Advanced Drug Delivery Reviews 200 (2023) 115009

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Advances in long-acting slow effective release antiretroviral therapies for treatment and prevention of HIV infection

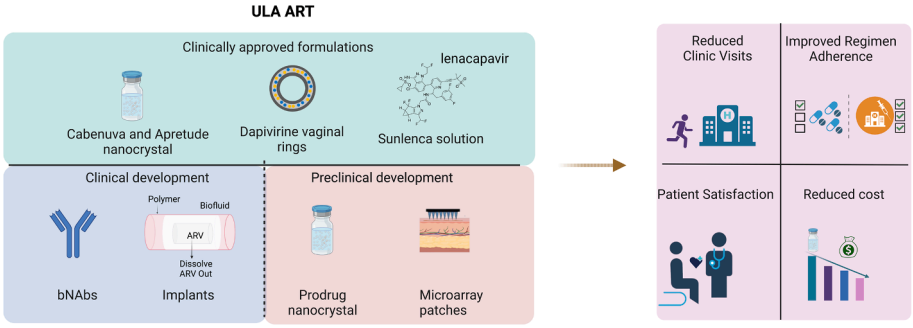
Mohammad Ullah Nayan [a], Brady Sillman [a], Mahmudul Hasan [b], Suyash Deodhar [a], Srijanee Das [c], Ashrafi Sultana [a], Nam Thai Hoang Le [a], Vicente Soriano [d], Benson Edagwa [a,*], Howard E. Gendelman [a,*]

[a] Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, NE, USA
[b] Department of Pharmaceutical Science, University of Nebraska Medical Center, NE, USA
[c] Department of Pathology and Microbiology, University of Nebraska Medical Center, NE, USA
[d] UNIR Health Sciences School & Medical Center, Madrid, Spain

HIGHLIGHTS

- Defined needs for long-acting (LA) antiretroviral therapy (ART)
- Current and future LA ART for HIV prevention and treatment.
- Extending antiretroviral (ARV) drugs half-lives.
- Optimizing ARV biodistribution to cell and tissue viral reservoirs.
- ARV implants, microbicides, and injectable prodrug formulations.
- Pathways towards an every six-month LA ART.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Long-acting slow effective release antiretroviral therapy
Pre-exposure prophylaxis

ABSTRACT

Adherence to daily oral antiretroviral therapy (ART) is a barrier to both treatment and prevention of human immunodeficiency virus (HIV) infection. To overcome limitations of life-long daily regimen adherence, long-acting (LA) injectable antiretroviral (ARV) drugs, nanoformulations, implants, vaginal rings, microarray

Abbreviations: AIDS, Acquired immune deficiency syndrome; HIV-1, Human immunodeficiency virus type 1; ULA, Ultra-long acting; ART, anti-retroviral therapies; INSTI, integrase strand transfer inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitors; PrEP, Pre-exposure prophylaxis; TDF, Tenofovir disoproxyl fumarate; FTC, Emtricitabine; TAF, Tenofovir alafenamide; DDS, Drug delivery systems; CAB LA, Long acting cabotegravir; RPV LA, Long acting rilpivirine; LATTE-2, Long-Acting Antiretroviral Treatment Enabling Trial 2; FLAIR, First Long-Acting Injectable Regimen; ATLAS, Antiretroviral Therapy as Long-Acting Suppression; HPTN, HIV Prevention Trials Network; MSM, Men who have sex with men; PI, Protease inhibitors; AZT, Zidovudine; PLWH, People living with HIV; PK, Pharmacokinetic; ART, Antiretroviral therapy; STRs, Single-tablet regimens; QOL, Quality of life; LAI, Long-acting injectable; EMA, European Medicines Agency; OLI, Oral lead-in; CVF, Complete virological failure; ISR, Injection site reaction; AEs, Adverse events; LASER ART, Long-Acting Slow Effective Release ART; DTG, Dolutegravir; BIC, Bictegravir; PLGA, Poly(lactic-co-glycolic acid; NMP, N-methyl-2-pyrrolidone; ISFI, In situ forming implants; MAPs, Microneedle array patches; HDAC, Histone deacetylase; HMT, Histone methyltransferase; PKC, Protein kinase C; TLR7, Tall-like receptor 7; ZFN, Zinc-finger nucleases; TALEN, Transcription activator-like effector nucleases; bNAbs, Broadly Neutralizing Antibodies.

* Corresponding authors.
E-mail addresses: benson.edagwa@unmc.edu (B. Edagwa), hegendel@unmc.edu (H.E. Gendelman).

https://doi.org/10.1016/j.addr.2023.115009
Received 24 April 2023; Received in revised form 21 June 2023; Accepted 12 July 2023
Available online 13 July 2023

Human immunodeficiency virus
Antiretroviral prodrugs
Pharmacokinetic testing
Adverse reactions
Medicinal and polymer chemistry
Pharmacodynamics
Nucleoside reverse transcriptase inhibitors
Nonnucleoside reverse transcriptase inhibitors
Integrase strand transfer inhibitors

patches, and ultra-long-acting (ULA) prodrugs are now available or in development. These medicines enable persons who are or at risk for HIV infection to be treated with simplified ART regimens. First-generation LA cabotegravir, rilpivirine, and lenacapavir injectables and a dapivirine vaginal ring are now in use. However, each remains limited by existing dosing intervals, ease of administration, or difficulties in finding drug partners. ULA ART regimens provide an answer, but to date, such next-generation formulations remain in development. Establishing the niche will require affirmation of extended dosing, improved access, reduced injection volumes, improved pharmacokinetic profiles, selections of combination treatments, and synchronization of healthcare support. Based on such needs, this review highlights recent pharmacological advances and a future treatment perspective. While first-generation LA ARTs are available for HIV care, they remain far from ideal in meeting patient needs. ULA medicines, now in advanced preclinical development, may close gaps toward broader usage and treatment options.

1. Introduction

Adherence to daily medicines remains the mainstay for chronic disease treatment and prophylaxis. This includes the human immunodeficiency virus type one (HIV-1) and hepatitis B, C, and delta viruses (HBV, HCV, HDV). Treatment of each remains challenging and even unattainable. Optimizing the therapeutic effectiveness of antiviral medicines necessitates maintaining a high therapeutic index, improving access, and sustaining regimen adherence. Adherence is a notable limitation, as patients commonly forget to take their medications. This is even more common during protracted treatment regimens such as life-long daily HIV-1 medicine requirements. Concurrent socioeconomic factors and stigmas associated with HIV-1 make the situation worse. Such socioeconomic factors include substance abuse, social stigmas, discouragement, complex regimens, pill fatigue, and medicine availability. Regrettably, for disease control, there is limited forgiveness for missed doses of antiretroviral (ARV) drugs. This is true both for HIV-1 prevention and treatment. Indeed, any effective pre-exposure prophylaxis (PrEP) regimen depends on medication dose consistency [1]. Thus, a long-acting (LA) drug regimen is an advantage. Less frequent dosages are forgiving, especially in precluding drug resistance and access. Indeed, LA medicines provide sustained therapeutic drug concentrations while enabling longer intervals of viral suppression and protection. Sustained viral suppression of viral infection also reduces chances for transmission from an infected person to an uninfected partner.

Thus, success in implementing any LA medicine regimen rests in improving access. One recent example was the success of LA therapies when used to treat chronic psychiatric conditions. LA antipsychotics delay hospitalizations for early-phase schizophrenia and improve treatment outcomes by preventing psychotic relapses [2,3]. Contraception is a second example for how effective treatments are affected by suboptimal regimen adherence. Notably following the introduction of LA medicines a significant increase in contraceptive utilization was achieved resulting in birth rate reductions [4]. For HIV-1 infection, the development of monthly or bimonthly injectable LA cabotegravir (CAB) and rilpivirine (RPV) has demonstrated improved outcomes for treatment and prevention. The HIV Prevention Network (HPTN)-083 and HPTN-084 clinical trials demonstrated viral risk reduction at levels of up to 89% for persons at risk of infection when LA CAB was used for PrEP compared against standard practice oral medicines [5]. The success of LA CAB extended into treatment. Here combination of LA CAB and LA RPV was proven as effective as the existing oral daily antiretroviral therapies (ARTs) when used for the treatment of HIV-1 infection in virally suppressed adults and adolescents [6]. Indeed, recent approvals of LA ARVs by the US Food and Drug Administration (FDA) serve as evidence of the therapeutic advantages of LA medicines over conventional oral ARTs.

Despite what LA medicines offer, several limitations exist. These include the number of clinic visits, comorbidities, high cost, variable pharmacokinetic (PK) profiles, injection volumes, injection site reactions, significant drug-drug interactions for the capsid inhibitor, extended ARV PK tail, and the emergence of drug-resistance viral mutants. Each affects the broader usage of the current LA medicines. Thus, further improvement of the existing LA medicines remains an immediate need. The needs can be met through ultra-long-acting (ULA) ARV nanoformulations, implants, vaginal rings (VRs), microarray patches (MAPs), and broadly neutralizing antibodies (bNAbs) [7]. These modalities can offer various options for HIV-1 treatment and prevention, ease of access, limited drug-drug interactions, and simplicity of administration. Each is in either preclinical or translational development [8] (Fig. 1). The preference of the target user is what drives the development of ULA ART. A simple survey conducted among men who have sex with men (MSM) for preference for ULA ARTs reported that 79.2% (n = 156/197) preferred every three months injectables over daily pills [9]. Preference focused on convenience, improved privacy, and limited adverse events [8].

With immediate needs in mind, we are now providing a comprehensive review of the current trends in LA ARTs in the clinic and in development. We offer a detailed analysis of commercially available LA ART's pharmacology, clinical trials, and critical results. The latter sections focus on recent advances in drug delivery technologies for ULA ART, including nanoformulations, implants, VRs, MAPs, and bNAbs. Notable improvements for each, together with key products and pharmacological characteristics, are covered. Furthermore, the review explores the developmental challenges associated with ULA ARV therapies, with a specific emphasis on the current successes and obstacles surrounding ULA prodrug formulations and ARV implants. The article also discusses the role of ULA ARVs in HIV cure.

2. Currently approved LA ARTs for HIV-1 treatment and prevention

2.1. Overview of available ARVs

There has been significant progress in the treatment of HIV-1 infection since the virus was first discovered in the early 1980s. In 1987, the first ARV, zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI), was introduced. AZT showed only temporary improvement and did not decrease disease-associated morbidities or mortality [10]. Problems included treatment-limiting toxicities, inconvenient dosing, viral drug resistance, pill burden, and limited virological suppression. Multiple AZT resistance virus mutations emerged rapidly [11]. In the proceeding 35 years since the introduction of the first ARV agent, more than 40 ARVs have been developed to improve disease outcomes for HIV-1 infection and associated immune impairment [11].

The mid-1990′s brought ART to a different stage. Treatment was now associated with three ARV combinations [12]. New classes of ARVs emerged that included protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [13]. Significantly improved clinical outcomes were observed due to the targeting of divergent stages of the viral life cycle with the new drug combinations. The decrease in morbidity and mortality in people living with HIV (PLWH) proved to be profound [14]. However, problems soon again emerged with early combinatorial ART regimens as the new regimens required taking multiple pills several times per day. This rapidly resulted in treatment fatigue and suboptimal adherence. Adherence to ARVs had to be ≥ 95%

as these levels were required to maintain a therapeutic viral suppression [15]. These classes of drugs also came with their unique issues, including poor tolerability and toxicities, stringent food requirements, drug-drug interactions, and resistances [11].

The mid-2010s brought another wave of ART innovations. It was the approval of the first-generation integrase strand-transfer inhibitors (INSTIs), the second-generation NNRTIs, and further improvements in PIs. These drugs demonstrated significant PK profile and therapeutic indices improvement. These ARVs facilitated new regimens. The new combinations further improved the suppression of viral replication leading to robust immune reconstitution. These improvements transformed HIV-1 infection from a life-ending disease to a manageable chronic disease [16]. The new drugs allowed the development of fixed-dose combination (FDC) products to use as a once-a-day single-tablet regimen (STR). This led to treatment simplification and increased the quality of life (QOL) for PLWH [11]. ART adherence rates also greatly improved [17]. Current oral triple-drug therapies consist of an INSTI or an NNRTI plus two NRTIs. Alternatively, a simplified dual-drug therapy consisting of one INSTI and one NRTI or NNRTI (for example, DTG and lamivudine (3TC) or DTG and RPV) has emerged. These regimens can achieve optimal clinical outcomes and high tolerability in virologically suppressed patients.

Due to the unsuccessful attempts at developing a preventive vaccine for HIV-1 infection, ART was used for PrEP and post-exposure prophylaxis [18–20]. In 2012, a fixed-dose combination of the NRTIs, emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada), was approved by the US FDA as a once-daily oral regimen for those who at high risk for HIV-1 acquisition [21]. In 2019, tenofovir alafenamide fumarate (TAF) was approved by the US FDA for use with FTC (Descovy) for once-daily oral PrEP [22,23].

Despite remarkable advances in oral ARTs, there is still a need for improvements, particularly in regimen adherence. Almost one-third of PLWH fail to maintain the required $\geq$ 90% ART adherence for sustained viral suppression [24]. The FEM-PrEP clinical trial was designed to assess whether a daily dose of the ARV Truvada was safe and effective at preventing infection in sub-Saharan African women. The results proved unsuccessful in preventing new HIV infections due to low adherence to the oral therapy [25]. A follow-up survey among the trial participants identified several underlying causes for non-adherence, including social stigma, discouragement from partners regarding daily oral pill intake, forgetfulness, and drug toxicities [26]. Other challenges linked to poor adherence included the need for discretion, comorbid mental illness, substance use disorders, societal and personal pressures, and pill fatigue [27]. Additionally, according to a sub-study cohort of Partners PrEP, maintaining high adherence levels (>80%) through counseling prevented HIV acquisition in heterosexual serodiscordant couples who are in intimate partnerships in which one person is HIV-positive and the other is HIV-negative [28]. Thus, any method that enhances adherence to therapy could greatly increase treatment effectiveness.

Current trends in HIV drug discovery involve the development of LA ART. Advances in nanoparticle technology and drug delivery systems (DDSs) have aided in converting several existing ARVs into LA

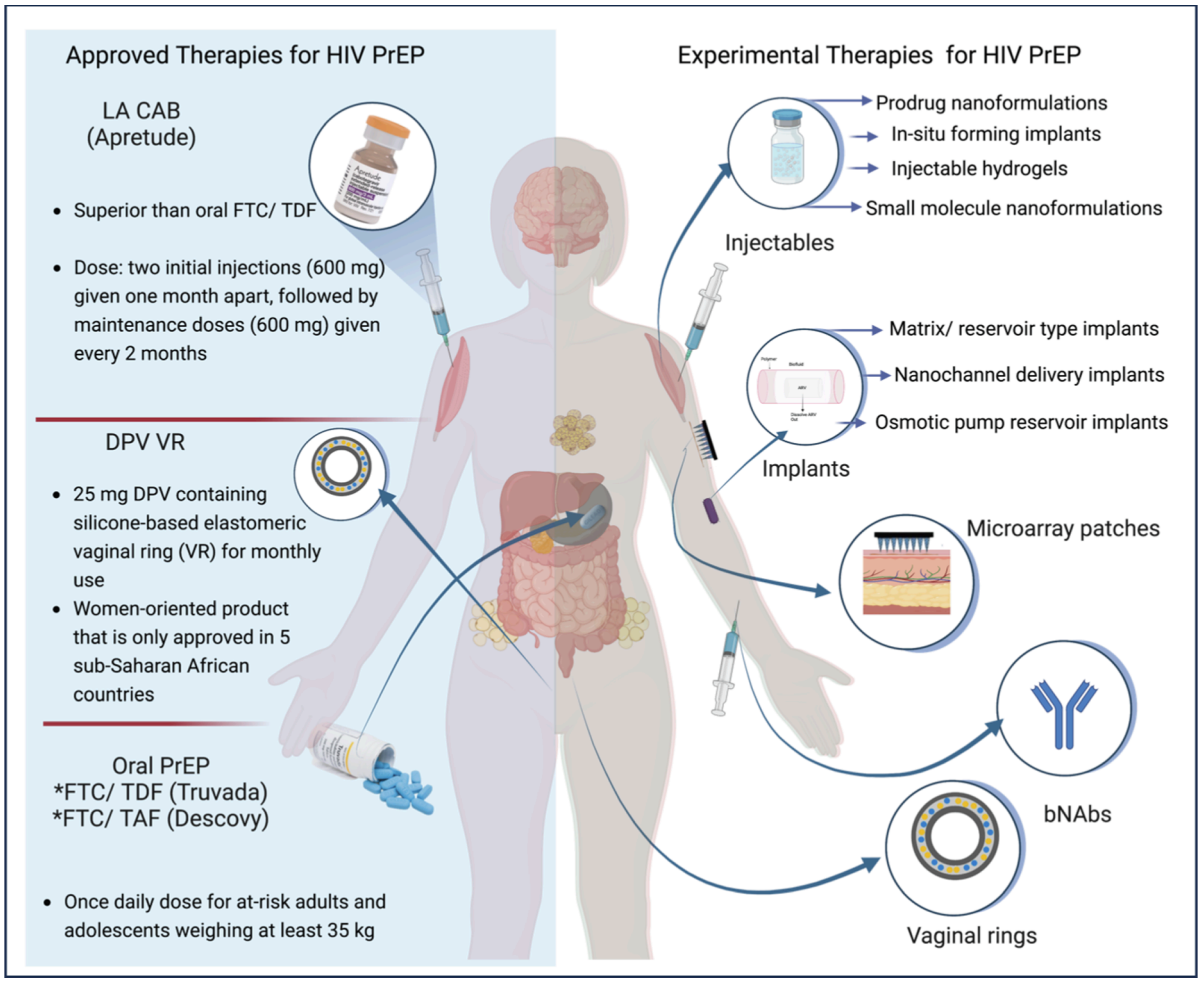


Fig. 1. Approved and experimental therapies for HIV Prevention. Left panel: Approved therapies for HIV prevention include LA CAB (Apretude), FTC/TDF (Truvada) and FTC/TAF (Descovy). **Right panel**: Experimental therapies that are either in clinical or advanced pre-clinical development include injectables (prodrug or small molecules nanoformulation, hydrogels, in-situ forming implants), implants, microarray patches, bNAbs, and vaginal rings.

formulations, which include LA CAB and LA RPV. Newly emerging highly effective LA ARVs include lenacapavir (LEN), islatravir (ISL), dapivirine (DPV), elsulfavirine (VM 1500), and ulonivirine (MK-8507) (Fig. 2).

