



IAS Corporate Partnership Programme

Industry Liaison Forum

Accessing long-acting HIV prevention and treatment innovations: Landscape, service delivery and pathways to affordability

IAS – International AIDS Society –
in collaboration with the Medicines Patent Pool

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Satellite report
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Background

The prevention and treatment landscape for HIV has come a long way since the U.S. Food and Drug Administration (FDA) first approved antiretroviral therapy (ART) in 1987. Numerous ART options are now available on the market. Lifelong treatment may pose several challenges to clients, including stigma, pill burden and non-adherence. It is, therefore, important to provide a variety of treatment and prevention options that meet the needs and wants of clients. With the first long-acting (LA) regimens being approved by the FDA in 2021, long-acting technologies are the exciting additions to the HIV treatment and prevention toolbox that could address some of these issues. However, there is a need to further explore opportunities and mitigate the anticipated challenges these options might create for the beneficiary populations and healthcare systems they cater to.

This satellite, co-organized by the IAS Industry Liaison Forum and the Medicines Patent Pool, brought together key stakeholders from ministries of health, civil society, industry, communities, funders, implementers and researchers. The aims were to:

- Provide the audience with knowledge of the current landscape of HIV prevention and treatment long-acting technologies.
- Discuss the differentiated service delivery models that can be used to ensure that these technologies reach the various communities vulnerable to HIV and do not burden the healthcare system.
- Discuss the technology transference possibilities for some of these technologies to increase their availability and affordability

Satellite programme

Welcome and introduction Adeeba KAMARULZAMAN , University Malaya, Malaysia Charles GORE , Medicines Patent pool, Switzerland
Landscape of long-acting HIV prevention and treatment innovations Charles FLEXNER , Johns Hopkins University, United States
Sustainable service delivery in the long-acting technology era Nittaya PHANUPHAK , Institute of HIV Research and Innovation, Thailand
Pathways for timely and at-scale access to quality affordable long-acting HIV innovations Cherise SCOTT , Unitaid, Switzerland
New WHO guidance: Long-acting cabotegravir for HIV prevention Rachel BAGGALEY , World Health Organization, Switzerland
Panel discussion Wesley KREFT , PFSCM, Netherlands Mitchell WARREN , AVAC, United States Anton POZNIAK , Chelsea & Westminster and LSHTM, United Kingdom Nina RUSSELL , Bill & Melinda Gates Foundation, United States David RIPIN , Clinton Health Access Initiative (CHAI), United States Lilian MWOREKO , International Community of Women living with HIV Eastern Africa (ICWEA), Uganda Kenly SIKWESE , AfroCAB, Zambia
Summary and closing Adeeba KAMARULZAMAN , University Malaya, Malaysia Charles GORE , Medicines Patent Pool, Switzerland

Key points from the presentations

What's in the pipeline: Long-acting drugs for treatment and prevention – Charles Flexner, Johns Hopkins University, USA

Charles Flexner presented an overview of the pipeline of long-acting drugs for HIV treatment and prevention. This included agents in development, but not cabotegravir and rilpivirine, which were covered in other sessions at the conference.

Long-acting oral ARVs

Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI), which has a unique mechanism of action and a unique resistance profile. It has extraordinary potency and a long half-life, which makes it an ideal candidate for a long-acting formulation. It has been in development as both an oral weekly formulation for treatment and an oral monthly formulation for pre-exposure prophylaxis (PrEP). Merck had to temporarily pause the development of ISL at the request of regulatory agencies due to participants experiencing unexpected toxicity, namely, lymphopenia associated with a significant drop in CD4 count in some clients.

ISL was in development with another NNRTI (MK-8507) in a once-weekly regimen, which was also paused. Several questions are yet to be answered. Toxicity may be related to the amount of drug given; lower doses of ISL may meet safety and efficacy targets. There may be populations for whom ISL would never be an appropriate drug. Other delivery platforms (for example, implants) may not lead to lymphopenia.

