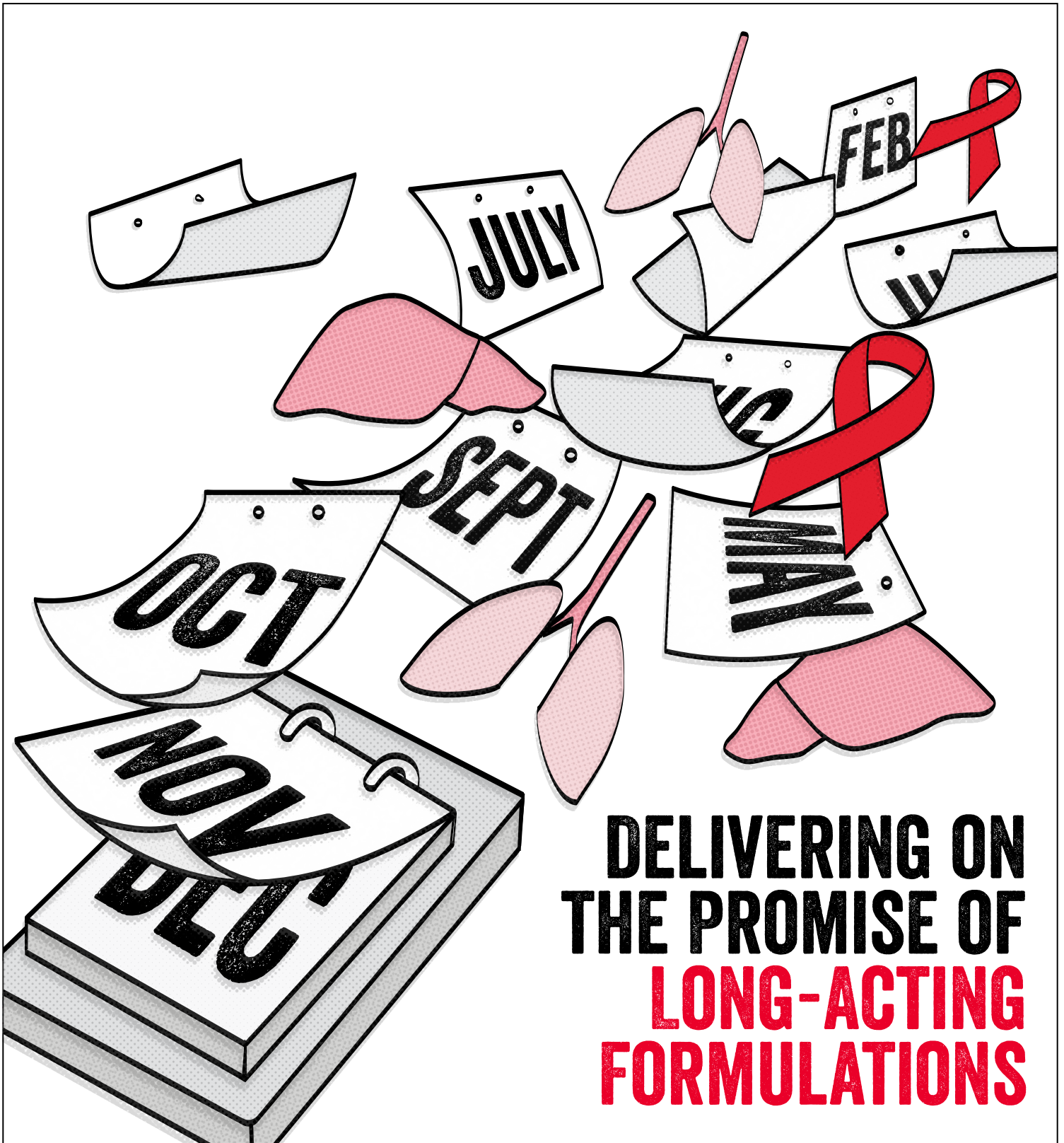


tagline

NEWS ON THE FIGHT TO END HIV/AIDS, HEPATITIS C, AND TUBERCULOSIS



**DELIVERING ON
THE PROMISE OF
LONG-ACTING
FORMULATIONS**

DELIVERING ON THE PROMISE OF LONG-ACTING TECHNOLOGIES

By Mark Harrington and Sue Swindells

This issue of *TAGline* explores the exciting opportunities and challenges that come with the development of long-acting formulations for the prevention and treatment of infectious diseases. For many years to date, patients and providers have welcomed long-acting medications for other conditions such as schizophrenia, osteoporosis, and contraception. These delivery systems improve adherence, which leads to improved clinical outcomes.^{1,2,3}

A serious concern regarding equity and access for novel long-acting antiretroviral agents will be the price.

The terms “long-acting” or “extended release” describe applications for multiple routes of administration, including oral, topical, and parenteral (which refers to implants and intravenous, intramuscular, subcutaneous injections). Generally, to be considered a long-acting technology (LAT), a drug should have dosing once weekly or less often orally, once monthly or less often by injection, or every six months by implant.⁴ Encouraging data from large clinical trials for HIV treatment recently led to the approval of long-acting cabotegravir and rilpivirine by the U.S. Food and Drug Administration.^{5,6} Ongoing community engagement and equitable access, however, are critical for this new strategy to fulfill its promise.

A serious concern regarding equity and access for novel long-acting antiretroviral agents will be the price. According to the U.S. Department of Health and Human Services, the monthly average wholesale price of cabotegravir plus rilpivirine for HIV treatment (sold as Cabenuva by ViiV Healthcare) ranges from \$4,752 to \$7,218 depending on dose – or as much

as \$86,616 per year.⁷ Comparator oral regimens’ annual average whole sale price costs range from \$23,532 for all-generic efavirenz/TDF/FTC to \$48,876 for bicitegravir/cobicistat/TAF/FTC.⁸ It’s not yet clear whether ViiV or other co-developers of long-acting injectable therapies intend to market these formulations globally or, if so, what prices will be required to make them maximally accessible (including the cost of supply chain, delivery, storage, administration, and pharmacovigilance).

Alongside ongoing efforts to develop other long-acting drugs for HIV prevention and treatment,⁹ other infectious diseases are now receiving attention. Unitaid¹⁰ is a global health initiative for innovations to prevent, diagnose, and treat major diseases in low- and middle-income countries, with an emphasis on tuberculosis (TB), malaria, and HIV. To that end, Unitaid is funding a consortium based at the University of Liverpool and including TAG called Longevity.¹¹ This project is developing a pipeline of long-acting medicines for malaria, TB, and hepatitis C virus (HCV) and infrastructure for sustainable translational capacity.

Each disease and each potential long-acting intervention poses a series of questions specific to the disease and proposed intervention. There are a number of shared, cross-cutting issues, among them community acceptability and involvement, how best to design the studies and in which groups of people, regulatory issues, manufacturing, cost, delivery, accessibility, and affordability. The introduction of safe and effective long-acting interventions could help speed the end of the HIV, HCV, malaria, and TB pandemics.

Affected communities are central to success in the development, approval, and safe distribution of LATs for HIV, HCV, malaria, and TB. Their involvement, participation, and endorsement of LAT research is key. To that end, TAG, in partnership with AfroCAB and the LONGEVITY team including the University of Nebraska Medical Center (UNMC), is supporting the development of a Long-Acting Technologies

Community Advisory Board (LAT-CAB). Recruited in 2021, the new LAT-CAB is now engaging this novel research area of great potential, as described in this edition by Bryn Gay and Joelle Dountio Ofimboudem of *TAGline* with Kenly Sikwese of the [AfroCAB](#).

[Annette Gaudino and Suraj Madoori](#) go on to explore how the health care delivery and policy landscape must be substantially altered in order to create enabling environments for the successful, effective use of LATs. Zooming in on the U.S. HIV epidemic, [Abraham Johnson](#) explores the issues of health equity raised by the advent of research into and regulatory approval of long-acting agents for preventing and treating HIV. Gaudino and Madoori emphasize that combatting racism and strengthening affected community

Affected communities are central to success in the development, approval, and safe distribution of Long-Acting Technologies for HIV, HCV, malaria, and TB.

involvement are essential every stage of the struggle to end HIV. [Richard Jefferys](#) reviews recent data indicating that when used for HIV prevention, current LA-PrEP (using injectable cabotegravir) can in rare cases miss early HIV infection that is undetectable using standard laboratory HIV antibody (serology) assays.

