REVIEW

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Promise, perils and cautious optimism: the next frontier in long-acting modalities for the treatment and prevention of HIV

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Purpose of review
This paper provides a critical review of recent therapeutic advances in long-acting (LA) modalities for human immunodeficiency virus (HIV) treatment and prevention.

Recent findings
LA injectable antiretroviral therapy (ART) has been approved in the United States, Canada and Europe; the United States also has approved LA injectable preexposure prophylaxis (PrEP) and the World Health Organization has recommended the vaginal PrEP ring. Current LA PrEP modalities in clinical trials include injections, films, rings, and implants; LA ART modalities in trials include subcutaneous injections and long-term oral pills. Although LA modalities hold incredible promise, global availability is inhibited by long-standing multilevel perils including declining multilateral funding, patent protections and lack of political will. Once available, access and uptake are limited by factors such as insurance coverage, clinic access, labor markets, stigma, and structural racism and sexism. These must be addressed to facilitate equitable access for all.

Summary
There have been tremendous recent advances in the efficacy of LA ART and PrEP modalities, providing renewed hope that 'ending the HIV epidemic' is within reach. However, pervasive socio-structural inequities limit the promise of LA modalities, highlighting the need for cautious optimism in light of the embedded inequities in the trajectory of research, development, and population-level implementation.

Keywords
health equity, HIV prevention and care, long-acting antiretroviral therapy and preexposure prophylaxis, long-acting injectable, therapeutic innovation

INTRODUCTION

The advent of highly active antiretroviral therapy (ART) in 1996 transformed human immunodeficiency virus (HIV) infection into a manageable chronic condition for those in locales where it was available and accessible. Recent biomedical advances in long-acting (LA) modalities for ART and preexposure prophylaxis (PrEP) are once again expanding what is possible as we move toward 'ending the HIV epidemic' [1]. As of February 2022, LA injectable (LAI) ART with two month dosing [2] had been approved by the United States Food and Drug Administration (FDA) and Canadian and European regulators [3]. In 2021, the US FDA approved LAI PrEP and the World Health Organization (WHO) recommended the monthly vaginal ring for PrEP.

Each new LA modality is an important tool in an ever-expanding toolkit and offers novel strategies to reduce barriers to daily pill taking [4,5]. Although LA modalities have the potential to change the course of the epidemic if provided as an option for all, they are not a panacea. The history of HIV and AIDS has underscored that framing biomedical treatment and

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KEY POINTS

- The tremendous recent advances in the efficacy of long-acting (LA) antiretroviral therapy and preexposure prophylaxis modalities have renewed optimism that 'ending the HIV epidemic' is within reach. However, medical innovations alone are insufficient to overcome pervasive health inequities both globally and within countries.
- The promise represented by LA modalities (e.g., injectables, implants, patches, enemas) must be approached with cautious optimism in light of the embedded inequities across all stages of research, development and, most critically, population-level scale-up. Social and behavioral science research can help identify and address these embedded inequities.
- To redress global inequities in LA modalities, we must name and address embedded biases in research by examining which individuals are able to enroll, choose to enroll and remain in the clinical trials themselves and who can subsequently benefit from the trial findings.
- Given inequities in adherence and viral suppression by factors such as age, sexuality, gender, socioeconomic status, race, and ethnicity, we must make changes to the social context that extend beyond implementing health-specific interventions to include such things as sustaining funding for multilevel initiatives, including those supported by PEPFAR and the Global Fund, and revisiting patent protections.

prevention as sufficient for 'ending the HIV epidemic' flattens the deeply embedded social, cultural and political processes that drive the epidemic [6,7]. Historically, this has all too often resulted in incredible HIV technological advances that take a myopic individual-level approach and thus have limited population-level impacts; effective approaches to scaling up LA HIV modalities will require keen attention to socio-cultural dimensions [8].

LA modalities will not improve adherence without addressing long-standing multilevel perils that continue to constrain uptake of oral ART and PrEP, particularly among marginalized communities. For example, geopolitical determinants including fluctuations in funding for major HIV initiatives, such as the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis, and Malaria [9,10▪,11], patent protections [12–14] and lack of political will [15–17] can limit the in-country availability of approved HIV therapies. Clinical trials are sometimes the only avenue for communities in resource-limited settings to access emerging HIV treatment and prevention modalities, creating ethical questions about engagement in, vs. benefits from, research [18–21]. Even countries with approved LA modalities have striking inequities in access and uptake due to factors including: provider education, training and attitudes, insurance coverage and access, ability to attend clinic visits (e.g., transportation, labor market restrictions), medical mistrust and broader factors such as racism and sexual oppression [22,23▪,24,25].

