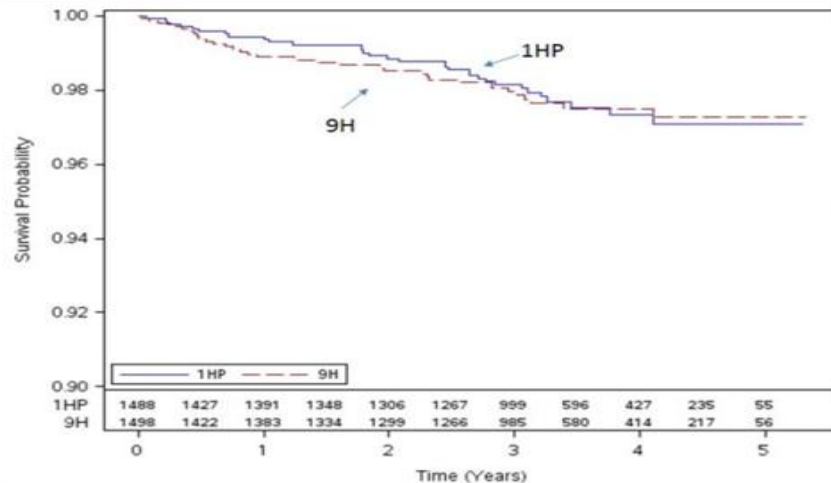


Figure Schematic representation of the three drug-specific properties influencing physicochemical and pharmacological compatibility with long-acting administration, as described in the text. The gray area represents the range for existing long-acting formulations for multiple disease areas (paliperidone palmitate, olanzapine pamoate, risperidone, medroxyprogesterone acetate, rilpivirine and cabotegravir; half-life >12 h, therapeutic concentrations <1000 ng/ml and water solubility <50 mg/ml). The axis spans across 0.1 to 10 000 (\log_{10} scale). Rifabutin, rifapentine, delamanid and bedaquiline have properties in the range of other long-acting medicines, whereas the other drugs currently used in anti-tuberculosis treatment do not.



LTBI can be treated with a 1-month course of drugs



Conference Dates and Location:
March 4-7, 2018 | Boston, Massachusetts

Abstract Number:
37LB

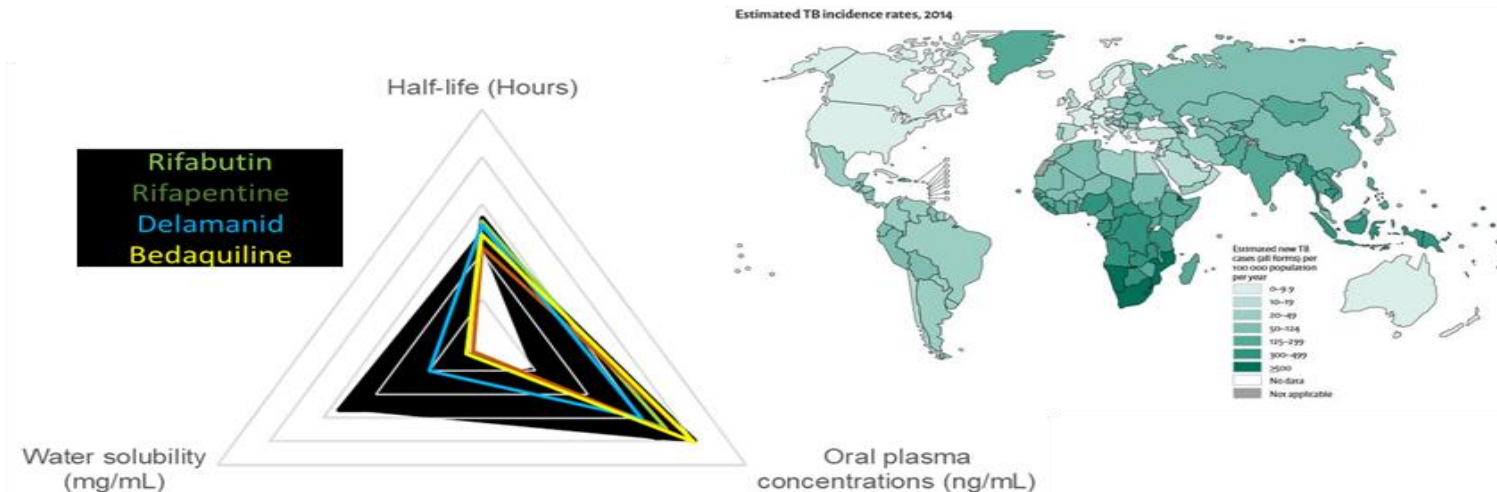
ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

Author(s):

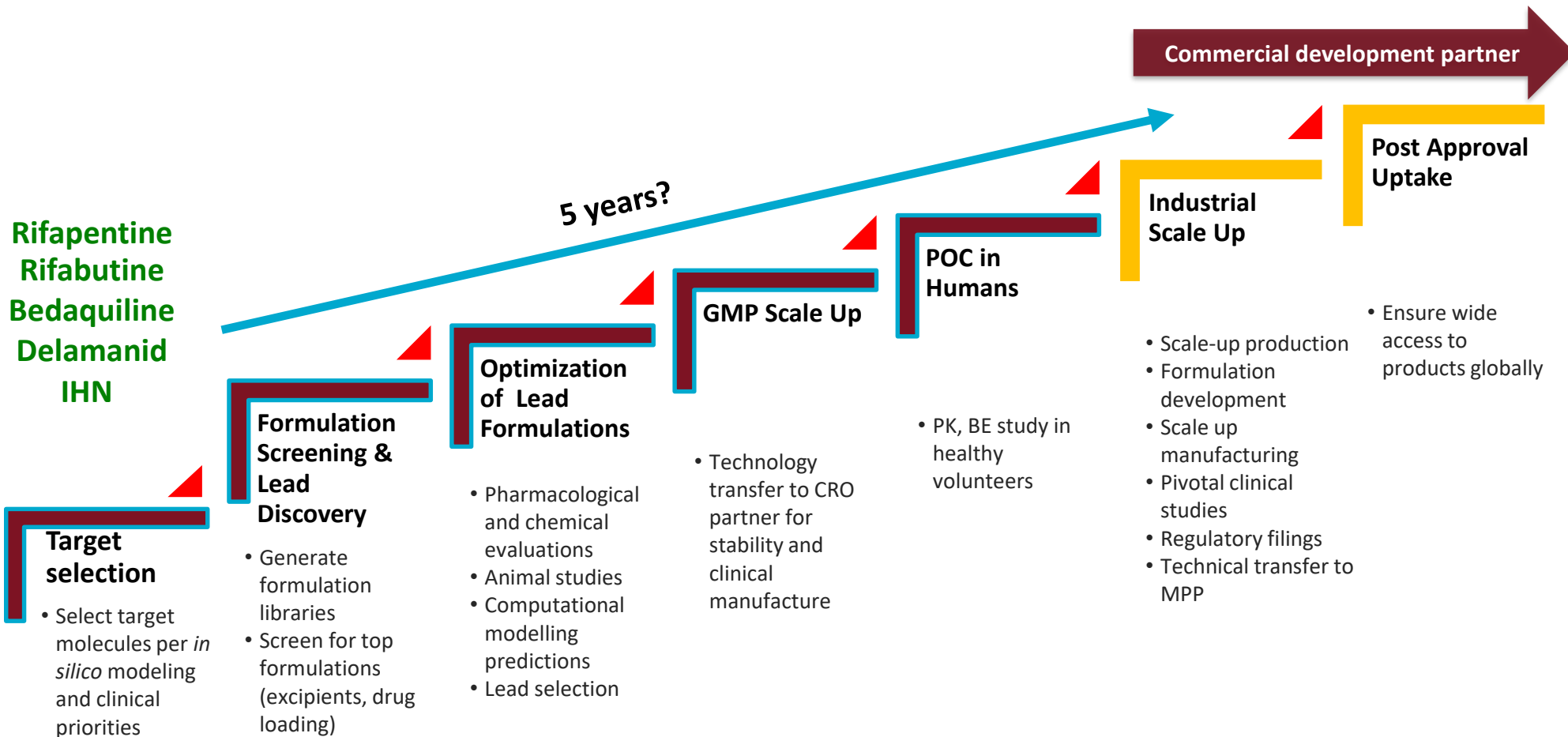
Susan Swindells¹, Ritesh Ramchandani², Amita Gupta³, Constance A. Benson⁴, Jorge T. Leon-Cruz², Ayotunde Omoz-Oarhe⁵, Marc Antoine Jean Juste⁶, Javier R. Lama⁷, Javier A. Valencia⁷, Sharlaa Badal-Faesen⁸, Laura E. Moran⁹, Courtney V. Fletcher¹, Eric Nuermberger¹⁰, Richard E. Chaisson¹⁰

In this study, 1month of INH + RPT was found to be non-inferior to 9 months of NIH for preventing TB, TB death or death from unknown cause in adults and adolescents living with HIV. Further confirmation of the data may be needed.

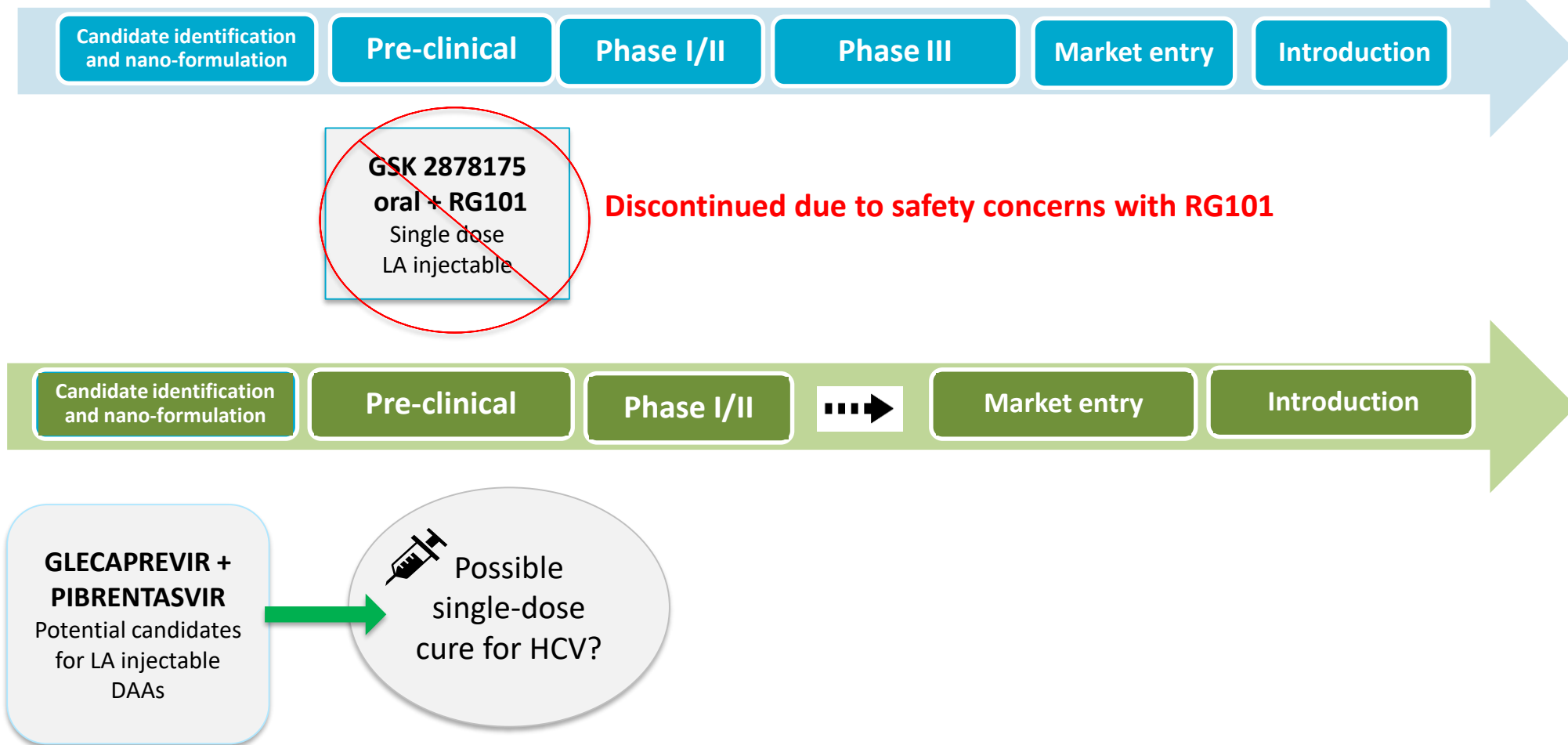
1-shot LTBI treatment possible?