[David Branigan](#) describes the paradoxical situation of using injectable agents in the TB space, after years of successfully struggling to end the use of toxic, antiquated, and unnecessary daily injectable treatments for drug-resistant TB. All stakeholders – including policymakers, national health and regulatory authorities, TB clinics, and communities where TB is prevalent – must become fully conversant with the potential for new, safe, and effective long-acting injectables for TB chemoprophylaxis or curative treatment.

Erica Lessem's interview with [David Thomas](#) of Johns Hopkins University explores the exciting possibility of what could be

a one-shot, single injectable cure for HCV infection. [Joelle Dountio Ofimboudem](#) outlines the potential of LA-malaria chemoprophylaxis or mass treatment to enable a significant step forward in global efforts to eliminate malaria, particularly in sub-Saharan Africa.

As the world continues to struggle with mainly uncontrolled and continuously evolving SARS-CoV-2, the importance of prompt drug, diagnostic, and vaccine development, sufficient funding, and deep community involvement has become clearer than ever. These elements were crucial in developing safe and effective vaccines to prevent infection, severe disease and death from SARS-CoV-2/COVID-19; and they will be just as essential in the upcoming work to roll out safe and effective LATs for HIV, HCV, malaria, and TB.

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KNOW YOUR CAB: COMMUNITY EXPERTS SHAPING THE LONG-ACTING TECHNOLOGIES PIPELINE

By Bryn Gay, Joelle Dountio Ofimboudem, and Kenly Sikwese*

Meaningful and equitable community engagement is essential to ensuring that long-acting technologies (LATs) clinical research is conducted in ways that are safe, ethical, appropriate, and responsive to community priorities and needs.¹ To advance the community engagement work, Treatment Action Group (TAG) and the African Community Advisory Board (AfroCAB) have partnered to coordinate and co-chair a new global, cross-disease Long-Acting Technologies Community Advisory Board (LAT CAB).

Meaningful and equitable community engagement is essential to ensuring that long-acting technologies clinical research is conducted in ways that are safe, ethical, appropriate, and responsive to community priorities and needs.

LAT CAB is a dedicated community body that will advance LAT research and uptake under the Unitaid-funded LONGEVITY project.² This will develop long-acting technologies for malaria and tuberculosis (TB) prevention, and a cure for the hepatitis C virus (HCV). The LAT CAB meets with clinical researchers, developers, contract manufacturing organizations, and project partners to address issues related to the science, costs and pricing, and access plans across countries, particularly those of low- and middle-income. LAT CAB can strengthen capacity and leadership among affected communities and advise on

the approaches used to introduce LAT generally—creating demand for the treatment. LAT CAB can develop research & development (R&D) recommendations to ensure LATs are acceptable and meet the needs of affected communities. These recommendations will inform national and global guidelines.

During LONGEVITY project, community experts will review the state of long-acting therapeutics and preventives research, facilitate community contributions in the design and review of research protocols, and create a platform to engage in the R&D process. Community experts will also advise on research questions, survey and trial design, price points, and access issues. LAT CAB, in consultation with external technical experts, will analyze and review materials at learning sessions, provide community perspectives, and bridge the gap among communities, clinical researchers, and pharmaceutical developers. This will strengthen research and scientific literacy among activists and affected communities.

LAT CAB recruitment occurred over six weeks in April to June 2021. Applicants from a high TB, HCV, HIV, and/or malaria setting, or familiar with access or health systems barriers in low- and middle-income countries, were encouraged. Three external, independent reviewers assessed 24 eligible candidates according to criteria based on knowledge across HIV, HCV, TB, and/or malaria (the infections for which Unitaid is supporting LAT R&D across several projects), technical skills, activism experience, engagement with civil society networks, and quality of application materials. The selection process also considered balanced representation from diverse geographic regions, gender identities, and affected communities, including but not limited to people who use and inject drugs, men who have sex with men, sex workers, people who are incarcerated, people who are migrants, or Indigenous populations. By the end of July 2021, a total of 12 members were confirmed for a four-year tenure (2021-2024). The first introductory and planning meetings to map learning needs took place in September 2021.

Meet the 11 LAT CAB Community Experts:

Affiliations are listed for context only; members participate in their individual capacity.

Alma de Leon

She/Her/Hers
International
Treatment
Preparedness
Coalition-Latin America
and The Caribbean
(ITPC-LATCA)
Guatemala



Belinda Ameterra

She/Her/Hers
Boland Research
Community
Advisory Board
South Africa



Ketho Angami

He/Him/His
Access to Rights
and Knowledge
(ARK) Foundation
India

Clovis Sangwe

He/Him/His
Rural Doctors
Cameroon



Obatunde Oladapo

He/Him/His
PLAN Health Advocacy and
Development Foundation
(PLAN Foundation);
African Community Advisory
Board (AFROCAB)
Nigeria

Dorothy Onyango

She/Her/Hers
Women Fighting AIDS
in Kenya WOFAK
Kenya



Raef Makar

He/Him/His
Doctors Without Borders/
Médecins sans Frontiers
(MSF)
Geneva/Jordan

Gisèle Takaléa

She/Her/Hers
Collective of
Organizations for
the Fight against TB
& Respiratory Diseases
(COLTMR)
Côte d'Ivoire



Sergiy Kondratyuk

He/Him/His
International Treatment
Preparedness Coalition-Global
(ITPC)
Ukraine

Iriebe Gboh

He/Him/His
African Community
Advisory Board
(AFROCAB)
Côte d'Ivoire



Yves Kugbe

He/Him/His
Community Expert,
Independent Consultant
Senegal/Togo

LAT CAB can strengthen capacity and leadership among affected communities and advise on the approaches used to introduce [long-acting technology] generally—creating demand for the treatment.

Among the myriad priorities, LAT CAB will cover R&D issues from conceptualization to lab bench to bedside:

- Basic epidemiology and current treatment landscapes of malaria, HCV, and TB;
- A review on how the LONGEVITY project addresses treatment and prevention gaps;
- Lessons from long-acting (pre-exposure prophylaxis) PrEP and antiretrovirals;
- Complementarity of LA malaria prophylaxis with other control measures, including the roll-out of the new malaria vaccine;
- Direct-acting antiviral treatment uptake, registration gaps, access/licensing challenges, and the role of long-acting glecaprevir/pibrentasvir (the lead candidate for an HCV LAT);
- Community perspectives on injectables for long-acting TB preventive therapy;
- The basics of clinical trials and clinical trial design;
- The basics of qualitative surveys;
- Diversity, equity, and inclusion in research;
- Considerations for inclusion of key populations, including pregnant individuals and children;
- Considerations for chronic diseases and comorbidities;
- Patent landscape and trends in long-acting technologies; and
- Strategies to incentivize generic manufacturers, bend cost curves for nanotechnology, increase production efficiencies, and address technology transfer.

**Kenly Sikwese is with the African Community Advisory Board*

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TERRAFORMING THE POLICY LANDSCAPE TO ENABLE ACCESS TO LONG-ACTING TECHNOLOGIES

by Annette Gaudino and Suraj Madoori

Let's Define Terraforming

Terraforming – or “earth-shaping” – the transformation of an alien planet into one where humans can live, is probably most familiar to science-fiction fans and Minecraft players. Terraforming is more intensive than landscaping, the term used to describe the need to understand local politics to win policy fights. Change requires more than knowing the key players and presenting compelling evidence, it also requires actively shaping the terms of the debate, including what’s considered “too radical.”

Terraforming for policy change requires time and patience. Vulnerable communities have immediate needs that advocates and allies must address before they can accept – and demand – emerging long-acting technologies (LATs) for HIV, hepatitis C virus (HCV), and tuberculosis (TB) prevention and treatment. These communities need technical information clearly communicated, non-health related needs (housing, income, safety) addressed, and understandable fears assuaged. This work should center around the most marginalized: those denied treatment due to active substance use or incarceration, criminalized LGBTQ+ people, unhoused individuals, the uninsured and underinsured, including immigrants. Policymakers must acknowledge and address the racism faced by Black, Indigenous, and people of color. Models of care and financing mechanisms must adapt to increase access and demand for LATs among the most marginalized. Struggles for care are not new, and advocates can learn from these histories to guide terraforming policy for LATs access.