Editor's note: Since this AIDS 2022 satellite session was held, Merck has stated that although it will continue exploring ISL for treatment, it has ceased any work on ISL for prevention as either an oral LA product or an implant.

Implantable ARVs

Tenofovir alafenamide (TAF) is in clinical development as a long-acting agent. Animal studies have shown that a single implant can maintain effective antiretroviral (ARV) levels of TAF for up to 40 days. With none of the approved long-acting ARVs and most of those in development having an effect against the hepatitis B virus, the development of this implant will facilitate the use of LA-ARV technology by people who also have HBV. Unfortunately, several implants have been associated with severe local toxicity, including tissue necrosis. Consequently, the Bill & Melinda Gates Foundation, which supported the development of this implant, decided to no longer fund the research. However, a recent animal study showed that the toxicity was related to the rate of release of the drug. Implants with slower release rates produced no or low toxicity and may provide a pathway for the development of a TAF implant. Several studies are currently running in South Africa.

Subcutaneous ARVs

Lenacapavir, a capsid inhibitor developed by Gilead Sciences, is a leading candidate. This drug has more than one site of activity and a unique mechanism of action and resistance profile. In the Phase 2/3 CAPELLA study involving treatment-experienced people living with HIV with resistance to other ARV classes, lenacapavir reduced the viral load in the short term following oral administration of the drug. The study is ongoing, with lenacapavir administered subcutaneously every six months. Because the drug has an exceedingly long half-life, it requires an oral loading dose given three times over eight days to bring its concentration quickly to antiretroviral levels, followed by a subcutaneous maintenance dose every six months. Therefore, two formulations will have to be developed for this product. Based on current data, Gilead has made an application for approval of lenacapavir in treatment-experienced people with resistance to other classes of ARVs.

Intravenous ARVs

Several broadly neutralizing monoclonal antibodies (bnAb) are currently in clinical development. Studies showed that a simple mutation in the Fc binding domain of the VRC-01 antibody

dramatically increases its plasma half-life. This was not seen with another bnAb, VRC07, which is a much more potent antibody than VRC-01.

Transdermal ARVs

Microarray/needle patches are providing a unique opportunity to deliver ARVs. These are devices cast in a mould with an adhesive border on the outside of the patch. The patch is pressed into the skin, so the microneedles can enter the subdermal space. Nano-formulated drugs are deposited in viable skin layers and provide sustained release and absorption by rich dermal microcirculation. Pharmacokinetic studies in animals of three different CAB-LA formulations showed that it is possible to deliver CAB-LA with two different kinds of microarray patches. Nano-formulated transdermal patches release CAB-LA over four weeks and achieve concentrations that exceed the target for inhibiting HIV. Clinical studies with placebo are ongoing in humans to assess tolerability and performance. Studies with ARVs are expected in the next two to three years.

More technologies are being developed, including bio-erodible polymer implants that degrade over time and will not need removal, gastric reservoirs and combination technology (ARVs with a hormonal contraceptive). Efforts to reduce the injection volumes are also ongoing. Flexner concluded by signposting the long-acting technologies patents and licences database ([LAPaL](#)), hosted by MPP, and the [Leap](#) database.

Sustainable service delivery in the long-acting technology era – Nittaya Phanuphak, IHRI, Thailand

Nittaya Phanuphak addressed two questions in her presentation. Why is the service delivery model such an important aspect when thinking about implementation of LA products? And what are the key considerations from a service delivery perspective? The presentation focused on LA PrEP products.

In the Asia Pacific region, Thailand and Vietnam are ranked second and third after Australia in terms of active PrEP users, with both countries sharing a key population-led service PrEP delivery model. In Thailand, 80% of PrEP users receive PrEP in key population-led PrEP clinics, which are not staffed with doctors or nurses although doctors are involved in decisions to prescribe and provide PrEP through a smartphone application.

