

https://dspace.org/

Impact of longacting therapies on the global HIV epidemic

Nomathemba Chandiwana; Celicia M Serenata; Andrew Owen; Steve Rannard; Carmen Perez Casas ...

https://hdl.handle.net/10539/35605
WOS

Downloaded from a DSpace repository. https://dspace.org/

OPEN

Impact of long-acting therapies on the global HIV epidemic

Nomathemba C. Chandiwana[a], Celicia M. Serenata[a,*], Andrew Owen[b], Steve Rannard[c], Carmen Pérez Casas[d], Cherise Scott[d], Andrew Hill[e], Polly Clayden[f] and Charles Flexner[g]

Long-acting antiretroviral drugs have emerged as exciting treatment and preexposure prophylaxis (PrEP) options for people with HIV and at risk of HIV. Long-acting regimens may improve dosing convenience, tolerability and cost compared with current daily-based oral therapy. They can also circumvent stigma associated with oral therapy for both treatment and PrEP, thereby improving adherence and outcomes. Yet, multiple challenges remain, many specific to low-income and middle-income countries (LMICs), where the epidemic is most concentrated and HIV prevention and treatment options are limited. To optimize the use of long-acting formulations, key outstanding questions must be addressed. Uncertain costing, scale-up manufacturing, complex delivery systems and implementation challenges are potential barriers when considering the scalability of long-acting ARVs for global use.

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

AIDS 2021, **35** (Suppl 2):S137–S143

Keywords: access and barriers, long-acting antiretrovirals, low-income and middle-income countries, treatment optimization

Downloaded from https://journals.lww.com/aidsonline by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 12/08/2021

Introduction

Current oral antiretroviral regimens are extremely effective at suppressing HIV with minimal toxicity. Wherever fixed-dose combinations are available, they offer the simplicity of once-daily single-tablet dosing and have enabled vast scale-up of antiretroviral therapy (ART) in low-income and middle-income countries (LMICs) during the last 15 years [1]. However, these gains might be threatened in the absence of sustained viral suppression [2]. Among the most common reasons for lack of adherence are forgetting, being away from home, and a change in daily routine [3]. Depression, pill fatigue, alcohol and substance use, secrecy/stigma, and health service-related barriers (e.g. distance to clinic, stockouts) are also reported [4].

Long-acting (LA) antiretrovirals with infrequent dosing, for example, weekly oral or long-acting parenterally administered agents, may be useful in circumstances where daily oral therapies are not feasible, difficult to administer, and/or when adherence may be inadequate [5,6]. Limitations of such approaches to drug delivery include the management of toxicities, given that exposure to these agents is not easily reversed; and prevention of drug resistance, when these drugs are discontinued, and drug concentrations are slowly reduced below targets over time. New agents with long-acting anti-HIV-1 activity and older antiretrovirals in modified delivery systems are being tested in both treatment of chronic infection and PrEP for people at high risk of infection [7–9].

[a]Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [b]Department of Molecular and Clinical Pharmacology, [c]Department of Chemistry, Centre of Excellence in Long-acting Therapeutics (CELT), University of Liverpool, Liverpool, United Kingdom, [d]Unitaid, Geneva, Switzerland, [e]Department of Translational Medicine, Liverpool University, Liverpool, [f]HIV i-Base, London, United Kingdom, and [g]Divisions of Clinical Pharmacology and Infectious Diseases, School of Medicine and Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.

Correspondence to Nomathemba C. Chandiwana, Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Building C, 32 Princess of Wales Terrace, Johannesburg 2193, South Africa.

Tel: +27 76 164 3215; e-mail: nchandiwana@ezintsha.org

[*] Celicia M. Serenata deceased.

Received: 9 September 2021; accepted: 29 September 2021.