This paper reviews the state of the science regarding LA ART and PrEP to underscore the tremendous recent advances. It also presents how embedded and deep-rooted inequities continue to exist in all phases of the research-to-implementation pipeline, and how these will limit who ultimately stands to benefit from LA modalities. We must attend to these perils, and approach LA HIV modalities with cautious optimism, in order to ensure availability, access and uptake for all.

THE STATE OF THE SCIENCE FOR LONG-ACTING ANTIRETROVIRAL THERAPY AND PREEXPOSURE PROPHYLAXIS MODALITIES

Long-acting injectable ART, administered every 2 months, has been approved by the US FDA, and Canadian and European regulators for virally suppressed people aged 18 years and over [2]. LAI PrEP, administered every 8 weeks, was approved by the US FDA in December 2021. The WHO recommended the vaginal PrEP ring in 2021 but the International Partnership for Microbicides (IPM) voluntarily withdrew its US FDA New Drug Application in December 2021 [26]. Additional LA ART and PrEP modalities are in all phases of clinical trials (Tables 1 and 2). In September 2021, there were 27 nonvaccine LA PrEP products in the pipeline [27]. LA ART modalities under study include injections and oral pills.

Long-acting antiretroviral therapy modalities

LAI ART is a combination of cabotegravir and rilpivirine, branded as Vocabria and Rekambys in Europe and Cabenuva in the United States. In initial clinical trials LAI ART required two injections in the buttocks every 4 weeks and was noninferior to oral ART [28]. In subsequent trials, LAI ART administered every 8 weeks was noninferior to monthly injections [29]; this has been approved in Europe, Canada, and the United States [30,31]. LAI ART is only available to virologically suppressed individuals [32] and requires an oral lead-in [33]. Thus, LAI ART cannot substantially expand the number of virally suppressed individuals, though it may facilitate long-term viral suppression among those with episodic oral ART adherence. Also, because nonadherence is higher among minoritized populations (e.g., by race and ethnicity, sexuality, gender, and socioeconomic

Table 1. LA ART and PrEP modalities that are approved or under review

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing	Main findings and/or comments
Phase III; ART	ATLAS [100▪▪]; two intramuscular injections (buttocks); cabotegravir and rilpivirine; ViiV Healthcare (sponsor) & Janssen Pharmaceuticals (collaborator) & GlaxoSmithKline (collaborator)	Start date: October 28, 2016; end date: May 29, 2018	618	18+ years old, all sexes. On uninterrupted current regimen for at least 6 months. Pregnant and/or breastfeeding participants excluded	United States, Argentina, Australia, Canada, France, Germany, Italy, South Korea, Mexico, Russia, South Africa, Spain, Sweden	Every 4 weeks	At 48 weeks, monthly injections of long-acting injectable cabotegravir and rilpivirine were noninferior to standard oral therapy. Adverse effects (injection site pain) were common (75%), but rarely resulted in study withdrawal [101]. Results were similar at 96 weeks [28]
Phase III; ART	ATLAS-2M [102]; two intramuscular injections (buttocks); cabotegravir and rilpivirine; ViiV Healthcare (sponsor) & Janssen Research and Development (collaborator)	Start date: October 27, 2017; end date: June 6, 2019	1049	18+ years old, all sexes. On uninterrupted current regimen for at least 6 months. Pregnant and/or breastfeeding participants excluded	United States, Argentina, Australia, Canada, France, Germany, Italy, South Korea, Mexico, Russia, South Africa, Spain, Sweden	Every 8 weeks	The efficacy and safety profiles of dosing long-acting injectable cabotegravir and rilpivirine every 8 weeks were similar to dosing every 4 weeks [29]
Phase III; ART	FLAIR [103]; two intramuscular injections (buttocks); cabotegravir and rilpivirine; ViiV Healthcare (sponsor) & Janssen Pharmaceuticals (collaborator) & GlaxoSmithKline (collaborator)	Start date: October 27, 2016; end date: August 30, 2018	631	18+ years old, all sexes. Treatment naïve (≤10 days of prior therapy with any ART following diagnosis). Pregnant and/or breastfeeding participants excluded	United States, Canada, France, Germany, Italy, Japan, Netherlands, Russia, South Africa, Spain, United Kingdom	Every 4 weeks	At 48 weeks, long-acting injectable cabotegravir and rilpivirine was noninferior to standard oral therapy. Injection-site reactions were common [104]. Results were similar at 96 weeks [105]
Phase IIb/III; PrEP	HPTN 083 [106▪▪]; one intramuscular injection (buttocks); cabotegravir; NIAID (sponsor) & ViiV Healthcare (collaborator) & Gilead Sciences (collaborator)	Start date: December 6, 2016; end date: March 16, 2020	4570	18+ years old, assigned male at birth (cisgender men and transgender women who have sex with men). Participants with surgically placed or injected buttock implants or fillers excluded	United States, Argentina, Brazil, Peru, South Africa, Thailand, Vietnam	Every 8 weeks	Long-acting injectable cabotegravir (CAB-LA) was superior to daily oral tenofovir-emtricitabine (TDF-FTC) in preventing HIV infection among MSM and transgender women [107]

