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 longstanding 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 LA 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...
The promise and perils of long-acting ART and PrEP

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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 status), LA ART will not be as effective among these groups as compared to those who can successfully dose CAB as a 6- month injection [34].

Conversely, LAI ART is noninferior to CAB every 4 weeks and has a dosing regimen that results in surprisingly high adherence in clinical trials. One review demonstrated 99% adherence to LAI ART [35] and another study found 78% adherence to CAB once every 8 weeks compared with 95% adherence to LAI ART [36]. However, it is not clear whether LAI ART will have similar adherence in real-world settings. Furthermore, LAI ART may be commercially unaffordable given the high costs of developing and delivering injectable ART: one study estimates the cost of LAI ART will range from $20,000 to $50,000 per patient per year [37].

LAI PrEP is a combination of cabotegravir and rilpivirine, branded as Cabenuva in the United States. In initial clinical trials LAI PrEP required two injections in the buttocks every 8 weeks was noninferior to monthly injections [28]. In subsequent trials, LAI PrEP administered every 4 weeks and was noninferior to oral ART [35]. In initial trials LAI PrEP was noninferior to oral ART every 8 weeks [38]. However, LAI PrEP requires a three-month lead-in of oral ART for those initiating ART who have never been on ART [39]. Furthermore, LAI PrEP is not approved for those who have never been on ART [40]. LAI PrEP was noninferior to oral ART every 8 weeks in downstream analysis [35]. However, LAI PrEP requires a three-month lead-in of oral ART for those initiating ART who have never been on ART [39]. Furthermore, LAI PrEP is not approved for those who have never been on ART [40].
## 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         | ATLAS2M [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 naive (≤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]. |
| 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] |

PHASE, phase; PrEP, preexposure prophylaxis; ART, antiretroviral therapy; IPM, International Partnership for Microbicides, Inc.; NIAID, National Institute of Allergy and Infectious Diseases; PrEP, pre-exposure prophylaxis.
| 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 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 |
| 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 | United States, Africa, Zimbabwe | Two time points 4 weeks apart and every 8 weeks thereafter | Study in progress, no results posted |
| Phase II; PrEP         | NCT04003103 [123]; one-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] |
| 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 (sponsors) & 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 States | 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 Hopkins 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          | DREAM03 [145]; enema; tenofovir; John’s Hopkins 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 |
| 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 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 LA 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 LA 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, focus on Drug Abuse: K01DA039804A and National Institute of Mental Health: R34MH124552 and the Canadian Institutes of Health Research (Canada Research Chair, Tier 2).

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Fast-Track – Ending the AIDS epidemic by 2030, Available at: https://www.unaids.org/en/resources/documents/2014/UC2686_WAD2014report [Accessed 1 December 2021]
2. ViV Healthcare Announces US FDA Approval of Cabenuva (CABOTEGRA-VIR, RILPIVIRINE) for Use Every Two Months, Expanding the Label, of the First and only complete long-acting HIV Treatment, https://vivhealthcare.com/news/pr-2022/2022/january/viv-healthcare-announces-fda-approval-of-cabenuva-for-use-every-two-months/ [Accessed 14th February]
3. Injectable HIV therapy would have to cost less than $131 a year to be cost-effective in Africa. aidsmap.com. Available at: https://www.aidsmap.com/news/apr-2021/injectable-hiv-therapy-would-have-cost-less-131-year-be-cost-effective-in-africa [Accessed 22 November 2021]
4. Scariati KK, Swindells S. The promise of improved adherence with long-acting antiretroviral therapy; what are the data? J Int Assoc Provid AIDS Care 2021; 20: 232598221109012.
5. Landovitz RJ, Kohren R, McCauley M. The promise and pitfalls of long acting injectable agents for HIV prevention. Curr Opin HIV AIDS 2016; 11: 122–128.
6. Kippax SC, Holt M, Friedman SR. Bridging the social and the biomedical: engaging the social and political sciences in HIV research. J Int AIDS Soc 2011; 14(Suppl 2):51.
7. Kippax S, Stephenson N. Beyond the distinction between biomedical and social dimensions of HIV prevention through the lens of a social public health. Am J Public Health 2012; 102:789–796.
8. Appleton P, Parker R. Moving beyond biomedicalization in the HIV response: implications for community involvement and community leadership among men who have sex with men and transgender people. Am J Public Health 2015; 105:1552–1558.
9. Benning L, Mantinos A, Kerrigan D, et al. Examining adherence barriers among women with HIV to tailor outreach for long-acting injectable antiretroviral therapy. BMC Womens Health 2020; 20:152.
10. Kanaan JM, Saberi P, Sauceda JA, et al. The LAIs are coming! Implementa-
tion science considerations for long-acting injectable antiretroviral therapy in the United States: a scoping review. AIDS Res Hum Retroviruses 2021; 37:75–88.

