The long wait for long-acting HIV prevention and treatment formulations

Willem Daniel Francois Venter, Monica Gandhi, Simiso Sokhela, Kenly Sikwese, Helen Bygrave, Louis Da Gama, Ndiviwe Mphothulo, Lise Jamieson, Mark J Siedner, Anton L Pozniak, Pablo Rojo, Solange L Baptiste, Jacque Wambui, Gesine Meyer-Rath, Brian Honermann, Mitchell Warren, Linda-Gail Bekker, Phumla Sinxadi, Simon Collins, Jessica Burry, Karlien Möller, Polly Clayden, Andrew Owen, Andrew Hill

Large randomised studies of new long-acting medications for the prevention and treatment of HIV have shown high effectiveness and acceptability. Although modelling studies indicate these agents could be fundamental in HIV elimination, coordination of their entry into health-care markets is crucial, especially in low-income and middle-income countries with high HIV prevalence, where coordination is low despite UNAIDS flagging that global HIV targets will not be met. Research and implementation projects are tightly controlled by originator pharmaceutical companies, with only a small percentage of eligible people living with or affected by HIV benefiting from these projects. WHO, financial donors, manufacturers, and governments need to consider urgent coordinated action from stakeholders worldwide, akin to the successful introduction of dolutegravir into treatment programmes across low-income and middle-income countries. Without this immediate coordination, large-scale access to long-acting agents for HIV will be delayed, potentially extending into the 2030s. This delay is unacceptable considering the established global HIV targets.

Lancet HIV 2024; 11: e711–16

Published Online August 16, 2024 https://doi.org/10.1016/S2352-3018(24)00173-5

This online publication has been corrected. The corrected version first appeared at thelancet.com/hiv on August 29, 2024

Wits Ezintsha (W D F Venter FCP, S Sokhela MBChB, K Möller MBChB) **and Health Economics and Epidemiology Research Office** (L Jamieson PhD, G Meyer-Rath PhD), **Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Division of HIV, Infectious Diseases, and Global Medicine, Department of Medicine, University of California San Francisco (UCSF), San Francisco, CA, USA** (M Gandhi MD)**; African Community Advisory Board (AfroCAB), Lusaka, Zambia** (K Sikwese)**; Médecins Sans Frontières Access Campaign, London, UK** (H Bygrave MBBS)**; Unitaid, Geneva, Switzerland** (L D Gama)**; Southern African HIV Clinicians Society, Johannesburg, South Africa** (N Mphothulo MBChB)**; The South African Department of Science and Innovation/National Research Foundation Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa** (L Jamieson, G Meyer-Rath)**; Harvard Medical School, Boston, MA, USA** (M J Siedner MD)**; Africa Health Research Institute, Durban, South Africa** (M J Siedner)**; Chelsea and Westminster NHS Foundation Trust and London School of Hygiene and Tropical Medicine, London, UK** (A L Pozniak)**; Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain** (P Rojo PhD)**; International Treatment Preparedness Coalition,**

Introduction

New technologies for therapeutic delivery are transforming health care for a range of conditions, including HIV. These advances allow for new medications, altered formulations of existing drugs, new drugs with a longer duration between dosing (weekly, once every month and 2 months and 6 months, and potentially even annually), and various modalities of administration (including intramuscular, subcutaneous, implantable, vaginal, and novel transdermal patches).[1] Antiretroviral potency and safety have substantially improved, with attention shifting to removing the need for daily pills, extending dosing intervals of existing and new antiretrovirals beyond daily fixed-dosed oral tablets used in first-line treatment, and improving uptake of pre-exposure prophylaxis (PrEP) in populations at risk.[1,2]