DOI:10.1097/QAD.0000000000003102

ISSN 0269-9370 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

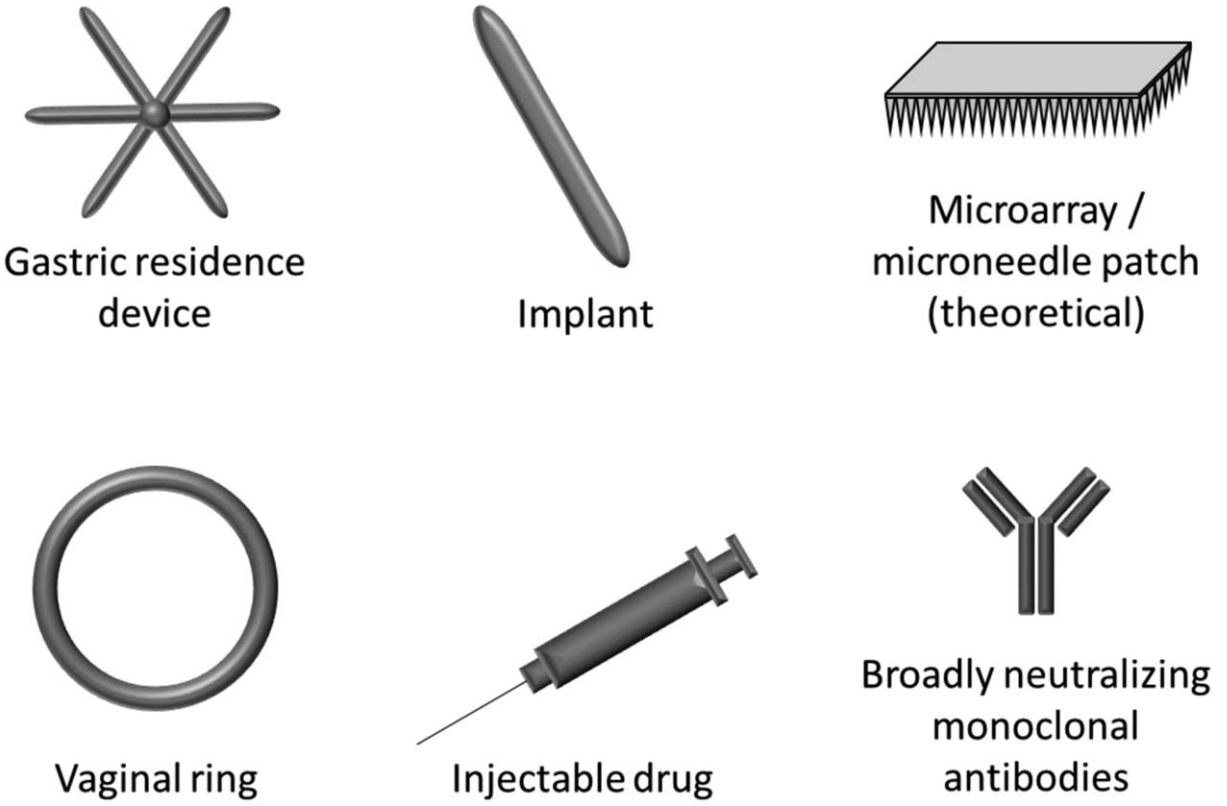


Fig. 1. Schematic of long-acting drug delivery technologies in clinical and preclinical development.

These approaches appear to be especially attractive for people complaining of pill fatigue, including adolescents, women during pregnancy and the postpartum period, and for those experiencing HIV-associated stigma [3,10]. However, in higher income countries, disparities in access are barriers to uptake of long-acting ART and PrEP for women and black MSM [11–14]. Due to high tuberculosis (TB) and hepatitis B (HBV) burdens, as well as cold chain requirements, currently available long-acting formulations, are not ideal for LMICs. Other barriers to the optimal implementation of long-acting antiretrovirals in LMICs, include the increased frequency of the injection appointments, provider concerns of identifying appropriate candidates for LA ART and operational challenges of the availability of single use needles [15,16]. As these formulations, are shown to be safe, well tolerated, more user-friendly, and economically viable, they are likely to gain broader appeal.

Current pipeline of long-acting antiretroviral therapy for treatment and prevention

Current clinical and experimental long-acting technologies can be classified as oral, parenteral, transdermal or implantable approaches (Fig. 1). Parenteral (intramuscular or subcutaneous) and implantable technologies have already proven clinically successful for other indications, while other approaches may be less invasive but are at earlier stages of development [9,17,18]. For HIV prevention, the pipeline is advancing quickly, with a diversity of long-acting options being developed [19], including the recently reported results of long-acting cabotegravir in preventing HIV among MSM and in cisgender women, and the recent approval of a monthly vaginal ring of dapivirine [20,21]. In the HIV treatment pipeline, a number of initiatives are looking into long-acting products, with multiple candidates at different stages of development (Table 1), and other products in a diverse number of platforms entering this dynamic pipeline that hold promise to radically change the way ART is taken [22–24].

The first long-acting injectable combination (cabotegravir with rilpivirine) shown to be noninferior to daily oral ART, with high patient satisfaction in research to date has recently approved been approved for use in North America and Europe [25–28]. This is an important landmark in ART development but its use may be limited in LMICs as long-acting rilpivirine requires cold chain preservation, two separate vials for injection every 8 weeks, occurrence of drug resistance, and there is interaction with anti-TB therapy [29,30]. New classes of antiretrovirals can now be formulated in long-acting forms, including capsid inhibitors, and nucleoside reverse transcriptase translocation inhibitors, such as islatravir [31,32]. In terms of biotherapeutic research, HIV broadly neutralizing antibodies (bnAbs) are becoming attractive strategies for treatment and prevention.