This scoping review article used the PRISMA model to review the ever-expanding literature on LAI ART implementation. The review revealed the need for more data and research on the acceptability of LAI ART among certain subgroups, cost effectiveness, patient satisfaction and outcomes, and additional ethical considerations.

11. KFF. The U.S. & the Global Fund to Fight AIDS, Tuberculosis and Malaria. 2021. Available at: https://www.kff.org/global-health-policy/fact-sheet/the-u-s-the-global-fund-to-fight-aids-tuberculosis-and-malaria/ [Accessed 14 January 2022]
12. Novogrodsky N. Duty of treatment human rights and the HIV/AIDS pandemic. Yale Hum Rights Dev Law J 2009; 12:1–61.
13. Grover A, Citro B, Mankad M, et al. Pharmaceutical companies and global lack of access to medicines: strengthening accountability under the right to health. J Law Med Ethics 2012; 40:234–250.
14. Boylan M. Medical pharmaceuticals and distributive justice. Camb Q Healthc Ethics 2008; 17:30–44.
15. Plot P, Russell S, Larson H. Good politics, bad politics: the experience of AIDS. Am J Public Health 2007; 97:1934–1936.
16. Sidibe M, Plot P, Dybul M. AIDS is not over. Lancet 2012; 380:2058–2060.
17. Berkman A, Garcia J, Muñoz-Laboy M, et al. A Critical analysis of the Brazilian response to HIV/AIDS: lessons learned for controlling and mitigating the epidemic in developing countries. Am J Public Health 2005; 95: 1162–1172.
18. Braude HD. Colonialism, Biko and AIDS: reflections on the principle of beneficence in South African medical ethics. Soc Sci Med 2009; 68: 2053–2060.

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This review problematizes the ‘one-size-fits-all’ approach to the administration of ARV-based PrEP and notes that future research must consider the significant individual variability in LAR ART pharmacokinetics. This review also offers therapeutic drug monitoring as a potential solution to improve the management of LAR ART in individual patients.

42. Gilead Sciences. A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination With an Optimized Background Regimen in Heavily Treatment Exposed People Living With HIV-1 Infection (MULTI-2M) [Clinical] Registration NCT041500068, clinicaltrials.gov, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT041500068 [Accessed 21 November 2021].

43. International Partnership for Microbicides. A Long-Acting Ring for Women’s HIV Prevention. Available at: https://www.ipmglobal.org/sites/default/files/attachments/publication/rpm_ring_backgrounder_sept_2021_final.pdf [Accessed September 2021].

44. Perez-Brumer A, Naz-McLean S, Huerta L, et al. The wisdom of mistrust: qualitative insights from transgender women who participated in PrEP research in Lima, Peru. J Int AIDS Soc 2021; 24:e25769.

45. Bogart LM, Takada S, Cunningham WE, Medico, and the domestic HIV epidemic. In: Ojukutu BO, Stone VE, editors. HIV in US communities of color. Cham: Springer International Publishing; 2021, 256 pages. Available at: https://link.springer.com/book/10.1007/978-3-030-48744-7#about.
In addition, it was found that racial/ethnic groups were disproportionately affected, suppression in this age group was suboptimal and transmission risk was high. This article assessed rates of sustained viral suppression among racial/ethnic women with a past history of substance use who had concerns about LAI ART interest for LAI ART. A particularly meaningful finding from this study came from through the research and development pipeline. It helps inform potential barriers for future uptake of LAI PrEP modalities as they move related health literacy and risk perception, difficulty assessing risk, provider bias, and viral suppression in adolescents receiving ART at a paeditric HIV clinic in South Africa. J Int AIDS Soc 2020; 23:e25644.

Phiblin MM, Tanner AE, DuVall S, et al. Factors influencing linkage to care and engagement in care for newly diagnosed HIV-positive adolescents within fifteen adolescent medicine clinics in the United States. AIDS Behav 2014; 18:1501–1510.

Flexner C, Thomas DL, Swindells S. Creating demand for long-acting formulations for the treatment and prevention of HIV, tuberculosis, and viral hepatitis. AIDS Behav 2018; 22:971–985.

Rice WS, Tunur B, Fletcher FE, et al. A mixed methods study of anticipated and experienced stigma in healthcare settings among women living with HIV in the United States. AIDS Patient Care STDS 2019; 33:184–195.