The term long acting is loosely applied to antiretrovirals administered at intervals longer than every 24 h, usually at least once per week or more, and given orally, vaginally, as an injectable (intramuscular or subcutaneous), or as implantable preparations. Currently, three long-acting HIV medications are approved by the US Food and Drug Administration (FDA). For treatment, cabotegravir (ViiV Healthcare, London, UK) and rilpivirine (Johnson and Johnson [J&J; previously known as Janssen] New Brunswick, NJ, USA), administered once per month or every 2 months as separate intramuscular injections, is licensed for the treatment of people living with HIV with no previous evidence of antiretroviral resistance to these drugs. This combination is co-packaged as Cabenuva and was approved in Botswana (2022) and the high-income countries Canada (2020) and the USA (2021), and separately in the EU (2020) as Vocabria (ie, cabotegravir) and Rekambys (ie, rilpivirine), as well as a growing number of different registrations in various countries.[3]

In 2021, the FDA approved cabotegravir as an injectable alone (manufactured as tradename Apretude by ViiV Healthcare, London, UK), administered once every 2 months intramuscularly. Approval was also granted in Australia in 2022, the EU in 2023, and multiple other countries, including seven countries in Africa between 2022 and 2023, after cabotegravir injectable alone initially showed efficacy in 2020. Cabotegravir for PrEP has been voluntarily licensed to the Medicines Patent Pool (MPP), an international organisation that aims to reduce drug prices through voluntary licensing and patent pooling. Generic manufacturers have to undergo 42-week bioequivalence testing per the WHO prequalification process, which sets a minimum standard for quality-assured health products for member countries and is often the criterion for purchase by governments and financial donors.[4]

Lenacapavir, a capsid inhibitor, is licensed as a treatment for people with extensive drug resistance as

Key messages

- Long-acting antiretrovirals are perhaps the greatest advance in HIV care in over a decade and provide great promise towards achieving global HIV prevention and control programme targets
- Current long-acting agents are firmly under the control of originator pharmaceutical companies and remain unavailable or cost-prohibitive across much of the globe
- If action from the broader HIV community is stagnant, the populations who are most in need of these long-acting agents are unlikely to receive any benefit until well into the 2030s, resulting in a large number of preventable HIV infections
- Coordination by international agencies, with assistance from relevant financial donors and stakeholders, will be needed in the complex research and access programmes required to provide widescale use of these indispensable products to people living with HIV or affected by HIV

Johannesburg, South Africa (S L Baptiste ScM); **AfroCAB, Nairobi, Kenya** (J Wambui); **amfAR, The Foundation for AIDS Research, Washington, DC, USA** (B Honermann JD); **AIDS Vaccine Advocacy Coalition (AVAC), New York, NY, USA** (M Warren BA); **Division of Clinical Pharmacology, Department of Medicine** (P Sinxadi PhD) **and The Desmond Tutu HIV Centre** (L-G Bekker PhD), **University of Cape Town, Cape Town, South Africa; i-Base, London, UK** (S Collins, P Clayden); **Médecins Sans Frontières Access Campaign, Geneva, Switzerland** (J Burry); **Centre of Excellence in Long-acting Therapeutics (CELT)** (A Owen PhD) **and Department of Pharmacology and Therapeutics** (A Hill PhD), **University of Liverpool, Liverpool, UK; Department of Global Health, Boston University School of Public Health, Boston, MA, USA** (G Meyer-Rath); **Department of Public Health Medicine, School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria, Johannesburg, South Africa** (W D F Venter)

Correspondence to: Willem Daniel Francois Venter, Wits Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg 2193, South Africa **fventer@ezintsha.org**

For more on **licensed long-acting therapies** see https://lapal.medicinespatentpool.org

a subcutaneous injection once every 6 months, administered with optimised daily oral therapy (manufactured by Gilead Sciences, San Francisco, CA, USA; registered in the EU, Canada, and the USA in 2022). Lenacapavir has recently been shown to have complete prevention efficacy in cisgender women, with a second study in cisgender men anticipated later in 2024.[3,5]