Table 1 (*Continued*)

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing	Main findings and/or comments
Phase III; PrEP	HPTN 084 [108]; one intramuscular injection (buttocks); cabotegravir; NIAID (sponsor)	Start date: November 7, 2017; end date: November 5, 2020	3200	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women and women who exclusively have sex with women excluded	Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe	Every 8 weeks	Long-acting injectable cabotegravir (CAB-LA) was safe and superior to daily oral tenofovir-emtricitabine (TDF-FTC) for HIV prevention among cisgender women in sub-Saharan Africa [109]
Phase III; PrEP	The Ring Study [110]; vaginal ring; dapivirine; IPM (sponsor)	Start date: March 2012; end date: December 2016	1950	18–45 years old, assigned female at birth. Self-reported sexually active. Pregnant and/or breastfeeding women excluded	South Africa, Uganda	Every month	The ring was reported safe, with no difference in safety concerns between the experimental and placebo groups. Any side effects were mild in nature [111]
Phase III; PrEP	ASPIRE [112]; vaginal ring; dapivirine; IPM (sponsor) & NIAID (collaborator)	Start date: June 2012; end date: June 2015	3540	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women excluded	Malawi, South Africa, Uganda, Zimbabwe	Every month	The ring was reported safe, with no difference in safety concerns or side effects between the experimental and placebo group [113]
Phase IIIb; PrEP	DREAM [114]; vaginal ring; dapivirine; IPM (sponsor)	Start date: July 13, 2016; end date: December 10, 2018	850	18–45 years old, assigned female at birth. Self-reported sexually active. Previously enrolled in The Ring Study. Pregnant and/or breastfeeding women excluded	South Africa, Uganda	Every month	Follow-up study to the Ring Study. Found to have similar safety profile [115]
Phase IIIb; PrEP	HOPE [116▪]; vaginal ring; dapivirine; IPM (sponsor)	Start date: August 2016; end date: October 10, 2018	1576	18–45 years old, assigned female at birth. Previously enrolled in the ASPIRE study. Pregnant and/or breastfeeding women excluded	South Africa	Every month	Follow-up study to ASPIRE. Found to have similar safety profile to ASPIRE. Moderate side effects related to dapivirine occurred in only two patients [117]

ART, antiretroviral therapy; IPM, International Partnership for Microbicides, Inc.; NIAID, National Institute of Allergy and Infectious Diseases; PrEP, preexposure prophylaxis.

Table 2. LA ART and PrEP products currently in the clinical trial phase

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing periods	Main findings and/or comments
Phase III; ART	LATITUDE [118▪]; two intramuscular injections (buttocks); cabotegravir and rilpivirine; NIAID (sponsor) & ViiV Healthcare (collaborator)	Start date: March 28, 2019; end date (estimated): October 1, 2025	350 (Est.)	18+ years old, all sexes. HIV-1 plasma viral load >200 copies/ml within 60 days prior to study entry. Evidence of nonadherence. Pregnant and/or breastfeeding participants excluded	United States, Puerto Rico	Every 4 weeks	Study in progress, no results posted
Phase II/III; ART	CAPELLA [42]; one subcutaneous injection (abdomen); lenacapavir; Gilead Sciences (sponsor)	Start date: November 21, 2019; end date: October 5, 2020	72	12+ years old, all sexes. HIV-1 plasma viral load >400 copies/ml at screening. Have multidrug resistance	United States, Canada, Dominican Republic, France, Germany, Italy, Japan, South Africa, Spain, Taiwan, Thailand	Every 6 months	Lenacapavir administered subcutaneously every 6 months maintained high rates of virologic suppression (73%) through 26 weeks in patients with multidrug resistance on failing regimen [119]
Phase III; PrEP	IMPOWER-022 [41]; once-monthly oral pill; islatravir; Merck Sharp & Dohme Corp. (sponsor)	Start date: February 24, 2021; end date (estimated): July 5, 2024	4500 (Est.)	16–45 years old, assigned female at birth (cisgender identifying only). Sexually active with male partner in 30 days prior to screening. High risk for HIV. Pregnant and/or breastfeeding women excluded	United States, South Africa	Every month	Study in progress, no results posted
Phase III; PrEP	IMPOWER-024 [120]; once-monthly oral pill; islatravir; Merck Sharp & Dohme Corp. (sponsor)	Start date: March 15, 2021; end date (estimated): September 27, 2024	1500 (Est.)	16+ years old, assigned male at birth (cisgender men and transgender women). Is sexually active (anal intercourse) with a cisgender male or TGW at least once in the past month. High risk for HIV	United States, France, Japan, Peru, South Africa, Thailand	Every month	Study in progress, no results posted