Kalichman SC, DiMarco M, Austin J, et al. Stress, social support, and HIV status disclosure to family and friends among HIV-positive men and women. J Behav Med 2003; 26:315–332.

Phiblin MM, Parish C, Kinnard EN, et al. A multisite study of women living with HIV’s perceived barriers to, and interest in, long-acting injectable antiretroviral therapy. J Acquir Immune Defic Syndr 2020; 84:263–270.

Phiblin MM, Parish C, Kinnard EN, et al. Interest in long-acting injectable preexposure prophylaxis (LAIPrEP) among women in the women’s interagency HIV study (WIHS): a qualitative study across six cities in the United States. AIDS Behav 2021; 25:667–678.

Phiblin MM, Parish C, Kinnard EN, et al. A qualitative exploration of women’s interest in long-acting injectable antiretroviral therapy across six cities in the women’s interagency HIV study: intersections with current and past injectable medication and substance use. AIDS Patient Care STDS 2021; 35:23–30.

This qualitative study conducted interviews with women living with HIV to assess interest for LAI ART. A particularly meaningful finding from this study came from women with a past history of substance use who had concerns about LAR ART triggering a recurrence. While other substance users did not have concerns, this insight has implications for LAI ART uptake among individuals in this at-risk group.

Phiblin MM, Bergen S, Parish C, et al. Long-acting injectable ART and PrEP among women in six cities across the United States: a qualitative analysis of who would benefit the most. AIDS Behav 2021. Oct 14. doi: 10.1007/s10461-021-03483-7. [Online ahead of print]

The ATLAS clinical trial found that the combination of cabotegravir and rilpivirine administered as an intramuscular injection every 4 weeks was noninferior to oral ART. This trial, in addition to the FLAIR clinical trial (which was conducted among treatment-naive individuals) lead to the approval of the use of LAI ART for people 18 years of age and older by regulatory bodies in the U.S., Canada, and Europe. ATLAS-2M is a subsequent clinical trial that found that LAI ART administered every 8 weeks is noninferior to injections every 4 weeks.

Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med 2020; 382:1112–1123.

ViiV Healthcare. A Phase III, Randomized, Multicenter, Parallel-group, Noninferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Among HIV-1-infected Adults Who Are Virologically Suppressed. Clinical Trial Registration NCT02998504, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02998504 [Accessed 18 November 2021]

ViiV Healthcare. A Phase III, Randomized, Multicenter, Parallel-group, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch From an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naive Adult Participants. Clinical Trial Registration NCT02938520, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02938520 [Accessed 19 July 2021]
116. Nel A, Niekerk N van, Baelen BV, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020; 382:1124–1135.

117. Orkin C, Arasteh K, Gorgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020; 382:1124–1135.

118. National Institute of Allergy and Infectious Diseases (NIAID). A Phase III Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-1 Uninfected Cisgender Men and Transgender Women Who Have Sex With Men. Clinical Trial Registration NCT02720094, clinicaltrials.gov. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT02720094 [Accessed 16 November 2021]

119. The LATITUDE trial found that cabotegravir administered as an intramuscular injection every 8 weeks was superior to oral PrEP regimens among cisgender men and transgender women. A similar clinical trial, HPTN 084, conducted among cisgender women also found that LAI PrEP was superior to oral PrEP, with even greater effectiveness than the 083 trial. Currently two additional clinical trials, HPTN 085-01 (cisgender men and transgender women) and HPTN 084-01 (cisgender women), are recruiting participants to assess the effectiveness of LAI PrEP in individual under the age of 18.

120. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med 2021; 385:595–608.

121. National Institute of Allergy and Infectious Diseases (NIAID). A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-1 Uninfected Men. Clinical Trial Registration NCT01646410, clinicaltrials.gov. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT01646410 [Accessed 16 November 2021]

122. HPTN 085 Study Demonstrates Superiority of Injectable Cabotegravir to Oral FTC/TDF for the Prevention of HIV in Cisgender Women in Sub-Saharan Africa | The HIV Prevention Trials Network. Available at: https://www.hptn.org/news-events/announcements/hptn-084-study-demonstrates-superiority-of-injectable-cabotegravir-to [Accessed 24 November 2021]

123. International Partnership for Microbicides, Inc. A Multi-Centre, Randomised, Double-Blind, Placebo-Controlled Safety and Efficacy Trial of a Dapivirine Vaginal Matrix Ring in Healthy HIV-Negative Women. Clinical Trial Registration NCT01598226, clinicaltrials.gov. 2011. Available at: https://clinicaltrials.gov/ct2/show/NCT01598226 [Accessed 21 November 2021]

124. Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV infection in women. N Engl J Med 2016; 375:2133–2143.