Table 1. Long-acting antiretroviral therapy formulations already in clinical evaluation or commercialized.

Agent	Class/type	Manufacturer/sponsor	Status
Treatment			
Cabotegravir LA and rilpivirine LA injections	Integrase inhibitor + nonnucleoside reverse transcriptase inhibitor (NNRTI)	ViiV Healthcare, Janssen	Approved (Canada, March 2020, EMA Dec 2020, FDA Jan 2021)
Ibalizumab	Monoclonal antibody	TaiMed Biologics	Approved FDA (Mar,2018) & EU approval (Sep-2019)
Islatravir (MK-8591)	NRTI	Merck	Phase 3
Elsulfavirine (VM-1500A)	NNRTI	Viriom	Phase 2/3; approved in Russia.
Rovafovir etalafenamide (formerly known as GS-9131)	Nucleoside reverse transcriptase inhibitor (NRTI)	Gilead Sciences	Phase 2
Leronlimab (PRO 140)	Monoclonal antibody	CytoDyn	Phase 3
UB-421	Monoclonal antibody	United BioPharma	Phase 1
VRC01	Monoclonal antibody	NIAID Vaccine Research Center	Phase 1
VRC01LS	Monoclonal antibody	NIAID Vaccine Research Center	Phase 1
Lenacapavir (formerly known as GS-6207) Gilead	Capsid inhibitor	Gilead Sciences	Phase 2
Albuvirtide	Fusion inhibitor	Frontier Biotechnologies Co., Ltd	Approved (China, June 2018)

The first monoclonal antibody (ibalizumab) was approved in March 2018 for treatment-experienced patients with multidrug-resistant HIV [33]. A rapidly growing number of HIV bnAbs are in development now, including combinations of different bnAbs and second-generation products, which might bring about important advantages for LMICs scaled use [5,34].

Perspectives/experience of long-acting antiretrovirals in low-income and middle-income countries

Long-acting formulations offer a promising new avenue for simplifying HIV treatment but most options are not adapted to the needs of LMICs (for example, several products now in clinical trials are infusions, or intravenous injectables) or are at very early stages of development. Long-acting antiretrovirals for either treatment or PrEP have primarily been studied in mostly men from higher income countries, which is not representative of the global HIV epidemic [8,35,36]. This leaves a large knowledge gap in the safety, efficacy, acceptability, and cost of long-acting antiretroviral options used in diverse populations in LMICs.

Several studies suggest that long-acting ART could be a preferred and cost-effective option compared with oral antiretrovirals in LMICs. In 2013, when long-acting ART was still in very early stages of development, a 400-patient survey found surprisingly high levels of enthusiasm for long-acting injectables for treatment. More than 80% of respondents indicated they would consider switching from oral to parenteral ART if the injection frequency were once per month; interest was less with more frequent injections [37]. Since then, several other surveys have confirmed these findings, including in female sex workers, adolescents, and people from predominantly minority communities [8,38,39]. Participants in phase 2 and 3 clinical trials of long-acting ART therapy have reported very high levels of acceptance but these results are not easily generalizable as they only included those who had agreed to participate [7,8,36,40]. In the HPTN 076 trial, despite nearly two-thirds of women reporting pain or tenderness at the injection site but despite this, long-acting rilpivirine was an acceptable option for longer term HIV protection, particularly among the African women included in the study [41].

The experience with long-acting injectable contraception, as well as extended release implants, seems to indicate a strong preference for these formulations over daily tablets [17]. However, injectable contraception is not without its pitfalls. For example, the risk of 'breakthrough' pregnancies, when women delay/miss a follow-up visit. For long-acting ARVs, the equivalent could be recurrent viraemia with risk for transmission and developing resistance.

Nevertheless, there is great enthusiasm for this mode of delivery to be available, including in LMICs [42]. Communities, donors, and policy makers see this as strategy to address stigma (no visible tablets to carry around) and suboptimal adherence [43]. Though providers were more reticent about its broader implementation [15,35], which will likely be the case in LMICs as well, especially given concerns of drug resistance from missed doses. In addition, when many countries have moved to multimonth dispensing, and the most common first-line regimen now comes packaged in 3-month supplies, any injectable ART that would require monthly visits with a healthcare worker is unlikely to be attractive to many countries, especially if at a higher cost.