Table 2 (*Continued*)

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing periods	Main findings and/or comments
Phase II; PrEP	HPTN 083-01 [121]; one intramuscular injection (buttocks); cabotegravir; NIAID (sponsor)	Start date: February 19, 2020; end date (estimated): May 31, 2023	50 (Est.)	Under 18 years old, assigned male at birth (cisgender men, transgender women, and gender nonconforming people who have sex with men). Participants with surgically placed or injected buttock implants or fillers excluded	United States	Two time points 4 weeks apart and every 8 weeks thereafter	Study in progress, no results posted
Phase II; PrEP	HPTN 084-01 [122]; one intramuscular injection (buttocks); cabotegravir; NIAID (sponsor)	Start date: November 4, 2020; end date (estimated): May 2024	50 (Est.)	Under 18 years old, assigned female at birth. Pregnant and/or breastfeeding women and women who exclusively have sex with women excluded	South African, Uganda, Zimbabwe	Two time points 4 weeks apart and every 8 weeks thereafter	Study in progress, no results posted
Phase II; PrEP	NCT04003103 [123]; once-monthly oral pill; islatravir; Merck Sharp & Dohme Corp. (sponsor)	Start date: September 19, 2019; End date (estimated): March 15, 2022	250 (Est.)	18–65 years old, all sexes. Low risk of HIV infection. Pregnant and/or breastfeeding women excluded	United States, Israel, South Africa	Every month	Study in progress, no results posted
Phase II; PrEP	MK-8591-043 [124]; implant (upper arm); islatravir; Merck Sharp & Dohme Corp. (sponsor)	Start date (estimated): December 13, 2021; end date (estimated): March 7, 2024	175 (Est.)	18–55 years old, all sexes. Low risk of HIV infection. Pregnant and/or breastfeeding women excluded	No location provided	Every year (52 weeks)	Study has not commenced, no results posted
Phase I; PrEP	NCT03422172 [85]; one intramuscular injection (buttocks); cabotegravir; ViiV Healthcare (sponsor) & PPD (collaborator)	Start date: April 10, 2018; end date: April 20, 2020	48	18–65 years old, assigned male at birth. At risk of HIV infection (a casual male or female partner in the last 2 years).	China	Two time points 4 weeks apart and every 8 weeks thereafter	Long-acting injectable cabotegravir (CAB-LA) was safe and well tolerated overall, with only one participant experiencing an adverse event

Table 2 (*Continued*)

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing periods	Main findings and/or comments
Phase I; PrEP	MTN-027 [125]; vaginal ring; vicriviroc and/or MK-2048; NIAID (sponsor)	Start date: May 2015; end date: March 2016	48	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women excluded	United States	Every 28 days	The rings were safe and well tolerated. Both VCV and MK-2048 were quantifiable in all matrices tested with peak compartmental drug concentrations similar for single and combination drug rings. Tissue-associated VCV and/or MK-2048 did not correlate with inhibition of HIV infection [126]
Phase I; PrEP	MTN-028 [127]; vaginal ring; vicriviroc and MK-2048; NIAID (sponsor)	Start date: June 2015; end date: March 2016	19	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women excluded	United States	Every 28 days	Both rings were found to be safe and well tolerated. Drug release and plasma drug exposure were higher for the original-dose than for the low-dose ring [128]
Phase I; PrEP	MTN-036/IPM 047 [129]; vaginal ring; dapivirine; IPM (sponsor) & NIH (collaborator) & NIAID (collaborator)	Start date: December 4, 2017; end date: January 23, 2019	49	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women excluded	United States	Every 13 weeks	The extended duration DPV rings (100 mg for 13 weeks) were well tolerated and achieved higher DPV concentrations when compared to the monthly (25 mg) DPV ring [130]
Phase I; PrEP	MTN-044/IPM 053/ CCN019 [131]; vaginal ring; dapivirine and levonorgestrel; IPM (sponsor) & NICHD, NIAID, NIMH, NIH, (collaborators)	Start date: July 17, 2018; end date: October 7, 2019	25	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women excluded	United States	Every 90 days (taking out every 28 days for 2 days)	The ring delivered sustained levels of each drug when used continuously for 90 days at levels likely sufficient to protect against HIV and unwanted pregnancy [132]