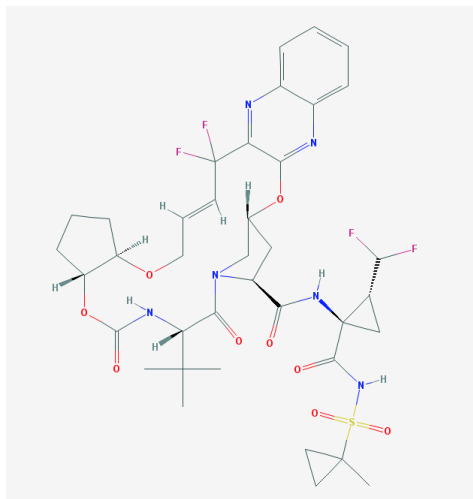
TB: Potential candidates for SDN development (University of Liverpool)



HCV LA pipeline: New and repurposed products

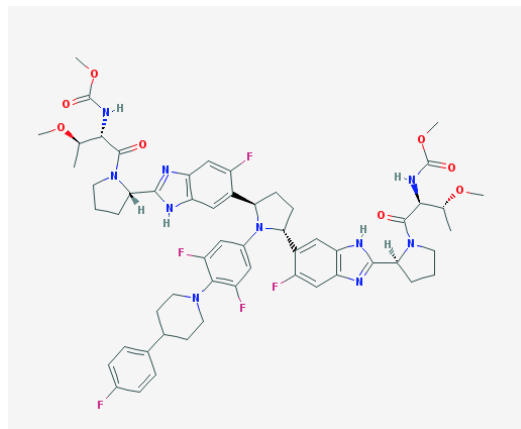


Glecaprevir and pibrentasvir: Safe, pangentotypic antiviral drugs, most people cured in 56 days



Glecaprevir 300 mg (three 100 mg tablets)

- HCV protease inhibitor
- Liver metabolized; renal safe
- Tmax 5 hrs
- Mol Wt 838 g/mol
- Water sol <0.1 to 0.3 mg/ml
- Charge 0; Polar surface 204 Å²



Pibrentasvir 160 mg (three 40 mg tablets)

- HCV NS5A
- Liver metabolized; renal safe
- Tmax 5 hrs
- Mol Wt 1113 g/mol
- Water sol <0.1 mg/ml
- Charge 0; Polar surface 200 Å²

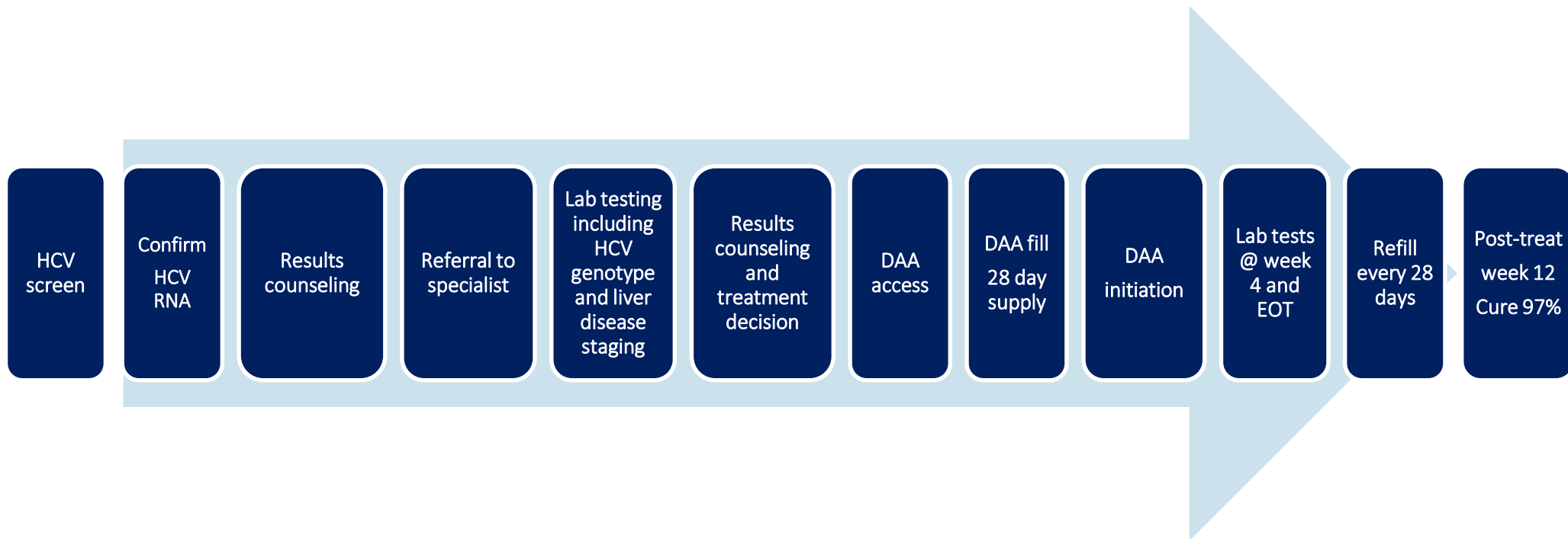
Source: <https://pubchem.ncbi.nlm.nih.gov>



Potential application
for LA formulation



The current patient journey to HCV cure is complicated



Potential simplified journey to one shot cure with LA approach

POC HCV screen
and confirm*

Counseling, exam
and POC lab
testing†

Long-acting injection of DAAs

Post-treatment
week 12 POC
Cure 97%‡‡

*if no access to HCV RNA or antigen, treat persons who are HCV antibody +

†Point of care: renal and liver chemistry, CBC, HIV antibody, HBsAg; calculate FIB-4

‡ With high adherence, proof of SVR is not essential

Potential elements of a test and cure approach

Point-of-care: HCV diagnosis

- Confirm POC HCV antibody and/or HCV antigen and/or HCV RNA (if confirmatory test not available, treat if HCV antibody +)
- No need for HCV genotype since pan-genotypic
- History and exam for liver disease and drug interaction
- Point of care: HIV, HBsAg, Chemistry panel, CBC
- Single dose of pangenotypic DAA regimen
 - No need for monitoring since safety is similar to placebo
- SVR rate >95% with perfect adherence

See approach from MINMON Study (ACTG 5360):

- Dispense 84 tablets of Sofosbuvir/Velpatasvir
- One follow-up visit to confirm cure



Hepatitis Extended Release Long Acting Injectable/Implantable Medication (HEP ELIM) Research Group

- **LEAP consortium** - Charlie Flexner and Sue Swindells
- **University of Liverpool** – Andrew Owen and Marco Siccardi
- **RTI** – Ginger Rothrock
- **Epidemiology** – Shruti Mehta, Sunil Solomon, Ethel Weld
- **Clinical** – Mark Sulkowski, Dave Thomas
- **DAIDS** - Carl Dieffenbach
 - CFAR - 5P30AI094189 (Dick Chaisson)
- **Clinton Health Access Foundation** – Paul Damanico



MPT LA pipeline (repurposed oral products only)

Candidate identification
and nano-formulation

Pre-clinical

Phase I/II



Market entry


Introduction

TDF + Levonorgestrel
Vaginal ring (90 days)
CONRAD

DPV + Levonorgestrel
Vaginal ring (90 days)
IPM, USAI

PrEP + contraception
"Schield" biodegradable
subdermal implant
(12-18 months)
RTI, USAID, PATH and others

Randomized, placebo controlled phase I trial of safety, pharmacokinetics, pharmacodynamics and acceptability of tenofovir and tenofovir plus levonorgestrel vaginal rings in women

Andrea Ries Thurman , Jill L. Schwartz, Vivian Brache, Meredith R. Clark, Timothy McCormick, Neelima Chandra, Mark A. Marzinke, Frank Z. Stanczyk, Charlene S. Dezzutti, Sharon L. Hillier, Betsy C. Herold, Raina Fichorova, Susana N. Asin, [...], Gustavo F. Doncel [view all]

Published: June 28, 2018 • <https://doi.org/10.1371/journal.pone.0199778>

This slide is not exhaustive:
a range of MPTs is
in development.
For more information, see
[the presentation from the
Initiative on Multi-purpose
Prevention Technologies
\(IPMT\)
at AIDS 2018 \(July 2018\)](#)

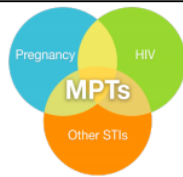


Selected resources on multi-purpose prevention technology

Multipurpose Prevention Technologies (MPTs)

An Introductory Factsheet

June 2016



This fact sheet provides basic information on multipurpose-prevention options. For more basic fact sheets in this series on emerging HIV prevention tools visit www.avac.org/intro.



MPT Product Development Database

This database includes MPT products that are currently available, as well as MPT products in active development. The database outlines detailed product information and can be searched to display products by desired criteria as selected from the drop-down boxes or by entering a keyword in the search box. Click on the product name to access detailed information on each product. [Click here to learn more about the inclusion criteria and information update methodology.](#)

Product Type	Delivery Route	Delivery Method
Show All Product Types	Show All Delivery Routes	Show All Delivery Methods
Indication	Product Developer	Product Sponsor/Funding
Show All Indications	Show All Developers	Show All Sponsors

Welcome to the MPT Resource Center!

As Secretariat for the [Initiative for Multipurpose Prevention Technologies \(IMPT\)](#), CAMI Health serves as the information hub for the multipurpose prevention technology (MPT) field. In addition to being organized by categories, the new **MPT Resource Center** features a [searchable resource database](#) to help you find what you are looking for.

Our resources include:

► Technical Webinars

Watch on-demand webinar recordings on priority topics for the MPT field, from regulatory issues to end-user research.

► Outreach Toolkit

PowerPoint presentations templates, fact sheets, and other materials developed to support your communication and advocacy around MPTs.

► IMPT Annual Reports

Read the latest IMPT Annual Report for a brief summary of progress in the IMPT network and across the larger MPT field.

► Technical Briefs & Reports

Find IMPT-developed tools, guidance, and other MPT-related information on a range of critical topics.



MPTs: Articles from the Field

The IMPT Secretariat distributes a monthly compilation of articles and other resources relevant to MPTs. [Click here to view current and past issues](#) or [join our mailing list](#)



BJOG Releases a Special Issue on MPTs. [Click here to read the IMPT Secretariat press release.](#)



Market Access Framework

[Updated 21 January, 2016]

Market Access Framework for Multipurpose Prevention Technology (MPT) Development and Introduction



4
Science

4c
Disease

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HIV/HCV harm reduction Long-Acting pipeline: Repurposed oral buprenorphine

Name	Manufacturer	Type
Sublocade Buprenorphine monthly depot	Indivior	OST
CAM 2038 Buprenorphine monthly depot	Braeburn	OST
Probuphine 6-monthly Buprenorphine implant	Titan	OST



HIV/HCV harm reduction LA pipeline:

Repurposed oral buprenorphine

Candidate identification
and nano-formulation

Pre-clinical

Phase I/II



Market entry

Introduction

FDA News Release

FDA approves first buprenorphine implant for treatment of opioid dependence

Expanded use and availability of medication-assisted treatment is a top priority of federal effort to combat opioid epidemic

f SHARE t TWEET in LINKEDIN p PIN IT e EMAIL p PRINT

For Immediate Release May 26, 2016

Psychiatry > Opioids

FDA Panels Like Long-Acting Buprenorphine — Backed two new products during two-day meeting

by Kristina Fiore, Deputy Managing Editor, MedPage Today
November 01, 2017

A joint FDA advisory committee has voted in favor of approval of two long-acting buprenorphine formulations, though they expressed concerns about higher doses of both products.

The Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 18-1 in favor of approval of Indivior's RBP-6000 monthly buprenorphine depot and 17-3 in favor of approving some doses of Braeburn's CAM2038 weekly and monthly buprenorphine depot.

CAM-2038

Buprenorphine
Weekly/monthly
SQ depot
Braeburn



SUBLOCADE

Buprenorphine
Indivior
Monthly SQ
injection



PROBUPHINE

Buprenorphine
Titan
6-monthly implant



4
Science

4c
Disease

Unitaid

HIV/HCV harm reduction LA pipeline:

Repurposed oral buprenorphine

- Options for opioid substitution therapy (OST) include methadone and buprenorphine.
- The opioid agonist **buprenorphine** has recently become available as a long-acting, monthly injectable and as a 6-monthly implant. While the impact of these innovations has not yet been widely studied, they may help to further improve adherence to OST, reduce risk behaviours for HIV and HCV and improve adherence to HIV and HCV treatment and care among PWID. Prices of the LA products are currently high than oral formulation (in the US, \$1500 per month for Sublocade injection, \$5000 for six-month implant, versus \$130 per month for daily oral formulation)
- Sublocade and Probuphine are only recommended by their manufacturers for people who are on a stable dose of a daily transmucosal/sub-lingual buprenorphine tablet
 - Only one cycle of the Probuphine implant is recommended in each upper arm
 - Sublocade is injected subcutaneously in the abdomen by a health care provider





Part 4d: Product summaries for approved LA drugs and those in Phase 2-3 trials

HIV

- Cabotegravir
- Rilpivirine
- VRC01
- DPV vaginal ring

HIV/HCV harm reduction

- Sublocade
- Probuphine
- CAM 2038



Product name: CABOTEGRAVIR

Originator company: Viiv Health Care

Drug type/class: Antiretroviral (Integrase inhibitor)

Delivery method and frequency: Intra-muscular injection every 8 weeks

Expected use: HIV prevention alone, and as combination treatment with RVP (Janssen)

Development status: In Phase 2b/3 clinical trials

Current studies:

HPTN 083 (CAB alone as PrEP compared to daily oral TDF/3TC): 7 countries, 4500 MSM and TG results expected 2021

HPTN 084 (CAB alone as PrEP compared to daily oral TDF/3TC): 7 countries, 3200 sexually active women, results expected 2022

ATLAS: Testing non-inferiority of switching from 2 NRTIs+INI/NNRTI/PI to LA injectable CAB/RVP every 4 weeks in ART-experienced patients (618 men and women in 13 countries); results expected 2022

ATLAS 2M: Testing non-inferiority of LA injectable CAB/RVP every 4 weeks compared to LA CAB/RVP every 8 weeks (48 week duration, 1020 participants); results expected 2022

FLAIR: Testing efficacy, safety and tolerability of LACAB/RVP every 4 weeks following switch from 20 weeks of oral ABC/DTG/3TC in ART-naïve patients (570 participants); results expected 2022

Development partners: NIAD sponsoring the PrEP trials; treatment trials with Janssen (RVP)

Regulatory status: Not approved

IP details: Patent families cover:

- Composition of matter of cabotegravir (CAB), dolutegravir (DTG) and analogues having inhibitory activity on HIV integrase; granted or pending in CN, EA, ID, MA, ZA, UA, VN; BR, IN (with opposition), but not filed in ARIPO, GT, OAPI, TH. Expected expiry in 2026 (except term extension in some EAPO countries)
- CAB-LAI, including its combination with RPV-LAI; granted or pending in CN, EA, ZA, UA; BR and IN, but not filed in ARIPO, GT, ID, MA, OAPI, TH & VN. Expected expiry in 2031
- GSK has additional filings covering CAB-LAI and GSK-2838232 (a Phase II maturation inhibitor) and combinations thereof.
- The Univ. of Nebraska has also filed for patent applications concerning other formulations of CAB-LAI and DTG-LAI in the US and Europe, but not in the majority of LMICs sampled by MPP. The status in MA and OA is unknown.

Considerations for use in LMICs: May be clarified in Ph3 studies: Oral lead-in, injection volume tolerability, PK tail. Other points: intra-muscular injection should ~~must~~ be given by a health care provider, large injection volume, current RVP-LAI formulation requires cold-chain

Next milestone/other notes: 48 week ATLAS data announced in August 2018 showed non-inferiority of monthly LA CAB/RVP compared to oral regimen. Current trials do not include pregnant women or people with active TB



Product name: RILPIVIRINE

Originator company: Janssen Pharmaceuticals

Drug type/class: Antiretroviral (Non-nucleoside reverse transcriptase inhibitor)

Delivery method and frequency: Intra-muscular injection every 8 weeks

Expected use: As part of dual combination HIV treatment with CAB

Development status: In Phase 2b/3 clinical trials

Current studies:

ATLAS: Testing non-inferiority of switching from 2 NRTIs+INI/NNRTI/PI to LA injectable CAB/RVP every 4 weeks in ART-experienced patients (618 men and women in 13 countries); results expected 2022

ATLAS 2M: Testing non-inferiority of LA injectable CAB/RVP every 4 weeks compared to LA CAB/RVP every 8 weeks (48 week duration, 1020 participants); results expected 2022

FLAIR: Testing efficacy, safety and tolerability of LACAB/RVP every 4 weeks following switch from 20 weeks of oral ABC/DTG/3TC in ART-naive patients (570 participants); results expected 2022

Development partners: Viiv (CAB)

Regulatory status: Not approved

IP details: Janssen's leading RPV-LAI formulation incorporated Alkermes' proprietary NanoCrystal® technology. The licensing arrangement between Janssen and Alkermes is not in the public domain. Janssen owns patent families covering:

- (AstraZeneca owns a patent family on the general formula covering RPV. Patent granted or pending in CN, ZA; BR, but not filed in ARIPO, EA, GT, IN, ID, TH, UA and VN. The status in MA and OAPI is unknown. Expected expiry in 2021).
- Composition of matter of rilpivirine (RPV), its salts and polymorphic forms. Patent granted or pending in ARIPO, CN, EA, IN (opposition), ID, OAPI, UA, VN, ZA; BR and TH, but not filed in GT. Status in MA unknown. Expiry in 2022. Janssen has signed bilateral licences with several generic companies for oral RPV, covering >100 LMICs.
- Solid oral composition of RPV salts. Patents granted or pending in ARIPO, CN, EAPO, IN, ID, OAPI, UA, VN, ZA; BR, but not filed in GT, MA & TH. Expected expiry in 2025.
- Several filings on parenteral formulations (intramuscular or subcutaneous) of RPV or its salt for the prevention and/or treatment of HIV infection. Patent granted or pending in ARIPO, EAPO, ID, OAPI, UA, ZA; BR, CN, IN, TH and VN, but not filed in GT or MA. Expected expiry 2026-2027
- Freeze-dried nanosuspension of RPV and a steric stabilizer, and compositions for injection. Patent granted or pending in RU; BR, CN, IN, but not filed in ARIPO, other EAPO countries, GT, ID, MA, OAPI, TH, UA, VN and ZA. Expected expiry in 2032
- Various filings on subcutaneous biodegradable implants for sustained release of HCV or HIV inhibitors, including RPV. Patent granted or pending in CN, RU, UA; BR, IN, ZA, but not filed in ARIPO, other EAPO countries, GT, ID, MA, OAPI, TH and VN. Expected expiry 2029-2030
- Additional Janssen patents on RPV polymorphic form and salt which are not contained in the marketed products are not mentioned here

Considerations for use in LMICs: May be clarified in Ph3 studies: Oral lead-in, injection volume tolerability, PK tail. Other points: intra-muscular injection should be given by a health care provider, large injection volume, current RVP-LA formulation requires cold-chain

Next milestone/other notes: Clinical development for use as PrEP has been discontinued



Product name: VRC01

Originator company: NIAID VRC

Drug type/class: Broadly neutralizing monoclonal antibody

Delivery method and frequency: Infusion every 8 weeks

Expected use: HIV prevention or treatment/therapeutic vaccine

Development status: In Phase 2b clinical trials

Current studies:

HPTN 081/HVTN 703: Men who have sex with men and transgender women in North and South America and Europe

HPTN 085/HVTN 704: Sexually active women in sub-Saharan Africa

Trials are also known as Antibody Mediated Prevention (AMP) trials, total 47 sites in 11 countries

Development partners: NIAID

Regulatory status: Not approved

IP details:

- The US Govt as represented by the DHHS owns a patent family covering neutralizing monoclonal antibodies against HIV gp120, including VRC01, VRC02, VRC03 etc and their expression vectors, for use in preventing or treating HIV infection or for testing a potential vaccine. Patents granted or pending in CN; IN and ZA, but not filed in other LMICs sampled by MPP. Expected expiry in 2030
- Univ. of Washington, and the US Gov as represented by the DHHS own a patent family covering VRC01-like mAbs such as VRC07 and their expression vectors, for use in preventing or treating HIV infection or for detecting HIV. Patents granted or pending in CN; IN and ZA, but not filed in other LMICs sampled by MPP. Expected expiry in 2032
- Xencor Inc. owns the Xtend Technology that has been applied to VRC01LS (VRC01 with Xtend) and VRC07-523LS (VRC07 with Xtend). Patents covering the Xtend Technology are granted or pending in CN, RU, IN; BR, but are not filed in the other LMICs studied by MPP. Expected expiry 2025-2028, earlier than the above VRC patents
- Licensing arrangement between Xencor and DHHS (or NIH) is not in the public domain

Considerations for use in LMICs:

Infusions can take several hours and must be performed by a health care provider; requires cold chain; likely to be costly to manufacture

Next milestone/other notes: Trial results expected 2021 or earlier. VRC01LS in pre-clinical studies has 4x the half-life of VRC01, with potential use as 6-monthly SQ injection



Product name: DAPIVIRINE VAGINAL RING

Originator company: International Partnership for Microbicides

Drug type/class: Antiretroviral (Non-nucleoside reverse transcriptase inhibitor)

Delivery method and frequency: Silicone vaginal ring with 30 day duration

Expected use: HIV prevention

Development status: Completed Phase 3 clinical trials (The RING Study and ASPIRE). HIV risk reduced by 30% overall. Higher risk reduction associated with increased use: women who used the ring at least some of the time saw HIV risk was cut by 45% among women who used the ring at least some of the time. Across both studies, HIV risk was reduced by 40% among women >21 years, while no risk reduction was seen among women <21 years, likely due to low product use on those studies. Preliminary results from open access studies (HOPE and DREAM) show increased adherence and modelling suggests risk reduction of 54%. New interim data from DREAM announced in October 2018 suggest a risk reduction of 59%.

Current studies: HOPE completed in October 2018; DREAM scheduled to complete in December 2018.

REACH study (MTN-034/IPM 045) to compare ring to oral PrEP (planned); safety studies among pregnant and breastfeeding women in Africa (planned)

Development partners: Ministry of Foreign Affairs Denmark, Flanders Dept of Foreign Affairs, Irish Aid, German Federal Ministry of Education and Research through the KfW Development Bank; Ministry of Foreign Affairs Netherlands; DfID UK; USAID with PEPFAR; Bill and Melinda Gates Foundation

Regulatory status: Submitted for Article 58 EMA opinion, expected 2019

IP details: IPM has received worldwide rights from Janssen Sciences Ireland UC to develop, manufacture and commercialize dapivirine-based products for use by women

Considerations for use in LMICs:

Next milestone/other notes: EMA opinion expected 2018 or 2019. REACH study to launch early 2019. Longer duration (90-day) DPV rings, rings using TDF and MPT rings (DPV or TDF plus hormonal contraception) in earlier stage (Phase 1) development.