Despite the small number of long-acting medications to date, there has been intense excitement among people living with HIV or at risk of HIV and clinician communities, as well as substantial preclinical activity reported in academic literature focusing on novel long-acting technologies. Modelling studies of the mass introduction of cabotegravir-based PrEP have shown promise for accelerated HIV prevention. The benefits for HIV treatment with cabotegravir plus rilpivirine as a switch agent in high-prevalence areas has also been modelled.[6,7] A 2024 randomised trial showed that cabotegravir plus rilpivirine was superior to oral antiretroviral therapy (ART) in people with HIV with poor adherence.[8] Among adolescents in five countries, cabotegravir plus rilpivirine maintained rates of virological suppression.[9] A 2024 trial in Africa showed that cabotegravir plus rilpivirine was non-inferior to oral ART in maintaining high rates of virological suppression (>97%) when switched to injectable ART.[10] Cabotegravir as an additional choice with standard-of-care oral PrEP reduced the HIV incidence rate from 1·8% to 0 in a 2024 study.[11] Data from people using these medicines suggest high acceptance and clinicians have begun prescribing the agents successfully in populations who are not able to adhere to oral agents. Since 2017, editorials, reviews, and entire editions of major HIV journals have been devoted to the promise of these agents.[2,3,12–14]

Access of low-income and middle-income countries to treatment

Initially, ViiV Healthcare announced plans to be the sole producer of cabotegravir globally, and proceeded to restrict access for operational research and not make the price of access public. These decisions came as a surprise, as ViiV Healthcare had a successful history of licensing crucial antiretrovirals (specifically dolutegravir) to generic manufacturers in low-income and middle-income countries, thus allowing access to the drug for millions of people with HIV in one of the most important public health advancements for HIV programmes in modern times. Reaction to the cabotegravir sole manufacturing decision from advocacy groups was immediate and angry. ViiV Healthcare subsequently retreated from this position, licensing cabotegravir to the MPP in July, 2022 (albeit excluding many middle-income countries from access).[15,16] This licence only allows the use of generic cabotegravir in the prevention of HIV, but not treatment. In March, 2023, the licence was awarded to three companies (Aurobindo, Hyderabad; Cipla, Mumbai; and Viatris, Canonsburg) with promised technology transfer (negotiated in a confidential contract between ViiV Healthcare and each manufacturer) after the bioequivalence testing required by WHO prequalification.

To date, neither Gilead Sciences (the manufacturer of lenacapavir) nor J&J (the manufacturer of rilpivirine) have taken action to grant a voluntary licence for their products, despite both products already being marketed in many high-income countries. Gilead Sciences has a long history of licensing other commonly used drugs to the MPP process, allowing direct licensing deals with generic manufacturers. J&J has not licensed injectable rilpivirine to the MPP or even bilaterally to generic manufacturers, which is a notable contrast to the near-immediate bilateral licensing of oral rilpivirine to generic manufacturers in 2011.[17]

ViiV Healthcare is the market authorisation holder for the combination of cabotegravir and rilpivirine in high-income countries, whereas J&J is responsible for the same role in an unpublished list of low-income and middle-income countries. No licence for generic manufacture of cabotegravir or rilpivirine for treatment has been granted. There is also minimal registration for the treatment combination in countries that are not high-income countries, which makes negotiation of research studies that use the drug combination exceedingly complex for researchers, who have to gain approval from both ViiV Healthcare and J&J. At least one such study has been cancelled in what appears to be concern for the absence of guarantee of post-trial cabotegravir, after J&J initially approved funding.

Multiple operational PrEP studies reliant on ViiV Healthcare-donated cabotegravir have been delayed by intensive company reviews and alterations, even when the company has not provided funding to these studies. ViiV Healthcare remained reluctant to publicly disclose the price for their list of eligible countries until after public pressure was applied (US$30 per vial in 2024 at the time of writing, not including distribution cost).[18] Médecins sans Frontières, who wanted to procure cabotegravir for operational research independent of ViiV Healthcare's approval process and without having to keep the price confidential, underwent lengthy negotiations for over 2 years before reaching an agreement to procure the medicine directly in January, 2024, for countries included in ViiV Healthcare's list of those eligible for the access price of £23·49 per vial (not including distribution cost).[19] Other feasibility studies by community-led organisations, for example Coalition Plus in Morocco and Mauritius, have failed to secure access from ViiV Healthcare.