Table 2 (*Continued*)

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing periods	Main findings and/or comments
Phase I; PrEP	CAPRISA 018 [133]; implant (upper arm); tenofovir alafenamide; Center for the Aids Programme of Research in South Africa, Stichting Amsterdam institute for Global Health and Development, & Université Jean Monnet Saint-Etienne (sponsors)	Start date: January 1, 2017; end date (estimated): December 31, 2022	40 (Part A); 490 (Part B) (Est.)	Assigned female at birth. At-risk of HIV infection. Other inclusion and exclusion criteria not stated	South Africa	Optimal dosage and frequency to be determined during Part A lead-in	Study in progress, no results posted
Phase I; PrEP	MTN-026 [134]; rectal gel; dapivirine; NIAID (sponsor)	Start date: October 26, 2017; end date: September 20, 2018	28	18–45 years old, all sexes. History of receptive anal intercourse, per participant report. Pregnant and/or breastfeeding women excluded	United States, Thailand	Single dose, followed by 2-week washout period, followed by 7 consecutive days of dose administration	Participants reported favorable acceptability of the study DPV gel, with half preferring the gel over condoms and about 30% reporting equal preference. Side effects included leakage, diarrhea, and soiling [135]
Phase 1; PrEP	NCT03082690 [136]; rectal gel; IQP-0528; Johns Hopkins University (sponsor) & ImQuest Pharmaceuticals, Inc, & NIAID (collaborator)	Start date: November 1, 2017; end date: June 2, 2019	10	18+ years old, all sexes. History of receptive anal intercourse, per participant report	United Sates	Single dose	The gel was determined to be safe with one mild adverse event and no effect on rectal tissue histology. Benefits of the gel include local safety with no systematic absorption, delivery of local high IQP-0528 concentrations, and reductions in *ex vivo* HIV infectivity. The gel is limited by its rapid clearance and inability to penetrate vaginal tissue following rectal dosing [137]
Phase I; PrEP	MTN-033 [138]; rectal gel; dapivirine; NIAID (sponsor)	Start date: May 10, 2018; end date: December 3, 2018	16	18+ years old, assigned male at birth. History of receptive anal intercourse, per participant report	United States	Single dose, followed by 2- to 4-week washout period, followed by a second dose	DPV gel was reported safe and easy to use. However, a roughly 3-fold lower DPV exposure in plasma and lack of detectable DPV in tissue biopsies indicated formulation changes may be necessary to achieve protective tissue concentrations [139]

Table 2 (*Continued*)

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing periods	Main findings and/or comments
Phase I; PrEP	OB-002H-101 [140]; vaginal or rectal gel; OB-002H; Orion Biotechnology Polska Sp. z o.o. (sponsor) & SCOPE International AG (collaborator)	Start date: October 5, 2019; end date: August 31, 2020	60	18–45 years old, all sexes. Pregnant and/or breastfeeding women excluded.	Poland	Single dose vs. 5 consecutive days of dose administration	Overall, the product had a positive acceptability profile, and most of the participants would consider using the product against HIV infection and/or pregnancy. Only two Grade 2 adverse events occurred in the multiple dose arm of the study [141].
Phase I; PrEP	DREAM-01 [142]; enema; tenofovir; John's Hopkin's University (sponsor) & University of California, Los Angeles (collaborator) & University of Pittsburgh (collaborator)	Start date: October 2016; end date: May 2019	21	18+ years old, assigned male at birth. History of receptive anal intercourse, per participant report	United States	Single dose	The product proved safe and acceptable with levels of TFV-DP reaching concentrations well above those linked to >90% efficacy. However, cumulative systemic tenofovir exposure was lower than seen with oral dosing. Only two adverse events were attributed to the study product [143]
Phase I; PrEP	PREVENT [144]; enema; Q-griffithsin; Rhonda Brand, University of Pittsburgh (sponsor) & NIAID (collaborator) & Intrucept Biomedicine LLC (collaborator)	Start date: July 10, 2019; end date: February 4, 2021	18	18–45 years old, all sexes. Pregnant and/or breastfeeding women excluded. Individuals undergoing gender reassignment excluded	United States	Single dose	Study permanently terminated due to the COVID-19 pandemic
Phase I; PrEP	DREAM-03 [145]; enema; tenofovir; John's Hopkin's University (sponsor) & NIAID (collaborator) & University of Pittsburgh (collaborator)	Start date: January 10, 2020; end date: April 27, 2021	9	18+ years old, all sexes. History of receptive anal intercourse, per participant report	United States	Three doses (sequence varies by experimental arm)	Study complete, but results not yet posted