See [what's next for the Dapivirine Ring?](#) (AVAC, March 2018) and IPM website <https://www.ipmglobal.org/our-work/our-products/dapivirine-ring>



Product name: CAM-2038

Originator company: Braeburn

Drug type/class: Partial opioid agonist (buprenorphine)

Delivery method and frequency: Pre-filled syringe, either weekly or monthly SQ injection by health care provider

Expected use: Opioid substitution therapy

Development status: Phase 3 trials completed, resubmitted for FDA approval May 2018

Current studies: Phase 3 efficacy study (HS-11-421) completed November 2016

Development partners: -

Regulatory status: FDA approval pending, action date 26/12/18

IP details: CAM2038 uses Camurus' proprietary FluidCrystal® injection depot technology and is covered by several patent families describing controlled release injectable buprenorphine formulations and preformulations (which form a depot upon injection and contact with aqueous fluid *in vivo*). Patents granted or filed in CN, EAPO (some patents only active in RU), ZA; BR, IN, ID, TH, but are not filed in other LMICs mentioned above. Expected expiry 2032-2035

- Camurus owns additional patents covering controlled release formulations for parenteral or non-parenteral use. These patents are granted or filed in CN, IN, RU, ZA; and BR. Expiry in 2025
- Tolmar Therapeutics Inc (formerly Atrix Labs, QLT) owns the patent on syringe device for CAM2038 as well as process for its filling and use. The patent was not filed in the majority of the LMICs sampled by MPP (the status in MA, GT and OA is unknown).

Considerations for use in LMICs:

SQ injection must be given by health care provider to avoid risks of depot with intravenous injection. Price likely to be significantly higher than oral formulation. Limited user preference data.

Next milestone/other notes:

The only LA buprenorphine available as both weekly or monthly depot



Product name: SUBLOCADE

Originator company: Indivior

Drug type/class: Partial opioid agonist (buprenorphine)

Delivery method and frequency: Pre-filled syringe, monthly SQ abdominal injection

Expected use: Opioid substitution therapy

Development status: FDA approved 2017

Current studies: N/A

Development partners: -

Regulatory status: FDA approved 30/11/17

- **IP details:** Indivior (rebranded from RECKITT BENCKISER HEALTHCARE - the original assignee of the patents - post demerger) owns patent families covering Sublocade composition and its approved indications and dosage regimens. Patents granted or pending in CN, ID, RU, ZA; BR and IN. Expected expiry in 2031. National phase filings have yet to be made regarding a more recent patent family, which is expected to expire in 2035
- Tolmar Therapeutics Inc (formerly Atrix Labs, QLT) owns the extended release Atrigel Technology which is used in Sublocade. Some patent families were not filed in LMICs, but other patents were granted or filed in CN, EA, IN and ZA, and national phase filings have not yet been made concerning other LMICs. Expiry expected in 2036. The licensing arrangement between Indivior and Tolmar is not in the public domain.

Considerations for use in LMICs:

Patients must be stable on daily sublingual/transmucosal buprenorphine tablet

SQ abdominal injection must be given by health care provider to avoid risks of depot with intravenous injection

Price: Approx \$1300-1800 per month in USA compared to around \$130 per month for oral buprenorphine

Limited user preference data

Next milestone/other notes: -



PRODUCT SUMMARY

Product name: PROBUPHINE

Originator company: Braeburn

Drug type/class: Partial opioid agonist (buprenorphine)

Delivery method and frequency: 6-monthly implant (4 rods in upper arm)

Expected use: Opioid substitution therapy

Development status: FDA approved 2016

Current studies: -

Development partners: -

Regulatory status: FDA approved 26/5/16

IP details: Titan owns patent families covering the Probuphine subdermal implant (based on the ProNeura™ implant technology) and indication. These patents were not filed in the majority of LMICs sampled by MPP. The US exclusivity related to New Product is set to expire on May 26, 2019.

Considerations for use in LMICs:

Patients must be stable on daily sublingual/transmucosal buprenorphine tablet

Must be inserted and removed by a health care provider

No more than 1 implant recommended per upper arm

Cost: Approximately \$5000 per implant in USA

Limited user preference data

Next milestone/other notes: -





Part 5: Target product profiles

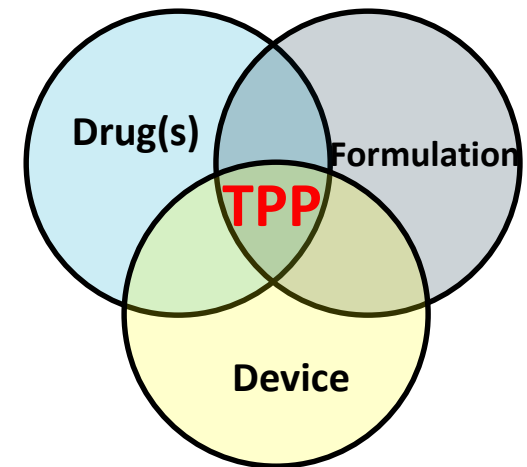
- Key considerations for all LA drugs
- Examples of ideal characteristics of drugs for use in innovative delivery devices
- HIV: TPP for LA injectable antiretroviral
- TPP for monoclonal antibody for HIV prevention
- TB: TPP for LA preventive treatment (LTBI)
- Malaria: TPP for chemoprophylaxis
- HCV
- MPTs: TPPs for rings and injectables
- Some implementation considerations



Key technical considerations for all LA drugs

(not mutually exclusive; for discussion)

- **Manufacturing-specific considerations**
 - Cost
 - Scalability
 - Sterility
 - Compatibility with preferred APIs
- **Drug-specific considerations**
 - Loading (volume of depot)
 - Combinations
 - Adverse drug reactions (need for oral lead-in?)
 - Drug-drug interactions
 - Cold-chain?
- **Release characteristics**
 - Achievable plasma (target) concentrations
 - Duration of exposure (plasma versus target); tail
 - Consistency / reproducibility
 - Tuneability?
 - Removal possibility



Examples of ideal physiochemical and pharmacokinetic characteristics of drugs for use in innovative drug delivery devices

Extended release gastric resident system (information provided by Lyndra)

- High potency
- Max 50 mg daily dose per drug, 200-300 mg total active ingredients
- Ph acidic resistant
- Stability at high temperature and high humidity
- Broader spectrum of possible APIs due to oral delivery
- Can use both hydrophobic and hydrophilic drugs



Implant (information provided by RTI)

- Small molecule, high potency, low dose
- Long half-life (intracellular persistence)
- Somewhat hydrophilic (not hydrophobic)
- Heat stable, chemically stable



Dissolving microarray needle patch (information provided by PATH)

- High-potency, low-dose drugs to minimize patch size
- Suitable for both hydrophobic and hydrophilic drugs
- Formulation, such as nanoparticles, that releases drug slowly over time to provide long-acting protection
- Compatibility with excipients that provide structural integrity for microneedles to pierce the skin, but dissolve quickly upon contact to minimize wear time
- Note: Molecules that are low-potency could be delivered with continuous-wear hydrogel microarray patches, rather than dissolving microarray patches



HIV: Ideal characteristics of target product for LA injectable antiretroviral (A.Hill for WHO, 2018)

Ideally, a target product for LA injectable treatment and prevention of HIV would possess the following characteristics. Any LA injectable intended to improve adherence must be safe and inexpensive in order to reach all populations:

- Exhibit similar or improved efficacy data to existing optimal oral therapies
- Be composed of a fixed-dose combination of injectable products
- Have a high genetic barrier to resistance
- Incur minimal injection-associated adverse events
- Be low in cost
- Be safe in patients with TB or viral hepatitis coinfection and pregnancy
- Have a low dosage volume on <2ml per injection
- Have no cold-chain requirement



HIV: Ideal and minimum acceptable profile for a long-acting injectable antiretroviral candidate (A. Hill for WHO, 2018)

Product Properties	Ideal profile	Minimum acceptable profile
Primary Indication	Viral suppression <50 copies/mL	Maintenance therapy
Patient Population	All HIV+ patients who are eligible for antiretroviral treatment	Patients excluded pregnant women and those with comorbidities
Resistance Profile	Improved resistance profile compared to oral regimens	Favorable resistance profile compared to oral regimens
Dosage Form	<2mL per injection	2mL per injection
Efficacy	Increased viral suppression when compared to oral therapy	As effective as oral therapy
Risk/Tolerability	No to mild risk of adverse events, no side effects, even at injection site	Mild to moderate side risk of adverse events, few side effects
Potency	Much higher potency compared to oral regimens, allowing for infrequent dosing	High potency compared to oral regimens



HIV: Target product profile for LA ARVs ([R. Tressler 2014](#))

	Minimum	Base Case	Optimum
Dosing Frequency	• Q Week	• Q Month	• \geq Q 2 Month
Route	• IV	• IV/IM/SC	• IM/SC
Safety Profile	• Similar to EFV	• No systemic allergic reactions • Similar to raltegravir	• No mitochondrial toxicity • Similar to FTC/3TC • Removable by hemofiltration
Metabolism • Includes drug-drug interactions	• No preference	• Not metabolized by CYP3A4 • CYP3A4 inhibition preferred to induction	• Not a substrate for CYP3A4 • No effect on CYP3A4 or glucuronidation
Tissue Penetration (viral suppression)	• LN • Genital Tract	• CNS • LN • Genital Tract	• CNS • LN • Genital Tract
Storage	• 2 yr, refrigeration acceptable	• 3 yr at 20-25 ^o C; or • 2 yr at \geq 40 ^o C	• \geq 3 yr at \geq 40 ^o C
Resistance Profile	• Similar to EFV • No cross resistance	• Infrequent • No cross resistance	• None • Protects other ARV's
Cost of Goods	• POC	• Affordable for RLC's	• < EFV



Target product profile for bNAb for HIV prevention

Product	Two IgG mAbs (or one bi-tri-specific)
Indication	Prevention of HIV infection
Efficacy Profile	Prevents infection by > 98% strains
Target Population	Adolescents/adults: high-risk of HIV infection Infants of HIV+ mothers: at birth; during breastfeeding
Dosage Administration	Adolescents/adults: 5 mg/kg SQ q3-6 months Infants: one dose (20 mg/kg SQ) at delivery
Safety/Tolerability	Adverse event frequency – rare but....
Cost of Goods	< \$50 per person, per year



Hinges on human efficacy data (AMP studies) and commercial interest in producing bNAbs for broad use



TB: Target product profile for LA approach for latent TB infection

([Swindells et al, 2018](#))

	Viability Parenteral Regimen	Ideal Parenteral Regimen
Mechanism of Action	Activity against drug susceptible TB	Activity against drug susceptible and drug resistant TB
# of Compounds in the Regimen	Monotherapy	Monotherapy
Indication	Treatment of presumed drug susceptible latent TB infection	Treatment of latent TB infection, including for contacts of MDRTB
Availability of Drug Susceptibility Testing (DST) for the Index Case	Rapid, low cost DST method that can be implemented at district level or below	No requirement for DST
Target Populations	Adults; irrespective of HIV or immune status	All age groups, irrespective of HIV status (pediatric formulation likely to come after adult indication)
Route of Administration	IV/IM/SC	IM/SC
Product Presentation	2 x 2 ml injections	Single injection (≤2 ml; 25-gauge or smaller) or implant
Dosage Form and Schedule	Suspension administered: 1 time per week or less frequently for up to 3-months; or 1 time per month for up to 6 months or longer. Implant lasting for up to 3 months.	Suspension administered less frequently than 1x per month; implant lasting for up to 1 year.
Expected Efficacy	Non inferior to SOC (e.g. RPT/INH - 3mo)	Superior to SOC (less incident TB, shorter duration of treatment)
Contraindications, Warnings, Precautions, Interactions, and Use During Pregnancy and Lactation	No additional monitoring required compared with current therapy; DDIs no worse than current therapy; mild injection site reaction	No contraindications or warnings; no significant side effects; no significant DDIs; safe for use in pregnant and lactating women; no injection site reaction
Shelf-life and Storage	2 yr at 4°C	3 yr at 40°C and 75% humidity
Product Registration and WHO Prequalification	Approved by FDA, EMA, WHO PQ, and national regulatory authorities of high-burden countries	
Manufactured Cost of Drugs	Total health system cost no greater than current	Total health system cost less than current