The US President's Emergency Plan for AIDS Relief announced a donation of cabotegravir to the Zambian Ministry of Health in February, 2024. Zambia was one of the few countries to receive the drug, and the donation was sufficient for only 2000 PrEP-eligible recipients for 1 year, accounting for less than 1% of the 275 000 Zambians initiated on PrEP in 2023.[14]

Potential future treatment combinations

Intramuscular cabotegravir plus rilpivirine, an available long-acting treatment combination for HIV, has limited availability, high cost, and reported cases of resistance; however, successful off-label use has been reported in populations with poor adherence for oral therapy.[20,21] Pharmacokinetic complexity in pregnancy requires further investigation.[22,23] Operationally, use of the drug combination faces substantial challenges, requiring health-care worker training in administration, a cold chain for rilpivirine, and two separate location-coordinated intramuscular injections, with a special needle for patients over a particular bodyweight. Concerns that pre-existing, high non-nucleoside reverse transcriptase (NNRTI) resistance would render the combination less effective have been challenged by the large, randomised clinical switch trial in Africa,[10] suggesting high efficacy rates.[24]

One proposed combination, especially among people with HIV with NNRTI resistance, is cabotegravir administered once every 2 months and lenacapavir administered once every 6 months.[25] A new longer-acting formulation of cabotegravir might allow both medications to be given more synchronously.[26] Both medications have noteworthy safety data in pregnancy.[12] An initial proposal to test lenacapavir and cabotegravir in a large trial was made by the AIDS Clinical Trials Group, but Gilead Sciences and ViiV Healthcare suggested a sample size of only 20 participants. Similar proposals by The European Treatment Network for HIV, Hepatitis, and Global Infectious Diseases and others have been rejected by Gilead Sciences and ViiV Healthcare. ViiV Healthcare and Gilead Sciences are commercial rivals, with a history of pursuing competitor products, although they have donated to independent investigator studies combining their products.[27]

Islatravir, a nucleoside reverse transcriptase translocation inhibitor in development by Merck (Rahway, NJ, USA), was explored as both a long-acting implant and oral tablet for PrEP and treatment, with PrEP and some treatment doses discontinued for toxicity reasons. A phase 2 study of lenacapavir and islatravir given orally once per week showed safety and efficacy in maintaining virological suppression.[28] Other treatment combinations using long-acting agents, including neutralising antibodies, are many years away from commercial availability and are unlikely to have any noteworthy pregnancy and lactation safety data by the time they are approved.[3,28] An exception is a potential long-acting version of the current first-line treatment.[28,29]

There are legitimate concerns about cost-effectiveness and operational issues regarding long-acting products for HIV treatment in public health programmes in low-income and middle-income countries at current prices.[15,30] However, as with many other novel products, including antiretrovirals themselves, changing ART is a question of health-care systems establishing how best to deploy medications in the field (eg, tenofovir disoproxil fumarate replacing stavudine and zidovudine in low-income and middle-income countries). Access to a large volume of long-acting medications, along with simultaneous operational research addressing the complexity of administration of the first generation of long-acting drugs in health-care systems of low-income and middle-income countries, is a necessary first step to working out how to deliver these innovative new medicines in low-income and middle-income countries. As with oral PrEP, supporting large enough pharmaceutical markets will allow economies of scale and eventually prices to be reduced to values that render the drugs cost-effective.[31] According to the Clinton Health Access Initiative, generic long-acting injectable cabotegravir could be introduced at US$30–40 per person per year in low-income and middle-income countries, similar to the current price of oral PrEP, and eventually reach as little as $14–18 per person per year.[32]

Timelines

The new projection is that, in a best-case scenario, cabotegravir for PrEP will only be available through generic manufacturers in 2027 (7 years after showing efficacy), in small volumes only, and at a price that remains uncertain.[33] Until that time, cabotegravir access will be through ViiV Healthcare. There is concern that generic manufacturers might refrain from scaling up the production of cabotegravir, which requires substantial capital investment. Generic manufacturers anticipate the increased use of lenacapavir as the preferred alternative for oral PrEP, which could displace cabotegravir. To make a drug commercially available and receive orders from donors and countries, generic manufacturers have already taken substantial investment risks by the time they have acquired manufacturing machinery, developed the drug-manufacturing process, completed bioequivalence studies, and garnered approval from regulatory authorities (including via the WHO prequalification process).