Although there are good networks working on initiatives relating to long-acting formulations, such as the Long-Acting/Extended Release Antiretroviral Research Resource Program, or LEAP, these do not include researchers from LMICs [23]. So complimentary studies will be needed in these settings to inform operational issues, efficacy, feasibility, and cost-effectiveness. For example, cabotegravir/rilpivirine long-acting formulations need to be studied in African and Asian populations to confirm its efficacy in the HIV sub-types prevalent in these settings. The use of long-acting injectable formulations in LMICs will also require a review of manufacturing capacity.

A 2018 WHO review of LAI ART candidates acknowledged both the advantages and disadvantages of long-acting formulations [44]. Issues around service delivery platforms, especially if long-acting formulations require more frequent healthcare visits can be overcome in using innovative delivery models, for example, providing ART/PrEP through private pharmacies and other nonpublic sector facilities [45,46]. These differentiated delivery models, could be considered for long-acting ART. Planning for implementation of long-acting formulations should build on experience gained from the expansive scale-up of HIV interventions/family planning innovations, such as prevention of vertical transmission, voluntary medical male circumcision, and more recently, oral PrEP programmes as well as self-injection of contraception [47].

Long-acting drugs and formulations for other infectious diseases in low-income and middle-income countries

If long-acting/extended release formulations for HIV are successful, this is likely to stimulate and facilitate the development, availability and adoption of similar formulations for other infectious diseases in LMICs. Similar to the HIV epidemic, global responses to TB, malaria and hepatitis C, diseases for which global goals for elimination have been established for 2030, face a range of serious challenges, including the lack of a highly efficacious vaccine, complex protocols for chemoprophylaxis, increasing burden on health services and supply systems, pervasive stigma and discrimination, poor drug quality, and emergence of resistance [48].

Long-acting products are in various stages of development for these diseases. For TB, a long-acting formulation of bedaquiline, a key component of MDR-TB regimens, showed antimicrobial activity for up to 12 weeks after a single dose in a mouse model of TB [49]. Long-acting antimalarials are being assessed for prevention and could even be used in place of a vaccine for regional eradication. New compounds and repurposing existing drugs as long-acting formulations are being explored. Formulations, analogous to that of rilpivirine and cabotegravir LA, could be used for prevention of malaria in humans to protect most vulnerable populations in endemic areas. [50,51]. Likewise, the potential for repurposing ivermectin as a long-acting malaria vector-control tool (and for other vector-borne neglected tropical diseases) is being investigated [52,53]. For control of hepatitis virus infections, the tenofovir alafenamide implants could be used in chronic hepatitis B virus (HBV) infection, although other long-acting antiretroviral formulations lack activity against HBV [54]. A test-and cure strategy for hepatitis C virus (HCV) may be possible if there were a two-drug injectable combination that could deliver effective antiviral concentrations for 8 to 12 weeks [55].

Cost of scale-up of long-acting antiretroviral therapy in low-income and middle-income countries

The economic argument for the use of long-acting antiretrovirals will be a primary concern. Long-acting products, although they may add some costs comparative to standard of care in the short-term, can bring substantial cost savings in the long-term to help alleviate burdens from existing and new health threats [23,56]. Their benefits enable national programmes and individuals to untap the maximum potential of available therapies leading to reduced transmission of target pathogens, improved clinical outcomes, and greater impact in disease burden, eventually reducing the total funding needs. A robust economic understanding will require a thorough interrogation of the costs associated with manufacturing and sourcing the product (manufacturing processes, selling prices, storage, and logistic costs), as well as with the economic impact of the intervention on wider healthcare provision.

Importantly, not all long-acting technologies are the same, and each have very different manufacturing considerations. Even particle dispersions for injection can be manufactured using different processes that are likely to differ considerably in terms of manufacturing cost [57–59], with 'syringeability' and drug/excipient ratios also dictating the ultimate drug concentration within an acceptable administration volume. Scale-up of manufacturing will require investment in capability to meet the needs of new technologies and/or additional demand in LMIC markets and the need for prodrug derivatization for compatibility with some approaches may also increase complexity and cost [57,58,60]. For parenterals and implantables, sterility is also of pivotal importance and selection of an appropriate manufacturing technology should consider the need for premanufacturing or postmanufacturing sterilization, which may also impact cost. Ultimately, there should be an effort to decrease the cost of goods manufactured, with careful thought on selection of technology and platform during product development. And also, efforts must be undertaken now to enabling a market where scaled production by different manufacturers can render LA market viable. There are precedents, notably in HIV

treatment and prevention, of large-scale manufacturing with limited margins serving high-volume markets. Notwithstanding the differences between such oral antiretroviral market, and the production of long-acting formulations that might require advanced manufacturing approaches to control drug release and perhaps complex platform for delivery (implants, patches, etc.), efforts to develop a sustainable market are warranted.