We Keep Us Safe

Harm reduction was born from the response of people who use drugs to the deadly HIV epidemic. Harm reduction embodies a whole society effort to support the well-being of people who use criminalized substances. The HIV transmission



risk from sharing syringes is high, so people who inject drugs developed ways to keep themselves and their communities safe. Unsanctioned syringe service programs (SSPs) challenged local laws against possession and distribution of so-called paraphernalia to save lives. Over time, leadership by those directly impacted – in partnership with clinical providers, researchers, and community leaders – created an enabling legal and political environment for SSPs to evolve from acts of civil disobedience to evidence-based infectious disease prevention.

Each averted infection built the case for sanctioned, funded SSPs, which serve as entry points to other services and support. While more was and is needed to create safe spaces in clinical settings for people who use drugs, the success of SSPs in preventing HIV gave people who use drugs the opportunity to be viewed as partners in public health. Inverting the traditional direction of public health education, so that people

with lived experiences educate the credentialed experts, is key to terraforming for policy change. When the targets of an intervention inform its design and implementation, the landscape becomes transformed and truly livable.

The formative period for SSPs provided additional lessons: it confronted and disproved the belief that people who use criminalized substances don't care for their health or the health of others. It framed health care, including access to the tools needed to stay safe, as a matter of human rights.

Change requires more than knowing the key players and presenting compelling evidence, it also requires actively shaping the terms of the debate, including what's considered "too radical"... Without the advance work of terraforming, a public health crisis risks entrenching approaches that further harm public health.

The U.S. South

Without the advance work of terraforming, a public health crisis risks entrenching approaches that further harm public health. The U.S. South is home to examples of this damaging dynamic.

In 2018, the Kanawha-Charleston syringe service programs (SSPs) in West Virginia – which served 400 people a week – chose to indefinitely suspend services following changes to local legal requirements.¹ Now, those seeking care would need to provide proof of residency and government-issued photo identification. Not only did this raise access barriers, it also violated the trust developed between SSP staff and

participants. While the overdose crisis is the result of multiple factors, the state reported a slight decrease in overdose deaths from 2017 to 2018.² West Virginia now has the highest rate of overdose deaths in the nation, suffering a nearly 50% increase in 2020 over the previous year.

Similarly, North Carolina's legislature has sought to eliminate SSPs by making their establishment as burdensome as possible: limiting neighborhoods in which prospective SSPs can operate, requiring approval from over half of the residents in a neighborhood, and barring site staff who have a conviction or misdemeanor on their record. Grandstanding political efforts to be "tough on crime" have also led to the closure of SSPs in Indiana, Michigan, and New Jersey.

SSPs remain illegal in 29 states, all of which have Republican-controlled legislatures and are predominantly in the U.S. South. Yet, we can find hope in local leaders such as the North Carolina Harm Reduction Coalition (NHRC), who are working to make it the first Republican-led state to authorize an SSP. Decriminalization of SSPs cannot be a Democrat-only effort, particularly in the South, where terraforming for policy change requires a bipartisan approach.

Locally-led efforts such as NHRC's offer lessons on what works best to decriminalize populations most vulnerable to HIV, HCV, and TB. Grassroots organizing of diverse, powerful stakeholders – including people who use drugs, veterans, Black clergy, and sex workers – underpins these efforts. Community mobilization can build and strengthen networks to push bold demands, such as integrating game-changing LATs into harm reduction sites and health hubs for people who use drugs. Most importantly, these efforts require lawmakers and public officials to respond to the demands of their constituents.

Paying for It

Even with a high level of community acceptance and demand, health systems must take a holistic approach to coverage in order to reach those most in need of care. This means providing all services at no out-of-pocket cost, from the screening stage all through lab test monitoring. In the U.S., this requires expanding and sustainably financing Medicaid, and subsidized private insurance.

Policymakers will determine how LATs will be funded based on what settings are deemed appropriate for their administration. These decisions will impact who gets access to treatment. Patients could potentially receive LATs in hospital-

based clinics, community health centers, pharmacies, or any combination of these settings. In each case, reimbursement rates and policies will generate revenue to these providers, a powerful motivation to lobby for mechanisms that benefit some providers over others. Providers may also use reimbursement mechanisms and logistics as justifications to override patient preferences or informed consent: prison staff may prefer the convenience of administering monthly injections over dispensing oral medicines (see interview with Dave Thomas, [page 18](#)). Logistics such as cold-chain storage requirements and package volumes will impact access, as it has for mass COVID-19 vaccination programs.

Decades of the HIV pandemic have clearly demonstrated that the most effective advocates for comprehensive services are those living with or at highest risk of illness. If patients are preemptively excluded due to their criminalized drug use, new clinic capacity cannot care for them. Without a mobilized community of patients demanding care, it would take rare political courage to change policies to finance diagnostics, treatment, and monitoring – to deliver cutting-edge LATs to the poorest and most marginalized.

Broad acceptance and use of LATs require nothing less than the transformation of the U.S.'s healthcare delivery and financing system. This possibility should not frighten advocates or be used as an excuse not to act. LATs are yet another opportunity to apply lessons learned and make concrete choices in favor of universal care.

Overcoming Histories of Harm

Medical mistrust is a rational response to the long, terrible history of harm done to Black, Indigenous, and other people of color by medical institutions and researchers. The responsibility for repairing the relationship between patients and their caregivers rests with the medical profession and other authorities and begins with listening to and learning from experiences of impacted communities. This is especially true for individuals whose behaviors are explicitly criminalized, including LGBTQ+ people, gender non-conforming people, and people who use and distribute illicit drugs.

In the case of LAT, advocates must engage those who fear malicious intentions on the part of pharmaceutical companies. Community wariness about locating services that may attract police attention due to the people they serve must be understood and worked through. Stigmatizing attitudes

that deny the humanity of marginalized individuals within marginalized communities must be confronted.

The shaky roll-out of COVID-19 vaccines have revealed a key insight – having a game-changing technology does not guarantee acceptance by the communities that need them the most. Vaccine hesitancy, a result of historically unaddressed medical mistrust and racism, remains a formidable challenge to overcome in reaching vaccination goals. For LATs to succeed, advocates and policymakers must change policies that criminalize and stigmatize. Clinicians, drug user unions, harm reduction advocates, and other community-based networks are central to tackling medical mistrust.

With the ever-closer horizon of LATs, policymakers have a window of opportunity to ensure their viability and acceptance. The time is now for brave, bold policymaking and terraforming the landscape for LATs:

- Significant scale-up in community mobilization among people who use and inject drugs, LGBTQ+ people, sex workers, and other marginalized communities.
- Resources to sustain key access points of care for vulnerable populations including SSPs and AIDS Service Organizations (ASOs).
- Undoing harmful policies – including laws that criminalize people who use drugs, HIV and other infectious diseases – to increase access to LATs and other care.
- In the U.S., Medicaid expansion, and payer mechanisms that include LATs in a comprehensive package of care (diagnostics, lab monitoring coverage, case management, and linkage to ancillary services).
- Community leadership by vulnerable and key population constituencies in the development and implementation of policies
- Systemic changes to promote the uptake of new technologies like LAT, and significantly diminish the effects of medical and institutional mistrust.

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PrEPARED? LONG-ACTING PREP ACCESS IN COMMUNITIES MARGINALIZED BY THE U.S. HEALTHCARE SYSTEM

By Abraham Johnson



The announcement that HIV Prevention Trials Network (HPTN) had two successful studies on long-acting technologies (LAT) to prevent HIV – HPTN 083 and 084 – came with much excitement. Populations most impacted by HIV could possibly have an even greater opportunity to prevent HIV. LATs provide for potentially easier adherence, fewer side effects, and are less noticeable which creates more privacy for users than pre-exposure prophylaxis (PrEP) in pill form. Yet, as the prevention toolbox continues to grow, there are still uncertainties on the effectiveness, cost, accessibility, and other structural barriers of long-acting technologies. This raises the question: just how prepared are we really for long-acting technologies? Ending the HIV epidemic requires everyone to have access to LATs regardless of race, geographic location, gender identity, income, and immigration status – ensuring that communities everywhere have the same chance of reducing their likelihood of contracting HIV. We spoke with some leading voices in HIV prevention to get their take on what we need to do to prepare for LATs.