WHO requirements for bioequivalence studies of new generic medications have been shortened from 52 weeks to 42 weeks; however, there is still a considerable extension to the timelines of drugs being marketed that could be shortened further if reviews could be conducted in parallel. Other medicines that might be longer acting and possibly less expensive could be reaching the market. ViiV Healthcare's restrictions on the market mean stakeholders, including generic manufacturers, have little idea of the true demand for cabotegravir. ViiV Healthcare itself might have little interest in marketing beyond targeting financially lucrative commercial markets, noting the administrative burden of registration and subsequent expanded manufacturing capacity to supply these markets, with the possibility of lenacapavir replacing cabotegravir as the preferred agent for PrEP almost immediately on approval.

The timeline for long-acting combinations for treatment of HIV is even more bleak. There is no patent, manufacturing, or operational expansion plan in place for cabotegravir plus rilpivirine. Moreover, there is no apparent plan to support a large-scale cabotegravir plus lenacapavir study, which is the only drug combination that seems feasible for an immediate clinical trial and could be accomplished within 4 years using a classic non-inferiority study design. Such a large-scale study would need a parallel focus on intellectual property barriers and facilitation of technology transfers (implying cooperation from originator companies) to allow voluntary licensing via the MPP to use both medicines. Moreover, preparation of health-care infrastructure to allow for efficient injection centres in key operational locations would be needed to allow for immediate scale-up for either drug combination. Several such trials, with multiple potential agents, would allow for a rapid launch of clinically interesting, long-acting ART combinations, and accommodate the likelihood that some drug combinations and approaches will not succeed.

Lessons from dolutegravir introduction

Increasing recognition of the side-effects associated with efavirenz and community-wide NNRTI resistance justified the introduction of the more potent antiretroviral dolutegravir, a major public health advancement in HIV treatment, with almost immediate benefits at a public health level.[34] However, the introduction required a massive coordination of resources, involving the entire expanded HIV community, including: originator and generic manufacturers, governments of high-prevalence countries, supply-chain actors, international agencies and donors, advocacy organisations, civil society organisations, and substantial investment in treatment literacy for both people with HIV and health-care worker communities.

The long-acting medicine field is in its infancy, with much of the fundamental technology development activity taking place in academia. Individual academics, technology transfer offices, and universities should familiarise themselves with the mechanisms available for alignment with downstream equitable access provision, including technology platforms developed within the public sector. Academic groups can play important roles in early voluntary licensing, facilitating earlier access to medicines, health benefits, and economic savings, as was the case with dolutegravir.[35]

Implications of the current status quo

Coordination among companies, agencies, and donors is fragmentary and disjointed. There is little supply of long-acting medication for investigator-driven studies, either to inform low-income and middle-income countries guidelines or for operational guidance. Even in high-income countries, access to novel combination treatment is restricted to a small minority of people who would benefit.

The informed consent form from the notable cabotegravir PrEP study conducted in Africa (HPTN 084), which supported FDA approval, states "the information gathered during this study may help to prevent the spread of HIV. This may be beneficial to you and your community."[36] There seems to have been little consideration as to how more cabotegravir as an HIV prevention option will become available for the 500 000 African women who are estimated to acquire HIV annually this decade, with little access to the cabotegravir initially tested on them.

Civil society organisations and HIV activists have been instrumental in holding pharmaceutical companies, financial donors, governments, and international organisations accountable for commitments to the international HIV treatment response for decades. These organisations and activists are needed to promote transparency in pricing, challenge restrictive patent practices, advocate for affordable and widespread availability of drug innovations, prevent companies from restricting broad access to medications, and require funding to allow this work to be done independently.