Key population-led PrEP services in Thailand aim to simplify, de-medicalize and differentiate PrEP services through close collaboration with hospitals. It has been very successful in scaling up oral PrEP programmes because of it's:

1. Accessibility: Hotspot locations, flexible hours, one-stop service
2. Availability: Needs-based and client-centred services (such as gender-affirming services for trans people, hormone monitoring, STI testing, legal consultation and harm reduction)
3. Acceptability: Staff drawn from key population communities and gender-oriented services and free from stigma and discrimination
4. Quality: Trained and qualified staff and strong linkage with and high acceptance by public health sector

The success of the intervention led the Ministry of Public Health to legalize key population-led providers, which can now provide a range of services, including dispensing PrEP as prescribed by doctors. There are now several certified key population-led providers throughout the country.

The three principles of key population-led PrEP services are:

1. De-medicalization: PrEP offered by lay providers or through healthcare workers, leading to task shifting
2. Simplification: Finding simpler ways to deliver care, promote increased access and lower cost while retaining efficacy and quality
3. Differentiation: Adapting the "when", "where", "who" and "what" based on a client-centred approach

Integrating CAB-LA injections into key population-led PrEP service will lead to:

1. Re-medicalization as product administration shift back to nurses and doctors

2. More complexity as HIV testing algorithm will need HIV RNA assay and it is not known whether third- or fourth-generation rapid test, self-testing and pooled POC HIV RNA can be used
3. The need to address various user patterns with more PrEP products available
4. Determining how to handle more frequent CAB-LA visits and switching between oral and LA products

Challenges and enablers to be considered for long-acting PrEP implementation include:

1. Convenience and comfortability
 - a. Simplification and differentiation: Moving CAB-LA from public hospital or clinic to community-led or key population-led clinic or home
 - b. Differentiation of the "who", "where", "what" and "when" for CAB-LA initiation, continuation, discontinuation and re-initiation and switching between oral and injectable products
 - c. Differentiation of the HIV testing algorithm according to PrEP status to understand the use of third- and fourth-generation rapid testing versus third- and fourth-generation HIV self-testing
 - d. Simplification through integration with family planning, gender-affirming and STI/HCV test-and-treat services
 - e. Provision of adherence support for a clinic visit (which now equals product administration)
2. Competence in product administration
 - a. De-medicalization: Task shifting from doctor, nurse to lay provider, oneself
 - b. Lack of clinical research data on self-injection, reduced volume, reduced visits, alternative injection sites (thigh muscle, subcutaneous injection) and difficulties in planning for implementation research
 - c. Capacity building and quality assurance for injection by lay providers and self-injection
 - d. Professional institution regulations and rules and mindset

Beyond CAB-LA, we need to think about other long-acting products for which there will be common and specific implementation considerations and challenges. CAB-LA may score better in terms of frequency of product use than oral PrEP, but we have no experience with integrating products that need to be injected in key population-led services, including who can be an injector and how to provide adherence support. Cost may also be an issue if more frequent and more specific HIV testing is needed. It is also unknown whether generic products will be available at an affordable price soon. The current CAB-LA agreement does not include medium-income countries like Thailand. For future long-acting products, the manufacturers may want to think about these implementation challenges in advance and include implementation research in the design of the clinical trial to move more quickly from trial to implementation.

Phanuphak concluded with the following points:

- LA products will not become a true choice without generic products.
- Creating demand for true choice is crucial.
- LA PrEP may also be stigmatizing for users if it is positioned as second-line PrEP, especially when it comes to oral PrEP.
- It is important to conduct research that will support implementation with plans that are regularly updated.
- Implementers need to know what will become available and when.
- We need better plans for delivery than we had for oral PrEP.

Cherise Scott started by saying that Unitaid recognizes the game-changing nature of LA technologies to prevent and treat infectious diseases. These products hold the potential to improve adherence, reduce transmission and the risk of drug resistance, and ultimately save lives. Unitaid has heard the message from communities that want to access these products and are calling for a paradigm change. The opportunities are there, with products at various stages of development, marketing and availability, including in low- and middle-income countries. A collaborative and holistic approach from all stakeholders involved is crucial to success. Unitaid has positioned itself at the forefront of the effort to advance LA technologies and has developed a strategy in the areas of innovation and access focusing on three key areas:

- Advance the technology pipeline.
- Accelerate the introduction of emerging products.
- Enable access pathways and scalability.