Likewise, for long-acting formulation based on biologic components (monoclonal antibodies), and given the particularity of these products, a clear strategy would be required to address the conditions for a future healthy market in LMICs that can deliver equitable access to populations most in need as early as possible [23]. For example, joint efforts by the International AIDS Vaccine Initiative (IAVI), Scripps Research and the US National Institutes of Health to accelerate affordable and sustainable global access when bnAbs are shown to be efficacious for HIV prevention and possibly for treatment [61]. Timely interventions are warranted to address affordability, scaled-up production by generic manufacturers, intellectual property, regulatory pathways for similar biotherapeutics, adaptability or ease of use, and simplified delivery supporting their scaled use.

In addition, many remaining challenges are pathogen-specific and use-case-specific, with cost implications being very different for prevention of malaria with a single agent for a single season, compared with a life-time commitment to a fully suppressive antiretroviral drug combination. A holistic approach to consideration of the wider healthcare implications is also required and many of the potential cost, equity, and/or healthcare benefits are not easy to directly quantify. For example, long-acting treatment of schizophrenia may represent a more relevant example than contraception, given the measurable benefits and cost-savings from long-acting injectable antipsychotics with reduction in mortality, rehospitalization, relapse, and caregiver burden (31%) [62–65].

As demonstrated by long-acting contraception, it is possible to see high uptake and impact in LMICs [17,66]. To supply the market in LMICs for modern contraception methods, generic products of long-acting formulations were included in the WHO Prequalification Programme and are currently supplied by the United Nations Population Fund (UNFPA). Market shaping interventions (enabling the increase in supplier-base and diversity of products) have led to significantly decreased prices and increased uptake in LMICs. Using similar pathways and interventions for emerging long-acting products for infectious diseases, especially when current standards of care are not adequate, may ensure their maximal impact.

In conclusion, long-acting antiretroviral agents have great potential to improve the way we both treat and prevent HIV. The two-drug combination of long-acting injectable cabotegravir and rilpivirine is likely to be approved in sub-Saharan Africa by the end of 2022, with a wider number of investigational long-acting antiretroviral formulations in clinical development that could be better adapted for use in LMICs. However, challenges include managing side effects, drug–drug interactions, use in pregnancy, and long-lasting drug concentrations after discontinuation of the formulations that could lead to the development of drug resistance. In addition, affordability, acceptability, and ability to deliver at scale must be anticipated. These products are likely to revolutionize the treatment and prevention of HIV, and this approach to drug delivery holds great promise for other infectious diseases as well.

Acknowledgements

We dedicate this work to our deceased co-author, colleague and friend, Celicia Serenata, a wonderful human being who lived her life improving the lives of others.

Funding for this AIDS journal supplement was provided by the US Agency for International Development (USAID) through the OPTIMIZE Cooperative Agreement AID-OAA-A-15-00069 to Ezintsha, University of the Witwatersrand. The content of this supplement is solely the responsibility of the authors and does not necessarily represent the official views of USAID, or any other agency.

Conflicts of interest

NC has received research funding from ViiV Healthcare, Merck, Janssen and Gilead, and speaker fees from Janssen.

A.O. and S.R. thank Unitaid for co-funding creation of CELT and for project LONGEVITY. A.O. and S.R. are Directors of Tandem Nano Ltd and co-inventors, with C.F., of patents relating to drug delivery for infectious diseases. A.O. has received research funding from ViiV Healthcare, Merck, Janssen and consultancy from Gilead, ViiV Healthcare and Merck. C.F. has served as a paid consultant to Merck, Mylan Pharmaceuticals, and ViiV Healthcare; is a paid Data Safety and Monitoring Board member for Algernon Pharmaceuticals; and has served as an expert witness in a legal case involving Gilead Sciences.

References

1. Nachega JB, Sam-Agudu NA, Mofenson LM, Schechter M, Mellors JW. **Achieving viral suppression in 90% of people living with human immunodeficiency virus on antiretroviral therapy in low- and middle-income countries: progress, challenges, and opportunities.** *Clin Infect Dis* 2018; **66**:1487–1491.

