

LONG-ACTING INJECTABLES FOR HIV TREATMENT AND PREVENTION

ACON Policy Paper, April 2022 Update

Introduction

Treatment and prevention of HIV is an evolving landscape. Now, many people living with HIV (PLHIV) in NSW have access to free and effective oral treatments. Some people only take one tablet once a day, and treatment can lead to someone achieving an undetectable viral load (UVL).

In recent years, an overwhelming body of evidence has established that an undetectable viral load = untransmittable, or U=U, is scientifically sound. This means that people with HIV who achieve and maintain an undetectable viral load by taking antiretroviral therapy (ART) daily as prescribed cannot sexually transmit the virus to others.

Since being made available in Australia in 2016, oral pre-exposure prophylaxis (PrEP) is an affordable and effective way to prevent HIV infection, and now there are [different ways to take PrEP](#) (e.g., daily, on-demand, periodic).

It is crucial that PLHIV and people using PrEP have access to a range of effective and affordable medications and are able to make informed choices about what treatment and prevention options suit them best.

As new biomedical technologies develop, the modalities of treatment and prevention can change. A new development in this space is the introduction of long-acting injectable forms of treatment and prevention.

A long-acting injectable is a form of treatment or prevention that is injected and has long-lasting effects. Long-acting

injectables represent a less frequent alternative to daily medications.

The *Eighth National HIV Strategy 2018-2022* argues for the need to capitalise on new technologies and advancements. The *NSW HIV Strategy 2021-2025* similarly identifies the need for innovation, and to trial new technologies such as injectable PrEP. Innovations in treatment and prevention are therefore part of the national and statewide efforts to end HIV transmission and stigma, and ACON continues to encourage innovation to respond effectively to the needs of our communities.

This paper outlines the evidence surrounding long-acting injectables, the benefits and disadvantages of these treatment modalities for PLHIV, their potential for use as an HIV-prevention method (PrEP), and the considerations for their integration into future HIV responses.

The potential of long-acting injectables for HIV treatment and prevention

The introduction of long-acting injectables has many potential benefits for both treatment and prevention, provided they are effective, affordable, and accessible.

- **Convenience:** long-acting injectables require fewer occasions of dosing, especially when compared to daily forms of treatment or prevention. This allows for greater convenience and flexibility, and the opportunity to travel without carrying medication or prescriptions.¹

- **Adherence:** with fewer doses come fewer opportunities to miss a dose, thus allowing for better adherence to both treatment and prevention regimens.
- **Stigma and discrimination:** studies have demonstrated the emotional advantage of long-acting injectables in their ability to eliminate a daily reminder of living with HIV, and the risk of inadvertent disclosure or adherence issues due to discovery of medications,² as well as the greater privacy of these treatment and prevention methods.³
- **Treatment alternatives for specific populations:** long-acting injectables provide an alternative to oral treatment for those with gastro-intestinal issues or other concerns with oral medications, and a solution to ‘pill fatigue’, especially for those on treatment or using daily PrEP. Long-acting forms of prevention may be especially worthwhile for those whom on-demand and event-based PrEP are not recommended, [including trans people](#). Long-acting forms of treatment may also represent a more appropriate treatment option (provided consent is given) for PLHIV who are subject to treatment orders, in residential care facilities, or those who are incarcerated.

What’s the current situation?

Interest in long-acting injectables for treatment and prevention is high. Patients in clinical trials of long-acting forms of treatment have [overwhelmingly preferred](#) the injectable over a daily tablet.

Among current users of PrEP in the [PrEPARE study](#), half indicated, in a hypothetical scenario given current availability of options, that their preferred method of taking PrEP (assuming all methods were available, affordable, and equally effective) was via long-acting injection (every 2 to 3 months), and 18% preferred the option of a long-acting implant. This was lower among non-PrEP users, but an injectable method was still

the most preferred option among this cohort, at 33%. A US study of trans MSM also found that just over half preferred, in a hypothetical setting, an injectable method of PrEP.⁴

While interest is high, there is currently only one form of long-acting injectable approved for treatment in Australia, with a few others in development.

Cabotegravir + Rilpivirine combination treatment

In February 2021, the [TGA approved](#) Cabenuva, a drug combination treatment consisting of long-acting Cabotegravir, a new form of integrase inhibitor, and Rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI). [Cabenuva](#) comes in the form of two intramuscular injections taken at the same time, either monthly or every other month. These injections need to be administered by a health professional, which means 6-12 clinical appointments per year.

The regime is recommended for people with an undetectable viral load, after they have completed a 30-day lead-in of oral medications Vocabria (Cabotegravir) and Rilpivirine, to ensure the medications are well-tolerated before commencing long-acting treatments. While ViiV have announced that the [oral lead-in is now optional](#), this treatment path is currently still recommended by the TGA.