The approach was guided through consultation and a landscaping exercise which started in 2018. This led to several publications and the LAPaL database.

Unitaid has a strong portfolio of products and is keen to collaborate with many partners to ensure that products reach people in need. Unitaid is also exploring multipurpose technologies and monoclonal antibodies and working with WHO and GAP-f to improve prevention and treatment in children.

For products being developed with Unitaid funding, access is built early in the research. This includes licencing agreements and access to ensure that products will reach people in need without delay. Unitaid also ensures that products are fit for purpose and can be administered in low-resource settings while advocating for access. It encourages all companies to coordinate efforts sooner rather than later to create an access pathway.

New WHO guidance: Long-acting cabotegravir for HIV prevention – Rachel Baggaley, WHO, Switzerland

The results of the cabotegravir trials have caused excitement in the global health community, Rachel Baggaley said, with an 80% reduction in risk of HIV acquisition compared with oral PrEP. This highly effective result was also shown in follow-up studies. WHO acted quickly to issue recommendations on the use of cabotegravir for HIV prevention. She stressed that those results did not mean that oral PrEP did not work and that it was very important to look at the difference in adherence between the two modalities. There are some concerns, with CAB adherence slipping slightly in follow-up studies, which is important when thinking about future delivery. Gaps were identified when looking at the evidence to develop the guidance. There is limited data for some populations and some geographic settings, as well as data on drug resistance – very few seroconversions were observed in the trial. Although there are no signals of safety issues when CAB is used during pregnancy and breastfeeding, there is limited data and this will have to be monitored through post-market surveillance. Evidence that CAB is safe and effective for people using hormonal gender-affirming therapy was provided at the conference.

WHO organized a broad survey of PrEP providers, including in low- and middle-income countries, to assess values and preferences of providers and users, which are important for successful rollout. Surprisingly, only 50% of service providers are aware of CAB, but 70% of those aware are considering providing CAB. This emphasizes the need to get information out about CAB-LA for HIV prevention.

WHO also conducted a systematic review of user preferences for PrEP products. These were largely based on hypothetical scenarios, and responses varied. There is a lot of interest in PrEP, with a preference for injectables, especially by people who do not want tablets or find it difficult to take tablets daily and who had experience with other injectable products, such as injectable contraceptives; there are also privacy motives.

WHO partnered with the global networks of key populations to understand their communities' values and preferences around PrEP products. The results were variable across geographies and

populations. Again, there is a lot of interest, but varying levels of awareness about PrEP choices, reinforcing the need to engage more with communities about CAB-LA. Choice is important, as well as the possibility of switching between modalities.

WHO looked at cost-effectiveness studies, which provided mixed results from the different models and inputs used (specifically, costs of products and testing and/or monitoring costs and incidence in the populations).

A critical issue for WHO is the requirement for HIV testing prior to initiating and during treatment with CAB and the potential for the development of drug resistance if detection of seroconversion is delayed. The FDA, in its approval of CAB and the company's instructions for use, stipulates that molecular testing is required when starting CAB and at every injection. This is a major concern as it would reduce feasibility and increase the cost, especially in low- and middle-income countries. After reviewing all available data and holding consultations, WHO CAB guidelines suggest that HIV testing should be more flexible and the use of the national testing strategy (usually serial rapid antibody tests) should be considered.

Following the publication of the guidance:

- WHO added CAB-LA to the WHO Expression of Interest, allowing manufacturers to apply for inclusion in the WHO list of prequalified products.
- WHO is supporting and pushing for rapid implementation research among populations that were not included in the randomized controlled trials (sex workers and people who inject drugs) and in settings where there is currently little implementation science planned, including in Asia.
- WHO is collaborating with the global effort led by Unitaaid and others to support product availability, access and low-cost pricing for low- and middle-income countries.
- WHO is updating all PrEP implementation guidelines to include CAB-LA alongside oral PrEP and the dapivirine vaginal ring.
- The Global Fund and other organizations can include CAB-LA in their lists of products for procurement.