2. UNAIDS Global HIV Update 2020 – Seizing the moment: tackling entrenched inequalities to end epidemics. 2020.
3. Hudelson C, Cluver L. **Factors associated with adherence to antiretroviral therapy among adolescents living with HIV/AIDS in low- and middle-income countries: a systematic review.** *AIDS Care* 2015; **27**:805–816.
4. Shubber Z, Mills EJ, Nachega JB, Vreeman R, Freitas M, Bock P, *et al*. **Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis.** *PLoS Med* 2016; **13**:e1002183.
5. Flexner C. **Antiretroviral implants for treatment and prevention of HIV infection.** *Curr Opin HIV AIDS* 2018; **13**:374–380.
6. Boyd MA, Cooper DA. **Long-acting injectable ART: next revolution in HIV?** *Lancet* 2017; **390**:1468–1470.
7. Orkin C, Arasteh K, Górgolas Hernández-Mora M, Pokrovsky V, Overton ET, Girard P-M, *et al*. **Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection.** *New Engl J Med* 2020; **382**:1124–1135.
8. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, *et al*. **Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression.** *New Engl J Med* 2020; **382**:1112–1123.
9. Sillman B, Bade AN, Dash PK, Bhargavan B, Kocher T, Mathews S, *et al*. **Creation of a long-acting nanoformulated dolutegravir.** *Nat Commun* 2018; **9**:443.
10. Psaros C, Remmert JE, Bangsberg DR, Safren SA, Smit JA. **Adherence to HIV care after pregnancy among women in sub-Saharan Africa: falling off the cliff of the treatment cascade.** *Curr HIV/AIDS Rep* 2015; **12**:1–5.
11. Benning L, Mantsios A, Kerrigan D, Coleman JS, Golub E, Blackstock O, *et al*. **Examining adherence barriers among women with HIV to tailor outreach for long-acting injectable antiretroviral therapy.** *BMC Women's health* 2020; **20**:152.
12. Goedel WC, Nunn AS, Chan PA, Duncan DT, Biello KB, Safren SA, Marshall BDL. **A shot at equity? Addressing disparities among Black MSM in the coming era of long-acting injectable preexposure prophylaxis.** *AIDS* 2019; **33**:2110–2112.
13. Philbin MM, Parish CL, Kinnard EN, Reed SE, Kerrigan D, Alcaide ML, *et al*. **Multisite study of women living with HIV's perceived barriers to, and interest in, long-acting injectable antiretroviral therapy.** *J Acquir Immune Defic Syndr* 19992020; **84**:263–270.
14. Fields EL, Hussen SA, Malebranche DJ. **Mind the gap: HIV prevention among young black men who have sex with men.** *Curr HIV/AIDS Rep* 2020; **17**:632–642.
15. Mantsios A, Murray M, Karver TS, Davis W, Galai N, Kumar P, *et al*. **Multilevel considerations for optimal implementation of long-acting injectable antiretroviral therapy to treat people living with HIV: perspectives of healthcare providers participating in phase 3 trials.** *BMC Health Serv Res* 2021; **21**:255.
16. Parker B, Ward T, Hayward O, Jacob I, Arthurs E, Becker D, *et al*. **Cost-effectiveness of the long-acting regimen cabotegravir plus rilpivirine for the treatment of HIV-1 and its potential impact on adherence and viral transmission: a modelling study.** *PloS One* 2021; **16**:e0245955.
17. Tsui AO, Brown W, Li Q. **Contraceptive practice in sub-Saharan Africa.** *Popul Dev Rev* 2017; **43 (Suppl 1)**:166–191.
18. Dhody K, Pourhassan N, Kazempour K, Green D, Badri S, Mekonnen H, *et al*. **PRO 140, a monoclonal antibody targeting CCR5, as a long-acting, single-agent maintenance therapy for HIV-1 infection.** *HIV Clin Trials* 2018; **19**:85–93.
19. Coelho LE, Torres TS, Veloso VG, Landovitz RJ, Grinsztejn B. **Preexposure prophylaxis 2.0: new drugs and technologies in the pipeline.** *Lancet HIV* 2019; **6**:e788–e799.
20. Health NIo. Long-acting injectable form of HIV prevention outperforms daily pill in NIH study. 2020.
21. Agency EM. Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden. 2020.
22. Collins S. HIV pipeline 2020: new drugs in development – March 2020. 2020.
23. Nachman S, Townsend CL, Abrams EJ, Archary M, Capparelli E, Clayden P, *et al*. **Long-acting or extended-release antiretroviral products for HIV treatment and prevention in infants, children, adolescents, and pregnant and breastfeeding women: knowledge gaps and research priorities.** *Lancet HIV* 2019; **6**:e552–e558.