Table 2 (*Continued*)

PHASE and PrEP vs. ART	Study name; modality; drug used; and pharmaceutical company	Start date and end date	Sample size	Study population and exclusion criteria	Global location	Treatment duration/ dosing periods	Main findings and/or comments
Phase I; PrEP	ATN DREAM [146]; enema; tenofovir; University of Pittsburgh (sponsor) & University of North Carolina Chapel Hill (collaborator) & Emory University (collaborator) & Johns Hopkins University (collaborator) & NICHD (collaborator)	Start date: April 1, 2021; end date (estimated): July 1, 2022	16 (Est.)	15–25 years old, assigned male at birth (cisgender MSM)	United States	Single dose	Study in progress, no results posted
Phase I; PrEP	DREAM-02 [147]; enema; tenofovir; John's Hopkin's University (sponsor) & NIAID (collaborator) & CONRAD (collaborator)	Start date: June 1, 2021; end date (estimated): December 31, 2021	16 (Est.)	18+ years old, assigned male at birth. History of receptive anal intercourse, per participant report	United States	Single dose of study product (sequence and additional alternate product varies by experimental arm)	Study in progress, no results posted
Phase I; PrEP	IPM 042 [148]; vaginal insert (tablet); DS003; IPM (sponsor)	Start date: November 18, 2015; end date: August 26, 2016	36	18–45 years old, assigned female at birth. Pregnant and/or breastfeeding women excluded	No location provided	One tablet on Day 0 and one on Day 17	DS003 tablets were safe and well tolerated [149], achieving local concentrations that are capable of protecting against HIV infection [150]
Phase I; PrEP	MTN-039 [151]; rectal insert; tenofovir alafenamide and elvitegravir; NIAID (sponsor) & CONRAD (collaborator)	Start date: December 11, 2019; end date: April 7, 2021	23	18+ years old, all sexes. History of receptive anal intercourse, per participant report. Pregnant and/or breastfeeding women excluded	United States	Single dose, followed by 7-day washout period, followed by two more doses	Study complete, but results not yet posted
Phase I; PrEP	NCT04319718 [152]; Vaginal film; MK-2048; Sharon Hillier, University of Pittsburgh (sponsor) & NIAID (collaborator)	Start date: August 19, 2020; end date (Estimated): December 21, 2021	48 (Est.)	18–45 years old, assigned female at birth	United States	Single use	Study in progress, no results posted

ART, antiretroviral therapy; IPM, International Partnership for Microbicides, Inc.; NIAID, National Institute of Allergy and Infectious Diseases; PrEP, preexposure prophylaxis.

status) [34,35], this requirement may exacerbate existing inequities. To address these challenges, the LATITUDE study [36] is currently investigating LAI ART feasibility among nonsuppressed individuals, who must first achieve suppression using an oral lead-in.

Long-acting preexposure prophylaxis modalities

LAI PrEP was superior to oral PrEP in HIV Prevention Trials Network (HPTN) studies among cisgender men, transgender women, and cisgender women [37,38]. These trials are continuing as open-label extension studies and expanding to include acceptability assessments among those under 18 years of age [39,40]. LA PrEP is also in various stages of clinical trials including: monthly oral pills; vaginal and rectal gels; vaginal rings, films, and inserts; intramuscular and subcutaneous injections; implants; enemas; and micro-array patches [27]. As of June 2021, LA PrEP products in Phase III/IV clinical trials include a once-monthly vaginal ring, a once-monthly oral pill and a twice-yearly subcutaneous injection. Further, with goals of increased inclusivity, these studies include recruitment targets to increase participation among African-American and gender non-binary individuals [41,42]. The WHO has recommended the vaginal ring for PrEP [43] even though it reduced HIV infection risk by only 27–35% in Phase III studies, likely due to challenges with long-term adherence (this compares with 95% efficacy for LAI PrEP) [39,43].