Conclusion

Leaving implementation and scale-up of phase 3 studies to pharmaceutical companies will not lead to mass introduction of long-acting treatments, as the cabotegravir example has shown. We need a large-scale programme, as seen with the introduction of dolutegravir, addressing long-acting agents for both PrEP and treatment, acknowledging that this class of drugs represents the next major step forward for people living with HIV and people at risk of HIV.

Contributors

WDFV completed the first draft and coordinated input from all authors. MG, SS, and AH had major input into the initial draft. All authors contributed to subsequent drafts.

Declaration of interests

WDFV receives grants paid to University of the Witwatersrand from the Bill & Melinda Gates Foundation, South African Medical Research Council, National Institutes of Health (NIH), Unitaid, Foundation for Innovative New Diagnostics, Children's Investment Fund Foundation, United States Agency for International Development (USAID), ViiV Healthcare, and Merck; drug donations from Gilead Sciences, ViiV Healthcare, Merck, and Johnson and Johnson; honoraria for educational talks and advisory board membership from Gilead Sciences, ViiV Healthcare, Mylan-Viatris, Merck, Adcock-Ingram, Aspen, Abbott, Roche, Johnson and Johnson, Sanofi, and Virology Education; conducts commercial drug studies for Merck and Novo Nordisk; and is a member of the international NIH HIV data safety monitoring board and WHO and Southern African HIV Clinicians Society HIV guideline committees. MG is supported financially by NIH. SLB is a member of the AIDS Vaccine Advocacy Coalition board, a Global Coalition of Tuberculosis Activists fiscal sponsor, and is a member of the Global Public Investment Network and Global Fund Advocate Network steering committees. LJ is financially supported by USAID and the Bill & Melinda Gates Foundation. BH receives grant support from ViiV Healthcare to amFAR. MW's receives support from the Bill & Melinda Gates Foundation to the AIDS Vaccine Advocacy Coalition. KM has received honoraria from Johnson and Johnson. LG-B has received honoraria for advisories to Merck, ViiV Healthcare, and Gilead Sciences;

is an unpaid board member for Access to Medicine Foundation, AIDS Vaccine Advocacy Coalition, and International AIDS Vaccine Initiative; and her unit (Desmond Tutu HIV Centre) has received a study drug from ViiV Healthcare and Johnson and Johnson for studies funded by the Bill & Melinda Gates Foundation. AO reports consulting fees for Gilead Sciences, ViiV Healthcare, and Assembly Biosciences; and is Director and Chief Science Officer for Tandem Nano, with patents issued and pending in drug delivery. AP receives grants paid to NEAT ID from NIH, National Heart, Lung, and Blood Institute, the EU (via the VERDI Consortium), Gilead Sciences, ViiV Healthcare, and Merck for commercial drug studies; receives honoraria for educational talks and advisory board membership from Gilead Sciences, ViiV Healthcare, Merck, and Virology Education; is on a data safety monitoring board for MRC–PENTA studies; is a member of the European AIDS Clinical Society and British HIV Association HIV treatment guidelines panels; is the President of NEAT ID; and is a board member of Doctor's with Africa CUAMM UK. PR has received grants from ViiV Healthcare and consulted for Gilead Sciences. All other authors declare no competing interests.

References

1 Flexner C, Siccardi M, Bunglawala F, Owen A. The LEAP process: streamlining the development of long-acting products and formulations for infectious diseases. *Clin Infect Dis* 2022; **75** (suppl 4)**:** S502–09.

2 Chandiwana NC, Serenata CM, Owen A, et al. Impact of long-acting therapies on the global HIV epidemic. *AIDS* 2021; **35** (suppl 2)**:** S137–43.

3 Thoueille P, Choong E, Cavassini M, Buclin T, Decosterd LA. Long-acting antiretrovirals: a new era for the management and prevention of HIV infection. *J Antimicrob Chemother* 2022; **77:** 290–302.