24. Jefferys R. HIV vaccines, passive immunization, and antibody gene transfer pipeline. 2020. 2020. https://www.treatmentactiongroup.org/wpcontent/uploads/2020/07/pipeline_HIV_vaccine_2020.pdf.
25. Jansssen. Janssen Announces U.S. FDA Approval of CABENUVA (rilpivirine and cabotegravir), the First Long-Acting Regimen for the Treatment of HIV. 2021.
26. Agency EM. First long-acting injectable antiretroviral therapy for HIV recommended for approval. 2020.
27. Healthcare V. ViiV Healthcare announces FDA approval of Cabenuva (cabotegravir, rilpivirine), the first and only complete long-acting regimen for HIV treatment. 2021.
28. Overton ET, Richmond G, Rizzardini G, Jaeger H, Orrell C, Nagimova F, *et al*. **Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2 M), 48-week results: a randomised, multicentre, open-label, phase 3b, noninferiority study.** *Lancet* 2021; **396**:1994–2005.
29. Havlir D, Gandhi M. **Implementation challenges for long-acting antivirals as treatment.** *Current opinion in HIV and AIDS* 2015; **10**:282–289.
30. Rizzardini G, Overton ET, Orkin C, Swindells S, Arasteh K, Górgolas Hernández-Mora M, *et al*. **Long-acting injectable Cabotegravir + Rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR Trials.** *J Acquir Immune Defic Syndr* 19992020; **85**:498–506.
31. Carnes SK, Sheehan JH, Aiken C. **Inhibitors of the HIV-1 capsid, a target of opportunity.** *Curr Opin HIV AIDS* 2018; **13**:359–365.
32. Molina J. Islatravir in combination with doravirine maintains HIV-1 viral suppression through 96 weeks. HIV Glasgow 2020, abstract O415. 2020.
33. Markham A. **Ibalizumab: first global approval.** *Drugs* 2018; **78**:781–785.
34. Cobb DA, Smith NA, Edagwa BJ, McMillan JM. **Long-acting approaches for delivery of antiretroviral drugs for prevention and treatment of HIV: a review of recent research.** *Expert Opin Drug Deliv* 2020; **17**:1227–1238.
35. Kerrigan D, Mantsios A, Gorgolas M, Montes ML, Pulido F, Brinson C, *et al*. **Experiences with long acting injectable ART: a qualitative study among PLHIV participating in a phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain.** *PloS One* 2018; **13**:e0190487.
36. Murray M, Antela A, Mills A, Huang J, Jäger H, Bernal E, *et al*. **Patient-reported outcomes in ATLAS and FLAIR participants on long-acting regimens of Cabotegravir and Rilpivirine over 48 weeks.** *AIDS Behav* 2020; **24**:3533–3544.
37. Williams J, Sayles HR, Meza JL, Sayre P, Sandkovsky U, Gendelman HE, *et al*. **Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients.** *Nanomedicine (Lond)* 2013; **8**:1807–1813.
38. Kerrigan D, Sanchez Karver T, Muraleetharan O, Savage V, Mbwambo J, Donastorg Y, *et al*. **A dream come true': perspectives on long-acting injectable antiretroviral therapy among female sex workers living with HIV from the Dominican Republic and Tanzania.** *PloS One* 2020; **15**:e0234666.
39. Murray M, Antela A, Mills A, Huang J, Jäger H, Bernal E, *et al*. **Patient-reported outcomes in ATLAS and FLAIR participants on long-acting regimens of cabotegravir and rilpivirine over 48 weeks.** *AIDS Behav* 2020; **24**:3533–3544.
40. Swindells S, Andrade-Villanueva J-F, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, *et al*. **Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression.** *N Engl J Med* 2020; **382**:1112–1123.
41. Tolley EE, Li S, Zangeneh SZ, Atujuna M, Musara P, Justman J, *et al*. **Acceptability of a long-acting injectable HIV prevention product among US and African women: findings from a phase 2 clinical Trial (HPTN 076).** *J Int AIDS Soc* 2019; **22**:e25408.
42. WHO Think-tank Meeting on Optimizing AntiRetroviral Therapy: meeting report, 12 March 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/338735/9789240016378-eng.pdf?sequence=1&isAllowed=y.
43. Smith JA, Garnett GP, Hallett TB. **The potential impact of long-acting cabotegravir for HIV prevention in South Africa: a Mathematical Modeling Study.** *J Infect Dis* 2020; **224**:1179–1186.
44. Hill A. Review of long-acting injectable candidates for HIV treatment and prevention. 2018.