Establishing Trust Within Communities

Progress toward increasing LAT access starts with building trust. As we have seen with the development of the COVID-19 vaccine, mistrust influenced vaccine hesitancy among underserved communities particularly among Black people living with HIV.¹ Before LATs are available, medical providers must foster trust within communities. Medical providers must provide community members with accurate and accessible information about LATs, including side effects and possible challenges that come with their use. For communities to believe in and feel comfortable with accessing LATs, researchers and manufacturers must do a better job at being transparent and trustworthy. In a recent interview with TAGline Sarit Golub, a professor at City University of New York said: “In order to build trust, we need to act trustworthy.” Lessons learned from the roll-out of once-daily oral dosage of PrEP show that, to date, uptake of PrEP in marginalized communities in the South is low.²

We need to get rid of the assumption that we continue to do business as usual. We must start by meeting and educating people around their options in the role that these options can play in the context of their lives,” Matthew Rose, the Director of the U.S. Policy and Advocacy at Health GAP, said (in an interview with TAG’s HIV Community Engagement Officer, Abraham Johnson). “Injectables will meet the same fate as everything else if we don’t roll out a new way of engaging people.”

No matter how effective LATs are, researchers must intentionally engage with community members who stand to benefit the most from using LATs. Sarit Golub notes, “We should see community members as ‘targets’ of our public health system. We need to recognize they are ‘agents’ of their own health and that an agentic mindset is one that centers community power and autonomy.”

No Population Left Behind in Research

Biomedical prevention research has historically excluded populations such as cisgender and transgender women. Black women are consistently excluded when it comes to biomedical prevention. From the moment PrEP was introduced, Black women were left out.) “Today, Black women are the least likely to take PrEP. This can’t be the case with long-acting technologies. We must make sure the language speaks to women. Women must see themselves in this from the beginning,” Gina Brown, Director of Strategic Partnerships and Community Engagement (SPaCE), said (in an interview with Abraham Johnson). “The same efforts that have been put into engaging Black Gay, Bisexual, and Same-Gender-Loving men in prevention have to be replicated with Black women.”

Although HPTN 084 avoided the missteps made by Gilead with F/TAF for PrEP (see table in Jeffery’s [page 14](#)) – for which no research was done in cisgender women and transgender men at the time of U.S. Food and Drug Administration approval – we must ensure that efficacy trials for LATs continue to cover all of the major HIV exposure risks. We must include people with current or a history of injection drug use in efficacy trials. For real-world effectiveness studies and demonstration projects, we must make it the norm to immediately and fully scale-up studies that intentionally look at the unique barriers to access for all major vulnerable populations, including transgender and gender-nonconforming individuals, people of color, cisgender women, and people who use drugs.

We also cannot forget about the rural South. There is a difference between the HIV Epidemic and health care access in urban cities in the South – such as Atlanta, Houston, Dallas, and Miami – distinctly differs from access in the rural South. Non-urban counties in the South have higher rates of new HIV infections compared to non-urban counties in other regions. Rural residents have limited access to PrEP: although the need for PrEP providers is evident because the South has the highest proportion regionally of PrEP-eligible persons living a 60-minute drive away from the nearest PrEP provider.³ Rural populations in the U.S. are generally underserved by HIV prevention services that offer HIV and sexually transmitted infections (STI) testing, don’t get a sufficient supply of free condoms, individual prevention services, and are less likely to have PrEP providers than those in urban cities.^{4,5} Even with the implementation of PrEP, the South has still felt the burden of the HIV epidemic for years. Integrating LATs in both the urban and rural South successfully

will require a collaborative effort among key stakeholders, health departments, and other service providers.

Preparing for Challenges Through Clear Communication

Like most new innovations, long-acting technologies will have their challenges. On a community level One challenge is ensuring that health information is provided in a way that is understandable. Generally, knowledge on PrEP is low in underserved communities. Therefore, the marketing of LA injectable PrEP must be creative. Perhaps this means veering away from the biomedical term “PrEP” to something more comprehensible. When developing materials, health communication specialists must tailor the medical information

Racism and provider bias have negatively impacted community members’ experiences with accessing PrEP.

for low-literacy settings. The lead-in phase required before starting long-acting cabotegravir (LA-CAB) injections bears a challenge for people using this specific treatment. (see Branigan, [page 15](#)). Although LA-CAB proved more effective than emtricitabine tenofovir (Truvada) in preventing HIV infection, users must take oral cabotegravir for five weeks and then start their injections. The delay in starting injections may be a challenge for people who struggle with taking their medication daily as prescribed.

Concern also surrounds the effectiveness of the injection once drug levels begin to wane – as noted in Jefferys’, [page 13](#), a few participants in a study acquired HIV after delayed injections. We will need to walk the fine line between overinflating the challenges of any prevention modality to the point of discouraging uptake, a mistake made often by healthcare professionals with oral PrEP. Healthcare professionals downplayed their significance to the point of losing community trust. We must be prepared to mitigate unintended negative outcomes.

For real-world effectiveness studies and demonstration projects, we must make it the norm to immediately and fully scale-up studies that intentionally look at the unique barriers to access for all major vulnerable populations, including transgender and gender-nonconforming individuals, people of color, cisgender women, and people who use drugs.

While some clinics are known for providing quality services to patients – particularly those owned and led by members from the most vulnerable communities – this is not the reality for all. Racism and provider bias have negatively impacted community members' experiences with accessing PrEP.⁶ Implementation of LATs require follow-up visits, ongoing health education, and culturally humble providers who can clearly communicate about potential side effects. Providers should allow patients to make informed decisions about whether LATs are the right choice for them.

Creating an Equity Framework

LATs must be affordable and accessible to all communities. For this to happen, funders and policymakers must address inequitable LAT distribution head-on. In an interview with TAG's HIV Community Engagement Officer Abraham Johnson, Sarit Golub said, "Funders must hold implementers accountable for equity metrics, not just volume metrics. In other words, any measure of quality or success in outcomes must examine not just how many new individuals are adopting a new prevention strategy, but whether adoption patterns are substantially reducing inequitable distribution in biomedical prevention adoption overall at an agency-, health system-, or jurisdictional-level."

Dismantling Systemic Racism

2020 taught us many lessons, underscoring that systemic racism is a public health issue. "There is literally no way that long-acting injectables enter the world and not be part of the racist system. The system is pervasive. It has long been part of our society," Matthew Rose said in an interview with

Abraham. "What we can do is we can try to ensure equity by shifting the paradigm – putting people of color in decision-making authority over the roll-out and program generation." All communities must have access to LATs, and policymakers have an obligation to make sure of this.

As LATs begin to enter communities, we must move toward dismantling systemic racism. Healthcare facilities need to offer cultural sensitivity training to doctors that provide services to Black, Indigenous, and people of color. Additionally, senate leaders need to directly infuse resources to communities of color, including local community-based organizations. In keeping with the Denver Principles and the rallying cry, "Nothing about us without us," more people of color should be in leadership positions to make decisions for their communities.

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THE CHALLENGE OF DIAGNOSING HIV INFECTION IN LA PREP USERS

by Richard Jefferys

Impressive results from two efficacy trials of a long-acting form of the integrase inhibitor cabotegravir (CAB LA) have boosted prospects for long-acting HIV pre-exposure prophylaxis (PrEP).^{1,2} In both cases, CAB LA proved superior to oral Truvada PrEP (see table).

The potential occurrence of masked infections in users of LA PrEP raises the question of how best to diagnose HIV in future studies and when LA PrEP becomes available on the market...Currently, it appears that monitoring for HIV infection will require intermittent use of sensitive viral load tests.

Analyses of the trial data have also revealed a wrinkle associated with the approach: among the small number of HIV infections that occurred, the capacity of CAB LA to suppress viral replication masked the presence of the virus by reducing viral load and preventing seroconversion to HIV antibody positive (delaying HIV diagnosis).^{3,4} In most cases, these HIV infections had occurred either immediately prior to PrEP initiation or during windows of suboptimal LA CAB levels associated with delayed (or lack of) receipt of scheduled drug doses. In two trial participants who acquired HIV despite adequate drug levels, the virus had mutations associated with resistance to CAB LA.