125. International Partnership for Microbicides, Inc. A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women. Clinical Trial Registration NCT01617096, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT01617096 [Accessed 21 November 2021]

126. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016; 375:2121–2132.

127. International Partnership for Microbicides, Inc. A Follow-On, Open-Label Trial To Assess Continued Safety Of And Adherence To The Dapivirine (25 Mg) Vaginal Ring-004 In Healthy, HIV-Negative Women. Clinical Trial Registration NCT02862171, clinicaltrials.gov. 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT02862171 [Accessed 21 November 2021]

128. Nel A, Niekerk N van, Baelen BV, et al. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. Lancet HIV 2021; 8:e77–e86.

129. International Partnership for Microbicides, Inc. A Phase 3B Open-Label Follow-On Trial To Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women. Clinical Trial Registration NCT02858037, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02858037 [Accessed 21 November 2021]

130. The Ring Study was the first clinical trial to assess the effectiveness of monthly dapivirine vaginal rings as long-acting PrEP among cisgender women in Sub-Saharan Africa. This trial and subsequent trials have found that the rings were safe and effective and have been recommended by the WHO in their HIV guidelines.

131. Baeten JM, Palanee-Phillips T, Mgodiso NM, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV 2021; 8:e77–e85.

132. National Institute of Allergy and Infectious Diseases (NIAID). A Phase III Trial to Study Evaluating Long-Acting Antiretroviral Therapy in Non-Adherent HIV-Infected Individuals. Clinical Trial Registration NCT03835788, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03835788 [Accessed 16 November 2021]

133. The LATITUDE study (anticipated completion October 2023) will investigate whether LAI ART is feasible among nonadherent individuals. This study also requires an oral lead prior to LAI ART initiation, the inclusion of nonadherent individuals in this trial has the potential to eventually expand the current patient eligibility for LAI ART (e.g. only virally suppressed individuals).

134. Orkin C, Arasteh K, Gorgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020; 382:1124–1135.

135. Orkin C, Arasteh K, Gorgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020; 382:1124–1135.

136. National Institute of Allergy and Infectious Diseases (NIAID). A Phase III Trial to Study Evaluating Long-Acting Antiretroviral Therapy in Non-Adherent HIV-Infected Individuals. Clinical Trial Registration NCT03835788, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03835788 [Accessed 16 November 2021]

137. The LATITUDE study (anticipated completion October 2023) will investigate whether LAI ART is feasible among nonadherent individuals. This study also requires an oral lead prior to LAI ART initiation, the inclusion of nonadherent individuals in this trial has the potential to eventually expand the current patient eligibility for LAI ART (e.g. only virally suppressed individuals).

138. Caprisa 018: A randomised controlled trial to assess the safety, acceptability and pharmacokinetics of a sustained-release tenofovir alafenamide sub-dermal implant for HIV prevention in women — ERA-LEARN. Available at: https://www.era-learn.eu/network-information/networks/edctp-il/research-innovation-action/strategic-actions-supporting-large-scale-clinical-trials/caprisa-018-a-randomised-controlled-trial-to-assess-the-safety-acceptability-and-pharmacokinetics-of-a-sustained-release-tenofovir-alafenamide-sub-dermal-implant-for-hiv-prevention-in-women [Accessed 22 November 2021]
Behavioral and social sciences

134. National Institute of Allergy and Infectious Diseases (NIAID). A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults. Clinical Trial Registration NCT0329483, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT0329483 [Accessed 22 November 2021]

135. Bauermeister JA, Tingler RC, Dominguez C, et al. Acceptability of a dapivirine/placebo gel administered rectally to HIV-1 seronegative adults (MTN-026). AIDS Behav. 2021. Oct 17. doi: 10.1007/s10461-021-03490-8. [Online ahead of print]

136. Johns Hopkins University. Phase 1 Study of the Safety, Toxicity, Pharmacokinetics, Pharmacodynamics and Luminal Distribution of Single-dose DucGel Through Rectal Administration. Clinical Trial Registration NCT03082690, clinicaltrials.gov. 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03082690 [Accessed 22 November 2021]

137. Al-Khouja A, Shieh E, Fuchs EJ, et al. Examining the safety, pharmacokinetics, and pharmacodynamics of a rectally administered ICP-0528 gel for HIV pre-exposure prophylaxis: a first-in-human study. AIDS Res Hum Retroviruses 2021; 37:444–452.