These LA ARVs are either approved or in clinical development. LEN is a first-in-class capsid inhibitor developed for both oral and subcutaneous (SC) injection. ISL is a unique LA nucleoside reverse transcriptase translocation inhibitor (NRTTI). DPV is a LA NNRTI, developed as VRs for the monthly administration to prevent HIV-1 infection acquisition. VM15500A is an investigational NNRTI and active metabolite of elsulfavirine, that is also in development as a LA agent for HIV treatment [29]. Other emerging LA and ULA technologies, such as prodrug nanocrystals, implants of existing ARVs, and MAPs, could extend dosing intervals to once every six months and improve patient privacy and convenience.

2.2. *Approved LA ARVs for HIV-1 treatment.*

Currently, two LA ARTs are approved for HIV-1 treatment. The first one is Cabenuva (co-packaged intramuscular (IM) injections of LA CAB and LA RPV, designated here as LA CAB and RPV). It is the only complete LA medicine approved for HIV-1 treatment for virologically suppressed adult and adolescent patients, weighing at least 35 kg [30]. Following the results of the phase IIb LATTE-2 trial and the phase III/IIb FLAIR and ATLAS trials, Cabenuva was first approved by Health Canada in March 2020, then by the European Medicines Agency (EMA) in October 2020, and by the US FDA in January 2021[31–33]. Currently, every 4-week and every 8-week administration regimens are approved [31,34]. Additionally, in March 2022, the US FDA announced a label update for Cabenuva to be initiated with or without an oral lead-in (OLI) based on the FLAIR clinical trial extension results [35,36]. The label update also cleared the use of LA CAB and RPV in adolescents weighing ≥ 35 kg who are on stable ART regimens with no history of treatment failure or

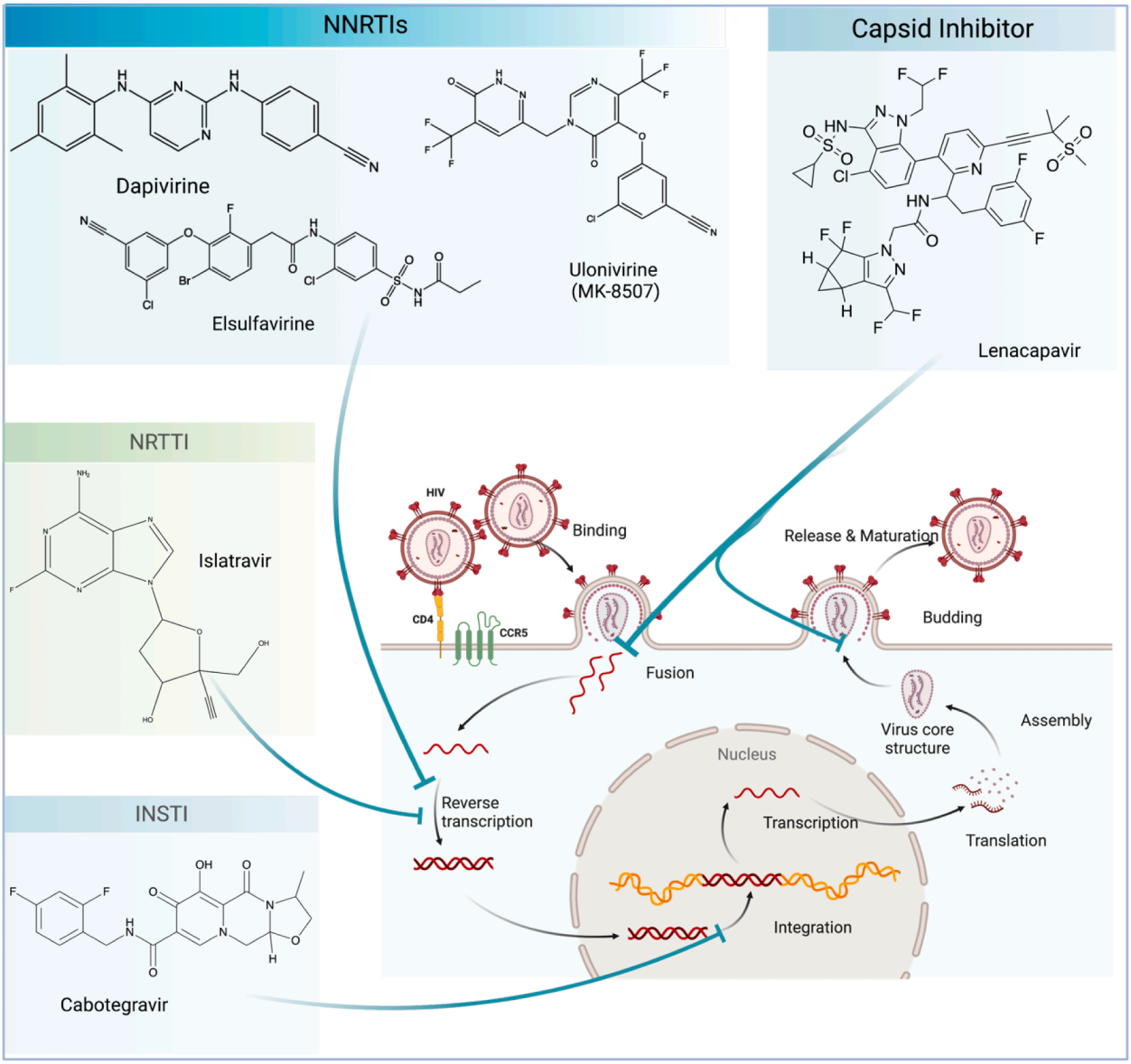


Fig. 2. LA ARVs. Lenacapavir (capsid inhibitor) binds to the NTD-CTD interface of capsid and inhibits several steps of the viral replication life cycle including capsid disassembly and nuclear transport, virus production, and capsid assembly. Dapivirine, ulonivirine, and elsulfavirine inhibit reverse transcription. Islatravir is an adenosine analog which inhibits the reverse transcription process through multiple mechanisms. Cabotegravir inhibits the integration of the viral DNA into the host DNA. NNRTIs – non - nucleoside reverse transcriptase inhibitors; NRTTI- nucleoside reverse transcriptase translocation inhibitor; INSTI- integrase strand transfer inhibitor.

resistance to CAB or RPV [37]. More patients could soon have access to this LA therapy to further improve efficacy, safety, tolerability, acceptability, adherence, and virological outcomes.

The second approved LA ARV is Sunlenca (LA LEN), the only capsid-inhibitor-based ART. In August 2022, the European Commission granted its approval, followed by the US FDA in December 2022, specifically for its utilization in heavily treatment-experienced individuals infected with multi-drug resistance (MDR) HIV-1 strains. LA LEN, as an SC injection, is administered twice a year in conjunction with an optimized background regimen. Notably, LA LEN has exhibited efficacy in both heavily treatment-experienced and treatment naïve PLWH. A comprehensive review of the performed clinical trials for Cabenuva and Sunlenca is now provided.

2.2.1. Cabenuva (LA CAB and RPV)

LA CAB formulation is an aqueous nanosuspension of crystalline-free acid of CAB, stabilized by polysorbate 20, polyethylene glycol 3350 (PEG-3350), and mannitol with an average particle size of 200 nm [38]. The smaller particle sizes of LA CAB influence the dissolution profile of CAB from the injection site drug depot. Owing to CAB's low aqueous solubility, it becomes a dissolution-controlled sustained-release depot after injection. LA CAB IM and SC injections pharmacology in healthy HIV uninfected persons was evaluated in a phase I study where participants received a single IM injection of doses ranging from 100 to 800 mg of LA CAB or SC injection of doses ranging from 100 to 400 mg of LA CAB. Plasma-time profile curves for both the IM and SC injections were comparable with each other, and the plasma CAB concentrations remained higher than protein-adjusted 90% inhibitory concentration (PA-IC_{90}) for at least 24 weeks in the participants who received $\geq$ 200 mg LA CAB doses [39].

On the other hand, LA RPV is an aqueous nanosuspension of RPV that is stabilized by poloxamer (P338) and has a mean particle size of 200 nm [40]. LA RPV was first developed for PrEP. However, the high prevalence of NNRTI drug resistance profile limited its further development as a single agent for PrEP [41]. LA RPV injection was reported to be well tolerated and safe in HPTN-076 trial. Participants in HPTN-076 study, who received at least one injection (1200 mg of LA RPV injection every 8-week), showed an average RPV trough concentration (C_{trough}) of 62.2 ng/mL, which is 4 times higher than PA-IC_{90} for RPV [42].

The effectiveness of LA CAB and RPV was studied extensively for HIV-1 treatment. LATTE-2 (NCT02120352), a phase IIb trial, was the first to evaluate the efficacy of a LA CAB and RPV regimen in treatment-naïve PLWH. Results from the LATTE-2 trial demonstrated that after 256 weeks, participants receiving LA CAB and RPV injections every 4 weeks (Q4W) or every 8 weeks (Q8W) achieved high rates of viral suppression, comparable to those receiving the standard triple-drug combination oral therapy [43,44]. Building on the success of LATTE-2, the phase III FLAIR trial (NCT02938520) was initiated to investigate the efficacy of LA CAB + RPV as maintenance therapy for treatment-naïve PLWH. After 48 weeks, the FLAIR trial revealed that Q4W administration of LA CAB and RPV maintained viral suppression at levels like the standard oral ART. These findings supported the efficacy of LA CAB + RPV as a viable alternative to conventional oral ARTs for the treatment of HIV-1 infection [45]. Participants in the FLAIR and LATTE-2 trials underwent an OLI phase before receiving LA ART injections. However, a comparison conducted during the FLAIR trial extension phase revealed that the efficacy of LA CAB and RPV was similar, regardless of whether an OLI was administered [36]. These findings supported the approval of a simplified dosing initiation for LA CAB and RPV, eliminating the need for an OLI phase. Additionally, the ATLAS (NCT02951052) and ATLAS-2M (NCT03299049) trials provided further evidence to support the effectiveness of LA CAB and RPV compared to standard therapy. The ATLAS trial assessed the effectiveness and tolerability of LA CAB and RPV in PLWH who had achieved viral suppression with standard oral therapy for at least 6 months. ATLAS trial also demonstrated similar efficacy results to LATTE-2 and FLAIR trials. Notably, participants expressed higher satisfaction with the LA treatment, and serious adverse events were infrequent [46,47]. The ATLAS-2M trial compared LA CAB and RPV administered either Q4W or Q8W. Both dosing regimens exhibited equal effectiveness in maintaining high levels of virological suppression [47–49]. These findings strongly support the efficacy of LA CAB and RPV as an excellent alternative to daily oral ARTs.

The effectiveness and safety of LA CAB and RPV Q8W are also reinforced by the ongoing phase IIb POLAR trial (NCT03639311), which involves individuals from the LATTE-2 trial who had been taking oral CAB and RPV daily and virologically suppressed for at least 5 years. The trial randomly assigned the participants to either LA CAB and RPV Q8W or oral DTG and RPV, and after a year, there were no instances of HIV-1 viral loads $\geq$ 50 copies/mL or virological failure in either treatment group [50]. The MOCHA trial (NCT03497676) is exploring oral and LA CAB and RPV (alone or in combination) in virologically suppressed adolescent patients. Clinical trial NCT04518228 is investigating the pharmacokinetics of LA CAB in pregnant and postpartum women with and without HIV-1 infection and their infants. The LATITUDE trial (NCT03635788) will evaluate the effectiveness of Q4W LA CAB and RPV injection in participants with suboptimal adherence and viral suppression. We have summarized the critical findings of the LA CAB and RPV clinical trials (Table 1).

2.2.2. Sunlenca (LA LEN)

LEN, formerly known as GS-6207, is the first-in-class HIV capsid (CA) inhibitor. Because of its ability to bind to the multistage of HIV capsid, specifically the NTD-CTD interface [52], it becomes a very potent inhibitor of HIV-1 virus replication, showing sub-nanomolar and picomolar potency against different isolates of HIV-1,2 viruses. LEN treatment causes the formation of a malformed capsid that is capable of penetrating new target cells but is unable to undergo replication to generate a new virion [53]. As a first-in-class agent, LEN resistance-associated mutations in treatment-naïve or heavily treatment-experienced patients are rare and do not show any significant contribution to the reduction of the drug's potency. CA sequences obtained from treatment-naive patient samples showed the absence of LEN resistance-associated mutations, which have recently been discovered in in-vitro [54]. The data indicated that genotypic resistance screening is not required prior to starting LEN treatment. Also, Gag polymorphisms or mutations in Gag cleavage sites associated with PI resistance do not affect the potency of LEN [55]. Additionally, the viruses associated with LEN resistance mutations were also susceptible to other ARVs [56]. This data indicated the usage of LEN as an add-on to the failing dosage regimen to treat treatment experienced PLWH.

The PK profile of LEN in both oral and SC injectable solution dosage forms was investigated in humans. In phase I, placebo-controlled, blinded, randomized study with HIV- uninfected persons, a single SC injection of 900 mg LEN showed plasma concentration $\geq$ 24 ng/ml (which is $\geq$ 6 fold of inhibitory quotient) for at least 26 weeks [57]. After the SC injection, an initial slow release of LEN from the injection site was observed, and it took the first few weeks to reach the target concentration. The C_{max} was observed between weeks 11 to 14. The plasma concentration of LEN also increases proportionately with the increase of doses from 300 mg to 900 mg. There was no report of clinically relevant adverse events graded 3 or 4. However, injection site reactions, including visible induration and nodules, were widely reported. The low plasma LEN levels soon after SC injection led to the consideration of oral LEN lead-in and PK lag time bridge. In Phase I study in healthy, non-HIV infected participants, LEN was well-tolerated up to 1800 mg single oral dose, and the $t_{1/2}$ was more than 13 days [58]. LEN is a CYP3A4, P-glycoprotein, and UGTA1 substrate. Therefore, strong inducers of CYP3A4 may significantly lower plasma concentrations of LEN; hence, dose adjustment should be considered.

The efficacy and safety of LEN, administered by SC injection and orally, were evaluated in two clinical trials. These trials were named

Table 1
LA CAB and RPV clinical trials for HIV-1 treatment.