As well as the TGA, this treatment option has been approved in the US, Canada, and Europe, following the success of three phase III clinical trials, [FLAIR](#), [ATLAS](#), and [ATLAS-2M](#). These clinical trials demonstrated the clinical effectiveness of injectable treatment, providing evidence that these treatments are non-inferior to oral treatments in treating HIV and maintaining a UVL.

There is [evidence to indicate](#) that there is a higher (but still small) chance of virological failure among people receiving the every other month treatment option (an estimated 1 in 40 chance of virological failure) compared to those dosing monthly (1 in 200).

A large majority of patients in these studies, 86% of ATLAS patients and 91% of FLAIR

patients, said they preferred injectable treatment to oral forms of treatment. 94% of participants in ATLAS-2M preferred injections every other month, while 3% preferred monthly dosing and 2% preferred oral therapy.

Following an [unsuccessful attempt](#) to have the medication listed on the Pharmaceutical Benefits Scheme, in November 2021 the Pharmaceutical Benefits Advisory Committee [recommended](#) the every other month regime of Cabenuva for the PBS. On the 1st April 2022, these processes were finalised, and Cabenuva is now available in Australia at a subsidised price.

Cabotegravir for HIV Prevention

Cabotegravir is also being investigated as a form of long-acting prevention, with one intramuscular injection every two months, administered by a health professional.

Two studies in particular, [HPTN083](#) which considered cisgender men and trans women, and [HPTN084](#), which studied cisgender women, have been terminated earlier than expected because the results clearly indicated that injectable PrEP was more effective at HIV prevention than oral PrEP.

This is not because oral forms of PrEP are ineffective, but rather that in these particular cohorts injectable PrEP helped to mitigate the low adherence of oral PrEP – that is, these populations were more likely to have an injection every other month, than take a daily pill.

Both oral and injectable PrEP, when administered correctly, provide an effective method of HIV prevention.

Cabotegravir, under the brand name Apretude, [was approved for use as PrEP for cisgender and transgender men and women in the USA in December 2021](#). It is not yet approved in Australia.

Other long-acting therapies for treatment and prevention

Other long-acting therapies are also being explored in early clinical trials, however, studies containing two of the most promising developments have been put on hold due to quality issues and safety concerns.

[Lenacapavir](#), a new class of drug known as a capsid inhibitor, has demonstrated effective viral suppression in phase II/III clinical trials, indicating a potential prevention option that could be self-administered by subcutaneous (under the skin) injection every 6 months.

Studies of lenacapavir have been [put on hold](#) following a quality issue with the glass vials the medicine is stored in. It is anticipated that this issue can be resolved in a relatively timely manner.

Lenacapavir was also being investigated as a treatment option in combination with [Islatravir](#), an NNRTI. Islatravir was also being investigated for use as a [prevention implant](#). However, all studies involving islatravir have been [put on hold](#) after some clinical trial participants experienced a decline in their CD4 T-cell counts.

Looking ahead

It is still early days for long-acting injectables. While clinical trials ensure their effectiveness, their uptake is contingent on whether the technology lives up to its potential, and how this could improve as the technology develops. There are several considerations for the integration of these technologies into future HIV responses.

Accessibility

Everyone deserves access to treatment and prevention of HIV. Increasing the available options for the treatment and prevention of HIV represents greater choice for those who need it.

In Australia, Cabenuva is now available for PLHIV at a lower price, but this is not the case in other parts of the world. There have been [calls to Viiv](#) to license the drug generically in order to enable widespread access, particularly in low and middle income countries.

In Australia, the PBAC justified the high price of subsidising the medication because it recognised the value this form of treatment would have for particular populations, including Aboriginal and Torres Strait Islander people, people living in rural or remote areas, and people with complex living or social circumstances.

As Cabenuva is so far only approved by the TGA for those with an already undetectable viral load of < 50 copies/mL, this treatment option is limited to those already adhering to treatment. This means it is not an option for many newly diagnosed people, who are then not able to access the benefits of this kind of medication in addressing stigma and discrimination during treatment initiation, a phase where [stigma has an impact](#).

Further clinical trials and cost analyses are needed to ensure equitable access for everyone, especially priority populations in the NSW HIV Strategy 2021-2025.

Convenience

Long-acting injectable forms of treatment and prevention have been heralded as a form of freedom from daily treatment. However, daily treatments and PrEP can be dispensed in amounts that require 2-4 medical visits a year, while Cabenuva must be administered by a doctor, thus representing 6-12 appointments per year.

The added inconvenience of extra medical appointments limits the benefit of the long-acting treatment or prevention for some people, especially those who have difficulty accessing medical care, whether due to cost, geographic location, stigma and discrimination, or other factors.

Participants in clinical trials reported that long-acting injections were convenient but expressed concern about the increased frequency of medical appointments, including for example, concerns around colleagues noting their time off work, and hoped for less-frequent options to be made available.⁵

Adherence

Clinical trials have proven that long-acting injectables allow for better adherence to treatment regimes, though it has to be noted that clinical trials are not the real world: there is more incentive for patients to adhere to treatment schedules and attend medical appointments than there is in daily life.