45. Dorward J, Msimango L, Gibbs A, Shozi H, Tonkin-Crine S, Hayward G, *et al*. **Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa.** *BMJ Open* 2020; **10**:e035412.
46. Fox MP, Pascoe S, Huber AN, Murphy J, Phokojoe M, Gorgens M, *et al*. **Adherence clubs and decentralized medication delivery to support patient retention and sustained viral suppression in care: results from a cluster-randomized evaluation of differentiated ART delivery models in South Africa.** *PLoS Med* 2019; **16**:e1002874.
47. Lerma K, Goldthwaite LM. **Injectable contraception: emerging evidence on subcutaneous self-administration.** *Curr Opin Obstet Gynecol* 2019; **31**:464–470.
48. Flexner C, Thomas DL, Swindells S. **Creating demand for long-acting formulations for the treatment and prevention of HIV, tuberculosis, and viral hepatitis.** *Curr Opin HIV AIDS* 2019; **14**:13–20.
49. Kaushik A, Ammerman NC, Tyagi S, Saini V, Vervoort I, Lachau-Durand S, *et al*. **Activity of a long-acting injectable bedaquiline formulation in a paucibacillary mouse model of latent tuberculosis infection.** *Antimicrob Agents Chemother* 2019; **63**:e00007-19.
50. Bakshi RP, Tatham LM, Savage AC, Tripathi AK, Mlambo G, Ippolito MM, *et al*. **Long-acting injectable atovaquone nanomedicines for malaria prophylaxis.** *Nat Commun* 2018; **9**:315.
51. Macintyre F, Ramachandruni H, Burrows JN, Holm R, Thomas A, Möhrle JJ, *et al*. **Injectable antimalarials revisited: discovery and development of new agents to protect against malaria.** *Malaria J* 2018; **17**:402.
52. Chaccour C, Hammann F, Rabinovich NR. **Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety.** *Malar J* 2017; **16**:161.
53. Slater HC, Foy BD, Kobylinski K, Chaccour C, Watson OJ, Hellewell J, *et al*. **Ivermectin as a novel complementary malaria control tool to reduce incidence and prevalence: a modelling study.** *Lancet Infect Dis* 2020; **20**:498–508.
54. Bollinger RC, Thio CL, Sulkowski MS, McKenzie-White J, Thomas DL, Flexner C. **Addressing the global burden of hepatitis B virus while developing long-acting injectables for the prevention and treatment of HIV.** *Lancet HIV* 2020; **7**:e443–e448.
55. Thomas DL. **Global elimination of chronic hepatitis.** *New Engl J Med* 2019; **380**:2041–2050.
56. Culhane J, Sharma M, Wilson K, Roberts DA, Mugo C, Wamalwa D, *et al*. **Modeling the health impact and cost threshold of long-acting ART for adolescents and young adults in Kenya.** *EClinicalMedicine* 2020; **25**:100453.
57. Hobson JJ, Al-khouja A, Curley P, Meyers D, Flexner C, Siccardi M, *et al*. **Semi-solid prodrug nanoparticles for long-acting delivery of water-soluble antiretroviral drugs within combination HIV therapies.** *Nat Commun* 2019; **10**:1413.
58. Kulkarni TA, Bade AN, Sillman B, Shetty BLD, Wojtkiewicz MS, Gautam N, *et al*. **A year-long extended release nanoformulated cabotegravir prodrug.** *Nat Mater* 2020; **19**:910–920.
59. Hu X, Lin X, Gu Y, Liu Z, Tang Y, Zhang Y, *et al*. **Biocompatible riboflavin laurate long-acting injectable nanosuspensions allowing sterile filtration.** *Drug Deliv* 2014; **21**:351–361.
60. Kalicharan RW, Oussoren C, Schot P, de Rijk E, Vromans H. **The contribution of the in-vivo fate of an oil depot to drug absorption.** *Int J Pharm* 2017; **528**:595–601.
61. IAVI. IAVI and Scripps Research Join Efforts with NIH to Expedite Development of Globally Accessible and Affordable HIV Antibody Combination Products. 2020.
62. Bhugra D. **The global prevalence of schizophrenia.** *PLoS medicine* 2005; **2**:e151.
63. Gopal S, Xu H, McQuarrie K, Savitz A, Nuamah I, Woodruff K, Mathews M. **Caregiver burden in schizophrenia following paliperidone palmitate long acting injectables treatment: pooled analysis of two double-blind randomized phase three studies.** *NPJ Schizophr* 2017; **3**:23.
64. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtälä J, Hoti F, *et al*. **Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia.** *Schizophr Res* 2018; **197**:274–280.
65. Phillips AN, Bansi-Matharu L, Cambiano V, Ehrenkranz P, Serenata C, Venter F, *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–e627.
66. Di Giorgio L, Mvundura M, Tumusiime J, Namagembe A, Ba A, Belemsaga-Yugbare D, *et al*. **Costs of administering injectable contraceptives through health workers and self-injection: evidence from Burkina Faso, Uganda, and Senegal.** *Contraception* 2018; **98**:389–395.