	LATTE-2	FLAIR	ATLAS	ATLAS-2M
Aim	Efficacy and safety evaluation of LA CAB and RPV regimen in treatment naïve PLWH	Safety and efficacy evaluation of LA CAB and RPV as maintenance therapy following a switch from an INSTI plus 2 NRTIs regimen in HIV-1 treatment naïve participant	Non-inferiority assessment of LA CAB and RPV compared to continuation of current daily oral therapy in virally suppressed PLWH	Effectiveness comparison of LA CAB and RPV as maintenance therapy, administered every 8 weeks versus every 4 weeks
Participants	Eligibility: PLWH ≥ 18 years old, receiving ART for ≤ 10 days, with ≥ 200 mm of CD4 + T-cell counts and ≥ 1000 copies/ mL of HIV-1 RNA. Participants: 286 (19–64 years old)	Eligibility: Treatment naïve PLWH ≥ 18 years old, and > 1000 copies/ml of plasma HIV-1 RNA. Participants: 566 (18–68 years old) with 127 females (22%).	Eligibility: HIV-infected patients ≥ 18 years of age and receiving un-interrupted ART with-out CVF. Participants: 618 (18–82 years old) and 74% had CD4 + T cell counts of 500/ ml^3.	Eligibility: Viral suppressed PLWH receiving 1st or 2nd oral standard-of-care regimen for ≥ 6 months. Participants: 1045 (34–50 years old)
Study design	An OLI of once-daily CAB (30 mg) plus two NRTIs (ABC, 600 mg and 3TC, 300 mg) for 20 weeks. 25 mg of oral RPV daily was added 4 weeks before randomizing. Gr- 1: continue oral CAB + ABC/3TC (n = 56), Gr- 2: LA CAB and RPV (400 mg of LA CAB + 600 mg of LA RPV) every 4 weeks (Q4W) (n = 115), or Gr-3: LA CAB and RPV (600 mg of LA CAB + 900 mg of LA RPV) every 8 weeks (Q8W) (n = 115). In week 256 (extension period), participants either transitioned to Q8W/Q4W LA (ex-tension-switch group) from oral therapy or continued their LA therapy.	Participants received 16 weeks of once-daily oral therapy, containing 50 mg of DTG + 600 mg of ABC + 300 mg of 3TC to achieve viral suppression. Then, randomized into 2 Groups. 1) continue oral DTG/ ABC/ 3TC, 2) switch to LA CAB and RPV (400 mg of LA CAB + 600 mg of LA RPV) every 4 weeks (Q4W) after switching to oral 30 mg of CAB and 25 mg of RPV for 4 weeks and an initial loading dose of 600 mg of LA CAB + 900 mg of LA RPV. Oral group participants were given choice to transition to LA therapy **at week 100** (extension switch). Those participants could select either direct-to-injection or with a 4-week oral lead-in (oral lead-in group) or withdraw.	Participants were randomized in either Gr-1: oral therapy or Gr-2: transition to LA therapy. Before the transition to LA therapy, participants received a 4-weeks once daily OLI (30 mg of CAB + 25 mg of RPV). After OLI, participants received initial IM injections (600 mg of LA CAB + 900 mg of LA RPV), followed by IM injections of LA CAB and RPV every 4 weeks (400 mg of LA CAB + 600 mg of LA RPV). After week 52, oral group participants were given 4 options ii) switch to LA therapy from oral therapy (Switch arm ii) withdraw, iii) transfer to ATLAS-2 M, iiv) enter the trial extension Phase to continue LA therapy.	Participants were randomized in two group, either Gr-1: LA CAB and RPV every 8 weeks (Q8W) (600 mg of LA CAB + 900 mg of LA RPV) or Gr-2. LA CAB and RPV every 4 weeks (Q4W) (400 mg of LA CAB + 600 mg of LA RPV). Participants who did not receive CAB/ RPV received a once daily OLI for 4 weeks (30 mg of CAB + 25 mg of RPV).
Results	**At week 96**, viral suppression rate was 84% (47 of 56 patients), 87% (100 of 115 patients), and 94% (108 of 115 patients) in the oral treatment group, Q4W group, Q8W group, respectively. CVF was observed in 2 and 1 participants in Q8W and oral treatment group, respectively. ISR were mostly mild (84%) or moderate (15%) in intensity. **At week 256**, viral suppression was observed in 81% (186 of 230 participants) in the Q4W or Q8W groups and 93% (41 of 44 participants) in the extension-switch group. Discontinuation due to CVF and ISR were rare.	**At week 48**, both the LA and oral therapy groups showed high rates of virological suppression, with 93.6% and 93.3% of participants, respectively. Mild to moderate ISRs were reported by 86% of participants in the LA group. **At week 96**, HIV-1 RNA levels ≥ 50 copies/mL were observed in only 3% of the participants in each group. AEs incident was comparable between the two groups, with 8%. **At week 124**, 99% (110/111) and 93% (113/122) of the direct-to-injection group participants and OLI group participants, respectively, remained virally suppressed. The proportion of participants with HIV-1 RNA levels ≥ 50 copies/mL was 5%, including 5 additional participants since the week 96 analysis.	**At week 48**, 92.5% (288/311) of participants in the LA group and 95.5% (286/300) of participants in the oral therapy group remained virally suppressed. CVF was reported in 3 and 4 participants in the LA group and oral therapy group, respectively. The most common reported AEs in the LA group were ISRs. **At week 96**, all 23 participants in the LA arm maintained virological suppression, while 1 participant in the switch arm (who switched from the oral ART arm, n = 29) had HIV-1 RNA levels > 50 copies/ml. No participants in either group met the CVF criterion.	**At week 48**, CVF was reported in 8 (1.5%) and 2 (0.4%) participants in Q8W and Q4W arm, respectively. 94.3% and 93.5% of participants in Q4W and Q4W arm were viral suppressed. **At week 96,** 2% of participants in Q8W (11 out of 522) and 1% in Q4W (6 out of 523) had HIV-1 RNA levels ≥ 50 cop-ies/mL. One person in Q8W met CVF criteria in week 48. This resulted in a total of 9 participants in Q8W and 2 in Q4W with CVF. **Between week 96 and week 152**, there were two additional CVFs.
Comments	LA therapy (LA CAB and RPV) whether administered every 4 weeks or every 8 weeks, had similar efficacy in maintaining viral suppression as daily three-drug oral therapy.	LA therapy (CAB and RPV) had similar efficacy in maintaining viral suppression as oral therapy with DTG/3TC/ ABC.	LA therapy (LA CAB and RPV) had similar efficacy as continuing the current oral therapy in virally suppressed PLWH.	LA CAB and RPV ad-ministered every 8 weeks, had similar effectiveness as administrated every 4 weeks.
Ref	[43,44]	[45]	[46,47]	[48,49]

PLWH- people living with HIV; IM- Intramuscular; OLI- Oral Lead-in; ISRs- Injection site reactions; CVF- Confirmed Virological Failure; AEs- Adverse Events; Q8W- Once every 8-week injection; Q4Q- Once every 4-week injection.

CAPELLA and CALIBRATE (Table 2). The CAPELLA trial focused on LEN as an add-on therapy for patients with MDR HIV-1. Results demonstrated that adding LEN to the failing regimen led to a significant reduction in HIV-1 RNA [59]. The CALIBRATE trial compared the effectiveness of oral and SC LEN, administered in combination with ARVs. At week 54, both the two and three-drug regimens of SC LEN given every six months had comparable effectiveness to a three-drug oral regimen [60].

Taken together, these clinical trials provided substantial evidence supporting the safety profile and effectiveness of LA LEN. LA LEN can be given to PLWH when the patient's current ARVs are failing, meaning the development of viral resistance and patients being unable to tolerate ARVs' side effects. What remains in need is finding a suitable drug partner for LEN so that a combination ARV therapy may be easily extended to longer intervals in administration.

2.3. *Currently approved LA ARVs for HIV-1 prevention.*

Currently, two LA ARTs are approved for HIV-1 PrEP, LA CAB and DPV VR. LA CAB, known as Apretude or Vocabria, is the only LA PrEP agent, authorized to use in the US for individuals weighing ≥ 35 kg who are at risk of acquiring HIV infection. The US FDA approved LA CAB as

Table 2
LA LEN clinical trials for HIV-1 treatment.

Clinical Trial	CAPELLA (NCT04150068)	CALIBRATE (NCT04143594)
Aims	Efficacy and safety evaluation of LEN plus an optimized background regimen in patients with MDR HIV-1 infection.	Efficacy and safety evaluation of LA LEN in combination with other ARTs in PLWH.
Participants	Eligibility: Participants $\geq$ 12 yrs. of age and weighing $\geq$ 35 kg who received ARTs for $>$ 8 weeks and have $\geq$ 400 copies/mL of HIV-1 RNA and have MDR infection. Participants: 72 participants aged between 23 and 78. Female-25%. Mean VL was $(4.17 \pm 1.03) \times \log_{10}$ copies/ml.	Eligibility: Treatment naïve participants $\geq$ 18 yrs. of age and have $\geq$ 200 copies/ml of HIV-1 RNA. Participants: 182 participants (7% female).
Study design	Participants were divided into two cohorts (36 participants per cohort). In cohort-1, participants either received LEN oral therapy or a placebo for the first 14 days. Then, LEN group participants received LEN SC injections (927 mg) every six months and the placebo group, first received 14 days of oral LEN, then LEN SC injections (927 mg) every six months. In cohort-2, participants received 14 days of oral LEN therapy, then LEN SC injections (927 mg) every six months. All participants received an optimized background regimen.	Participants were randomized into 4 groups. Group 1 and 2 received 14 days oral LEN lead-in, followed by LEN SC injections every six months. In addition, all the participants received oral FTC/TAF. At week 28, group 1 participants continued SC LEN injections every six months and oral TAF and group-2 participants switched to SC LEN injections every six months and oral BIC. Group 3 and 4 received daily oral LEN + FTC/TAF and BIC/FTC/TAF, respectively.
Virological efficacy and adverse events	In cohort I, 88% and 17 % of participants in oral LEN group respectively and control group had at least 0.5 $\log_{10}$ copies/ml HIV-1 RNA reduction from baseline in the first 14 days. After 26 weeks, 81% and 83% of cohort-I and cohort-ii participants, respectively were virally suppressed. No AEs lead to study discontinuation. 2 participants among 72 developed emergent capsid mutation that were highly resistance to LEN.	At week 28, The rate of viral suppression in groups 1,2,3, and 4, was 94%, 92%, 94%, and 100%, respectively. At week 54, the viral suppression rate was 90, 85, 85, and 92% in groups 1,2,3, and 4, respectively. No serious AEs were reported. However, grade-1 ISRs were reported by three participants and led to LEN injection discontinuation.
Comments	In patients with MDR, LEN treatment significantly improved treatment outcomes.	Both oral or SC injections of LEN in combination with TAF, BIC, or FTC/TAF are well tolerated and maintain a high rate of virological suppression in the treatment naïve PLWH.
Ref	[59]	[60]

PLWH- people living with HIV; MDR- Multi drug resistance; VL-viral load; LEN-lenacapavir; SC- subcutaneous; AEs- adverse events; ISRs- injection site reactions; TAF- tenofovir alafenamide; BIC- bictegravir; FTC- emtricitabine.

PrEP in December 2021, and the EMA approved it in October 2022. Its approval as PrEP was based on the results from HPTN-083 and 084 clinical trials [61,62]. LA CAB has also been approved as PrEP in Australia, Zimbabwe, and South Africa. The WHO also updated its guidelines in July 2022 regarding using LA CAB as PrEP for HIV-1 infection. These guidelines support the global efforts to plan and provide LA CAB in conjunction with other HIV-1 infection prevention measures [63].

Alternatively, DPV VR is a women-focused LA prevention strategy approved in five African countries: Kenya, Zimbabwe, South Africa, Uganda, and Zambia. DPV VR is a flexible silicone ring designed to release DPV directly into the vagina, offering month-long protection against HIV-1 infection [64]. It was initially developed by the International Partnership for Microbicides (IPM) and then acquired by the Population Council. Following the results from two Phase 3 clinical trials, Ring and ASPIRE, the EMA issued a positive opinion in July 2020, endorsing the use of the ring by women aged 18 years or older in developing countries. Subsequently, in January 2021, WHO recommended the ring as an additional prevention option for women at considerable risk of acquiring HIV-1 infection. Since then, it has received approval in five African countries, with expectations of further approvals in several other sub-Saharan African countries.

2.3.1. Apretude or Vocabria (LA CAB)

The safety and efficacy of LA CAB demonstrated in the LATTE-2 and FLAIR trials as a component of LA ART underscored its potential as a LA PrEP agent [65]. Following successful efficacy outcomes in non-human primate models using LA CAB as PrEP [64,66], two Phase III clinical trials were initiated to assess the utility of LA CAB in PrEP applications. The HPTN-083 and 084 clinical trials (Table 3) have provided compelling evidence of the remarkable effectiveness of LA CAB as PrEP compared to daily oral regimens. The current dosing schedule for LA CAB requires two initial injections (600 mg) given 4 weeks apart for the first 8 consecutive weeks, followed by maintenance doses (600 mg) given every 8 weeks (Q8W) thereafter. Before starting LA CAB, a CAB OLI may be given for one month to evaluate tolerability.

In HPTN-083, which focused on cis and transgender men who have sex with men, LA CAB demonstrated remarkable effectiveness, resulting in a 66% risk reduction compared with the TDF/FTC group [67,68]. Similarly, HPTN-084 evaluated the efficacy of LA CAB in HIV-uninfected women and reported an impressive 89% risk reduction for the LA CAB group compared to the TDF/FTC group. These findings highlight the potential of LA CAB as a highly effective preventive measure in different populations [69].

Surveys from the ÉCLAIR and HPTN-076 studies also indicated that participants prefer LA injectables over daily oral pills. Results from the ÉCLAIR trial showed that participants receiving LA CAB favored (74%), were satisfied with (75%), were willing to continue (79%), and would recommend (87%) the therapy over daily oral TDF/FTC [70]. Additionally, 88% of women in the HPTN-076 study somewhat/strongly agreed that they would “definitely use an injectable PrEP product for some time” if it were available [71].

The 2016 UN Declaration on Ending AIDS by 2030 aimed to provide PrEP to 3 million people at high risk of HIV infection by 2030. However, only 940,000 people across 83 countries received it at least once in 2020. Improvements are needed to address training, supply chains, monitoring, evaluation, and cost [72]. With recent US FDA and WHO guidance on LA CAB for PrEP and a licensing agreement between ViiV Healthcare and the Medicines Patent Pool, more people may gain access to LA CAB in the next few years.

2.3.2. DPV vaginal ring

DPV vaginal ring (DPV VR) contains 25 mg of DPV dispersed in a platinum-catalyzed silicone ring. The PK profile evaluation of the ring showed a rapid increase of DPV concentrations in plasma, vaginal fluid, and cervical tissue within 4 h post-insertion, which then sustained therapeutic drug levels approximately 3000 times the reported in-vitro IC_{99} values in vaginal fluids and between 14 and 1000 times the reported in-vitro IC_{99} values in cervical tissue for a month. Even though concentrations of vaginal fluid were reduced during menstruation, DPV level remained 100 times more concentrated than the IC_{99} values obtained through the in-vitro testing [73].

Table 3
LA CAB clinical trials for HIV-1 prevention.