The researchers identified these masked infections retrospectively by testing stored blood samples for low levels of HIV viral load. Once identified, antiretroviral treatment (ART) regimens were successfully initiated. In a few cases, HIV had developed CAB LA resistance due to the trial participants having spent an extended period on monotherapy after acquiring HIV, rather than appropriate combination ART.

The potential occurrence of masked infections in users of LA PrEP raises the question of how best to diagnose HIV in future studies and when LA PrEP becomes available on the market. (ViiV Healthcare announced the submission of a new drug application to the U.S. Food and Drug Administration on May 4, 2021.⁵)

Currently, it appears that monitoring for HIV infection will require intermittent use of sensitive viral load tests. This approach is under evaluation in the open label extension phases of HPTN 083 and 084. The researchers are assessing a variety of point-of-care and rapid viral load tests to better understand whether their use in the context of LA PrEP can identify incident HIV infections sooner and prevent the emergence of drug resistance.

Another idea in development that might offer enhanced convenience is home viral load testing. For example, the pharmaceutical company Merck is collaborating with researchers at the BEAT-HIV Martin Delaney Collaboratory in Philadelphia to assess whether a system that allows an individual to draw blood at home and mail for testing can be used to monitor for HIV viral load rebound in clinical trials involving an ART interruption.⁶ The National Institutes of Health is also supporting research into finger-prick viral load tests that could be self-administered at home.⁷

Before these tests could become HIV diagnostics for people on LA PrEP, they would need to overcome an important hurdle: the need for very low thresholds of viral load detection (e.g., 20 copies/mL of HIV RNA). Currently the Merck at-home

The researchers are assessing a variety of point-of-care and rapid viral load tests to better understand whether their use in the context of LA PrEP can identify incident HIV infections sooner and prevent the emergence of drug resistance.

testing technology has a lower cut-off of 1,000 copies/mL; in the ART interruption trial in which it's being evaluated, 1,000 copies/mL or greater is the viral load level that triggers restarting treatment. There is hope, however, that this lower limit of viral load detection can be improved.

As long-acting approaches to HIV prevention become more widely used, attention will also need to be paid to developing appropriate tools for diagnosing HIV infection among recipients. The issue highlights how new and successful interventions can sometimes create novel challenges that need to be addressed for optimal implementation.

Study	HPTN 83	HPTN 084
Population	4,566 cisgender men and transgender women who have sex with men	3,223 cisgender women
HIV infection endpoints (CAB LA / Truvada)	12 / 39	3 / 36
HIV incidence per 100 person-years (CAB LA / Truvada)	0.37 / 1.22	0.15 / 1.85
Incidence reduction (CAB LA vs. Truvada)	68%	92%

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INJECTABLES REDUX:

Developing Acceptable Long-Acting Formulations for TB Prevention Amidst a Push for All-Oral Treatment

by David Branigan

Ensuring access to tuberculosis (TB) preventive treatment for people most at risk of developing active TB is one of the key interventions required to end TB.¹ Central to these efforts is the push to scale up short course, rifapentine-based TB preventive treatment (TPT) in countries with high burdens of TB – similar to pre-exposure prophylaxis (PrEP) for HIV. Regimens include 3HP (3 months of rifapentine and isoniazid taken weekly) and 1HP (1 month of rifapentine and isoniazid taken daily). Yet, a number of barriers have hindered uptake of rifapentine-based TPT, including limited global supply and high prices of rifapentine, substantial pill burdens of 3HP and 1HP, and concerns regarding poor adherence given TPT dosing and treatment duration requirements.²

Now, imagine a long-acting TPT regimen that can be administered in a single injection. A long-acting TPT regimen could offer several advantages over existing TPT regimens administered orally on a daily or weekly basis. These advantages include a potentially more convenient and discrete mode of drug administration than pill-taking, and improved TPT adherence and thereby effectiveness. The Unitaid-funded LONGEVITY project, led by the University of Liverpool, is in the early stages of developing long-acting forms of rifapentine and isoniazid for TB prevention. If successful, an injection into muscle or subcutaneous tissue would deliver a drug depot that would gradually release TPT into the body at a rate that provides a therapeutic concentration for weeks or even months.

Long-acting TPT could help improve TPT adherence, advance TPT scale-up among people most at risk of developing active TB, and move the world closer toward ending TB. Yet, questions remain regarding whether communities will accept long-acting injectable (LAI) TPT.

LAI TPT in the Time of All-Oral Drug-Resistant TB Treatment

The TB community only recently succeeded in advocating for the removal and replacement of toxic injectable agents from

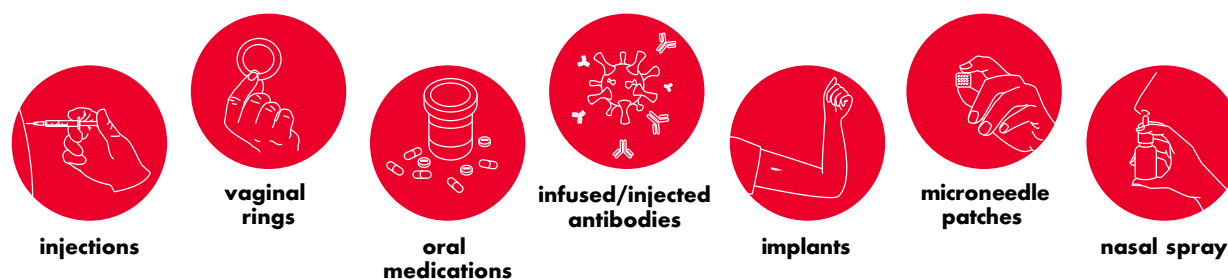
drug-resistant TB (DR-TB) regimens. Daily injections of these toxic drugs caused severe, debilitating side effects, including hearing loss.

“[T]he doctor called and said I was eligible for [DR-TB] treatment involving daily injections for two years... Although I was told about side effects, they were never monitored. After three months, I realized I was losing my hearing. I alerted the medical staff. My treatment was switched, but the deterioration continued. Today I have lost about 80% of my hearing and 60% of my sight.”³

The above testimonial of a DR-TB survivor is representative of the experiences of those who have received DR-TB treatment regimens containing injectables such as amikacin, kanamycin, or capreomycin.⁴ After a longstanding campaign led by TB survivors and affected communities to “Cap the Jabs,” the World Health Organization (WHO) issued updated guidance urging all countries to fully make the switch to all-oral DR-TB treatment regimens, replacing the injectable agents with bedaquiline instead.⁵ This follows an earlier move by the WHO to recommend against the addition of streptomycin – another injectable agent with severe adverse side effects – to first-line retreatment regimens. Instead, the WHO recommended drug-susceptibility testing to inform more optimized regimen selection.⁶ Memories of toxic injectables for TB treatment are still fresh. Meanwhile, advocacy for national policy changes to support access to all-oral DR-TB treatment regimens is ongoing.

While the medicines being explored for LAI TPT are not the same as the painful and toxic daily injections included in past (and in some instances presentⁱ) DR-TB treatment regimens, negative associations among members of TB-affected communities may persist.⁷ Making this distinction clear and

i. According to the Stop TB Partnership and MSF *Step Up for TB 2020* report, 46% of the 37 high-TB-burden countries surveyed still report using toxic injectables kanamycin and/or capreomycin in DR-TB treatment regimens, counter to WHO recommendations. See: <https://www.msf.org/step-tb-report-2020>.

FIGURE 1: Wide Array of Long-Acting Technologies

sensitizing TB-affected communities to the idea and potential advantages of new, injection-based treatment technologies for TB prevention will require robust community engagement and rigorous, community-responsive science.

Acceptability of LAI TPT Will Depend on Robust Community Engagement

Developing LAIs guided by patient preferences and values will lay the foundation for clinical trials and the future acceptability of long-acting TPT by TB-affected communities and activists. This will require engagement early on and throughout the development process to: (1) elucidate community perspectives on the acceptability of LAIs for TPT and how they will be evaluated through research; and (2) build treatment literacy in communities, including to dispel myths or false associations between LAI TPT and the toxic injectable agents now phased out of treatment for DR-TB. Community engagement will also be key to understanding the acceptability of injectables among certain high-risk populations, such as people who inject or used to inject drugs.