Panel discussion

The panel discussion started with an impromptu demonstration of advocates and activists calling for access to products, especially for communities that had contributed to the clinical trials and are in dire need of the technology.

Anton Pozniak commented that the demonstration reflected the concerns that the panel aimed to discuss. He asked the panel whether there are enough generic companies that can manufacture the product and how fast they can do it.

David Ripin commented that there are several suppliers able to make the product, but the question is: how much investment is needed to manufacture it and to perform bioequivalence work? He thought that it would take longer than oral PrEP, expecting that three or four years would be needed to get generics to the market, with cost depending on donors, risk-sharing strategies and funding mechanisms.

Wesley Kreft confirmed that there is an interest from generic suppliers and asked if there is an overall market and appetite for the product. Interest will result in a longer-term market. He believes that generics will be available in three or four years. As more products are available, prices will go down, potentially in five years, with multiple generics coming to the market.

Nina Russell added there is a need to better understand what the market, demand and potential maximal volume and, therefore, the lowest associated price will be. As a community, we need to explore mechanisms that can be used to mitigate pricing issues (for example, buying guarantees).

Lillian Mworeko said that communities have been waiting for a long time for effective HIV prevention and the demonstration showed that there is a crisis, as did the latest UNAIDS global report. In her region, women and young girls have been waiting for options, and 40 years into the epidemic, there are still new HIV acquisitions. Products are available and there is a menu for

everybody to choose from, but people are not able to access these products. She felt that the community is not taken seriously. She asked how to engage with young women who are disempowered and stigmatized to tell them that there are options they can choose but can't access. Mworeko drew attention to the contradictions of clinical research: for example, requesting that women use contraceptives while in a trial, but when successful products are developed, they are not available for trial participants. She called on all stakeholders to make products available immediately.

Audience questions

An audience member asked what can be learned from the successful TLD rollout. Mitchell Warren acknowledged the failure of HIV prevention. He pointed out that timelines can be achieved sooner only if people come together and collaborate, by getting volume guarantees, and by making policy decisions. This is doable in a couple of years through building partnerships and a sustainable market. A sustainable market requires demand creation, providers being training, HIV testing, guidance and products. More than one generic is needed to create competition. We also need to determine the cost of the full programme. Success will come from a programme that is comprehensive, strategic and collaborative. There are roadmaps to do this and there is a need to begin to act.

An audience member suggested that all this may come from following a traditional model of recouping investment and paying by prescription. We could learn from the development of antibiotics, which is difficult. People are advocating for different models, and a fixed fee to bring the product to the market could be considered. Dave Ripin commented that this is suitable for ultra-niche products that sell in very small volumes. In the case of cabotegravir, an incredibly high volume of product is needed. He added that we need to collectively place our bet on CAB-LA and make the investment based on a guaranteed volume.

Establishing proactive partnerships with communities well in advance is key to the success of TLD rollout. This was not done with PrEP, which resulted in early stigmatization and slow uptake. The predicted market size for oral PrEP was also incorrect. Tens of millions of PrEP users per year are needed to support rollout and we must rethink our targets. Ripin concluded by saying that three years should be our target for CAB-LA and we should start to scale up today.

Anton Pozniak asked how to remove the barriers to funding that are determined by countries' income. Nina Russell noted that anything we do with LA-CAB should be done in a way that anticipates a pipeline of products that will come quickly.

According to Mitchell Warren, it is the moment to build a prevention platform for each one of the products to come and for every country. If we do it only in a handful of countries, we will repeat what we did with the COVID-19 response and end up with a similar situation since epidemics do not know borders.

Lillian Mworeko said that although we are a learning movement, taking difficult decisions is required. There is a need to learn from the COVID-19 experience and move forward. The tools are there, and the question is how we can make them work. We cannot continue living in a world where inequality defines us.

Helen McDowell concluded the meeting by thanking all participants and adding that she is looking forward to continuing the dialogue.