Clinical Trial	HPTN-083 (NCT02720094)	HPTN-084 (NCT03164564)
Aims	Comparison between LA CAB and daily oral PrEP (TDF/FTC) for HIV prevention in HIV-uninfected but at-risk cisgender men and transgender women who have sex with men.	Comparison between LA CAB and daily oral PrEP (TDF/FTC) for HIV prevention in HIV-uninfected but at-risk women.
Participants	Participants: 4566 participants with median age 26 (22–32). 3992 MSM, 570 transgender women who had sex with men, 4 preferred not to answer.	Participants: 3224, aged between 22 and 30. 54.7% reported having two or more partners in past month.
Study design	Participants were randomized into 2 groups. Gr-1: initial LA CAB injection (600 mg) + placebo FTC/TDF, 2nd injection after 4 weeks, and injections every 8 weeks thereafter for up to 185 weeks (Q8W) Gr2: TDF, 300 mg + FTC, 200 mg. During the OLI phase, all participants in Gr-1 received two oral tablets: CAB 30 mg + placebo TDF/FTC, and Gr-2 received TDF/FTC (300 mg/200 mg) + placebo CAB for 5 weeks.	Same as HPTN-083.
Virological efficacy and adverse events	There were 13 and 39 incidents of HIV infection in LA CAB and TDF/FTC groups, respectively. 81.4% and 31.3% of the participants in the LA CAB and TDF/FTC groups, respectively, reported ISRs. Serious AEs events were similar in both groups.	There were 4 infections reported in LA CAB group and 36 infections were reported in the TDF-FTC group. Both groups had similar rates of AEs reports. ISRs were more frequent among AEs but did not result in injection discontinuation.
Comments	LA CAB was better than daily oral PrEP in preventing HIV among MSM and transgender women.	LA CAB was better than daily oral PrEP in preventing HIV among women.
Ref	[67]	[69]

HPTN- HIV Prevention Trial Network. LA CAB- long acting cabotegravir, Tenofovir disoproxil fumarate; FTC- Emtricitabine; MSM- Man who have sex with men.

The DPV-VR has been shown to be safe, well tolerated, and acceptable in sexually active adolescents (age range 18–35) [74,75] and postmenopausal women (age range 45–65) [76]. Two pivotal studies, RING and ASPIRE, conducted in several sites in sub-Saharan Africa have shown promising results in preventing HIV-1 infection. The Ring study, a phase 3 clinical trial, showed a 31% lower rate of HIV-1 infection in the DPV-VR group than in the placebo group, with no difference in efficacy among age groups (Table 4) [77]. ASPIRE study, another phase 3 trial of the monthly DPV VR, also showed similar results. In this study, there were 27% lower incidents of HIV infection in the DPV-VR group as compared to the placebo (Table 4) [64].

Both DREAM and HOPE trials, the extension of RING and ASPIRE trials, respectively, have expanded the positive safety and efficacy profiles observed in the original trials. HIV-1 incidence rates were 1.8 and 2·7 per 100 person-years in DREAM and HOPE clinical trials, respectively. Both studies revealed no new safety concerns [78,79]. However, the results from both trials showed that ring usage had increased among participants and was associated with an increased protection rate. Research focusing on PK, bioavailability, adherence, combined DPV/levonorgestrel rings, and combination therapy with oral FTC/TDF for adolescent, pregnant, and breastfeeding females are still ongoing.

3. ULA ARVs in development

The recent approval of LA ARVs has widened the spectrum of alternative ARTs available for the end users. Despite this progress, there are still obstacles and limitations that inhibit their widespread acceptance and utilization. These challenges span both user compliance difficulties and pharmacological restrictions. LA CAB and RPV necessitate a gluteal muscle injection administered by a healthcare professional (HCP) monthly or bimonthly. Globally, HIV-related stigma remains a significant concern across diverse cultures and communities. Regular clinic visits for Cabenuva injection may unintentionally reinforce this stigma associated with HIV-1. Additional societal pressure due to HIV-related stigma could adversely impact patients' mental health, potentially influencing their overall health outcomes. On the other hand, SC injection of LA LEN offers a less frequent clinic visit schedule with a six-month dosing regimen. However, it doesn't constitute a complete LA ART regimen, and necessitates the concurrent intake of daily oral pills. These limitations compromise its appeal to patients and physicians. DPV VR, while offering the advantage of self-administration, has sub-optimal efficacy of 31% and is no longer under consideration for the US FDA approval. The DPV VR is only approved in five African countries and is a women-oriented monthly product. The use of DPV VR is linked with metrorrhagia or intermenstrual bleeding (experienced by 18.6% of DPV VR users). It carries risks of gynecological chlamydia infection, urinary tract infection, and vaginal candidiasis (affecting over 10% of DPV VR users) [80]. Moreover, patient discomfort is associated with all LA injections, as these injections require a volume exceeding 3 ml. A significant percentage of clinical trial participants who received these LA injections reported experiencing injection pain and temporary local site reactions. After the SC injections of LA LEN, nodules remained for extended periods, reflecting its depot properties [66]. Compared to other PrEP agents, LEN exhibits significant drug-drug interactions with concomitant agents that are frequently used by the target PrEP populations. Furthermore, the logistics involved in storing and transporting frequently administered formulations can be complex, particularly in low-resource settings. This is an important consideration, given the global nature of the HIV pandemic.

The pharmacological limitations of the approved LA ARVs include the high person-to-person PK variability, lengthy terminal phase PK tail, requirement of OLI during treatment initiation for some agents, and non-removability of the dosage forms in case of adverse events. Owing to the dissolution-controlled depot-eluting nature of the IM or SC injectable LA formulations, drugs can persist in the body at a subtherapeutic concentration for a long time after the treatment discontinuation. This prolonged subtherapeutic plasma drug level is referred to as PK tail and may be prone to the selection of drug resistance mutations.

A prolonged PK tail can provide forgiveness and extended protection in case of missed or delayed doses if the target exposures are sustained. However, the length of extended protection needs further investigation as the PK tail length and drug concentration during this tailing phase are highly variable in terms of sex and body mass index (BMI). From tail phase safety, PK, and tolerability data of HPTN-077 trial, it has been estimated that LA CAB can remain detectable after the last injected dose for at least 3 years in men and 4 years in women [81]. PK tail is also longer in patients with higher BMI, irrespective of sex [82]. The observed PK variability of LA CAB underscores the need for understanding such differences in special populations. These populations include pregnant or childbearing women. Specifically, despite the discontinuation of LA CAB in the pre-pregnancy period, neonates can be exposed to LA CAB. Therefore, neonatal health outcomes after exposure to suboptimal CAB levels need to be thoroughly investigated.

Centers for Disease Control and Prevention (CDC) recommends people at risk of HIV infection to continue oral CAB or PrEP medication for at least 1 year after LA CAB [83]. However, transitioning LA medicines to oral PrEP will be challenging for some patients as individuals who prefer LA medicines generally show less inclination towards the

Table 4
DPV VR clinical trials for HIV-1 prevention.

Clinical Trial	RING	DREAM (extension of RING trial)	ASPIRE	HOPE (extension of ASPIRE Trial)
Aims	Safety and efficacy of DPV VR as HIV-1 PrEP among sexually active women in south Africa and Uganda.	Extension of RING study to evaluate safety, efficacy, and adherence of DPV VR in those using open-label DPV VR.	Safety and efficacy of DPV VR as HIV-1 PrEP in women in Malawi, South Africa, Uganda, and Zimbabwe.	Extension of ASPIRE study to evaluate safety, efficacy, and adherence of open-label DPV VR in high HIV-1 infection settings
Participants	1959 sexually active women (18—45 years old) from seven centers in South Africa and Uganda.	Former participants from Ring study, who were HIV-1 negative and had not withdrawn from the study due to any AEs.	2629 sexually active HIV-1 seronegative women (18 – 45 old) at 15 research sites.	1456 (median age 31 years) who were former participants of ASPIRE study and were HIV-1 negative.
Study design	Participants were randomly assigned in a 2:1 ratio to receive either DPV VR or placebo VR every month for up to 24 weeks.	All participants were given DPV VR for 12-months. The returned used VRs were tested for residual DPV to determine adherence.	Women were randomly assigned in a 1:1 ratio to receive either DPV VR or placebo VR.	All participants were given access to 12-months of DPV VR. They decided to accept or decline the VR at every visit. The returned used VRs were examined for residual DPV.
Virological efficacy and adverse events	77 and 56 participants using DPV VRs and placebo, respectively, experienced HIV-1 seroconversion (4.1 and 6.1 seroconversions per 100 person-years, respectively). DPV VRs effectiveness did not significantly vary between different subgroups.	No serious treatment-related AEs were observed. Consistently lower averages of residual DPV were observed in returned VRs. HIV-1 infections were confirmed in 1.9% of participants, corresponding to a 62% lower incidence rate than the simulated placebo rate.	168 HIV-1 infections occurred: 71 in the DPV VR group and 97 in the placebo group. Notably, women aged over 21 showed higher protection rates, while those aged 21 or under didn't, correlating with lower adherence.	Over 92% of women in the study opted to use the DPV VRs, with over 73% choosing to use them consistently at all visits. Most of the returned VRs indicated some use in the past month. The incidences of HIV-1 were lower than expected compared to a similar demographic from the placebo group of a previous trial. No severe AEs related to the DVR were observed.
Comments	DPV VR showed no safety issues and demonstrated a lower HIV-1 infection rate compared to the placebo among women in sub-Saharan Africa	DPV VR efficacy improved with better adherence, which was observed when women were aware of the established safety and efficacy of the device	DPV VR decreased HIV-1 infection risk, showing heightened effectiveness in subgroups demonstrating better adherence.	High uptake and persistent use of DPV VRs in this open-label extension study support the DPV VR as an HIV-1 prevention option for women.
Ref	[77]	[78,79]	[64].	[78,79]

DPV VR: dapivirine vaginal rings; AEs: adverse event; VRs: vaginal ring.

daily oral ARTs [84]. The non-removability of the injectable LA ARVs in case of adverse events also underscores the importance of robust initial patient screening and ongoing monitoring during treatment.

Various potential drug delivery technologies, including implants, micro- and nanoparticles, transdermal patches, VRs, and bNAbs, offer unique opportunities to optimize LA ART and better meet the demands of end users. ARV implants provide improved control over drug release and hold promise for ULA ARTs. Biodegradable or non-biodegradable implants containing potent ARVs like ISL, TAF, and CAB, with varying design and drug-release mechanisms, are in clinical and advanced preclinical development. Surveys on end-user preferences have shown positive attitudes towards implants due to their ability to provide highly effective systemic protection with reduced clinical visits, particularly benefiting individuals facing extreme adherence challenges [85,86]. Biodegradable implants eliminate the need for surgical removal, simplifying clinical translation and resource considerations, while non-biodegradable implants may require surgical removal. Complementing implants, efforts are underway to develop ULA ARV injectable nanoformulations, such as polymeric and lipid formulations, as well as prodrug nanocrystal formulations. These innovative nanoformulations also enable the targeted delivery of ARVs to viral reservoirs [87,88].

Inspired by the successful application of VRs that deliver exogenous hormones for contraception and estrogen therapy, these technologies are being harnessed and adapted in the development of ULA ARTs. Approval of DPV VR has already demonstrated VRs utility in HIV-1 prevention. Several other potent ARVs, including TAF, CAB, and TDF, can be delivered through VRs. These rings provide a discreet and convenient option for sustained drug release. Microarray patches (MAPs), a minimally invasive technology, have emerged as promising alternatives. These patches consist of microscopic projections that penetrate the skin or mucosal tissues, allowing for painless self-application and quick removal, enabling ULA drug delivery without needing prolonged wearing periods.

Nanoformulations, implants, MAPs, VRs, and other innovative approaches hold great potential in providing optimized and effective ULA drug delivery options for HIV infection management. However, before clinical testing, further investigation is required into various factors, including manufacturing scalability and reproducibility, the influence of individuals' biological variabilities, and integration of the end-user perspectives for better acceptability. These considerations will contribute to the development of robust and patient-centric ULA ARTs. Additionally, providing multiple ULA ART options may enhance the broader acceptance of these medicines as each approach has its own attributes that can address the various needs and challenges of distinct patients. We have summarized the recent advances of ULA ARV technologies, highlighting the key formulation parameters and developmental challenges. Due to the distinct advantages offered by nanoformulation and implant technologies in ULA ARVs, special attention is placed on providing detailed descriptions of these approaches.

3.1. *ARV nanoformulations*

Nanoformulation as an ARV drug delivery platform offers numerous advantages, including ease of production, higher drug loading, improved product stability, increased bioavailability, and the ability to target specific cells and tissues. Various types of nanoformulations, such as nanocrystals, prodrugs nanoformulations, solid drug nanoparticles (SDNs), lipid nanoparticles (LNPs), and polymeric nanoparticles, have been developed to extend the apparent half-life of existing ARVs. ARVs with low aqueous solubility, high partition coefficient (log P), high potency, and low pKa are suitable for LA nanoformulations preparation [89,90]. Nonetheless, ARVs that are not inherently suitable for LA nanoformulation can be modified through prodrug strategies. The unique scope of ARV prodrug nanoformulations is discussed in a separate section.

When administered via SC or IM injection, nanoformulations form a drug depot at the injection site, leading to sustained drug release. The drug release from the depot is influenced by the size and shape of the nanoparticles, the route of administration, and the physicochemical properties of the ARVs [91]. For example, RPV nanosuspension with a

particle size of 200 nm demonstrated higher drug loading and sustained plasma concentration compared to formulations with larger particle sizes of 400 nm and 800 nm [92]. Furthermore, IM injections exhibit faster drug release and absorption rates than SC injections. Additionally, nanoparticles can be sequestered from the depot into lymphocytes or macrophages, forming a secondary depot. Numerous investigations into ARV prodrug nanocrystals, SDNs, polymeric nanoparticles, and LNPs have shown promise in the development of LA ARTs. For instance, Owen et al. developed a LA maraviroc SDNs, which prolonged maraviroc's plasma duration threefold compared to a maraviroc-free solution [93].

LNPs are particularly suitable for ARV delivery due to their balanced lipophilic/hydrophilic nature [94–96]. In addition, specific targeting strategies can be employed to deliver ARVs to latent HIV reservoirs, including the spleen, gut mucosa, and lymph nodes. However, optimizing the performance of LNPs for ARV delivery necessitates meticulous fine-tuning of various parameters, such as lipid composition, size, surface charge, and coating. Prolonging the circulatory residence time of nanocarriers is critical for ensuring sufficient distribution to target tissues. To prolong the circulation time, certain strategies can be applied, such as adjusting size, avoiding positive charge, and using hydrophilic polymers as surface coatings to prevent serum protein opsonization. Rodney J. Y. Ho and his team have conducted a comprehensive investigation into the use of LNPs for targeted delivery of combination ARVs [87,88,97–100]. They have reported a novel LNP-based technology, named TLC-ART101, which allows for a lymphocyte-directed sustained release of combination ARVs. Following SC injections, these anti-HIV LNPs achieved successful delivery of the encapsulated ARVs to lymph nodes, resulting in sustained drug concentrations in both the plasma and lymph nodes for at least one week. Furthermore, LNPs can be strategically developed for vaginal administration to enhance the uptake of ARVs by virus-infected cells. For instance, TFV-loaded LNPs functionalized with a combination of peptides to enhance intracellular drug uptake for vaginal administration [101].

Polymeric nanocarriers have also gained attention for simultaneous ARV sustained delivery [102–107]. The efficacy of poly(lactic-co-glycolic acid) (PLGA)-based nanocarrier formulations for simultaneous delivery of two or three ARVs (elvitegravir, EVG/TAF/FTC, FTC/TAF, TAF/EVG, BIC/TAF) were demonstrated [105,108]. These nanoformulations improved the studied drugs' half-lives and increased the drug concentrations in the vaginal and rectal tissues [107,109]. Despite the attractiveness of nanoparticles for LA ARVs development, there are certain product and translational challenges that have hindered their broader application in the field. These challenges include the control of drug burst release, limited PLGA based nanoparticle sterilization options, finding alternative solvents to mitigate the toxicity concerns associated with organic solvents, long-term stability of the biodegradable PLGA polymers, and lower drug loading. Addressing these challenges is crucial for the successful translation and implementation of nanoparticle-based drug delivery strategies.

3.1.1. *ARV prodrug nanoformulations*

Prodrugs are not themselves pharmacologically active but are reversible modifications designed to improve upon the physicochemical and PK properties of the parent active molecule. An example where the prodrug approach has successfully been used to overcome the limitations of an existing ARV is TDF and TAF, two prodrugs of TFV. TFV was first converted to TDF to improve upon oral absorption and bioavailability of the highly ionizable parent molecule. However, the rapid conversion of TDF to TFV in the plasma was associated with a higher risk of renal and bone toxicities [110]. To limit plasma TFV levels and improve upon intracellular drug delivery, TFV was converted into a more stable phosphoramidite prodrug, TAF [111]. Our laboratory has employed LASER ART technology to further improve the physiochemical properties of TFV, making it suitable for ULA ARVs development. Long-acting slow effective release ART (LASER ART) is a state-of-the-art technology developed by our laboratory. LASER ART utilizes nanoparticle and prodrug technologies to transform both water-soluble and insoluble ARVs into ULA formulations. The prodrug synthesis process in LASER ART technology is novel and scalable. The prodrug nanocrystals are produced in aqueous buffers and stabilized by surfactants that are widely used in other US FDA-approved parenteral products. Top-down micro fluidization and milling processes are utilized to formulate the aqueous nanosuspensions with a target particle size range of 300–400 nm.