5
TPPs

Malaria: Target product profile for chemoprophylaxis

Parameter to be demonstrated	Minimum essential	Ideal
MoA	At least one molecule has activity protecting against establishment of infection of hepatocytes	Both molecules show activity protecting against establishment of infection of hepatocytes; in addition, one or more should have activity against the erythrocytic stages; drug resistant mutations should not be transmitted
Dosing regimen	Once per month, intramuscular	Once per three months, intramuscular or sub-cutaneous if quick onset of action and appropriate volume of administration achievable
Rate of onset of action	Rapid onset of protection within 72 hours of initial injection	Immediate protection (no lag prior to onset of action)
Clinical efficacy	<p>≥ 80% Protective Efficacy: reduction in incidence of symptomatic malaria.</p> <p>No fit drug resistant parasites identified in volunteer infection studies; no mutants identified preclinically with cross resistance against potential combination partner</p>	<p>≥ 95% Protective Efficacy: reduction in incidence of symptomatic malaria.</p> <p>No fit drug resistant parasites identified in volunteer infection studies; no mutants identified preclinically with cross resistance against potential combination partner</p>
Drug-drug interactions	No unmanageable risk in terms of solid state or PK interactions	No risks in terms of solid state or PK interactions with other co-administered PrEP or therapeutics
Safety and tolerability	No drug-related SAEs; minimal drug-related AEs that do not result in clinical study exclusion. No unacceptable pain, irritability of inflammation at injection site.	Idem
Use in patients with reduced G6PD activity	Testing not required; no enhanced risk in mild-moderate G6PD deficiency	No enhanced risk
Use in infants/children	Use in children >6 months old	All age groups
Formulations	Suitable for intramuscular injection with minimal preparation; maximum volume of 2 ml for adults and 0.5 ml for infants administered with 21-27 gauge needle; partner drugs injected separately	Liquid pre-filled injection device for intramuscular; maximum volume of 1 mL for adults and <0.5 ml infants administered with 27-30 gauge needle; fixed dose combination of the drugs; or subcutaneous injection if volumes smaller than above for intramuscular injection
Cost of treatment	<5 USD per injection	< 2 USD per injection for children under 5 years
Shelf life of formulated product (ICH guidelines for Zones III/IV)	≥ 2 years	≥ 3 years

[McIntyre, F et al, 2018](#)
[Injectable antimalarials revisited: Discovery and development of new agents to protect against malaria](#)



HCV: Target product profile - a one-shot cure?

- HCV cure rates with current 8-12 week oral treatment approaching 99%
- There is currently no TPP for LA HCV products, but there is increasing interest in developing a safe, effective LA single-injection cure to improve adherence (especially in high-risk groups) and outcomes and minimize burden on the patient and health system



MPTs: Target product profiles

MPT Intravaginal Ring Target Product Profile

Product Name: ARV + HC MPT IVR

MPT Long Acting Injectable Target Product Profile

Product Name: ARV + HC Long Acting Injectable/Systemic MPT

Some implementation considerations

For each product, understand and balance

- Dosing frequency
- Side effect profile
- User burden
- User preferences
- Health system burden and capacity
- Delivery channel(s)
- User- or provider-initiated?
- Product cost
- Program cost, including demand creation
- Provider training
- Reversibility
- Continuity/consistency of use
- Discretion of use/
potential to reduce stigma



Part 6: User and patient preferences for long-acting technologies



- Injectable HIV treatment
- HIV prevention
- Multi-purpose prevention
- Opioid substitution therapy



LA-injectable HIV treatment: User preferences

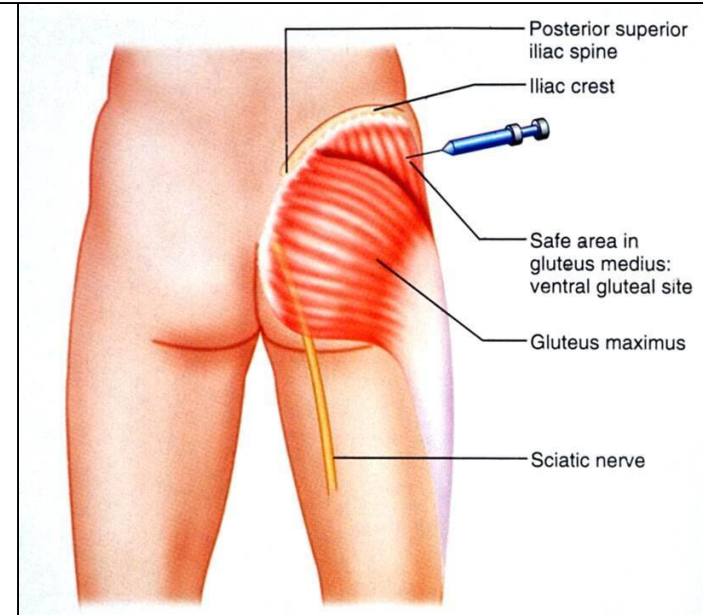
- 73% of 400 HIV-positive adult patients surveyed in Omaha and Baltimore indicated that they would definitely or probably try injectable nano-formulated antiretroviral therapy; 61% with weekly dosing, 72% every two weeks and 84% every month.
- 48% were concerned about possible side effects and 35% were concerned about needle use.
- Interest in injectable ART was higher among those who reported having missed doses or injected drugs ([Williams et al, 2013](#))

Published in final edited form as:

Nanomedicine (Lond). 2013 November ; 8(11): 1807–1813. doi:10.2217/nmm.12.214.

Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients

Jennifer Williams¹, Harlan R Sayles², Jane L Meza², Patrick Sayre³, Uriel Sandkovsky¹, Howard E Gendelman^{1,4}, Charles Flexner³, and Susan Swindells^{1,*}



Readiness of youth living with HIV for LA ARVs

TUPEB0460

IAS 2017 – no hyperlink available

Readiness of youth living with HIV for long-acting antiretrovirals

E.D. Weld¹, R. Dallas², A. Camacho-Gonzales³, S. Rana⁴, L. Thomas-Seaton², A. Gaur², P. Ryscavage⁵, C. Flexner⁶, R. Chakraborty³, A. Agwu⁷

- 303 youth (13-24 years; median age 22 years) living with HIV surveyed at 4 clinics in Baltimore, Atlanta and Memphis
- 87% would probably/definitely try intramuscular injectable LA-ARVs. Willingness to try increased with less frequent injections – 3 monthly administration preferred
- 77% would probably/definitely try surgically-placed implant containing ARVs
- Major concerns included side effects and longer duration of side effects, injection site pain/swelling
- Conclusion: High levels of acceptability “may be important given the high rates of attrition in care and non-adherence of this vulnerable group. LA-ARV should be given high priority as a potentially viable treatment option to improve clinical outcomes in HIV-infected youth”.



LA-injectable HIV treatment: patient satisfaction and adherence in LATTE-2 Phase 2b trial



THPEB042 - Poster Exhibition

TITLE
Patient satisfaction, tolerability and acceptability of Cabotegravir (CAB) and Rilpivirine (RPV) Long-Acting (LA) therapy in HIV-1 infected adults: LATTE-2 week 96 results

PRESENTER
Miranda Murray

AUTHORS
M. Murray¹, F. Pulido², A. Mills³, R. Moti⁴, R. Leblanc⁵, H. Jaegar⁶, V. Chounta¹, D. Dorey⁷, S. Griffith⁸, J. Mrus⁸, V. Cannon⁹, D. Margolis⁹, W. Spreen⁹



- Injection site pain was the most frequently reported adverse event (97% of those receiving the injection every 4 weeks; 95% of those receiving it every 8 weeks)
- Patients receiving the injection every 8 weeks and every 4 weeks reported higher satisfaction with HIV treatment at 96 weeks, compared to those maintained on daily oral therapy
- Patients receiving treatment every 8 weeks demonstrated numerically higher levels of satisfaction compared to those receiving it every 4 weeks



THPEB084 - Poster Exhibition

TITLE
Patient adherence to long-acting CAB and RPV injections through 96 weeks of maintenance therapy in LATTE-2

PRESENTER
Kenneth Sutton

AUTHORS
K. Sutton¹, M. Shaefer¹, D. Margolis¹, D. Dorey¹, F. Zhang², V. Chounta³, S. Griffith¹, V. Canon⁴, W. Spreen¹



- Adherence defined as the number of injection visits within a 7-day dosing window of projected visit divided by the number of expected visits over 96 weeks
- At 96 weeks, 98% of injections were within the 7-day window
- 2% were outside the 7-day window
- <1% missed an injection with/without oral bridging



LA approaches for HIV PrEP: Women's preferences

J Int AIDS Soc. 2016; 19(1): 20875.
Published online 2016 May 30. doi: [10.7448/IAS.19.1.20875](https://doi.org/10.7448/IAS.19.1.20875)

PMCID: PMC4887458
PMID: 27247202

Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study

Ellen H Luecke,^{S,1} Helen Cheng,¹ Kubashni Woeber,² Teopista Nakyanzi,³ Imelda C Mudekunye-Mahaka,⁴ Ariane van der Straten,^{1,5} and on behalf of the MTN-003D Study Team

Author information ► Article notes ► Copyright and License information ► Disclaimer

- Given a theoretical choice between several PrEP option (oral tablets, vaginal gel, vaginal film or suppository or LA products such as injectables, implants or vaginal ring), **81% of the women surveyed in South Africa, Zimbabwe and Uganda (n=68) preferred the LA products.**
- Attributes described as important in a preferred product formulation included duration of activity, ease of use, route of administration, clinic- versus self-administration and degree of familiarity with the product.

AIDS PATIENT CARE and STDs
Volume 31, Number 7, 2017
© Mary Ann Liebert, Inc.
DOI: 10.1089/apc.2017.0075

BEHAVIORAL AND PSYCHOSOCIAL RESEARCH

Favoring "Peace of Mind":
A Qualitative Study of African Women's HIV
Prevention Product Formulation Preferences
from the MTN-020/ASPIRE Trial

Ariane van der Straten, PhD^{1,2} Mary Kate Shapley-Quinn, MPH¹ Krishnaveni Reddy, MB BCH³
Helen Cheng, MS¹ Juliane Etima, MA⁴ Kubashni Woeber, MBA, MMed Sc⁵ Petina Musara, BSc⁶
Thesla Palanee-Phillips, MMed Sc, PhD³ Jared M. Baeten, MD, PhD⁷
and Elizabeth T. Montgomery, PhD¹, on behalf of the MTN-020/ASPIRE Study Team

- Given a theoretical choice between several HIV prevention options (condoms, oral tablets, injectables, implants and a vaginal gel, film or insert) **women in Malawi, South Africa, Uganda and Zimbabwe expressed most interest in LA options** (rings, implants, injections).
- Dislike of vaginally-administered products was strongest among young women.
- Attributes described as important were continuous protection, discreet and simplified use.

VACCINE AND PHARMACEUTICAL TECHNOLOGIES



ACCEPTABILITY OF MICROARRAY PATCHES FOR DELIVERY OF HIV PRE-EXPOSURE PROPHYLAXIS (PrEP) AMONG WOMEN AND HEALTH CARE PROVIDERS IN SOUTH AFRICA

A. Rein-Weston¹, C. Jarrhian¹, B. Blair¹, Y. Moyo¹, B. Creelman¹, E. Saxon¹, R. Donnelly², D. Zehrung¹
¹PATH (www.path.org), ²Queen's University (www.qub.ac.uk)

- User acceptability focus groups of women at high risk for HIV in **South Africa** discussed both an adhesive skin patch and a dissolvable vaginal patch for delivery of a LA ARV drug.
- Women particularly favoured a vaginal patch due to the potential for discreet use and familiarity with other vaginal products such as tampons. Reassurance was sought that the patch would not increase vaginal lubrication or discharge.
- The skin patch was less favoured due to concerns about efficacy and ability to wear the patch continuously and discreetly.

One size will not fit all: Divergent stated preferences for new antiretroviral-based HIV prevention products across adults, adolescents and female sex workers in South Africa

Matthew Quaife^{1,2}, Robyn Eakle^{1,2}, Maria Cabrera², Peter Vickerman^{1,3}, Sinead Delany-Morettiwe², Fern Terris-Prestholt¹



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& TROPICAL
MEDICINE



- In a discreet choice experiment to elicit preferences among **South African women** for five PrEP delivery methods (oral pill, microbicide gel, diaphragm, vaginal ring and injectable ARV), Injectable PrEP was favoured by all groups, particularly adult women and female sex workers
- Understanding user preferences is critical to ensure new HIV prevention products are appropriately implemented among key groups
- Uptake and impact modelling should consider differential uptake and use by group accounting for variations in preferences
- Results support the integration of HIV prevention into sexual health and contraception services



LA HIV PrEP: Preferences of young MSM

Share <http://programme.ias2017.org/Abstract/Abstract/4831>  

TITLE
Acceptability of emerging technologies for sustained, long-acting HIV pre-exposure prophylaxis (PrEP) among young men who have sex with men (MSM) in the U.S.