4 WHO. Notes on the design of bioequivalence study: cabotegravir. 2023. https://extranet.who.int/prequal/sites/default/files/document_files/BE_cabotegravir_July2023_1.pdf. (accessed March 19, 2024).

5 Bekker LG, Das M, Abdool Karim Q, et al, Twice-yearly lenacapavir or daily F/TAF for HIV prevention in cisgender women. *N Engl J Med* 2024; published online July 24. https://www.nejm.org/doi/10.1056/NEJMoa2407001.

6 Smith J, Bansi-Matharu L, Cambiano V, et al. Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. *Lancet HIV* 2023; **10:** e254–65.

7 Phillips AN, Bansi-Matharu L, Cambiano V, et al. The potential role of long-acting injectable cabotegravir–rilpivirine in the treatment of HIV in sub-Saharan Africa: a modelling analysis. *Lancet Glob Health* 2021; **9:** e620–27.

8 National Institutes of Health. Long-acting HIV treatment demonstrates efficacy in people with challenges taking daily medicine as prescribed. 2024. https://www.nih.gov/news-events/news-releases/long-acting-hiv-treatment-demonstrates-efficacy-people-challenges-taking-daily-medicine-prescribed (accessed Aug 3, 2024).

9 Gaur A, Capparelli E, Baltrusaitis K, et al, Long-acting cabotegravir plus rilpivirine in adolescents with HIV: week 24 IMPAACT 2017 (MOCHA) study. Conference on Retroviruses and Opportunistic Infections; March 3–6, 2024.

10 Kityo CM, Mambule IK, Sokhela S, et al. Randomized trial of cabotegravir and rilpivirine long-acting in Africa (CARES): week 48 results. Conference on retroviruses and opportunistic infections; March 3–6, 2024.

11 Kamya MR, Balzer LB, Ayieko J, et al. Randomized trial of SEARCH dynamic choice HIV prevention including injectable cabotegravir (CAB-LA). Conference on retroviruses and opportunistic infections; March 3–6, 2024.

12 Delany-Moretlwe S, Flexner C, Bauermeister JA. Advancing use of long-acting and extended delivery HIV prevention and treatment regimens. *J Int AIDS Soc* 2023; **26** (suppl 2)**:** e26126.

13 Boyd MA, Cooper DA. Long-acting injectable ART: next revolution in HIV? *Lancet* 2017; **390:** 1468–70.

14 US Mission Zambia. US government delivers first shipment of injectable PrEP to Zambia. 2024. https://zm.usembassy.gov/first-shipment-of-injectable-prep-to-zambia/ (accessed Aug 3, 2024).

15 Pepperrell T, Cross S, Hill A. Cabotegravir—global access to long-acting pre-exposure prophylaxis for HIV. *Open Forum Infect Dis* 2023; **10:** ofac673.

16 Collins S, HIV i-Base. ViiV Healthcare licenses long-acting cabotegravir (CAB-LA) for generic access. 2022. https://i-base.info/htb/42974 (accessed Aug 3, 2024).

17 PR Newswire. Tibotec signs multiple agreements with generic manufacturers to provide access to new HIV treatment. 2011. https://www.prnewswire.com/news-releases/tibotec-signs-multiple-agreements-with-generic-manufacturers-to-provide-access-to-new-hiv-treatment-114714404.html (accessed Aug 3, 2024).

18 Médecins Sans Frontières. Open letter to ViiV to improve access to HIV prevention drug CAB-LA. 2023. https://www.msfaccess.org/open-letter-viiv-improve-access-hiv-prevention-drug-cab-la (accessed Aug 3, 2024).

19 Médecins Sans Frontières. MSF refuses to sign ViiV Healthcare's last-minute NDA for access to most-effective HIV prevention drug CAB-LA. 2023. https://www.msfaccess.org/msf-refuses-sign-viivs-last-minute-nda-access-most-effective-hiv-prevention-drug-cab-la (accessed Aug 3, 2024).