LASER ART generated a lipophilic TFV ProTide, M1TFV, which sustained the levels of TFV active metabolite, TFV-diphosphate (TFV-DP) $\geq$ four times the 90% effective dose over two months in PBMCs and other key HIV and HBV target tissues and cells after a single IM injection of M1TFV nanoformulation in rats [112]. M1TFV nanoformulation exhibited sustained antiviral activities for at least three months in both HBV-infected transgenic and human hepatocyte transplanted TK-NOG mice, while an equivalent dose of a TAF control formulation (NTAF) had limited effect on suppression of HBV DNA replication [113].

Subsequent improvements in generating LA FTC formulations also included the synthesis of a carboxylate ester prodrug of FTC (MFTC) [114]. A single IM injection of the nanoformulated MFTC (NMFTC) into rats provided a modest improvement in the PK profile of the drug, producing FTC triphosphate levels in PBMCs that were eight-fold higher than those recorded for the unmodified FTC-treated animals at day 7. A similar trend was observed for myristoylated ester prodrugs of 3TC and ABC [115,116]. Given the limited PK profile of the FTC ester prodrugs, our laboratory then developed novel potent LA ProTides. Notably, such modifications for ABC (M3ABC), 3TC (M23TC), and FTC (M2FTC) enabled enhanced and sustained intracellular delivery of the active triphosphate metabolites with improved potency and long-term efficacy [117].

Notable improvements in PK properties of INSTIs were made through LASER ART approach. Esterification of the phenolic alcohols in INSTIs with fatty acids drastically enhanced their lipophilicity and hydrophobicity, enabling the creation of ULA nanoformulation. Since the derivatizing fatty acids are endogenous and commonly used in nutritional and pharmaceutical products, the safety profile of the cleavage byproducts from LASER ART prodrugs is well established. The first-generation CAB and DTG LASER ART prodrugs, designed as MCAB and MDTG, respectively, were esterified using a 14-carbon chain fatty acid, myristic acid [118,119]. PK studies of nanoformulated MCAB and MDTG in Balb/cJ mice demonstrated that plasma CAB and DTG levels were higher than 4x PA-IC_{90} for at least two months and one month, respectively.

The second-generation LASER ART INSTIs prodrugs were identified through screening of different modifications. It was unexpected and surprising to find that modification of INSTIs with 18 carbon chain fatty ester produced crystalline prodrugs that significantly extended the drug's apparent half-life, providing sustained therapeutic drug levels for at least six months [7,120]. A single IM injection of NM2CAB at 45 mg. CAB eq. dose per kg in NSG mice demonstrated plasma CAB levels higher than PA-IC_{90} at day 364. The PK properties for NM2CAB were also observed in rhesus macaques, affirming the ability of NM2CAB to extend the half-life of CAB. Similarly, a single IM injection of NM2DTG at a dose of 45 mg. DTG eq. per kg in Sprague Dawley rats produced sustained plasma DTG levels that remained above the PA-IC_{90} for at least 10 months. Improvements in PK profile of DTG for NM2DTG were also observed in rhesus macaques.

The prolonged half-life of LASER ART prodrug formulations is the cumulative effect of several unique attributes of LASER ART nanocrystals (Fig. 3). These attributes include but are not limited to i) prodrug physicochemical properties and stabilizing effect of surfactants, ii) controlled dissolution and absorption of the aqueous nanoparticles from the depot formed at the injection site, iii) uptake of the lipophilic prodrugs into the lymphatic tissues and their slow hydrolysis. PK testing, featuring diverse carbon chain fatty acid modifications, established a correlation between compound physicochemical properties and drug

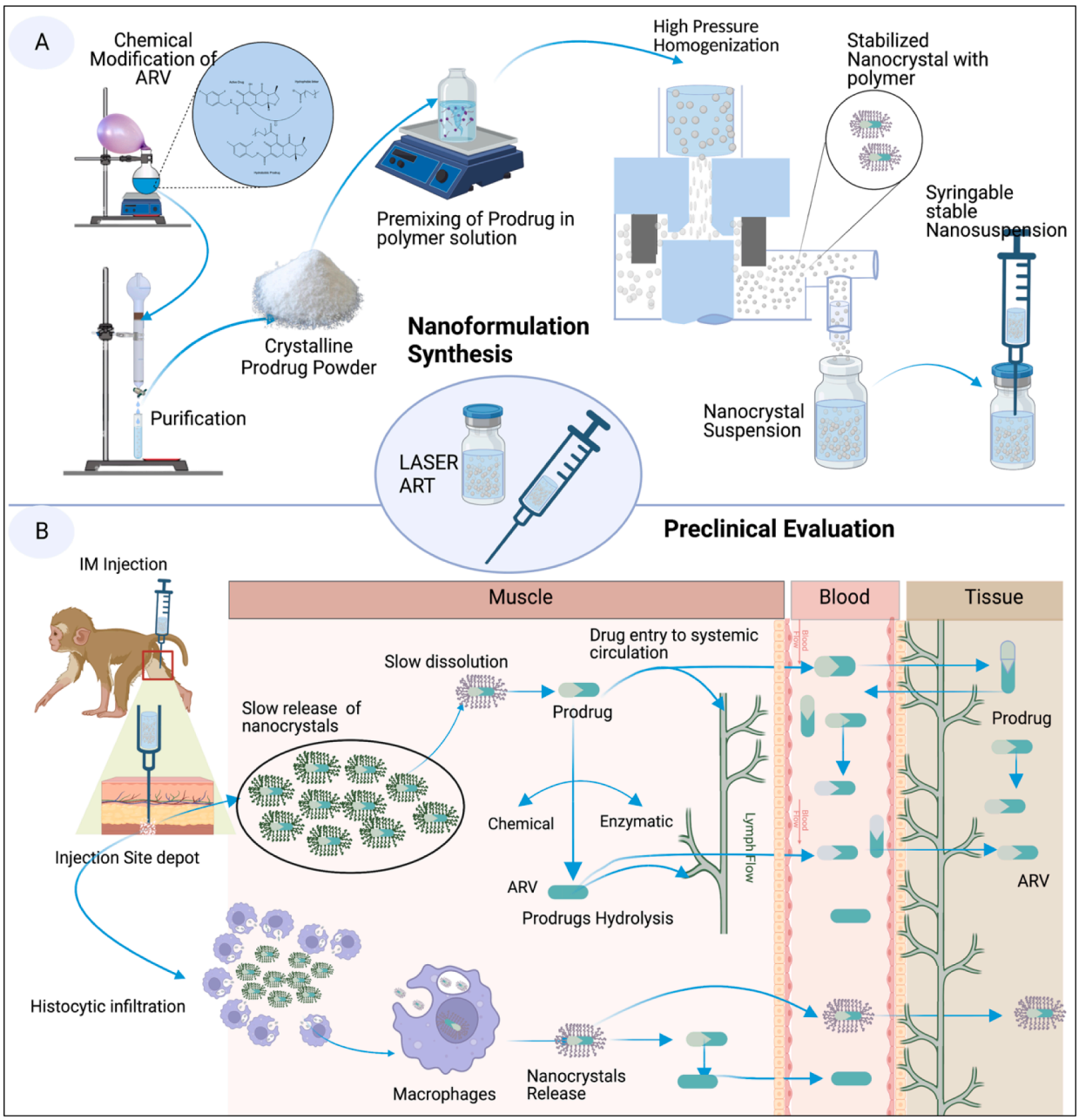


Fig. 3. Nanocrystal suspensions in development. A. Nanocrystals suspension formulation: ARV converted to hydrophobic prodrug by chemical modification. Then, high-pressure homogenization is used to formulate the polymer stabilized aqueous nanosuspension of prodrug. **B** Preclinical evaluation of formulated nanocrystals suspension following intramuscular (IM) injection. Nanosuspension formed a drug depot at muscle injection site, followed by slow release and dissolution of prodrug nanocrystals. The nanocrystal is hydrolyzed to the active drug and get biodistributed to the lymphoid and solid tissue. A histiocytic infiltration to the injection site was observed, causing the phagocytosis of the nanocrystals. Nanocrystals' low pH stability at macrophagic endosomes causes a cellular depot formation and causes slow release and dissolution of the nanocrystals over time.

release/clearance profiles. The least hydrophobic native CAB and DTG showed higher clearance rates than the first-generation INSTI LASER ART prodrugs (MCAB and MDTG). These prodrug modifications extended the half-life of CAB and DTG by 6.5 and 5.5-fold, respectively [119,120].

Further extension in the hydrocarbon chain length of the fatty acid from 14 to 18 increased the plasma half-life of CAB and DTG by 21- and 23-fold. However, extending the carbon chain length beyond 18 does not significantly improve the plasma half-life of DTG. PK testing of M3DTG, a DTG prodrug linked to a 22-carbon chain fatty acid, demonstrated plasma DTG levels above the PA-IC_{90} for only one week and inferior to what was recorded for the unmodified native DTG formulation. These unexpected findings demonstrate that subtle changes in prodrug linkages can remarkably influence the PK profile of prodrug nanocrystals. Systemic concentrations of the prodrugs after IM injection of NM2CAB or NM2DTG into rats, mice, and rhesus macaques were found to be much lower than the corresponding CAB or DTG (hydrolyzed active drugs) concentrations suggesting rapid nanoparticle dissolution and ester hydrolysis in blood and plasma. However, high prodrug concentrations were observed at the injection site, lymph nodes, and tissues, strongly suggesting that the nanocrystals accumulate as solid prodrug nanocrystals at these sites to serve as drug depots. A representative summary of ART prodrugs reported by our laboratory is listed in Fig. 4. Comprehensive studies on these prodrugs provided a strong

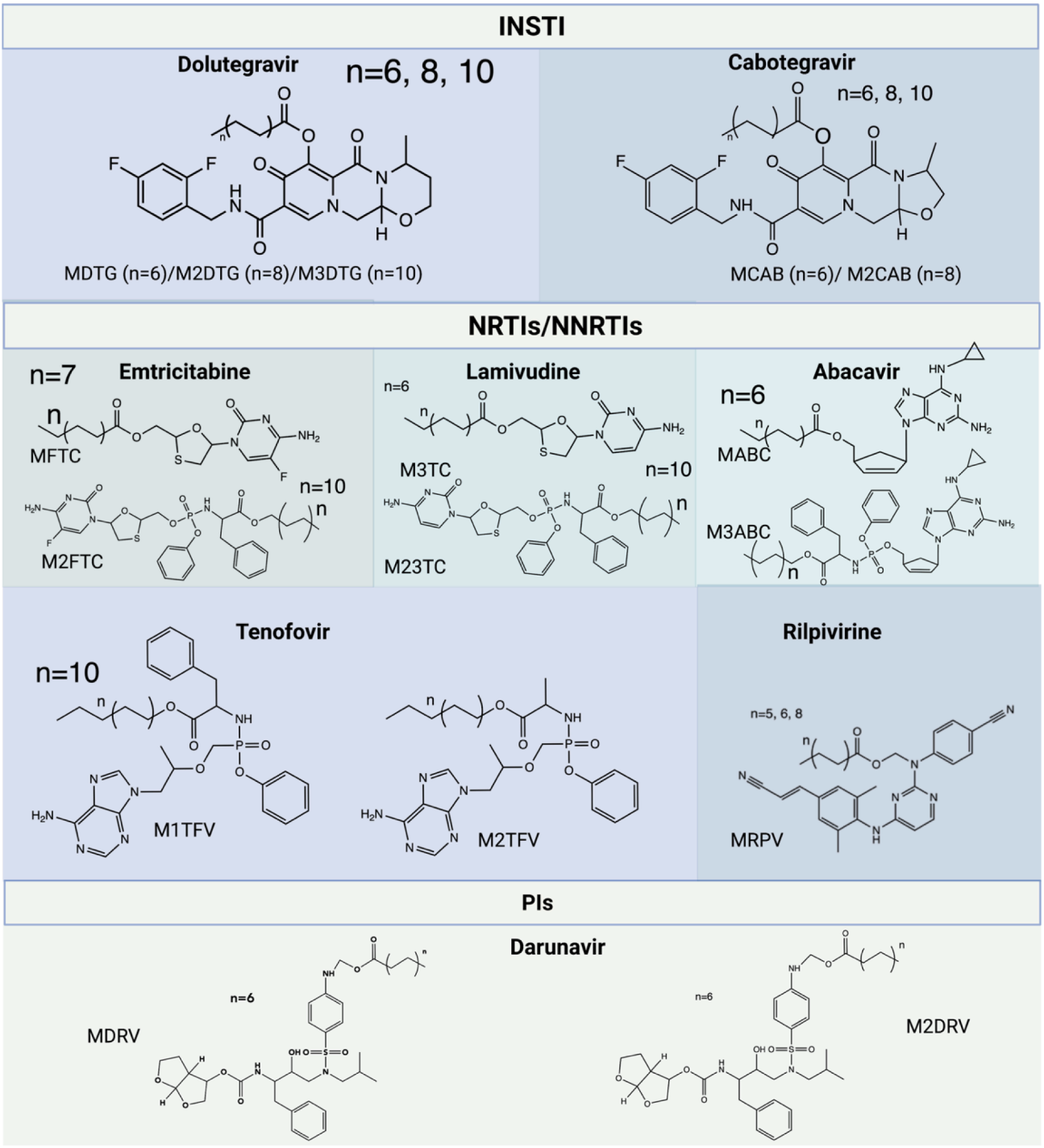


Fig. 4. Chemical structures of common LASER ART prodrugs: INSTI - integrase strand transfer inhibitor, NRTI - nucleoside reverse transcriptase inhibitor, NNRTI - non-nucleoside reverse transcriptase inhibitor, PI- protease inhibitor.

understanding of the complex interaction between drug nanocrystals and in vivo environments. Investigational new drug (IND)-enabling studies to support clinical development of the most promising ULA INSTI prodrug candidates are in progress.

Several other laboratories have also begun to explore prodrug strategies for ULA ARVs. PLGA microparticles encapsulating DTG palmitate prodrug were reported, where plasma DTG concentration was sustained $>$ 4x PA-IC_{90} for at least 60 days. The experiments were performed in albino New Zealand white rabbits, and data was recorded after a single subcutaneous injection [121]. Other studies modified FTC's chemical structure to make it compatible with LA formulation approaches [24,114,122]. *Hobson et al.* developed eight FTC prodrugs by modifying FTC at both the 5′-hydroxyl and amino groups with alkyl chloroformates to form carbamate and carbonate prodrugs that were evaluated for in vitro drug release [122]. Inspired by the data generated from the carbamate/carbonate FTC prodrugs, the same group synthesized polymeric versions of these prodrugs to make them amenable to biodegradable implant production [123]. The implant rods demonstrated sustained in vitro drug release. Evaluating these prodrugs in vivo could potentially identify alternative approaches for a LA FTC.

3.2. Implants

Implants can offer several advantages over other LA modalities, including the opportunities to remove the implant in events of adverse events or therapy discontinuation and the ease of combining multiple drugs in the same implant. However, limitations of implants also exist, such as the requirement for implant removal after the end of the product lifespan. Also, implant insertion is a sterile and careful procedure that requires the intervention of healthcare professionals and frequent clinic visits. Insertion of implants often involves patients' discomfort and implant site adverse events [124].

Drug selection criteria for implant formulation include high potency, molecular weight $\leq$ 500 Da, melting point $\leq$ 250 °C, and moderate aqueous solubility [125,126]. The restriction on the maximum drug that can be loaded into an implant makes less potent drugs unsuitable for implant development. Owing to the high potency of hormones, implant technology is widely used in contraception delivery, such as low dosages of progestin for an extended duration of contraception. Several well-tolerated contraceptive implants have a usage duration of 3——5 years [127]. The acceptability of these implants is very high among women, and in some developing countries, the percentage of contraceptive implant usage is more than 50% among all contraceptive methods [125].