PRESENTER
George J. Greene

AUTHORS
G.J. Greene¹, M. Matson², A. Carballo-Diéguez³, T.J. Hope², P.F. Kiser², R.T. D'Aquila²

- 6 focus groups of young MSM 18-29 years old; Chicago, USA, 2016
- **Injections** were viewed favourably in terms of privacy and familiarity; concerns existed with regard to irreversibility in the event of HIV infection
 - Desired attributes: Duration of 2-6 months, 1-3 injections per dose
- **Implants** were viewed favourably in terms of privacy and duration; apprehension about surgical procedure for implant and removal for non-biodegradables; concerns about removability in the event of HIV infection
 - Desired attributes: Duration of 6-12 months, 1-2 implants per insertion



Multi-purpose prevention technologies (MPTs): Women's preferences for combined HIV prevention and contraception

AIDS and Behavior
<https://doi.org/10.1007/s10461-018-2078-5>

ORIGINAL PAPER



Young Women's Ratings of Three Placebo Multipurpose Prevention Technologies for HIV and Pregnancy Prevention in a Randomized, Cross-Over Study in Kenya and South Africa

Alexandra M. Minnis^{1,2} · Sarah T. Roberts¹ · Kawango Agot³ · Rachel Weinrib¹ · Khatija Ahmed⁴ · Kgahliso Manenzhe⁴ · Fredrick Owino³ · Ariane van der Straten^{1,5} on behalf of the TRIO Study Team

© The Author(s) 2018

Injectables preferred over rings and tablets

Strong preferences among African women for LA MPT products

Straten Avd et al. *Journal of the International AIDS Society* 2018, **21**:e25094
<http://onlinelibrary.wiley.com/doi/10.1002/jia2.25094/full> | <https://doi.org/10.1002/jia2.25094>

JIAS
 JOURNAL OF THE
 INTERNATIONAL AIDS SOCIETY

Check
 update

RESEARCH ARTICLE

The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention

Ariane van der Straten^{1,2} Kawango Agot³, Khatija Ahmed⁴, Rachel Weinrib¹, Erica N Browne¹, Kgahliso Manenzhe⁴, Fredrick Owino³, Jill Schwartz⁵ and Alexandra Minnis^{1,6} on behalf of the TRIO Study Team

Corresponding author: Ariane van der Straten, 351 California Street, Suite 500, San Francisco, California 94104. Tel: 415-848-1324. (arlane@rti.org)

Tablets, rings and injections preferred over condoms for HIV and pregnancy prevention. 62% preferred injections over tablets and rings.



6
 Users

Unitaid

LA buprenorphine for opioid substitution therapy

- Reported high satisfaction (86%) and sustained improvements in mental health, addiction severity, treatment effectiveness and proportion employed with Sublocade monthly injectable ([Ling et al, 2018](#)).
- Available data on user preferences for Probuphine (6-monthly implant) are very limited.

[Ther Adv Psychopharmacol](#). 2017 Mar; 7(3): 119–134.
Published online 2016 Dec 19. doi: [10.1177/2045125316681984](#)

PMCID: PMC5354129
PMID: [28348732](#)

Probuphine® (buprenorphine implant): a promising candidate in opioid dependence

[Preeti Barnwal](#), [Saibal Das](#), [Somnath Mondal](#), [Anand Ramasamy](#), [Tanay Maiti](#), and [Arunava Saha](#)

[Author information](#) ▶ [Copyright and License information](#) ▶ [Disclaimer](#)

“Although the safety and efficacy of buprenorphine implant have been confirmed in several studies, how many patients and physicians would prefer buprenorphine implants instead of the available forms of the medicine is a big question and has never been measured in these studies”.

Real-time patient reviews
at [drugs.com](#)

Drugs Used to Treat Opiate Dependence

The following list of medications are in some way related to, or used in the treatment of this condition.

Drug Class

Rx OTC Off Label Only Generics [Update](#)

Drug name	Rx / OTC	Preg	CSA	Alcohol	Reviews	Rating	Popularity
Suboxone	Rx	C	3	X	537 reviews	8.0	<div style="width: 80%;"></div>
buprenorphine / naloxone	Rx	C	3	X	691 reviews	8.0	<div style="width: 60%;"></div>
buprenorphine	Rx	C	3	X	112 reviews	9.0	<div style="width: 40%;"></div>



Additional resources on user preferences

END USER RESEARCH MAPPING, REVIEW & ANALYSIS LONG-ACTING INJECTABLES SUB-ANALYSIS

**HIV Prevention
Market Manager**

Accelerating Product Introduction
Informing Product Development
Reducing Time to Impact

April 2017



Supported by the Bill & Melinda Gates Foundation

NEXT WAVE OF PREVENTION OPTIONS



Next PrEP: Insights from users

Ariane van der Straten and Alexandra Minnis
Women's Global Health Imperative
RTI International – San Francisco, CA USA

Satellite Session:
Sunday, 23 July 2017, 14:45-16:45

OPTIONS CONSORTIUM: Optimizing Prevention Technology Introduction On Schedule

Core Implementers: FHI 360, Wits RHI, AVAC

Primary Partners:
Avenir Health
FSG
LSHTM
LVCT Health
McCann Global Health
Pangaea Global AIDS

A Review of Social and Behavioral Factors Influencing
Dapivirine Ring Use

Cooperative Agreement No. AID-OAA-A-15-00035
Prepared by: Jack Clancy, AVAC
January 2017



Part 7: Towards a healthy market for LA technologies



- **The example of the market for LA hormonal contraception in LMICs**
- **5 dimensions of a healthy market: Issues for consideration**
 - Innovation/availability**
 - Quality and regulation**

Regulatory pathways for new chemical entities and existing oral drugs repurposed as LA products
 - Affordability**

Intellectual property considerations and MPP LA landscape
 - Global supply**
 - Country adoption**



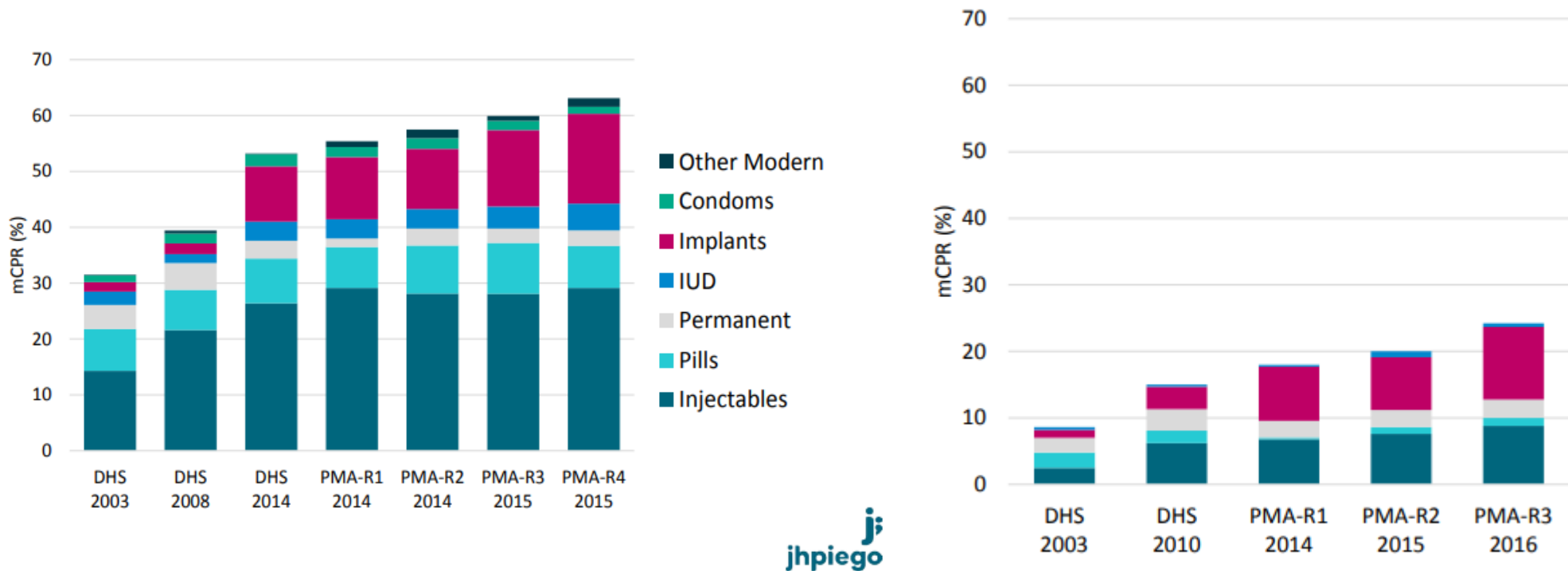
Example of long-acting contraceptive market in LMICs

Is the LA hormonal contraception market healthy and how did we get there?

- The expanded use of LA contraception in LMICs has been possible due to improvement in market conditions and availability of adequate formulations
 - A number of LA products (injectables, implants) are eligible for procurement by UNFPA after WHO prequalification
 - Donor and public health markets are supplied centrally
 - Prices in the public sector have decreased substantially
 - Community delivery is possible
- Access still remains limited in some areas



LA contraception: Rapid introduction and increased use over traditional methods in Africa

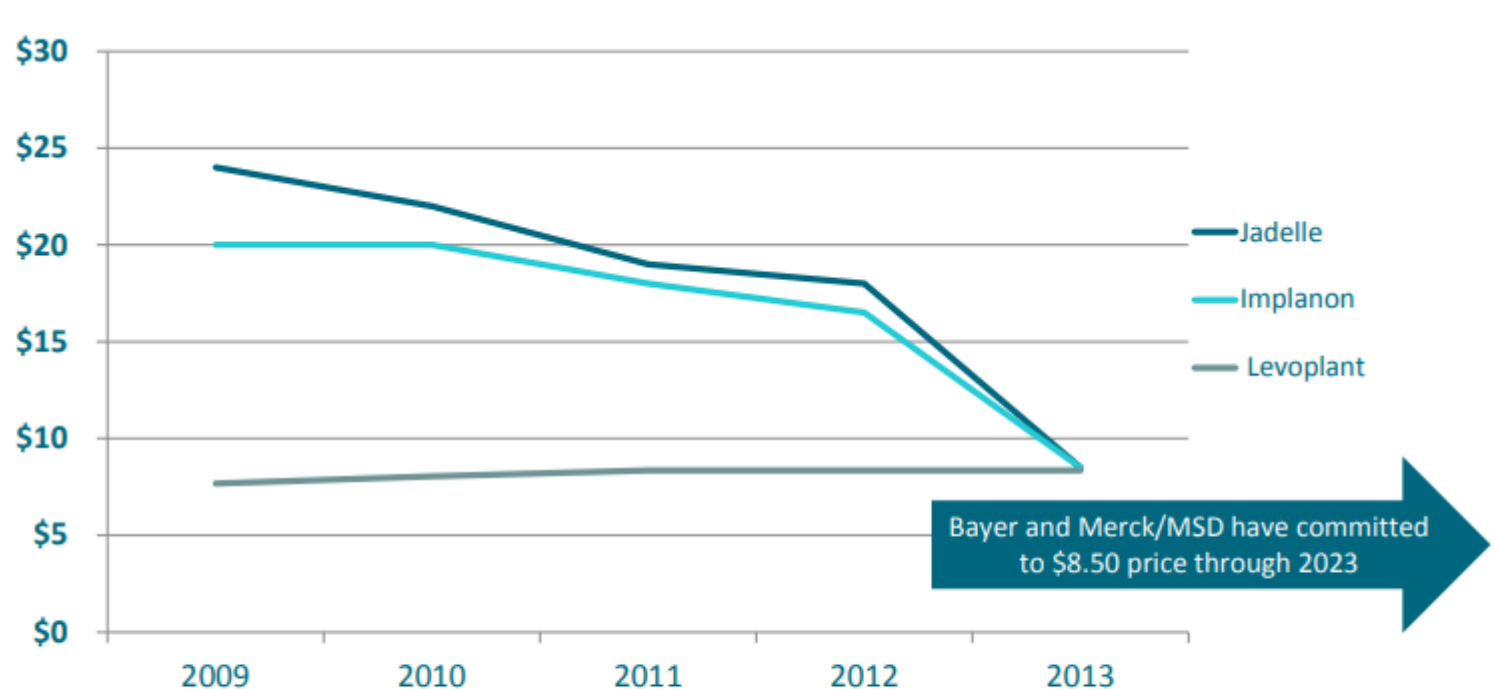


Kenya and Burkina Faso examples of mCPR and Method Mix among Married Women, 2003–2015. Source: DHS and PMA2020

[Source: Global trends and considerations in contraceptive implant scale-up, Jhpiego, 2017](#)



LA contraception: Price decrease in LMICs



7

Slide adapted from M. Steiner, FHI360



Contraceptive implant prices 2009-2013

[Source: Global trends and considerations in contraceptive implant scale-up, Jhpiego, 2017](#)



Example of market-shaping intervention to increase affordability of and access to LA hormonal contraception implants



CASE STUDY

Expanding global access to contraceptive implants

CHAI AND PARTNERS ACHIEVED A PRICE REDUCTION AGREEMENT FOR CONTRACEPTIVE IMPLANTS THAT INCREASED TOTAL IMPLANT DISTRIBUTION BY 56% FROM 2012 TO 2013 AND WILL RESULT IN PROCUREMENT SAVINGS OF MORE THAN US\$300 MILLION OVER SIX YEARS.