20 Sax PE, Thompson MA, Saag MS. Updated treatment recommendation on use of cabotegravir and rilpivirine for people with HIV from the IAS-USA guidelines panel. *JAMA* 2024; **331:** 1060–61.

21 van Welzen BJ, Van Lelyveld SFL, Ter Beest G, et al. Virological failure after switch to long-acting cabotegravir and rilpivirine injectable therapy: an in-depth analysis. *Clin Infect Dis* 2024; published online Jan 11. https://doi.org/10.1093/cid/ciae016.

22 van der Wekken-Pas L, Weiss F, Simon-Zuber C, et al. Cabotegravir and rilpivirine long acting injectables in a pregnant woman living with HIV. *Clin Infect Dis* 2024; published online May 3. https://doi.org/10.1093/cid/ciae242.

23 Atoyebi S, Bunglawala F, Cottura N, et al. Physiologically-based pharmacokinetic modelling of long-acting injectable cabotegravir and rilpivirine in pregnancy. *Br J Clin Pharmacol* 2024; published online Feb 10. https://doi.org/10.1111/bcp.16006.

24 Orkin C, Schapiro JM, Perno CF, et al. Expanded multivariable models to assist patient selection for long-acting cabotegravir + rilpivirine treatment: clinical utility of a combination of patient, drug concentration, and viral factors associated with virologic failure. *Clin Infect Dis* 2023; **77:** 1423–31.

25 Gandhi M, Hill L, Grochowski J, et al. Case series of people with HIV on the long-acting combination of lenacapavir and cabotegravir: call for a trial. *Open Forum Infect Dis* 2024; **11:** ofae125.

26 Han K, D'Amico R, Sievers J, et al. Phase 1 study of cabotegravir long-acting injectable formulations supports ≥4-monthly dose interval. Conference on retroviruses and opportunistic infections; March 3–6, 2024.

27 Sokhela S, Venter WDF, Bosch B, et al. Final 192-week efficacy and safety results of the ADVANCE Trial, comparing 3 first-line antiretroviral regimens. *Open Forum Infect Dis* 2024; **11:** ofae007.

28 Colson A, Crofoot G, Ruane PJ, et al. Efficacy and safety of weekly islatravir plus lenacapavir in PWH at 24 weeks: a phase 2 study. Conference on retroviruses and opportunistic infections; March 3–6, 2024.

29 Perazzolo S, Stephen ZR, Eguchi M, et al. A novel formulation enabled transformation of 3-HIV drugs tenofovir-lamivudine-dolutegravir from short-acting to long-acting all-in-one injectable. *AIDS* 2023; **37:** 2131–36.

30 Meyer-Rath G, Jamieson L, Pillay Y. What will it take for an injectable ARV to change the face of the HIV epidemic in high-prevalence countries? Considerations regarding drug costs and operations. *J Int AIDS Soc* 2023; **26** (suppl 2)**:** e26106.

31 Jamieson L, Johnson LF, Nichols BE, et al. Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis. *Lancet HIV* 2022; **9:** e857–67.

32 Clinton Health Access Initiative. Cost of goods sold (COGS) analysis: generic long-acting injectable cabotegravir (CAB-LA). 2023. https://chai19.wpenginepowered.com/wp-content/uploads/2022/10/Generic-CAB-LA-COGS-Analysis.pdf. (accessed Aug 3, 2024).

33 ViiV Healthcare. CATALYST satellite meeting. International AIDS Society Conference on HIV Science; July 23–27, 2023.

34 Dorward J, Sookrajh Y, Khubone T, et al. Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study. *Lancet HIV* 2023; **10:** e284–94.

35 Medicines Patent Pool. Long-acting injectable HIV drug combination technology. 2021. https://medicinespatentpool.org/licence-post/long-acting-injectable-drug-combination-for-hiv-treatment-prevention (accessed Aug 3, 2024).

36 Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. *Lancet* 2022; **399:** 1779–89.