Highly potent and low aqueous soluble ARVs, such as TAF, CAB, DTG, and ISL, have been explored for implant formulation. Implants may be designed as in situ forming implants (ISFIs) or solid implants. ARVs are usually formulated into two types of solid implants: matrix and reservoir. In matrix-type implants, the drug is dispersed in a biodegradable polymer, and polymer biodegradation controls the dissolution and release of the active drug. In reservoir-type implants, the active drug reservoir is encapsulated or inserted in a drug-eluting core polymer. In ISFIs, drugs are first formulated in solution or suspension, which forms a solid or semi-solid depot following SC or subdermal administration [128]. ISFIs offer a distinct advantage, as there's no need for future removal of the implant. However, if an adverse drug event occurs and the implant needs to be removed, this becomes increasingly difficult, potentially to the point of impossibility, as the implant disperses over the subsequent months post-injection.

3.2.1. Islatravir implants

Islatravir (ISL) is a novel investigational potent reverse transcriptase-translocation inhibitor, with a unique structure and mechanism of action. It has been previously investigated as an implant and LA oral tablet for the treatment and prevention of HIV-1 infection. ISL's active metabolite, ISL triphosphate (ISL-TP), exhibits an extended intracellular half-life in human cells, enabling it to demonstrate sustained antiretroviral efficacy following a single dose.

ISL possesses several unique structural features, including a 3′–OH group that makes it more like natural substrates than other NRTIs. It also features a 4′-ethynyl group (4′-E) on the pseudo-sugar ring and a 2-fluoro (2-F) on the adenine base ring. ISL-TP exhibits exceptional stability due to the fluorinated adenosine ring being resistant to adenosine deaminase. The intracellular half-life of ISL-TP in humans after oral dosing is between 130 and 210 h, whereas the half-life of the parent drug, ISL, in plasma is between 50 and 60 h in humans [129]. The potency of ISL is also increased by the presence of the 4′-ethynyl group (4′-E), which creates a strong hydrophobic interaction at a conserved hydrophobic pocket in the polymerase active site [51].

ISL has been explored for both LA oral and subdermal implant administration. A single dose of ISL, ranging from 0.5 to 30 mg, has been reported to be safe and well-tolerated. Notably, a 10 mg single oral dose of ISL decreased plasma viral load by 1.67 $\log_{10}$ copies/ml within a week [130]. Subdermal ISL solid implants, showed promising outcomes in clinical and preclinical models [131–133]. *Barrett et al.* have reported an ISL implant composed of a poly (lactic acid) (PLA) and poly (ethylene vinyl acetate) (EVA), demonstrating the potential for every six-month dosage regimen [131]. Results from a phase 1 clinical trial evaluating the PK and tolerability of a prototype subdermal ISL implant for an extended dosage regimen showed promise in clinical settings [134].

However, many trials (MK-8591–016, MK-8591–022, MK-8591–024, MK-8591–034, MK-8591–035, MK-8591–043) were halted in December 2021 due to concerns associated with CD4 + T-cells and total lymphocyte counts reduction in participants receiving ISL [135]. Its originator company, Merck, announced in September 2022 that a phase 2 study to evaluate an oral combination of ISL and LEN for potential weekly dosing was to resume, albeit with a reduced dose of ISL [136]. However, monthly PrEP study with ISL implants was not resumed as of the writing of this article.

3.2.2. Tenofovir alafenamide fumarate implants

TAF is an ideal candidate for LA delivery due to its high potency and lower daily dose requirements. Its active metabolite, TFV-DP, has an exceptionally long intracellular half-life of 60–100 h and high potency [137]. It is estimated that a yearlong TAF implant would need to release only 51 mg of TAF, which is equivalent to a daily dosage of 0.14 mg over 365 days, to achieve a therapeutic level of TFV-DP. This estimation was based on scaling the PK data of TFV-DP from dogs to humans and targeting a TFV-DP concentration in PBMCs equal to its reported EC_{90} [132]. Moreover, TAF's potency is ten times greater than the other TFV analog, TDF [138]. It is also effective against Hepatitis B Virus (HBV), which could aid in preventing HIV-HBV co-infection [139]. Given these characteristics, TAF stands out as an appealing candidate for creating ULA drug delivery systems.

Multiple strategies are being explored to develop TAF implants. These include implants made of biodegradable polycaprolactone (PCL), titanium osmotic mini-pumps, non-degradable nanofluidic implants that can be refilled transcutaneously, and silicone reservoir implants [140–142]. A silicone tube-based TAF implant, which can dispense TAF at a broad range of release rates for preclinical in vivo evaluation was developed [132]. The implant was a cylindrical silicone tube specifically designed with one or more delivery channels, each less than 1 mm in diameter. It contained a reservoir housing TAF freebase in the form of either compacted pellets or micro tablets. To better control in vivo drug delivery kinetics, a controlled-release polymer, such as heat-treated poly (vinyl alcohol) (PVA), coated the implant's exterior. The drug release profile from implants can be modified by adjusting the surface area, the number of channels, and the features of the outer coating of the implants. The PK properties of this prototype implant had been tested across various animal species, including dogs, mice, and sheep. A dose escalation study in dogs demonstrated no safety issues for doses under 1.0 mg/day TAF. Nevertheless, safety concerns were noted at higher doses, highlighting the necessity for careful dosage selection [143]. Interestingly, these implants exhibited high concentrations of TFV and its active metabolite, TFV-DP, in the skin tissues surrounding the implant without substantial local tolerability issues. To address the safety and PK concerns associated with these TAF free-base implants, the researcher is conducting an ongoing human clinical trial known as CAPRISA-018. This trial aims to further investigate the safety and PK of the implants in humans.

Another innovative approach of LA TAF delivery platform is the non-degradable transcutaneously refillable nanofluidic implant [144,145]. This technology uses silicon nanochannel membranes to regulate the release of TAF through diffusion. The drug delivery is facilitated by slit nanochannels that are densely stacked within a titanium reservoir implant. To ensure long-term bio-inertness and biocompatibility, the nanochannels are coated with silicon carbide. This type of implant can be used to deliver both solid and liquid formulations of drugs, irrespective of their physiochemical properties [146]. In non-human primates (NHPs), these implants demonstrated sustained levels of TFV-DP in PBMC that exceeded the anticipated protective threshold against HIV infection. The animals were subjected to rectal challenges with the simian-human immunodeficiency virus (SHIV) to assess the efficacy of

the implant. Following 10 weekly rectal exposures, two animals in the PrEP group remained uninfected. The control group had a 3.04 times higher likelihood of infection following the fourth rectal challenge dose [147].

Non-biodegradable polyurethane (PU) tube-based reservoir implants have also been employed for ULA TAF development. The construction of these implants involves the encapsulation of TAF formulation pellets within PU tubes. PU tubes act as mechanical capsules and rate-controlling membranes. By adjusting the implant's geometry and the composition of the PU membrane, the release rate of TAF could be precisely controlled. Several configurations of these implants were developed to deliver TAF and tested them in New Zealand white rabbits and rhesus NHP models [148]. In rabbits, granulomatous inflammation around the implanted area was observed at day 28, progressing to necrosis by 90 days. In NHPs, fibrosis, hemorrhagic abscesses, and severe granulomatosis were observed around the implanted area. Additionally, some implants were lost or disintegrated in vivo.

PCL-based reservoir-type implants have also been reported for SC TAF delivery [140,149]. The implants were prepared by fabricating a cylindrical structure through hot melt extrusion of PCL. One end of the cylinder was sealed, and then TAF formulation was loaded into the implant. The release rate of TAF from the implant can be adjusted by modifying the thickness of the implant wall, altering the oil excipient, and manipulating the physical properties of PCL. This implant was tested in different animal species, where a low plasma TFV and high intracellular TFV-DP level in PBMC were observed [140,149]. However, site lesion/dermal inflammation was observed in the species for those implants.

The titanium osmotic mini-pump implant presents an innovative approach for SC delivery of TAF. This implantable device utilizes a titanium alloy construction, with one end sealed by a water-permeable membrane and the other end equipped with a control diffusion modulator (DM) for drug expulsion. The implant incorporates an engine compartment containing sodium chloride, creating an osmotic gradient across the membrane. This gradient enables the absorption of fluid from the external environment into the osmotic engine compartment. As the volume of fluid increases within the engine compartment, it exerts pressure on a piston, propelling the formulated drug from the reservoir through an open channel in the control diffusion modulator. This unique design ensures the controlled and regulated release of the drug for effective SC delivery.

3.2.3. Cabotegravir implants

Numerous strategies involving implantable technology are currently under investigation to address the hurdles associated with IM injection of LA CAB. Current initiatives strive to develop a self-administrable, removable, and ULA formulation of CAB, potentially extending the dosage interval to six months or more.

A nanofluidic implantable device was developed that contains a 2-hydroxypropyl-β-cyclodextrin CAB formulation in the implant reservoir. It was made from either polyether ether ketone (PEEK) or 6AI4V titanium [150]. Each implant was fitted with a nanofluidic membrane that houses over 340,000 channels, each 13 nm in size, strategically arranged and connected through microchannels. The PK study of the implant in SD rats showed that the plasma CAB concentration stayed above PA-IC_{90} for at least three months. A CAB implant was manufactured using a hydrophilic PU membrane [151]. In preparing the implant, the CAB formulation was converted into cylindrical pellets and then, loaded into heat-sealed PU membrane. PK testing of the implants in rhesus macaque demonstrated a high level of plasma CAB for at least 90 days. The implants were well tolerated without signs of tissue damage.

In-situ forming implants (ISFIs) using bioerodible PLGA and N-methyl pyrrolidine (NMP) were made for sustained release delivery of CAB. An CAB ISFI showed extended protection against rectal SHIV challenge in female rhesus macaques [152]. These CAB ISFIs proved safe in female mice and macaques, exhibiting no signs of chronic inflammation or toxicity. Following implant removal from the macaques, a rapid decrease in CAB plasma levels was observed. Table 5 summarizes all the significant implants that are in clinical or advanced preclinical development.

3.3. Vaginal rings

Vaginal rings (VRs) are torus-shaped flexible devices made of elastomeric materials. They are designed to provide controlled drug exposure to the vaginal epithelium. VRs are widely used among adolescent girls and women for delivering hormone replacement therapy and contraceptives. They can be discreet and offer ease of self-insertion and removal when needed. For the greater part of development, VR delivery systems were developed for hormone replacement therapy. VRs allow localized, low-dose estrogen delivery for treating urogenital atrophy in women, while also capable of providing higher, systemic doses for estrogen replacement therapy.

VR delivery can also be utilized as a LA therapeutic modality for infectious and sexually transmitted diseases (STD). Young women and adolescent girls have the highest prevalence and incident rate of new HIV infections [154]. ARV-loaded VR can provide them with a fully women-initiated, discrete options for the prevention of HIV. It is also preferred over daily oral pills for HIV prevention. According to the REACH trial, 67% of young women and adolescent girls preferred to use the VRs over daily oral pills [155].

Generally, VRs are formulated with silicone elastomers, particularly polydimethylsiloxane (PDMS) or various thermoplastic polymers, such as poly (ethylene vinyl acetate) (EVA) and PU [156]. Generally, drugs are either dispersed in the polymers and then molded in ring shapes (matrix type VRs), or drugs containing polymer matrices are encased in an inert polymer core (reservoir type VRs) [41]. There are also pod-type VRs where polymer-coated drugs are loaded at different locations along the ring. Innovations in VRs design and advances in different elastomeric polymers also allow simultaneous delivery of partner drugs from the ring. ARVs that have been explored in VR delivery systems include DPV and TAF, owing to their suitable physiochemical properties and high potency [157,158]. Other investigational drugs that are also being developed for VR delivery include MK-2048, Vicriviroc (MK-4176), MK-2048A, MIV-150, IQP-0528 [159,160]. Table 6 outlines the vaginal rings that are either in clinical or preclinical development.

3.4. Microneedle array patches

Microneedle array patches (MAPs) could address some of the limitations associated with injectables and implants due to the minimally invasive nature of the microneedles themselves [165,166]. MAPs consist of projections or microneedles attached to a substratum that typically penetrate the stratum corneum to deliver the drug to the dermis [166,167]. The therapeutic strategies that could potentially benefit from MAPs include vaccination and ARVs.

The potential use of MAPs technology for developing LA ARVs has been reported in preclinical studies. A poly (vinyl alcohol) based soluble MAPs containing a LA nanosuspension of RPV was developed by *Mc Crudden et al.* The PK study of the developed MAPs in rats demonstrated sustained levels of RPV in plasma for 2 months [168]. Elsewhere, dissolving MAPs loaded with etravirine nanosuspension have been reported and demonstrated extended plasma drug levels in rats for a month [169]. Hydrogel-forming microarray patches (HF-MAPs) for delivery of CAB were reported in another study where the drug was complexed with hydroxypropyl-β-cyclodextrin to enhance solubility in the interstitial fluids [170]. Compared to LA CAB at one month, higher plasma CAB levels were reported for the HF-MPAs composed of poly (vinyl pyrrolidone) 58 kDa + poly (vinyl alcohol) 85–120 kDa [170]. Tekko et al. developed bilayer micronized MAPs fabricated by a two-step casting approach, fusing CAB-loaded hydrogel with drug-free hydrogel, and reported the PK outcomes from in vivo studies in rats

Table 5
ARV implants in development.

Drug	Year[a*] and Dosage Regimen[b*]	Design types and coating polymer	Implant description	PK/BD studies	Ref
TAF	Ongoing Phase I/II clinical trial (2022); 6–12 month	Reservoir, silicone with PVA-coated polymer	TAF pellet was loaded in a silicone tube. The implant length, inner diameter, and wall thickness were 40–45 mm, 2.01 ± 0.051 mm, 0.19 + 0.051/–0.25 mm, respectively. The in vitro release rate was 1.07 ± 0.02 mg/day.	Preclinical studies in beagle dogs demonstrated a substantial level of TFV-DP in PBMCs, exceeding the reported human concentration required for PrEP efficacy by at least 30 times.	[142]
	Advanced Preclinical Development (2022); 6–12 months	Reservoir, PCL	TAF in castor oil formulation was filled in PCL extruded tube. The outer diameter and length of the implant were 2.5 mm and 40 mm, respectively. The in-vitro release rate of TAF was (0.28 ± 0.06) mg/day.	Efficacy studies against vaginal SHIV infection in pigtailed macaque showed 100% protection against infection when two devices, one in each arm are implanted. The median TFV-DP concentration was 1519 fmol/10^6 cells in PBMCs.	[140]
	Preclinical Developed-discontinued (2020); 3 months	Reservoir, PU	Compressed TAF pellet was impulse sealed into PU tube to formulate the implant. The length and OD of the implant were 20 mm and 2.6 mm, respectively. The in-vitro release rate of the two types of implants was 0.39 mg/ml and 0.78 mg/ml.	PK studies in macaques showed sustained levels of TFV-DP over 90 days. The median TV-DP level from one generation of implants from 1 to 12 week was 42 fmol/10^6 cells in rhesus macaques. However, there were severe adverse reactions at the implant site.	[124]
	Preclinical Development (2021); 12 months	Refill Reservoir, Titanium within silicon nanofluidic membrane PU	Implant contained a drug reservoir, made with medical-grade titanium, which was mounted in a non-fluidic membrane. The membrane contained 199 circular microchannels and each microchannel had 1400 parallel slit-nanochannels. The in-vitro cumulative TAF release over 20 days was 81.85 ± 12.55 mg.	62.50% reduction in risk of infection per challenge was seen in PrEP efficacy studies with the implant compared to the control when rhesus macaques were challenged rectally with repeated low-dose SHIVs. The reported median TFV-DP concentration in PBMC was 9 times higher than clinically protective levels.	[147,153]
Cabotegravir	Preclinical Development (2021; 3 months)	Reservoir, PU	Hydrophilic PU membrane-based implant. Lumen length, outer diameter, and wall thickness of the implant were 47 mm, 3.6 mm, and 200 μm, respectively. In vivo release studies in rhesus macaques demonstrated a total release of 348 ± 107 μg/day of CAB.	PK in macaques with an increasing dose of CAB by increasing the number and length of implanted devices demonstrated high CAB plasma levels for at least three months. 5 implants generated an average CAB plasma concentration of 373 ng/ml. CAB plasma levels became undetectable within two weeks of implant removal.	[151]
	Preclinical Development (2021); 3 months	Titanium within silicon nanofluidic membrane Polyurethane	Silicone nanochannel membrane, containing a drug reservoir made of either PEEK or 6AI4V titanium is used to prepare the implant. CAB was formulated as βCAB. The dimension of nanochannel was 5 mm × 13 mm × 13 mm. In-vitro release rate of βCAB from implant was 7.84 ± 1.29 μg/ day.	PK study in rats demonstrated CAB plasma levels above 2x PA-IC_{90} for at least 91 days with no significant histopathological adverse reaction at the implant site.	[150]
ISL	Hold on clinical Trial (2022); 6–12 month	Reservoir, EVA	N/A	Clinical studies associated with ISL are on clinical hold because of the observed reduction in CD4 + T-cell and total lymphocyte counts in some of the clinical trial participants.	[131]

PVA- Polyvinyl Alcohol; PU – Polyurethane; EVA- Ethylene-vinyl acetate; PCL- Polycaprolactone; PEEK- polyether ether ketone; βCAB – 2-hydroxypropyl-β-cyclodextrin NHP - Nonhuman primate model; a*= Recent publication date is considered as developing year; b*= The length of PK/PD experiments is considered as the projected dosage regimen.