The LONGEVITY project determined that repositioning rifapentine and isoniazid (orally administered drugs already indicated for TB prevention) as long-acting medicines would be the most direct and least expensive approach to bringing long-acting TPT options to communities in need. Delivering doses of rifapentine and isoniazid high enough to ensure their release in adequate concentrations over an extended period is best achieved with injections.⁸ In the future, new chemical entities that are more potent may be more suitable for delivery via other forms of long-acting technologies, such as microneedle patches (see Figure 1).⁹

While the acceptability of LAI TPT requires special consideration given the history of toxic injectables for DR-TB treatment, there is precedent for LAI acceptability for HIV treatment. Two clinical trials of long-acting cabotegravir and rilpivirine (ATLAS and FLAIR) for HIV treatment showed that, while the majority

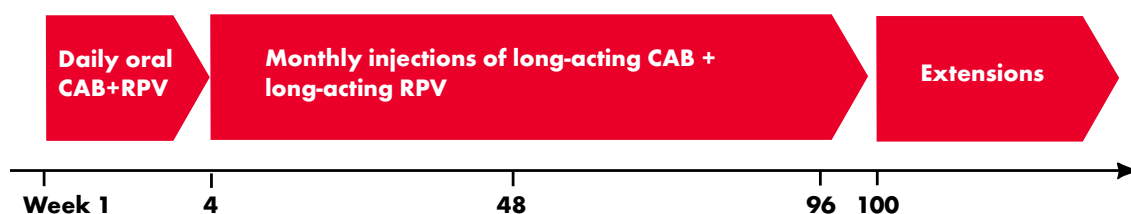
of participants reported injection site reactions such as pain or tenderness, overall acceptability of LAIs was high.^{10,11} An editorial on the two trials noted that the results clearly showed that “the benefits of not taking a daily oral pill outweighed this inconvenience [of injection site reactions] for participants in the first year of treatment.”¹²

While some may prefer LAI TPT to daily or weekly oral dosing, others may prefer pills or a different form of long-acting technology. A recent informal IMPAACT4TB survey of TB activists helped to draw out this nuance. One respondent said that “[m]embers of the community would have different acceptance to LAI TPT. Some would prefer the injection, but then a number of them would not accept injections simply because they fear needles. In conclusion, to provide a client centered service, both options of TPT (tablets and injectable) should be the option.”¹³ Community engagement to further elucidate these preferences will be critical for ensuring that the long-acting TPT development pathway is responsive to community needs.

Clinical Trials Should Be Designed to Answer Questions Important to Communities

Acceptability of LAI TPT will depend not only on robust community engagement but also on how effectively clinical trials can demonstrate the safety, efficacy, and other potential advantages of delivering rifapentine and isoniazid via long-acting injections. While rifapentine and isoniazid have been proven safe and effective when delivered orally, especially in combination for the treatment of TB infection, both of these drugs carry risks of hepatotoxicity, and rifapentine has been linked to hypersensitivity reactions in a small percentage of people who take it, a phenomenon that might be more common when rifapentine is dosed intermittently (as is the case for 3HP).¹⁴

Once LAIs are administered, if adverse events do occur, one cannot simply stop taking the medication like one can with

FIGURE 2: Long-Acting Cabotegravir and Rilpivirine Oral Lead-in Schema for HIV Treatment

Adapted from trial design schema. Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. *N Engl J Med*. 2020 Mar 19;382(12):1124-1135. doi: 10.1056/NEJMoa1909512.

daily pills. The long-acting medication has already been deposited and will continue to release the drug into the body.¹⁵ To reduce the risk of adverse events, cabotegravir and rilpivirine LAIs for HIV treatment are administered only after an oral lead-in period of taking the drugs in pill form for four weeks (see Figure 2).¹⁶ If an adverse event occurs within that period, the medication in pill form can be immediately discontinued to minimize its severity.

For TPT, the treatment duration may be as short as four weeks (i.e., 1HP), so is an oral lead-in necessary? If so, how long should the oral lead-in be, and how does this affect its acceptability? What if someone who has received LAI TPT begins to show signs of hepatotoxicity from the isoniazid – will there be any way to stop the release of the long-acting drug? Will the intermittent dosing of rifapentine (weekly or monthly) cause hypersensitivity reactions similar to those observed with once weekly 3HP? Rifapentine is a member of the rifamycin class of drugs, known for interactions with antiretroviral and other medications. Will LAI TPT interact with HIV antiretrovirals, hormone-based contraceptives, and methadone or buprenorphine opioid substitution therapies? These and other questions important to community acceptability must be taken into consideration and addressed in the clinical trials ahead for LAI TPT.

Preparing for the Introduction of Safe, Effective, and Acceptable Long-Acting TPT

As we engage communities and other stakeholders to prepare for future long-acting forms of TB preventive treatment, we will need to clearly explain our shift from advocating to “Cap the Jabs” to advocating for injectable TPT as a community-friendly option. To introduce safe, effective, and acceptable long-acting TPT that communities will want, the development pathway for long-acting TPT under the LONGEVITY project will need to advance in a way that is responsive both to community preferences and concerns and to science.

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DEVELOPING LONG-ACTING CURES TO ACCELERATE THE END OF HEPATITIS C

Interview with Dr. Dave Thomas*

With interview questions and editing by Erica Lessem, Bryn Gay, Joelle Dountio Ofimboudem, Annette Gaudino, and Elizabeth Lovinger

The World Health Organization set ambitious targets for eliminating the hepatitis C virus (HCV) among the 58 million people living with the disease, but most countries are far from reaching them. How could long-acting technologies, which extend the release of a drug over a period of time, such as over weeks or months, accelerate reaching these targets, especially in low- and middle-income countries, where most people living with HCV reside?



The current all-oral treatment regimen is safe, tolerable, and effectively cures HCV in over 95 percent of people when they also have access to diagnostics and linked to care. The current pathway to diagnosis and starting treatment still has many steps, and establishing the required infrastructure demands sustained financing, health trainings, political

leadership, and an enabling policy environment. Creating that infrastructure for HIV took almost ten years and billions of dollars with the support of the U.S. President's Emergency Plan for AIDS Relief and Global Fund. A long-acting treatment that can cure in one health visit could couple point-of-care testing