138. Nuttall J, Arieën K, Michiels J, et al. Comparing applicator vs. ‘as lubricant’ delivery of rectal dapivirine gel (MTN-033). Int AIDS Soc. 2021; 24:40–41.

139. Orion Biotechnology Polska Sp. z o.o. A Monocentric Phase I Safety, Acceptability, and Pharmacokinetic Trial of OB-002H Gel Administered Vaginally and Rectally in Open-Label and Randomised, Double-Blind, Placebo-Controlled Cohorts of HIV-1 Seronegative Adults. Clinical Trial Registration NCT04791007, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04791007 [Accessed 22 November 2021]

140. Hussain K, Islas CD, Szydlo D, et al. Comparing applicator vs. ‘as lubricant’ delivery of rectal dapivirine gel (MTN-033). Int AIDS Soc 2021; 24:40–41.

141. McGowan IM, Tzakis N, Kosak B, et al. Acceptability of a dapivirine/placebo gel administered rectally to HIV-1 seronegative adults (MTN-026). AIDS Behav. 2021. Oct 17. doi: 10.1007/s10461-021-03490-8. [Online ahead of print]

142. Johns Hopkins University. A Randomized, Double-Blind Phase 1 Safety and Pharmacokinetic Study of Tenofovir Rectal Douch. Clinical Trial Registration NCT04016233, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04016233 [Accessed 22 November 2021]

143. Johns Hopkins University. A Phase I, Open-label Multiple Dose Safety, Pharmacokinetic, Pharmacodynamic, and Acceptability Study of Tenofovir Rectal Douch. Clinical Trial Registration NCT04686279, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04686279 [Accessed 22 November 2021]

144. University of Pennsylvania. Safety, PK/PD, Acceptability, and Desirability of a Novel HIV Prevention Douché Among Adolescent Men (DREAM). Clinical Trial Registration NCT044686279, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT044686279 [Accessed 22 November 2021]

145. Johns Hopkins University. A Phase I Open Label Study Evaluating the Distribution of a Tenofovir Douché in Combination With Tap Water Douching and Simulated Receptive Anal Intercourse (DREAM-02). Clinical Trial Registration NCT04196776, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04196776 [Accessed 22 November 2021]

146. International Partnership for Microbicides, Inc. A Double-blind, Randomised, Placebo-controlled, Dose Escalation Trial to Evaluate the Safety and to Assess Local and Systemic Pharmacokinetics of DS003 Vaginal Tablets Administered to Healthy HIV-negative Women. Clinical Trial Registration NCT02877979, clinicaltrials.gov. 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02877979 [Accessed 21 November 2021]

147. Friend C, Steyler J, van Niekerk N, et al. DS003, a Novel gp120 Blocker, When Administered to Women as a Vaginal Tablet. Presented at: HIV Research For Prevention (HVR4P); 2018 October 21–22; Madrid, Spain. Available at: https://www.professionalabstracts.com/hvr4p2018/IPlanner/#/presentation/1300 [Accessed 24 November 2021]

148. Bunge K. A Randomized, Double Blinded Study of the Safety and Pharmacokinetic Activity of DS003, a Novel gp120 Blocker, When Administered to Women as a Vaginal Tablet. Presented at: HIV Research For Prevention (HVR4P); 2018 Oct 21–25; Madrid, Spain. Available at: https://www.professionalabstracts.com/hvr4p2018/IPlanner/#/presentation/1452 [Accessed 24 November 2021]

149. International Partnership for Microbicides, Inc. A Phase 1 Double-Blind, Placebo- Controlled, Dose Escalation Trial to Evaluate the Safety and to Assess Local and Systemic Pharmacokinetics of DS003 Vaginal Tablets Administered to Healthy HIV-negative Women. Clinical Trial Registration NCT02877979, clinicaltrials.gov. 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02877979 [Accessed 21 November 2021]

150. Friend C, Steyler J, van Niekerk N, et al. DS003, a Novel gp120 Blocker, When Administered to Women as a Vaginal Tablet. Presented at: HIV Research For Prevention (HVR4P); 2018 Oct 21–25; Madrid, Spain. Available at: https://www.professionalabstracts.com/hvr4p2018/IPlanner/#/presentation/1452 [Accessed 24 November 2021]

151. National Institute of Allergy and Infectious Diseases (NIAID). A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels. Clinical Trial Registration NCT04047420, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04047420 [Accessed 22 November 2021]

152. Bunge K. A Randomized, Double Blinded Study of the Safety and Pharmacokinetics of Two Vaginal Film Formulations Containing the Integrase Inhibitor MK-2048. Clinical Trial Registration NCT04319718, clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04319718 [Accessed 22 November 2021]