[171].

TAF-based MAPs were also explored for PrEP. *Puri A. et al.* described a silicone-based transdermal patch that was developed to deliver TAF for HIV-1 prevention [172]. In another study, *Jiang et al.* reported on a transdermal patch based on an adhesive-matrix TDS formulation for weekly administration of TAF [173].

MAPs are also being explored for HIV-1 vaccine development. *Pattani A. et al.* described polymeric MAPs that can deliver recombinant CN54 HIVgp140 and TLR4 agonist adjuvant monophosphoryl lipid A to induce antigen-specific immunity against HIV [174]. MAPs were also formulated to deliver a live recombinant human adenovirus type 5 vaccine vector encoding HIV-1 gag in mice. These successfully induced long-lasting antigen-specific CD8 + T cells [175]. Another MAP was constructed with solid pyramidal microneedle arrays, composed of polyacrylic acid with silk fibroin protein tips. These tips encapsulated a stabilized HIV envelope trimer immunogen, comprising BG505 SOSIP and MD3940 trimers [176].

While MAPs offer several benefits, such as the ability for self-administration, they also pose certain challenges. These include potential variability in host skin characteristics, which can influence drug absorption and PK profiles. Therefore, comprehensive PK studies should be conducted to ensure optimal MAPs provide consistent drug exposures under varying skin conditions.

3.5. Broadly neutralizing antibodies

Passive immunization with highly potent broadly neutralizing antibodies (bNAbs) has emerged as a potential therapeutic strategy for the prevention and treatment of HIV-1 infection. Following the discovery of the first HIV-1 bNAb in 1994, a significant number of highly potent bNAbs has been identified and characterized that can target seven regions of the HIV- envelop, including CD4 binding site, membrane-proximal external region, gp120-41 interface, fusion peptide, the silent-face center, V2-glycan apex, and V3-glycan [177,178]. bNAbs have a very long half-life, which enables them to persist in the bloodstream for several weeks or months after administration [179]. Ultra-long plasma half-life of these bNAbs, in addition to their good tolerability and higher safety, makes them attractive options for both treatment and prevention [180].

Prior to clinical trials, non-human primate (NHP) studies have shown that bNAbs are highly effective in preventing and treating HIV-1 infection. By administering low doses of the virus repeatedly via mucosal

Table 6
ARV VRs in development.

Drug	Year[a*] and Projected Dosage Regimen[b*]	Coating and Design	Implants	PK/BD study	Ref
TFV	Clinical Development (2018); 15 days	PU; Reservoir types	To prepare VR, a semisolid paste of TFV/glycerol/water was filled and then end-sealed in PU tubing. The outer and cross-sectional diameter of the VR was 55 mm × 5.5. The in-vitro release rate was ~ 10 mg/d.	A phase I, randomized, placebo-controlled trial (CONRAD A13-128) demonstrated safety and well acceptability of VR. The mean TFV-DP concentrations after 3 days of ring removal in vaginal tissue was > 1,000 fmol/mg tissue.	[161,162]
TDF	Clinical Developed-(2019); 1 month	HPEU, Reservoir types	Ring was prepared by filling HPEU tubing with TDF formulation containing 14% NaCl. Then, the tubing was made into a torus by induction-melt welding. The in-vitro TDF release rate was 5–7 mg/day for 1 month.	In preclinical studies, VR protected 100% of macaque from repeated low-dose challenges with SHIV and the mean vaginal fluid TFV concentration was 1.8×10^5 ng/ml. In the phase I clinical trial, two-thirds of the participants developed ulceration due to vaginal insertion of the ring which resulted in VR discontinuation.	[163,164]
Vicriviroc and MK-2048 combination	Clinical Development (2018); 1 month	EVA, Matrix types	VRs are smooth, flexible, and off-white in appearance. Drugs were dispersed in EVA matrix to prepare the VR. The outer diameter and cross-sectional diameter were 54 mm × 4 mm. It contains 182 mg and 30 mg of vicriviroc and MK-2048, respectively.	VR was reported acceptable and well-tolerated among the participants in a phase I PK and safety study. However, the vaginal fluids DPV concentration suggests the need for further dose modifications to improve therapeutic efficacy.	[160]

VR- Vaginal Rings; PU – Polyurethane; EVA- Ethylene-vinyl acetate; a* - Recent publication date is considered as developing year; b* - The length of PK/PD experiments is considered as the projected dosage regimen.

routes, NHP models can accurately replicate the natural transmission of HIV-1 infection. Additionally, chimeric simian-human immunodeficiency viruses (SHIVs) infected NHPs, and their immune response is comparable to that observed in humans [181]. In these models, passive immunization with bNAbs before exposure to chimeric SHIVs can effectively study the protective efficacy of bNAbs against various modes of SHIV infection. Several bNAbs targeting the CD4 binding site (VRC01, 3BNC117, VRC07-523.LS), the V3-glycan site (PGT121, 10-1074), the V2-glycan site (PGDM1400, CAP256-VRC26.25), and the MPER epitope (10E8) are in advanced clinical development and have shown varying degrees of protection against SHIV infection [181].

In early-phase human clinical trials, various leading bNAbs candidates, alone or as combination therapy, have demonstrated promising PK and safety profiles [182,183]. One major challenge is HIV-1 env sequence diversity, which can lead to resistance to bNAbs. Moreover, certain bNAbs exhibit clade-specific resistance patterns, complicating their use in regions where these HIV-1 subtypes are dominant [184]. To effectively target the diversity of HIV-1 ENV sequences, the use of a combination of bNAbs may be necessary. Such combinations can enhance potency and efficacy against various viral isolates [181].

For optimal therapeutic efficacy, the combination and number of bNAbs may need to be tailored based on their clinical applications. For instance, smaller combinations of bNAbs may be sufficient for preventing HIV-1 acquisition, whereas larger combinations may be required for therapeutic treatment strategies. Recent results from a phase Ib clinical trial (NCT04811040) showed the potential of every six-month dosage regimen of the combination therapy of LEN and two bNAbs (Teropavimab and Zinlirvimab) [185].

However, several other challenges must also be addressed to make bNAbs as a viable option for widespread use in HIV-1 treatment and prevention. One of the main challenges is the high production and administration cost, making them inaccessible to many individuals in resource-limited settings. Overall, bNAbs hold great promise as a novel approach to HIV-1 treatment and prevention. Continued research and development in this area will be critical to optimize their effectiveness and make them more accessible to PLWH.

4. ULA ARV translation

ULA ARVs are increasingly being considered to prevent new infections, as these agents can significantly improve the uptake and utilization of PrEP agents. However, five major concerns need to be considered while developing those ULA agents (Fig. 5).

The first recommendation is to prioritize ARVs with high resistance barriers for PrEP. The second is to evaluate potential drug-drug interactions before selecting an agent for PrEP [186]. Third, it's essential to monitor the long-term side effects of ARVs, especially in pregnant, breastfeeding, or reproductive-age women. Fourth, the total cost of treatment should be considered when prescribing ULA ART for prevention. Finally, the potential for increased sexual activity due to the high efficacy of PrEP agents should be addressed by providing proper counseling and education on risk reduction strategies [187].

5. HIV-1 elimination

In more than 40 years since the first identified case of acquired immunodeficiency syndrome (AIDS), there are only three reports of HIV cure, including the London and the Berlin patients. Berlin and London patients received a complicated, expensive, and costly intervention that included a bone marrow transplant, which is impractical for the 38 million people living with HIV. However, HIV infection is no longer considered a terminal illness, but rather a chronic condition that can be well managed. PLWH who take ART regularly can live a long and healthy life and will not transmit HIV to a negative partner through sex. However, treatment cost, drug adverse reaction and interaction, persistent inflammation, and inability to affect HIV-associated neurological diseases all together necessitate a cure. To control and end the HIV pandemic, 3 steps need to be fulfilled: First, identification, testing, and treatment for PLWH. Second, curing a proportion of PLWH. Third, preventing new HIV infections with widespread awareness and PrEP programs [188]. Even in 2023, we are well behind our 90–90–90 goals. More than 10 million people still do not know their HIV status. In 2021, approximately 1.5 million new cases of HIV infection were reported, and 22% of the 38 million individuals living with HIV do not have access to antiretroviral therapy (ART). Unfortunately, no established strategies currently exist for curing HIV. HIV cure strategies can be broadly categorized as either sterilizing or functional (Table 7, Fig. 6). Sterilizing cure encompasses eradicating all the intact integrated proviral DNA, preventing any chance of a viral rebound. A functional cure is defined as the control of HIV replication in the absence of ARVs. ARVs can be stopped without the return of subsequent viremia due to a near-complete or partial elimination of proviral DNA [189]. Depending on

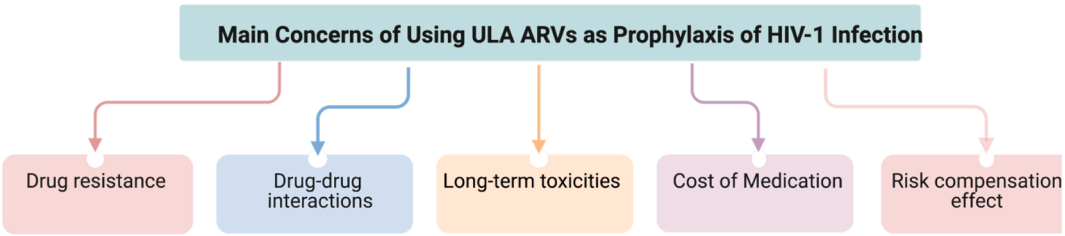


Fig. 5. Five major concerns of using ULA ARVs for prophylaxis of HIV-1 infection.

Table 7
HIV cure strategies.

Cure strategy	Class of Drugs	Sub-class of drugs	Example
Shock and kill	Latency reversing agent and ARVs	Inhibitors of HDAC, HMT, PKC, TLR7 agonist	Romidepsin, Entinostat, Vorinostat, Decitabine, Ionomycin
Gene therapy	Gene therapy with ARVs	CRISPR/Cas9; ZFN; TALENs	EBT-101
Block and Lock	Latency inducing agents with ARVs	Inhibitors of Tat, HSP90	didehydro Cortisan A (dCA)
Immune based therapies	Immune modulating agents	Vaccines; CAR-T cells; bNAbs	VRC01, 3BNC117, 101,074

(ARV- Antiretrovirals; HDAC- Histone deacetylase, HMT- Histone methyl-transferase; PKC- Protein kinase C; TLR7- tall-like receptor 7; ZFN- Zinc-finger nucleases; TALEN- transcription activator-like effector nucleases; and bNAbs).

the mechanism of action, HIV curative strategies can be further divided into four broad classes [190,191]. Over the last four decades, considerable scientific and therapeutic advances have been made in the field of ART. We now have a once-every-two-month injectable therapy for viral suppression or PrEP in the clinic and once-every-year therapies in pre-clinical IND-enabling studies. However, neither daily oral ARV therapy nor LA injectables have shown any decrease in the reservoir size. Discontinuation of ART results in viral rebound and viremia from latently infected cells harboring integrated full-length proviral DNA.

Although ARVs themselves cannot cure HIV, it is evident from Table 7 that all four of the HIV cure strategies still rely on viral suppression using ARVs. The use of LA ART can be advantageous in this aspect as patients will have a steady-state plasma concentration of the ARVs, allowing for easier adherence, durable suppression, and a more predictable landscape of viral reservoirs. Once every month injection of LA CAB and RPV was very acceptable among virologically suppressed patients in a Phase IIIb clinical trial [192]. Our lab has developed ULA therapies that could potentially be administered twice yearly. With the increased acceptance and durable suppression, LA ART can make it much easier for any of the cure strategies to work more reliably.

In fact, our laboratory has, for the first time, shown HIV elimination in one-third of humanized mice treated with sequential long-acting therapy and AAV-delivered gene editing cargo. In these mice, infected animals were virally suppressed using LA ART and were dosed with HIV-targeted gene therapy. Analytical treatment interruption showed that in one-third of the animals, no rebound occurred even after 12 weeks. Deep sequencing of the tissues of these animals showed no trace of full-length proviral DNA [193].

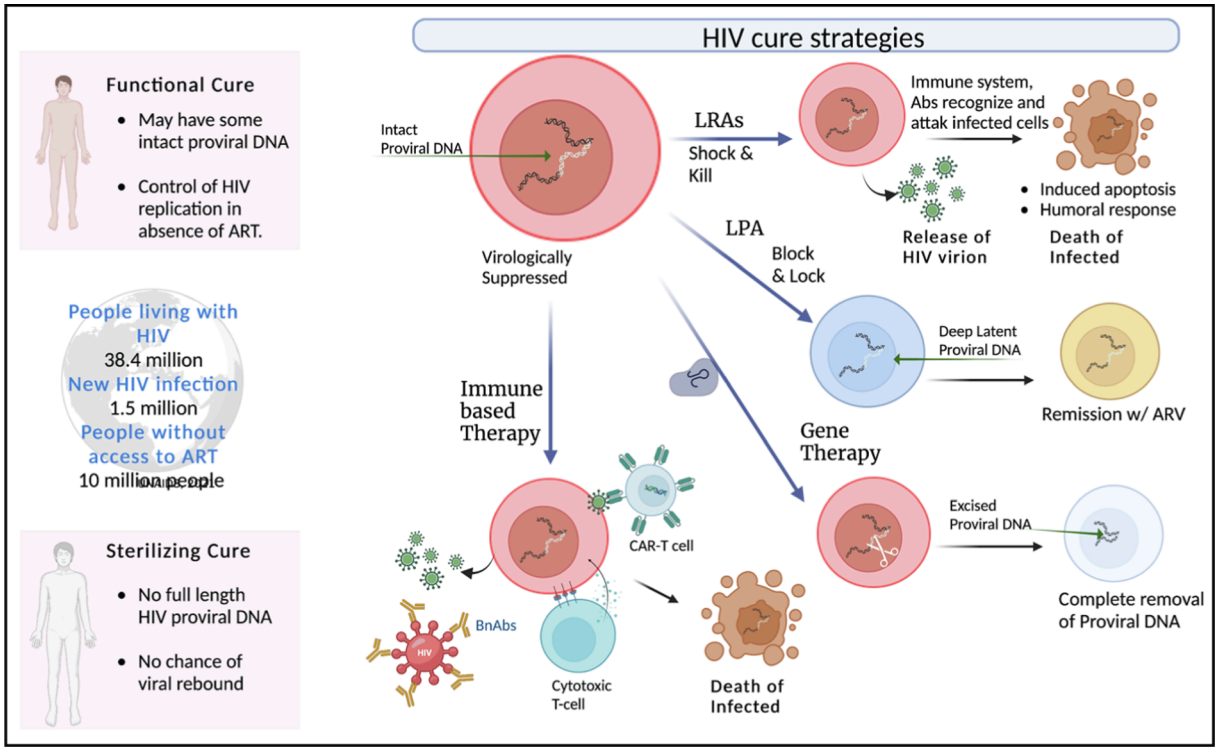


Fig. 6. Schematics of four boarder class of HIV curative strategies. These include (1) Shock and kill; (2) Block and lock; (3) Gene modification; and (4) Immune based therapies.

The above-mentioned landmark study from our lab also bolstered one crucial point, neither LA therapies nor gene therapies alone were able to produce any cure. It laid the foundation for future curative work where both LA therapies as well as the curative therapies will need to be improved. Although there were reports of HIV cure before [194], the methods were neither scalable nor applicable to the wider population and were marred with complications. Our study has shown an experimental approach that is scalable and can be tuned for better outcomes.