OVERVIEW

Access to voluntary contraception saves the lives of mothers and infants by allowing women to better space and limit their pregnancies, improves health outcomes, strengthens the financial wellbeing of families, and helps achieve national health and economic goals.¹ Of the widely available family planning methods, three- and five-year contraceptive implants are two of the most highly effective at preventing pregnancy (Figure 1) and are well suited for many women and health systems in low- and middle-income countries (LMICs).² Despite the efficacy and availability of quality-assured implants, evidence from national family planning programs has suggested a significant unmet need. CHAI identified several market barriers preventing access: high pricing compared to other contraceptive methods (which limited donor purchasing), no coordinated global supply planning or forecasting, and lack of trained health workers providing implants as part of routine family planning services.

THEORY OF CHANGE

An increase in demand, secured by donors through a volume guarantee, allows implant suppliers to achieve scale efficiencies and thus reduce prices. Price reductions for implant contraceptives increase access in LMICs and reduce the number of unwanted pregnancies, contributing to improved health outcomes, and ensuring that women have access to a broad range of contraceptive choices.

IMPACT

Price reductions for Jadelle (Bayer) and Implanon (Merck) will result in procurement savings of over US\$300 million, averting thousands of deaths over the six years of the agreements.

KEY PARTNERS

- BMGF
- DFID
- UNFPA
- USAID
- Norad
- SIDA
- CIFF

The price of implants has halved as a result of the multi-donor volume guarantee. With the price reduction, combined orders of contraceptive implants increased by 62 per cent in 2014 compared to 2012, resulting in large savings to governments in LMICs (ciff.org)

JAN 2013 – DEC 2018

CONTRACEPTIVE IMPLANT VOLUME GUARANTEE

To increase access to long-acting reversible contraception for women in 69 countries prioritised by Family Planning 2020.

PARTNERS
Bayer - Merck

OTHER FUNDERS
Bill & Melinda Gates Foundation - Government of Norway - Swedish International Development Corporation



5 dimensions of a healthy market to consider

Innovation/ Availability



- There is a robust pipeline of new products, regimens or formulations intended to improve clinical efficacy, reduce cost, or better meet the needs of end users, providers or supply chain managers (including relevant populations)
- New and/or superior evidence-supported adapted products are timely introduced in the market and made available in LMICs

Quality and regulation



- The medicine or technology is available at stringent standard of quality, and there is reliable information on the quality of the product
- This includes also the quality of starting and intermediary materials

Affordability



- The medicine or technology is offered at the lowest possible price that is sustainable for suppliers and does not impose an unreasonable financial burden on governments, donors, individuals, or other payers
- Market concentration is adequate

Global supply



- There is a reliable, sustainable and consistent supply of products to meet demand

Country adoption



- Supply chain systems (including quantification, procurement, storage, and distribution) function effectively to ensure that products reach end users in a reliable and timely way.
- Countries, programmes, providers (e.g., healthcare providers, retailers), and end users rapidly introduce and adopt the most cost-effective products (within their local context)



Towards a healthy market for LA technologies

1/5: Availability/innovation

Issues for consideration

- Dynamic product pipeline, with HIV the most advanced, but not necessarily meeting the needs of LMICs
 - Large injection volumes for current molecules
 - Lack of fixed-dose/triple combination formulations for ART
 - Requirement for oral lead-in
 - Need for cold chain (e.g. rilpivirine)
 - Most research is based in injectables which cannot be removed, risk of adverse events or infection with drug resistant virus (tail)
- Currently no LA products in TB or HCV
- Growing funding for early pre-clinical research, with expected gaps in moving forward through clinical development to implementation



Towards a healthy market for long-acting technologies

2/5: Quality and regulation

Issues for consideration

- Challenges for clinical trial design and regulatory approval (e.g. equivalence with oral therapy, interpatient variability, requirement for oral lead-in)
- Need for clear regulatory pathways at global level for drug-device combinations
 - WHO has experience prequalifying two LA hormonal contraceptives
- Lack of capacity/standards for post-marketing surveillance (Quality Control) at country level





Regulatory challenges in developing long-acting antiretrovirals for treatment and prevention of HIV infection

Curr Opin HIV AIDS 2015, 10:278–281

Vikram Arya^a, Stanley Au^a, Yodit Belew^b, Peter Miele^b, and Kimberly Struble^b

Purpose of review

To outline some of the regulatory challenges inherent to the development of long-acting antiretrovirals (ARVs) for the treatment or prevention of HIV infection.

Recent findings

Despite advances in drug development that have reduced ARV dosing to once daily, suboptimal drug adherence remains an obstacle to successful HIV treatment. Further, large randomized trials of once daily oral ARVs for preexposure prophylaxis (PrEP) have shown that drug adherence correlates strongly with prophylactic effect and study outcomes. Thus, the prospect of developing long-acting ARVs, which may mitigate drug adherence issues, has attracted considerable attention lately.

Summary

Because of their pharmacokinetic properties, the development of long-acting ARVs can present novel regulatory challenges. Chief among them is determining the appropriate dosing regimen, the need for an oral lead-in, and whether existing data with an approved oral agent, if available, can be leveraged for a treatment or prevention indication. For PrEP, because validated biomarkers are lacking, additional nonclinical studies and evaluation of tissue concentrations in multiple compartments may be necessary to identify optimal dosages. Study design and choice of controls for registrational trials of new long-acting PrEP agents might also prove challenging following the availability of an oral PrEP drug.

Keywords

antiretroviral therapy, HIV preexposure prophylaxis, HIV/AIDS, long-acting



Regulatory scenarios for LA ARVs for HIV treatment or prevention

LA products are either

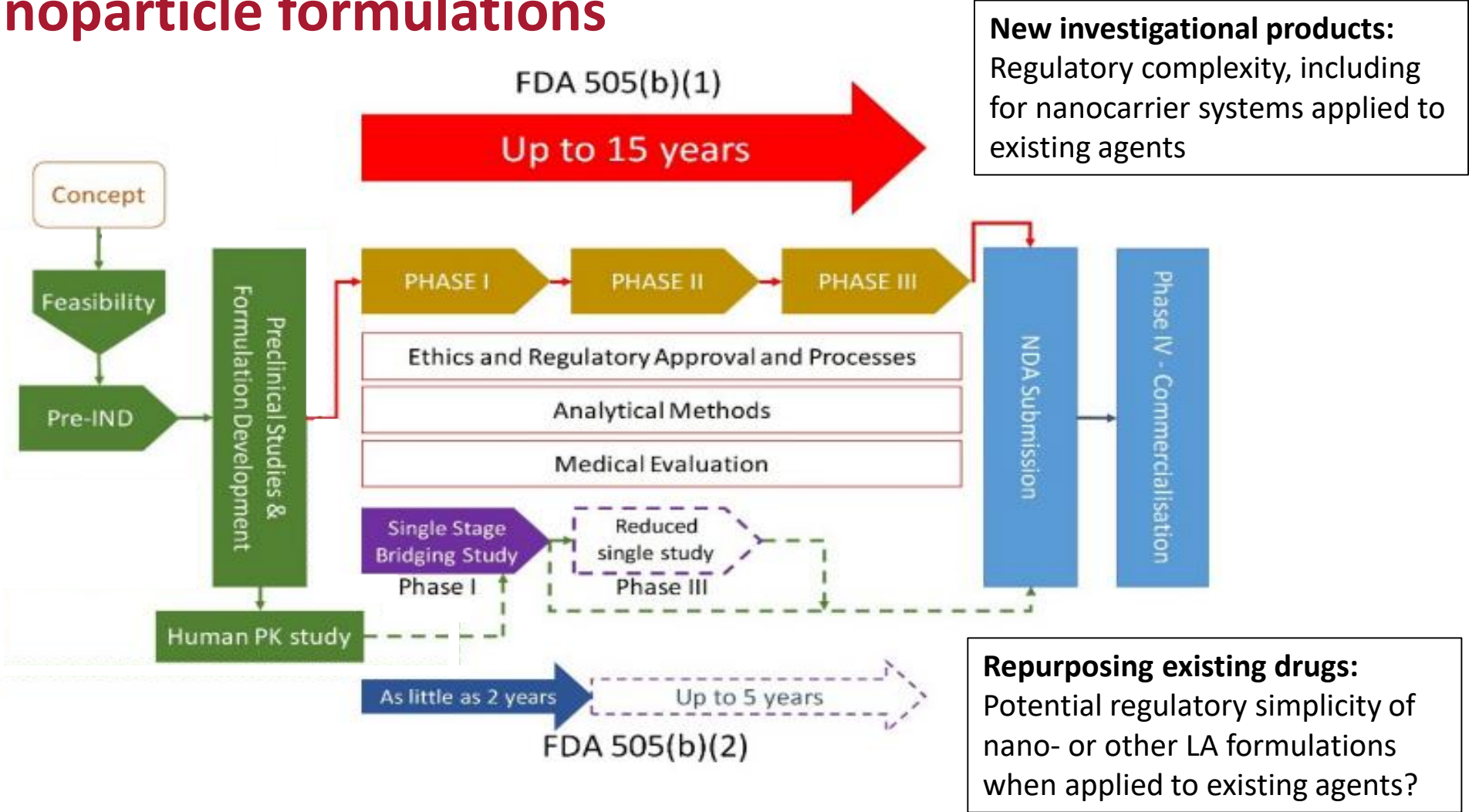
- A new investigational LA product

or

- Repurposing of an approved oral product for the same indication as an LA injectable (or other delivery system)



Example: Regulatory scenarios in the case of solid drug nanoparticle formulations



Regulatory pathways: New investigational ARV for LA treatment

- Can be developed in absence of immediate release formulation
- Typical pathway similar to small molecules
 - Single and multiple ascending dose trials
 - Proof-of-concept trials
 - Phase 2 Dose-finding trials
 - Phase 3 trials



Regulatory pathways for repurposed oral ARVs for LA treatment: Types of data needed to support approval

- PK data alone may be sufficient to support approval
- But if scientific rationale does not support use of PK data alone, a full safety evaluation is likely needed
 - At least 300 patients depending on what is observed during phase 1/2 trials and what is known about the parent drug
 - e.g. liposomal compounds have a variety of host reactions and safety trials are needed
- Efficacy data could also be needed if PK data are not supportive



Regulatory pathways for repurposed oral ARVs for LA treatment: types of data needed to support approval