Monthly or every-other-month injections represent fewer occasions of dosing, and

therefore fewer chances to miss a dose and compromise adherence. However, because the treatments are long-acting, missing a dose has a greater impact than missing a daily treatment.

The extra medical appointments required by patients opting for this form of treatment or prevention represent an added burden on the healthcare system.

It is important for the effective use of long-acting injectables that any issues with adherence are mitigated. This could be via greater access to appointments, via expanded community health services, investigating the possibility of self (or peer) administering, and other interventions to ensure adherence.

Long-acting injectables have a long half-life, and so developing a resistance to these drugs is therefore possible if treatment regimens aren't properly adhered to. It is [recommended](#) that a new anti-retroviral regimen starts one or two months (depending on frequency of injections) after stopping a long-acting regimen.

In clinical trials of Cabotegravir as prevention, participants were asked to take [oral PrEP for 48 weeks after their last injection](#), but it is not yet clear whether that is long enough to cover the long-tail period. This is important because a seroconversion during the tail period could mean a resistance to Cabotegravir and other integrase inhibitors, which can limit treatment options. This requirement could negate the benefit of an injectable form, especially among people with low adherence to oral PrEP.

Stigma and discrimination

As long-acting injectables are currently administered at a medical facility, these regimens mean no need to carry medication.

However, some benefits of reduced stigma and discrimination may be compromised by the need for additional clinic visits, particularly for those who experience stigma and discrimination in healthcare settings.

In a [recent study](#), one third (33%) of PLHIV reported being treated negatively or differently by healthcare workers because of their HIV status.

While long-acting injectables also help to address internalised stigma by eliminating the daily reminder of HIV, more holistic approaches, such as counselling, peer support and measures to reduce stigma in the broader community, are needed to accompany this treatment regime in order to fully address internalised stigma.

Treatment alternatives for specific populations

Injectable PrEP has been demonstrated to be favourable among trans MSM,⁶ and [effective for trans women](#). This is especially important given that event-based dosing of oral PrEP has [not been recommended for trans men, and there is no evidence to demonstrate the efficacy of this method for trans women](#). FDA approval of Apretude indicates that trans men and women, as well as cisgender men and women, are able to use the medication. It is important to note that very few trans men were involved in the clinical trials of cabotegravir as PrEP.

Injectable PrEP therefore represents an important option for those wanting an alternative to daily PrEP. Self-administering options for treatment and prevention may also prove suitable for trans people, especially those who are self-administering injectable hormone therapy.

The introduction of long-acting injectables into the treatment space may have consequences for those subject to treatment orders under the Public Health Act, as well as those in residential care or carceral facilities. In complex cases,

where treatment may be mandatorily administered, long-acting injectables represent fewer occasions of mandatory treatment, and therefore may be beneficial in reducing the stress of these instances on the person subject to treatment.

Side effects

[76-83% of participants](#) in clinical trials of Cabenuva as treatment reported experiencing pain at the site of injection. Fewer than 1% of participants discontinued treatment because of this side effect. Other side effects include fever, muscle pain, tiredness, weakness, depression, dizziness, abnormal dreams, diarrhoea, nausea, vomiting, abdominal pain and rash.

Further investigation into side effects may help determine who these forms of treatment and prevention are best suited to.

Conclusion

Long-acting injectables represent an important innovation in the treatment and prevention of HIV. As the technology improves, the benefit of long-acting modalities has the potential to be maximised via continued innovation in methods and frequency of administering, as well as the ability to streamline it with other forms of healthcare, including testing and gender affirming care. It is crucial that as these innovations develop, we can ensure equitable access for all, especially priority populations.

ACON supports the ongoing innovation of long-acting forms of treatment and prevention so that our communities may continue to make informed choices about what is best for their health and circumstances.

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Notes

¹ Spring, S., O'Bryan, J., McMahon, J. and Woolley, I., (2021), Acceptability of Injectable Antiretroviral Therapy in Australian Travelers With HIV. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 86(1), pp.e13-e15.

² Fernandez, C. and van Halsema, C.L., (2019) Evaluating cabotegravir/rilpivirine long-acting, injectable in the treatment of HIV infection: emerging data and therapeutic potential. *HIV/AIDS (Auckland, NZ)*, 11,

³ D'Amico, R., & Margolis, D. A. (2020), Long-acting injectable therapy: An emerging paradigm for the treatment of HIV infection. *Current Opinion in HIV and AIDS*, 15(1), 13-18.

⁴ Reisner, S.L., Moore, C.S., Asquith, A., Pardee, D.J. and Mayer, K.H., (2021), The Pre-Exposure Prophylaxis Cascade in At-Risk Transgender Men Who Have Sex with Men in the United States. *LGBT health*, 8(2), pp.116-124.

⁵ Fernandez and van Halsema, (2019)

⁶ Reisner et al. (2021)

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