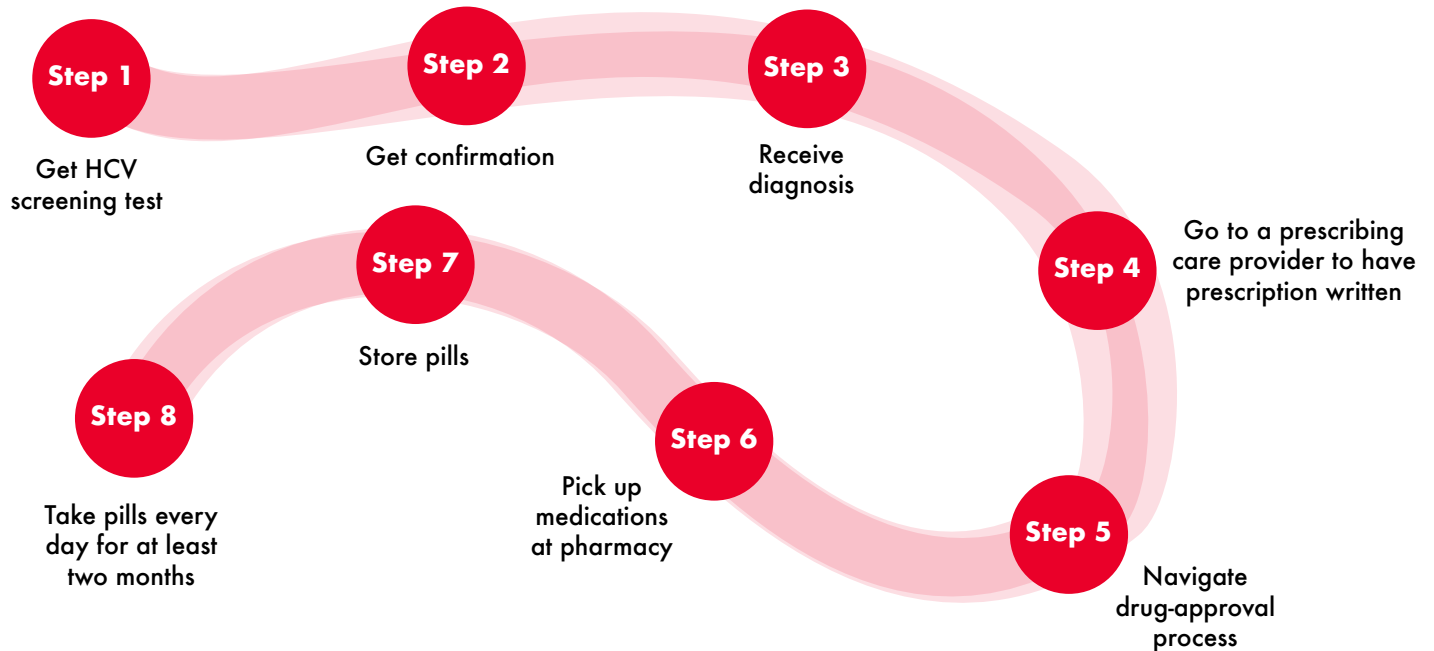
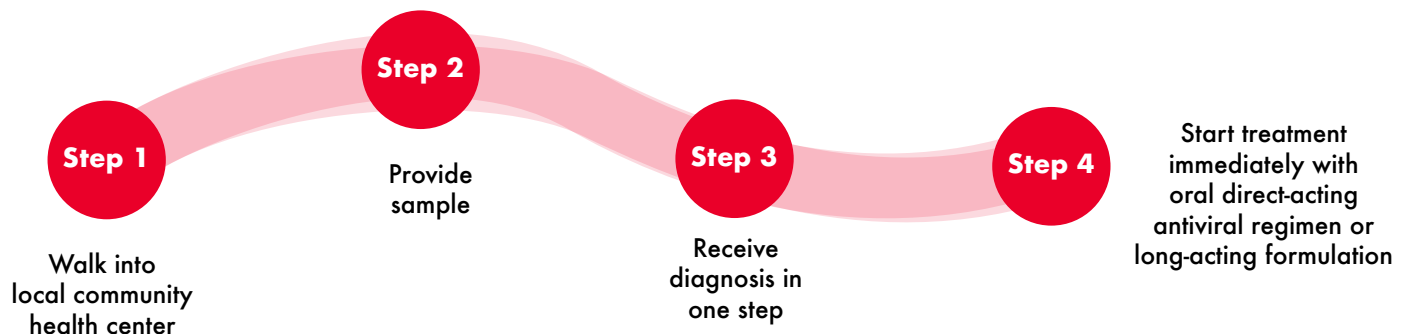
for HCV (which already exists) with immediate treatment initiation. Public health programs could deploy it in settings where there is no permanent infrastructure for medical care, pharmacies, or even a home where the medications can be stored.

Are there health systems capacity issues that need to be addressed in the drug development itself to ensure broad access in low- and middle-income countries?

Some long-acting technologies require cold storage or mixing on-site, and there are concerns that would add layers of cost, training, time, and quality assurance. In my view, developing a long-acting HCV cure that does not have those requirements is ideal but not necessary. My sense is that a public health campaign approach could still manage that type of preparation. Imagine an HCV elimination van that moves around and offers free testing and cure. Those on the van can certainly be trained to prepare the formulation.

You have started to survey providers and patients about their preferences when it comes to different formulations. Could you share anything from your findings so far?

Our findings have not yet been published. However, in general, we find that there is high acceptability for long-acting treatments – highest for injections, and highest when someone already has experience with that form (for example, already had an implant once). That said, there are some who prefer pills and a small fraction who really hate getting injections.

Figure 1: Current versus ideal diagnosis and treatment pathway**Current pathway (three months +)****Ideal pathway (Under 30 minutes)¹**

In those respects, persons who inject drugs are similar to other persons living with HCV. Long-acting treatments are particularly advantageous for persons who might not have stable housing that provides a place to store medications. We also are aware of research that shows you can safely hand out an entire HCV treatment course of pills.² So taken together, we believe in a model where both are offered.

You have done extensive work on HCV treatment and care in prisons in Louisiana. How would long-acting HCV cure work in a detention setting?

A long-acting HCV treatment would be ideal for carceral settings. Incarcerated people frequently are moved around within and between facilities, which poses interruptions to longer courses of treatment. Frequent medical care also

The current pathway to [HCV] diagnosis and starting treatment still has many steps, and establishing the required infrastructure demands sustained financing, health trainings, political leadership, and an enabling policy environment.

requires transporting incarcerated people to get treatment, which is a lot of work and cost for the system. A one-time test and cure approach is preferable.

Unitaid's LONGEVITY project is supporting the development of a long-acting formulation of glecaprevir and pibrentasvir (G/P). What are the challenges with developing long-acting formulations of drugs, and how did this drug combination become the frontrunner for a long-acting formulation?

I am new to this and have learned a lot from the pharmacologists and chemists on our team. In short, properties that make a drug great for oral use (water-soluble and fast uptake into the liver from the gut) are the opposite of what is ideal for a long-acting injection. That is particularly true for sofosbuvir. The rapid uptake of sofosbuvir from the gut into the liver contributes to its efficacy as a pill but makes it harder to formulate as a long-acting treatment. Also, with pills, one can overcome lower potency by ingesting more, while with injections, the amount that can be injected is limited. The release of a medicine must be chemically managed instead of just taking the pills at a certain frequency. It is much harder. Other helpful properties of G/P include not inducing hypersensitivity allergic reactions (so that oral test doses aren't needed), working for all HCV genotypes, and being the shortest approved therapy (eight weeks).

If the LONGEVITY project successfully develops long-acting formulations of HCV for treatment, what's next? Is there potential for long-acting prevention of HCV, similar to pre-exposure prophylaxis (PrEP) for HIV or tuberculosis preventive therapy?

I do not envision medical PrEP for HCV. One simple reason is that no one has received these medications for more than 3–6 months, so we don't have any sense of the safety. Also, HCV can be cured. So, in my view, it just makes a lot more sense to have a program that rapidly tests and cures – along with harm reduction – versus trying to develop PrEP for HCV.

But there is certainly more to do after developing the product. We need to engage with those who can use it, ideally before approval. I like the example of HIV pre-exposure prophylaxis (PrEP). It was absolutely crucial to engage the community and potential recipients to develop a formulation that matches what women in sub-Saharan Africa needed. We certainly have to do that for HCV as well. We also need to consider the other stakeholders. For example, ministries of health and carceral medical facilities need to be convinced of the potential and prepare teams to deploy the treatments.

Sir Houghton, one of the Nobel Prize recipients for discovering HCV, says an HCV vaccine could be ready in five years,³ roughly along the timeline of the LONGEVITY project. How would a long-acting treatment formulation complement a vaccine?

Michael is super smart and a terribly thoughtful person who has been working on a vaccine since early 1990s. Developing a vaccine is great but doesn't help the 58 million people who already have HCV.

**Dr. David Thomas is Professor of Medicine and Director of the Division of Infectious Diseases at Johns Hopkins Medicine. He is Principal Investigator of the Johns Hopkins project for developing long-acting technology for HCV and the lead investigator on HCV clinical development under the Unitaid LONGEVITY grant.*

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LONG-ACTING THERAPY FOR MALARIA PREVENTION: TOWARD A MALARIA-FREE WORLD

by Joelle Dountio Ofimboudem

Malaria is a life-threatening disease prevalent in the world's poorest countries, particularly in sub-Saharan Africa. Preventing malaria hits close to home for me. I am a mother to two children, aged three and five. We are originally from Cameroon, where we all have contracted malaria multiple times. As an intellectual property lawyer and global public health advocate, I know that geography – the fact that we live in the “neglected” part of the world in terms of research and development (R&D) priority – is the main reason for the constant battle with malaria. It is appalling to know that the multiple trips to the hospital and hospitalizations resulting in my kids missing school or not playing with their friends can be avoided.