EXISTING PERILS JEOPARDIZE THE PROMISE OF LONG-ACTING MODALITIES

One of the perils of LA modalities is that people who participated in the research that demonstrated their efficacy may not have equitable access to LA modalities once the modalities are approved and distributed. To some extent, this results from embedded biases in research that include where the trials are conducted, who is recruited for clinical trial enrollment, who is able to – and chooses to – enroll, and who benefits from post-research findings.

The need to ensure global availability

Though clinical trial eligibility criteria are necessary to determine a drug's efficacy, a lack of transparency regarding these criteria can directly affect participant trust [20,44,45] and willingness to engage with LA modalities once approved. For example, cisgender women were excluded from the initial DISCOVER trial (2016–2019) [46] that tested Descovy for PrEP among cisgender men and transgender women. Due to activism around their exclusion, a trial with cisgender women [47] began in 2021. Also, while the HPTN LAI PrEP trial [37] had an enrollment quota of 10% transgender women, it excluded individuals with buttock implants or fillers, a common practice among transgender women [48]. These exclusions are particularly salient since transgender women face increased HIV vulnerability [49].

Not all people choose to participate in clinical trials, and it is important to understand what motivates these choices for different people. Given the large number of LA modalities in development, sustained attention must also be given to informed refusal [50], namely individuals' decisions to not consent for research participation, or the ways they may assert their own agency during trial participation. The two major oral PrEP trials among cisgender women, FEMPrEP [51], and VOICE [52], demonstrated the unique ways that cisgender women may choose to 'opt out' or engage in 'informed refusal' regarding PrEP use [53]. Studying informed refusal will make visible key silences and identify these individuals not as data omissions but rather as points of resistance and opportunities that offer insight into potential barriers to future access, uptake and sustained use [50,54,55,56▪▪]. Such insights are particularly important as new modalities are becoming more invasive (e.g., injection vs. pill) and may have different gender-based pharmacokinetics [57].

The vast majority of LA ART and PrEP clinical trials occur in South America, Asia, and sub-Saharan Africa due to high HIV incidence in these regions. While Global South participants often constitute the majority of clinical trial participants, the availability of the drug under study in these regions is often limited to clinical trial participation due to scant posttrial access. Yet, trial results are often used as the basis for the approval of HIV treatment and prevention modalities in the United States, Canada, and Europe (i.e., paralleling current LAI ART approval) vs. distribution in the Global South [20,58]. Also, despite differences in risk reductions (95% vs. approximately 30%), LAI PrEP was approved in the United States while the (less effective) ring is under review in sub-Saharan Africa, and has been approved in Zimbabwe [39,43,59]. Availability is also tempered by continued decreases in multilateral funding (e.g., PEPFAR) and patent protections that make medications prohibitively expensive. Though collaborations are forming to accelerate availability (e.g., by the International AIDS Vaccine Initiative, Scripps Research, and the US National Institutes of Health), affordable LA modalities will also require generic drug pricing and patent waivers [60,61].

The need to ensure equitable access and uptake

Even once ART and PrEP are available, deep-seated inequities can still affect their access and uptake. For example, in the United States, AIDS-related mortality overall decreased once oral ART was developed, but declines were greater among white and economically-advantaged populations [62]. Similarly, with oral PrEP, 40% of white individuals in the United States with PrEP indications received a prescription in 2018, vs. 6% of African Americans and 11% of Latinx individuals [63,64]. Oral PrEP use was 3-times lower for women than men relative to new HIV diagnoses [63] and average length of use was 5.8 months for women vs. 8.4 months for men [65,66].

Potential pathways through which socioeconomic status, race and ethnicity, sexuality, and gender may affect ART and PrEP access and uptake in the United States include whether providers offer them [67▪]; healthcare and insurance access (e.g., Medicaid expansion) [68]; medical mistrust [69]; perceived risk [70]; clinical support and wrap-around services [71]; caregiving demands [71,72]; food insecurity [73]; drug use [74]; stigmatization [75,76]; and transportation and employment [24,25,77,78]. Patients' social contexts are unlikely to change alongside the advent of new biomedical modalities; many barriers to access and uptake of oral formulations will still exist for long-acting modalities [72,77,78,79▪▪,80]. These systemic barriers may also be perpetuated by LAI ART eligibility criteria – namely viral suppression – as this differs by age [81], race and ethnicity [82▪], public insurance [83], and gender [84].