- **PK Comparison**
 - Evaluate PK profile between reference and test product to determine if safety and efficacy extrapolation is possible
 - Ratio AUC, Cmax and Cmin [90% CI 0.8-1.25 (80-125%)]
- **Exposure-Response (E-R)**
 - Target exposures are different
 - E-R data may make it possible to determine if differences are not meaningful
- **Clinical Data**
 - E-R not understood and/or PK significantly differs and E-R not supportive
 - Single clinical trial may be sufficient to change formulations



LA ARVs for treatment: PK/PD considerations

- Residual drug exposure (PK tail)
 - Safety
 - Potential development of viral resistance once dosing of LA product is discontinued
- Drug interactions (DDI)
 - Relevant DDI trials as needed based on metabolism profile
 - Also consider DDIs between LA ARV and oral ARVs during PK tail period



LA ARVs: Risk mitigation strategies in studies for no oral lead-in

- Stringent enrollment criteria
- Start with small number of subjects
 - Dose 1-2 subjects
 - Stagger dosing between subjects for specified interval
- Stringent stopping rules for individual subjects, cohorts and the study
- Consideration of an independent unblinded medical monitor or data monitoring committee to oversee safety



Regulatory pathways for LA ARVs for PrEP (1): Considerations for study design

- Can be developed in absence of immediate release formulation
- Clinical trials are needed for HIV prevention indications
 - Approved formulation, new formulation of approved drug or new investigational agent
 - Exposure response for prevention not known and no validated biomarkers
 - Exposure-response data from treatment are insufficient to link treatment and prevention efficacy
- Trial design considerations:
 - Choice of comparator
 - Placebo vs active control
 - Non-inferiority challenges: MSM vs high risk women
 - Large sample sizes needed due to low incidence of sero-conversion even in high-prevalence populations; risk-reduction interventions e.g. condoms can reduce overall infection rate and further increase the sample size needed



Regulatory pathways for LA ARVs for PrEP (2): Considerations for study design

- Phase 2b/3 lead-in design
 - Enroll sexually active or high-risk and not restrict to low-medium risk
 - Advantage
 - Enroll fewer subjects than separate phase 2 and 3 trials
 - Allow more safety evaluations before expand enrollment
 - Provide some preliminary data on efficacy and may facilitate faster development timeline
- Patient population diversity
 - High-risk women
 - MSM
 - Sero-discordant couples
 - PWID



Regulatory pathways for LA ARVs for PrEP (3): PK/PD considerations

- Oral lead-in is not absolute
- Role of drug concentrations in plasma vs other biologic matrices (cervicovaginal/rectal issue)
 - Identifying appropriate biologic matrix, if feasible, to assess drug concentrations = challenge, reliability and feasibility concerns
 - Drug exposures may be different depending on biologic matrix
 - Exposure of tenofovir and emtricitabine was wide ranging depending on type of mucosal tissue ([Patterson, et al 2011](#))
- Tissue collection
 - Relationship between plasma and tissue concentrations is not well understood
 - Exploratory analyses to advance field
- Other
 - Window of protection
 - PK tail



Summary of regulatory issues in LA ARVs

Repurposing long-acting formulation of an approved ARV

- In most situations, not possible to match AUC or C_{max}
- Maintaining same or higher trough or pre-dose concentration compared to oral formulation is important
- Can use E-R data but likely clinical trial data needed

New Investigational LA ARV for treatment

- Clinical trial data (safety and efficacy) needed
- **Oral lead-in is not absolute (but the FDA currently requires it to evaluate adverse events)**

Other PK/ PD considerations

- Residual drug exposures (PK tail)
- Drug interactions



Towards a healthy market for LA technologies

3/5: Affordability

Issues for consideration

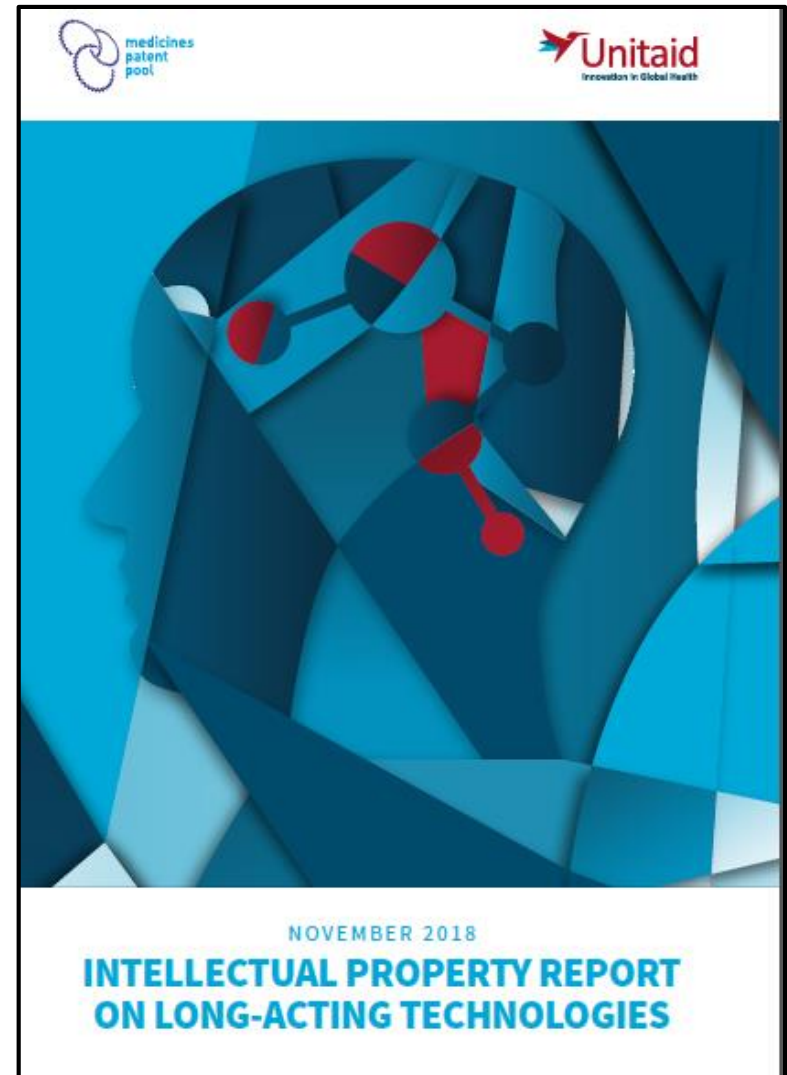
- High unit price in HICs for most existing LA formulations
- Increased delivery costs could contribute to high total costs of procurement (e.g. nurse to administer injection, injection-related commodities, safe disposal, cold chain; these may be offset by savings → modelling needed)
- Marketed products do not yet have access programs for LMICs
- Cost of generic production for LA products likely higher than for current oral therapy
 - What price will make them feasible? How can generic manufacturers be helped to minimize risk?
 - Potential regulatory complexities for a generic product
- Lack of market preparedness and potentially limited initial demand in absence of market-shaping efforts → Risk of persistent high price
- Modelling of prevention markets is especially important for market shaping (cost, demand, risk levels, etc.)
- Complex IP (drug, formulation process, delivery system/device)
 - Intellectual property barriers need to be addressed for competition to take place
 - Market visibility and risk-sharing are also needed to boost generic market
 - Large upfront investments (e.g. sterile plant) might be needed for generic companies to develop capacity
 - Capacity development or technology transfer might be required



Medicines Patent Pool: Intellectual property landscape for LA technologies

Medicines Patent Pool has worked with Unitaid to develop a summary of the intellectual property status of selected LA technologies for HIV, HCV, TB, malaria and harm reduction, including most of the drugs, devices and processes referred to in this compendium.

Some of the platform technologies may also be applicable to other therapeutic areas.



Challenges for generic manufacturing of LA technologies

- **The patent landscape for a novel LA product is potentially very complex**
 - May involve multi-layered patent protections covering drug/molecule, formulation process and materials (e.g. nanotechnology), the delivery device, and the process of manufacturing each component
 - There is wide geographical variation in patent protection by product/technology
- **Novel drug delivery approaches are technologically intensive**
 - Generic manufacturers would need to possess/acquire different capacities than for manufacturing conventional oral pills e.g. nano-formulated drug reservoir combined with device platform
 - Potentially substantial capital investments needed, but demand may be uncertain
 - Technology transfer, technical support and IP rights management may be needed
 - Potential need for financial support for generic manufacturers to enter market and decrease investment risks
- **Regulatory pathways may also be complex, especially for novel drugs**
 - Need for developers to seek early regulatory guidance
- **Coordinated efforts of stakeholders are needed to ensure demand**
 - E.g. Demand forecasts; market intervention to decrease price at launch (volume guarantees or other incentives); catalytic procurement for early adoption; demand generation.



Background on tertiary patents for drug-device combinations

Tertiary patenting on drug–device combination products in the United States

Reed F Beall & Aaron S Kesselheim

Drug–device combination products are becoming increasingly prevalent, with many lasting years beyond the expiration date of primary and secondary patents on the drug itself.



Drug–device combination products are becoming increasingly prevalent, with many lasting years beyond the expiration date of primary and secondary patents on the drug itself

Posted on April 30, 2018 by jdarrow

Tertiary Patents: An Emerging Phenomenon

By Jonathan J. Darrow

Brand-name pharmaceutical manufacturers have long been known to try to protect and extend their market exclusivity periods by obtaining patents on a drug's substance ("primary patents") and also on its peripheral features, such as formulations or methods of manufacture ("secondary patents"). A [new study](#) describes an emerging phenomenon of "tertiary patents," which have the potential to further delay and discourage market entry in the context of drug-device combination products.

Combination products are defined by the U.S. Food and Drug Administration (FDA) to include therapeutic products that combine a drug with a device, such as an inhaler or injector pen. These products can sometimes offer life-changing or life-sustaining treatment, as with naloxone (Narcan) for opioid overdose or epinephrine (EpiPen) for severe allergic reactions. In recent years, these and other similar products have been the subject of [substantial controversy](#) related to their prices and prolonged lack of [generic competition](#).



- Combination products are defined by the U.S. Food and Drug Administration (FDA) to include therapeutic products that combine a drug with a device. In recent years, these and other similar products have been the subject of substantial controversy related to their prices and prolonged lack of generic competition
- Tertiary patents are distinguishable from other types of patents and are increasingly becoming a central form of intellectual property protection on drugs delivered through inhalers and injector pens once primary and secondary patents expire. In addition, because there is virtually no limit to the number of times a device can be altered in a patentably-distinct (but not necessarily clinically important) manner, the potential for serial device modification and subsequent patenting is high.
- Secondary patents may outlast (and outnumber) primary patents, since they are typically filed at a later point in time, and tertiary patents outnumber and outlast secondary patents—in some cases by many years.
- The expansion of drug delivery device patenting will permit extended market exclusivity periods that are likely to further delay generic competition and increase prices.



Towards a healthy market for LA technologies

4/5: Global supply

Elements for consideration

- Uncertainties regarding product uptake
- Lack of demand forecasting
- Limited supply-base and single-source markets
- Lower API and drug volumes required could offset costs



Towards a healthy market for long-acting technologies

5/5: Country adoption

Elements for consideration

- Very limited experience with LA in LMICs in any disease, except for LA hormonal contraception
- Strong efforts will be required to ensure efficient uptake of radically different tools (provider to end-user)
- Some advantages of more choices for different populations, but comprehensive decision-making matrix needed, rather than implementation of single products
- More data needed on demand creation and issues related to user preference and acceptability (current data are limited)
- Task-shifting and community-based delivery models for HIV may be compromised or require adaptation; shift from public health approach could support differentiated care
- Potentially increased health facility burden may pose challenges for capacity, workforce, funding
- In rural areas, additional challenges if health facilities/posts required to give injection
- Cold chain unlikely to be viable in LMICs
- Safe disposal of biohazards and waste management



*It is the framework which changes
with each new technology,
and not just the picture within the frame.*

Marshall McLuhan



The development of this compendium was coordinated by **Unitaid (Carmen Pérez-Casas) and Health Hounds (Craig McClure and Ian Grubb)** with contributions from several other individuals and organizations. All errors and omissions are the responsibility of the authors. We thank the following for kindly contributing, commenting or sharing resources:

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