By offering an easier way to protect people living in endemic regions against malaria, a long-acting formulation for malaria prevention would indirectly address drug resistance by sparing people from taking medications and eventually eliminating the market for unverified antimalarials.

Today, 14 of the 15 countries – which account for 80% of the malaria burden – are in sub-Saharan Africa. Yet, elimination efforts do not focus on these countries.¹ While malaria remains a leading cause of death in sub-Saharan Africa, the disease was eradicated in the United States and Europe in 1951 and 1975 respectively.² This is a stark reminder of the inequities in global health.

Malaria is a common comorbidity for people living with HIV. HIV infection can increase the risk and the severity of malaria, and the prevalence of symptomatic malaria is high among people who are coinfecting with HIV.³ Moreover, malaria increases HIV plasma viral load and decreases CD4+ T cells,⁴ and both diseases cause complex activation of immune cells and dysregulated production of cytokines and antibodies.⁵ Coinfection can also accentuate the progression of anemia.

As we explore long-acting technologies (LATs) for preventing malaria and HIV, many of the communities with whom we work are dramatically impacted by both and face similar access and linkage to care barriers (see Johnson, [page 10](#)). As a partner on the LONGEVITY project, which aims to develop LATs for preventing malaria and tuberculosis and curing hepatitis C, Treatment Action Group (TAG) applies our technical and community engagement expertise to follow and translate the science of LATs to benefit patients, affected communities, providers, researchers, and other stakeholders across these diseases.

Global Malaria fast facts (2019)⁶

Prevalence	229,000,000 people
Deaths	409,000 people
Deaths of children under 5	274,000 (67%) children
Rate in sub-Saharan Africa	Represents 94% of cases and deaths

Current Malaria Prevention Measures and Challenges

Malaria persists because current prevention measures do not go far enough, hence, the need for more comprehensive approaches in the battle against malaria. Currently, prevention revolves around three main interventions: (1) sleeping under insecticide-treated nets; (2) spraying insecticides indoors; and (3) providing malaria prevention medications to people traveling to malaria endemic countries, pregnant individuals,

and infants living in high-transmission areas.⁷ Yet, each of these approaches presents challenges. People do not always use insecticide-treated nets because they increase heat,⁸ reduce airflow and cause breathing difficulties.⁹ The chemicals on these nets sometimes cause skin reactions; and the nets can be inconvenient for daily set-up in homes that lack space.¹⁰ Moreover, these nets are not typically replaced or re-treated in time to provide continuous protection against mosquito bites. With respect to indoor spraying, Pyrethroid – a chemical contained both in insecticide spray and insecticide-treated nets that kill mosquitoes— although affordable and having a

The high prevalence of malaria in low- and middle- income countries (LMICs) over 50 years after its eradication in high-income countries is a glaring example of global health inequity. Malaria eradication in LMICs would ensure a “malaria-free” world for all and enhance global health equity. Long-acting technologies offer a critical opportunity for advancing that goal.

long residual action, has developed resistance across most of malaria endemic sub-Saharan Africa due to increased use.¹¹ The high cost of alternative insecticide sprays and their low community acceptance have also contributed to minimal spraying of insecticides indoors across sub-Saharan Africa.¹² Lastly, insufficient capacity and funding for malaria prevention constrains countries’ ability to set their own agendas for reducing the disease burden.¹³

Current Malaria Treatment and Challenges

While there are several approved Artemisinin-based Combination Therapies for malaria treatment which are recommended by the World Health Organization,¹⁴ malaria treatment also faces many challenges. Historically, due to high

malaria prevalence in endemic countries such as Tanzania, health providers treated people with suspected cases of the disease with relatively cheap antimalarial medications, a practice known as presumptive treatment.¹⁵

In Cameroon, due to insufficient health staff, people stock and self-administer anti-malarial medications at the onset of any fever, especially in remote areas. The failure of authorities to effectively regulate medicines imports and quality floods the market with unverified/low quality antimalarials. Ineffective regulation provides patients with antimalarials through street vendors and even at pharmacies without prescriptions. There are also high costs: transportation, hospital consultation, and laboratory exams which, combined, cost more than the full treatment course for malaria from street vendors.

Due to these factors, and the frequency of symptoms, adults and parents self-administering malaria medication when they, or their children, have a fever is a common practice, despite healthcare guidelines and providers’ dissuasion. They often use unverified, low quality antimalarials that fuel drug resistance, or seek traditional herbal treatments at the onset of symptoms, and present too late at healthcare facilities with severe illness.

The LONGEVITY Project and Malaria Elimination

A long-acting malaria preventive – if proven safe, effective, acceptable, and accessible – could address many of the shortcomings of the current approaches to both treatment and prevention. By offering an easier way to protect people living in endemic regions against malaria, a long-acting formulation for malaria prevention would indirectly address drug resistance by sparing people from taking medications and eventually eliminating the market for unverified antimalarials.

Given the shortage of healthcare staff in most sub-Saharan African countries, a long-acting preventive for malaria would significantly reduce the workload on health providers and enable them to focus on other health problems – hence, enhancing public health overall. A long-acting malaria prevention therapy would also drastically reduce adult and infant mortality. More children could live more fulfilling and healthy lives, and parents like myself and their children would no longer have the burden of frequent visits to the hospital and hospitalizations. Apart from the health benefits, malaria elimination would reduce economic loss in the form of disability-adjusted life years in endemic countries.¹⁶

A long-acting formulation will hopefully eliminate the need for insecticide-treated nets, which cause skin reactions and exacerbate the already warm, tropical climates where malaria is endemic. People could sleep better, enhancing their overall well-being.

Malaria endemic countries usually have very fragile healthcare systems. Malaria prevention could help avert complications that arise with the onset of malaria, including anemia, miscarriage, liver failure, kidney failure, premature and stillbirth, and cerebral malaria. Given the high out-of-pocket cost, and the limited number of specialists available to provide care for these complications, especially in rural areas, prevention would be a tremendous public health win for malaria endemic countries.

The LONGEVITY Project – Redefining Pharmaceutical Research and Development

The pharmaceutical industry's status quo has failed to develop new antimalarials and antibiotics because these medications have a lower return on investment than treatments for conditions that turn higher profits in high-income countries, such as cancer.¹⁷ The access-to-medicines movement has called for "push," "pull," and "pool" mechanisms to incentivize pharmaceutical developers and donors to invest in R&D for neglected diseases, such as malaria. The LONGEVITY Project encapsulates both the "push" (i.e., incentivizes industry by reducing R&D costs and absorbs upfront risks) and "pull" (i.e., creates incentives for private sector engagement by creating viable market demand) mechanisms. The project invests in R&D for long-acting injectables of existing treatments; in the case of malaria, it investigates atovaquone. The LONGEVITY Project also involves community engagement and advocacy to ensure accessibility and acceptability of long-acting formulations and prepare stakeholders for eventual introduction.

The high prevalence of malaria in low- and middle-income countries (LMICs) over 50 years after its eradication in high-income countries is a glaring example of global health inequity. Malaria eradication in LMICs would ensure a "malaria-free" world for all and enhance global health equity. Long-acting technologies offer a critical opportunity for advancing that goal.

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Our cover was inspired by a variety of images Unitaid (<https://unitaid.org>) created for their series of web articles on long-acting medicines.

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Now in our 29th year, Treatment Action Group advocates for treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, hepatitis C virus, and COVID-19. The progress is palpable, but there's still much to be done to end these epidemics. We need your support to continue saving lives in 2021.

Make a donation today: treatmentactiongroup.org/support-us/donate

ABOUT TAG

Treatment Action Group (TAG) is an independent, activist, and community-based research and policy think tank committed to racial, gender, and LGBTQ+ equity; social justice; and liberation, fighting to end HIV, tuberculosis (TB), and hepatitis C virus (HCV).

TAG catalyzes open collective action by affected communities, scientists, and policymakers to ensure that all people living with or impacted by HIV, TB, or HCV – especially communities of color and other marginalized communities experiencing inequities – receive life-saving prevention, diagnosis, treatment, care, and information.

We are science-based activists working to expand and accelerate vital research and effective community engagement with research and policy institutions for an end to the HIV, TB, and HCV pandemics.

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