Variations in access and uptake may also differ by LA modality type. LAI ART and PrEP may increase adherence because they are clinic vs. patient administered. However, LAI modalities tether patients to clinics with little room for variation, increasing the cost of administration. In contrast, LA oral and subcutaneous formulations are self-administered and may increase patient autonomy, but also potentially lower adherence. Patients' social contexts must be acknowledged to address known challenges to adherence, such as oral lead-in concerns, and issues related to long pharmacokinetic tails and the potential need to return to oral medications [4,85]. Patients have expressed concerns about switching from oral to LA ART as it requires a new drug regimen, may have different adverse effects, and it limits their control over daily dosing [77,86,87]. Patients have also noted potential stigma and workplace-based challenges associated with the frequency of LA ART-related clinic visits [72,79▪▪,88].

Access to LA ART will not be equally distributed in settings like the United States that lack universal healthcare. Cabenuva costs approximately $50 000 annually and there is no generic equivalent. Although the US-based AIDS Drug Assistance Program (ADAP) provided HIV medication to 284 973 low-income individuals in 2018 [89], ADAP access is state administered and not universal. As of October 2021, only 22 US states had updated their ADAP formulary after Cabenuva's approval: of these, 10 covered Cabenuva, and 12 did not. Thus, patients outside those 10 states that cover Cabenuva may be unable to access LAI ART, especially since the manufacturer's patient assistance program does not currently cover ADAP patients, nor those outside of the United States. Similar financial inequities will likely exist with LA PrEP. Although its cost remains unknown, it will likely be more expensive than oral PrEP, making it cost-prohibitive for many [90]. Unless structural supports (e.g., insurance, universal healthcare) are introduced, LA HIV modalities will exacerbate the cost-related inequities evidenced in oral ART and PrEP access.

Issues of availability, access, and uptake must also be contextualized within intersecting inequities – such as homelessness, incarceration, mental health and substance use [91–93]. LA modalities are also available to treat mental health and substance use conditions [94,95], and patients' experiences with those modalities (e.g., Vivitrol for opioid use disorder) may affect their willingness to engage in LA ART and PrEP [79▪▪]. The additional clinical steps for delivering LA HIV modalities to vulnerable communities may also complicate the provision of a 'one stop shop' approach to service integration, including for unhoused or recently incarcerated individuals.

Future directions

As LA HIV treatment and prevention modalities continue to advance, research and practice must acknowledge and address the historical and social contexts that limit global availability and access. The integration of social and behavioral scientists into clinical trial design and subsequent implementation studies may be of particular use to identify multilevel approaches to increase inclusion and equity at all stages of the research-to-implementation pipeline [96]. In contexts where LA HIV modalities are available, further research should address access and uptake within healthcare settings, for example how providers may serve as gatekeepers who determine which patients are 'ready' to switch from oral to LA formulations (e.g., by developing patient-provider decision aids to choose between LAI vs. oral ART or whether to begin PrEP, and in which modality) [97]. Various healthcare delivery models (e.g., telehealth and mobile vans) should be

explored to facilitate equitable and person-centered utilization of prevention and treatment methods, as these models have been successful for delivering naloxone, clean syringes and COVID-19 vaccines. Research also needs to address the multilevel drivers of health policy initiatives and patent protections, including incorporating intersectionality-enhanced frameworks, [98] to facilitate an equitable scale-up of LA treatment and prevention modalities for all.

CAUTIOUS OPTIMISM WITH ADDITIONAL TOOLS IN THE TOOLKIT

There have been tremendous advances in LA ART and PrEP modalities, with even more products in the pipeline. Yet the perils that constrain their availability, access and uptake demonstrate the need for *cautious* optimism as to whether 'ending the HIV epidemic' is within reach. Biomedical technologies, no matter how innovative, cannot reach their full promise without applying social and behavioral strategies to address context-specific factors. Such approaches will improve how these LA modalities are developed and tested, distributed, and who can access them (or opt-out if they so choose). This is particularly salient for scale-up in low-resource settings where context-specific challenges have historically impeded wide-scale rollout of HIV prevention and treatment technologies [99]. As the history of the HIV and AIDS response has demonstrated, focusing solely on the medication, clinic, and patient–provider interactions is insufficient: tackling the social and political dimensions that limit equitable access requires political struggle, social movements, and global accountability. Social and behavioral sciences should be leveraged as complementary tools to biomedical advances to better understand the lived experiences of marginalized community members; the failure to do so will increase medical paternalism and hinder patient–provider relationships. In order for LA HIV modalities to truly fulfill their promise of 'ending the HIV epidemic', equity in availability, access and uptake must be addressed on a global scale.

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Conflicts of interest

There are no conflicts of interest.

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