6. Conclusions and future directions

HIV treatment and prevention have entered a new era through the introduction of LA ART. This includes CAB, RPV, LEN, and DPV lifting barriers for the prevention and treatment of HIV-1 infection. The pressing needs include the identification of more simplified ART regimens with dosing intervals extended to every six months or longer, improved access, limited drug-drug interactions, reduced injection volumes and site reactions, optimal PK profiles, broader numbers of combinatorial treatments, and synchronization of healthcare support. Addressing these concerns requires careful consideration of factors such as ULA ARVs manufacturing processes, long-term storage and transportation stability of the ULA ARVs, and overall cost analysis.

Even though the excipients used in formulations and ARVs are identified as safe by the US FDA, safety and tolerability of ULA ARVs should be carefully investigated through long-term preclinical studies. The HIV epidemic burden is highest in resource-limited settings. So, it is crucial to ensure that ULA ARVs are suitable for transportation and storage in resource-limited settings. ULA ARVs should also be stable for their entire shelf-life as uniform physicochemical properties throughout the shelf life of the product are crucial for patient compliance and dosing integrity. Pharmacological considerations include the potential for self-administration, injection volume, removability in case of adverse events, individual PK variability, terminal phase PK behaviors, and the impact of physicochemical properties on injectability and safety. Timely testing of products in local populations and early engagement of key stakeholders are essential to gather feedback and support the successful introduction and implementation of ULA ARVs. Incorporating end-user preferences at the early product developmental stage can also enhance successful clinical translations.

As HIV weakens the immune systems, another important consideration is to emphasize on developing ULA ARVs that are also active against frequent HIV co-infections. For instance, approximately 7.5% of PLWH are co-infected with HBV. HBV is a leading cause of chronic liver disease and liver cancer and is projected to cause more deaths annually than HIV, tuberculosis, or malaria by 2040. Co-infection of HIV and HBV increases liver-related mortality rates compared to mono-infection. There are only 5 FDA- approved ARVs (TAF, TDF, entecavir, FTC, 3TC) that have activity against HBV [195]. TAF and TDF are preferred for HBV infection treatment, given their high resistance barrier to HBV. HBV-active ARVs are effective in preventing HBV acquisition, and therefore, switching to an LA ART with no anti-HBV NRTI backbone can cause reactivation of HBV or high HBV acquisition, as HBV also uses the same mode of transmission as HIV [196]. The development of ULA TAF or FTC can significantly improve uptake and treatment outcomes in HIV/HBV co-infected patients. Furthermore, there needs to be a strong linkage between ULA ARVs research and fundamental HIV virology research. This connection is pivotal for comprehending the impact of ULA ARTs on HIV viral reservoirs and the occurrence of HIV-1 infection relapses. Such understanding will be instrumental in advancing the utilization of ULA ARVs in the eradication of HIV-1. Moreover, fundamental HIV virology research can aid in the identification and creation of suitable animal models for efficient testing of ULA ARVs. By investigating the behavior of immune cells, particularly macrophages, in the uptake and transportation of ULA ARVs in depot-forming formulations, valuable insights can be gained for the innovation and design of these novel therapies.

In summary, there are promising experimental ULA technologies. These include nanoformulations, ARV implants, and VRs. These are complementing new potent LA ARVs development to foster widespread usage of ULA ARVs. These innovative technologies possess the potential to effectively address the outstanding requirements for preventing, adhering to, and treating HIV/AIDS and HIV-associated co-infections, thus presenting a promising pathway toward ending the HIV pandemic. Notably, there are still specific challenges that persist in resource-limited settings, where HIV infection poses significant individual and public health risks in terms of infection spread, disease burden, and mortality. Through current and future creative approaches, the successful clinical implementation of essential medications at an affordable cost can be ensured in these settings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The figures in this review article were created using BioRender®, a web-based tool for designing scientific illustrations. The work is supported by National Institutes of Health grants R01 NS034239; R01 NS036126; R01 MH115860; R01 NS126089 (HEG); R01 AI145542 (BE and HEG); R01 AI158160 (HEG and BE).

References

[1] D.T. Dimitrov, B.R. Mâsse, D. Donnell, PrEP adherence patterns strongly affect individual HIV risk and observed efficacy in randomized clinical trials, J. Acquir. Immune Defic. Syndr. 72 (4) (2016) 444–451.
[2] C.U. Correll, et al., The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence, J. Clin. Psychiatry 77 (suppl 3) (2016) 1–24.
[3] J.M. Kane, et al., Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial, JAMA Psychiat. 77 (12) (2020) 1217–1224.
[4] J. Ross, J. Stover, Use of modern contraception increases when more methods become available: analysis of evidence from 1982–2009, Glob Health Sci Pract 1 (2) (2013) 203–212.
[5] Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States, 2023.
[6] A. Mills, et al., Long-acting cabotegravir and rilpivirine for HIV-1 suppression: switch to 2-monthly dosing after 5 years of daily oral therapy, AIDS 36 (2) (2022).
[7] S. Deodhar, et al., Transformation of dolutegravir into an ultra-long-acting parenteral prodrug formulation, Nat. Commun. 13 (1) (2022) 3226.
[8] D.A. Cobb, et al., Long-acting approaches for delivery of antiretroviral drugs for prevention and treatment of HIV: a review of recent research, Expert Opin. Drug Deliv. 17 (9) (2020) 1227–1238.
[9] K. Meyers, et al., High interest in a long-acting injectable formulation of pre-exposure prophylaxis for HIV in young men who have sex with men in NYC: a P18 cohort substudy, PLoS One 9 (12) (2014) e114700.
[10] M.A. Fischl, et al., The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial, N. Engl. J. Med. 317 (4) (1987) 185–191.
[11] A. Tseng, J. Seet, E.J. Phillips, The evolution of three decades of antiretroviral therapy: challenges, triumphs and the promise of the future, Br. J. Clin. Pharmacol. 79 (2) (2015) 182–194.
[12] M. Ray, et al., The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals, AIDS 24 (1) (2010) 123–137.
[13] R.P. van Heeswijk, et al., Combination of protease inhibitors for the treatment of HIV-1-infected patients: a review of pharmacokinetics and clinical experience, Antivir. Ther. 6 (4) (2001) 201–229.
[14] F.J. Palella Jr, et al., Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators, N. Engl. J. Med. 338 (13) (1998) 853–860.
[15] D.L. Paterson, et al., Adherence to protease inhibitor therapy and outcomes in patients with HIV infection, Ann. Intern. Med. 133 (1) (2000) 21–30.
[16] K. Maeda, et al., Discovery and development of anti-HIV therapeutic agents: progress towards improved HIV medication, Curr. Top. Med. Chem. 19 (18) (2019) 1621–1649.
[17] J.B. Nachega, et al., Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials, Clin. Infect. Dis. 58 (9) (2014) 1297–1307.

[18] T. Kelesidis, R.J. Landovitz, Preexposure prophylaxis for HIV prevention, Curr. HIV/AIDS Rep. 8 (2) (2011) 94–103.
[19] M.V. Sivay, et al., Characterization of HIV Seroconverters in a TDF/FTC PrEP Study: HPTN 067/ADAPT, J. Acquir. Immune Defic. Syndr. 75 (3) (2017) 271–279.
[20] I. Massud, et al., Efficacy of oral tenofovir alafenamide/emtricitabine combination or single-agent tenofovir alafenamide against vaginal simian human immunodeficiency virus infection in macaques, J Infect Dis 220 (11) (2019) 1826–1833.
[21] Administration, U.S.F.D., Truvada for PrEP Fact Sheet: Ensuring Safe and Proper Use. 2012: www.fda.gov.
[22] Administration, U.S.F.D., FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic. 2019: www.fda.gov.
[23] J.M. Baeten, et al., Antiretroviral prophylaxis for HIV prevention in heterosexual men and women, N. Engl. J. Med. 367 (5) (2012) 399–410.
[24] S.A. Krovi, et al., Injectable long-acting human immunodeficiency virus antiretroviral prodrugs with improved pharmacokinetic profiles, Int. J. Pharm. 552 (1–2) (2018) 371–377.
[25] L. Van Damme, et al., Preexposure prophylaxis for HIV infection among African women, N. Engl. J. Med. 367 (5) (2012) 411–422.
[26] M.E. Clement, R. Kofron, R.J. Landovitz, Long-acting injectable cabotegravir for the prevention of HIV infection, Curr. Opin. HIV AIDS 15 (1) (2020) 19–26.
[27] K.K. Scarsi S. Swindells The Promise of Improved Adherence With Long-Acting Antiretroviral Therapy: What Are the Data? J Int Assoc Provid AIDS Care 20 2021 23259582211009011.
[28] J.E. Haberer, et al., Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa, PLoS Med. 10 (9) (2013) e1001511.
[29] V. Agrahari, et al., Long-acting HIV pre-exposure prophylaxis (PrEP) approaches: recent advances, emerging technologies, and development challenges, Expert Opin. Drug Deliv. 19 (10) (2022) 1365–1380.
[30] E. Taki, et al., Cabotegravir/Rilpivirine: the last FDA-approved drug to treat HIV, Expert Rev. Anti Infect. Ther. 20 (8) (2022) 1135–1147.
[31] E.M. Agency, First long-acting injectable antiretroviral therapy for HIV recommended for approval. 2020: www.ema.europa.eu.
[32] V. Healthcare, ViiV Healthcare announces first global regulatory approval of CABENUVA; the first complete, long-acting, regimen for the treatment of HIV. 2020: www.viivhealthcare.com.
[33] Administration, U.S.F.D., FDA Approves Cabenuva and Vocabria for the Treatment of HIV-1 Infection. 2021: www.fda.gov.
[34] V. Healthcare, ViiV HEALTHCARE ANNOUNCES US FDA APPROVAL OF CABENUVA (CABOTEGRAVIR, RILPIVIRINE) FOR USE EVERY TWO MONTHS, EXPANDING THE LABEL OF THE FIRST AND ONLY COMPLETE LONG-ACTING HIV TREATMENT, in Cabenuva is now approved for administration as few as six times a year for virologically suppressed adults living with HIV without prior treatment failure or resistance to cabotegravir or rilpivirine. 2022: www.viivhealthcare.com.
[35] V. Healthcare, ViiV HEALTHCARE ANNOUNCES LABEL UPDATE FOR ITS LONG-ACTING HIV TREATMENT, CABENUVA (CABOTEGRAVIR, RILPIVIRINE), TO BE INITIATED WITH OR WITHOUT AN ORAL LEAD-IN PERIOD, in US FDA approval of updated label streamlines the initiation process for the first and only complete long-acting HIV treatment by allowing people to start directly with injections. 2022, www.viivhealthcare.com.
[36] C. Orkin, et al., Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study, Lancet HIV 8 (11) (2021) e668–e678.
[37] J. Johnson, U.S. FDA Approves CABENUVA (cabotegravir and rilpivirine) for Adolescents, Expanding the Indication of the First and Only Complete Long-Acting Injectable HIV Regimen in CABENUVA offers virologically suppressed adolescents 12 years of age or older living with HIV-1 an injectable treatment option with as few as six dosing days per year. 2022: www.jnj.com.
[38] C. Trezza, et al., Formulation and pharmacology of long-acting cabotegravir, Curr. Opin. HIV AIDS 10 (4) (2015) 239–245.
[39] W.R. Spreen, D.A. Margolis, J.C. Pottage Jr., Long-acting injectable antiretrovirals for HIV treatment and prevention, Curr. Opin. HIV AIDS 8 (6) (2013) 565–571.
[40] L. Baert, et al., Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment, Eur. J. Pharm. Biopharm. 72 (3) (2009) 502–508.
[41] S.A. Krovi, et al., Advances in long-acting injectables, implants, and vaginal rings for contraception and HIV prevention, Adv. Drug Deliv. Rev. 176 (2021), 113849.
[42] L.G. Bekker, et al., Safety and tolerability of injectable Rilpivirine LA in HPTN 076: A phase 2 HIV pre-exposure prophylaxis study in women, EClinicalMedicine 21 (2020), 100303.
[43] D.A. Margolis, et al., Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial, Lancet 390 (10101) (2017) 1499–1510.
[44] G.H.R. Smith, et al., Efficacy, Safety, and Durability of Long-Acting Cabotegravir and Rilpivirine in Adults With Human Immunodeficiency Virus Type 1 Infection: 5-Year Results From the LATTE-2 Study. Open Forum Infect Dis **8**(9) (2021) ofab439.
[45] C. Orkin, et al., Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection, N. Engl. J. Med. 382 (12) (2020) 1124–1135.
[46] S. Swindells, et al., Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression, N. Engl. J. Med. 382 (12) (2020) 1112–1123.
[47] S. Swindells, et al., Week 96 extension results of a Phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment, AIDS 36 (2) (2022) 185–194.
[48] E.T. Overton, et al., Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study, Lancet 396 (10267) (2021) 1994–2005.
[49] H. Jaeger, et al., Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study, Lancet HIV 8 (11) (2021) e679–e689.
[50] A. Mills, et al., Long-acting cabotegravir and rilpivirine for HIV-1 suppression: switch to 2-monthly dosing after 5 years of daily oral therapy, AIDS 36 (2) (2022) 195–203.
[51] M. Markowitz, S.G. Sarafianos, 4'-Ethynyl-2-fluoro-2'-deoxyadenosine, MK-8591: a novel HIV-1 reverse transcriptase translocation inhibitor, Curr. Opin. HIV AIDS 13 (4) (2018) 294–299.
[52] L. Sun, et al., An insight on medicinal aspects of novel HIV-1 capsid protein inhibitors, Eur. J. Med. Chem. 217 (2021), 113380.
[53] S.M. Bester, et al., Structural and mechanistic bases for a potent HIV-1 capsid inhibitor, Science 370 (6514) (2020) 360–364.
[54] M. Perrier, et al., Prevalence of gag mutations associated with in vitro resistance to capsid inhibitor GS-CA1 in HIV-1 antiretroviral-naive patients, J. Antimicrob. Chemother. 72 (10) (2017) 2954–2955.
[55] N. Margot, et al., Absence of lenacapavir (GS-6207) phenotypic resistance in HIV gag cleavage site mutants and in isolates with resistance to existing drug classes, Antimicrob. Agents Chemother. 65 (3) (2021).
[56] J.O. Link, et al., Clinical targeting of HIV capsid protein with a long-acting small molecule, Nature 584 (7822) (2020) 614–618.
[57] R. Begley, J. L., M. Rhee, et al., GS-6207 sustained delivery formulation supports 6-month dosing interval, in: 2020 International AIDS Conference; Virtual; July 6–10. 2020.
[58] R. Begley, R.M., S.K. West, et al., PK, food effect, and safety of oral GS-6207, a novel HIV-1 capsid inhibitor, in: 2020 Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, USA, 2020.
[59] S. Segal-Maurer, et al., Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 Infection, N. Engl. J. Med. 386 (19) (2022) 1793–1803.
[60] S.K. Gupta, et al., Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial, Lancet HIV 10 (1) (2023) e15–e23.
[61] Administration, U.S.F.D., *FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention*, in *Drug Given Every Two Months Rather Than Daily Pill is Important Tool in Effort to End the HIV Epidemic*. 2021: www.fda.gov.
[62] V. Healthcare EUROPEAN MEDICINES AGENCY VALIDATES ViiV HEALTHCARE'S MARKETING AUTHORISATION APPLICATION FOR CABOTEGRAVIR LONG-ACTING INJECTABLE FOR HIV PREVENTION 2022.
[63] W.H. Organization, WHO recommends long-acting cabotegravir for HIV prevention, in New WHO guidelines advise countries to deliver long-acting cabotegravir as part of comprehensive approach to HIV prevention. 2022: www.who.int.
[64] J.M. Baeten, et al., Use of a vaginal ring containing dapivirine for HIV-1 prevention in women, N. Engl. J. Med. 375 (22) (2016) 2121–2132.
[65] S.H. Bares, K.K. Scarsi, A new paradigm for antiretroviral delivery: long-acting cabotegravir and rilpivirine for the treatment and prevention of HIV, Curr. Opin. HIV AIDS 17 (1) (2022) 22–31.
[66] J. Tuan, O. Ogbuagu, Lenacapavir: a twice-yearly treatment for adults with multidrug-resistant HIV infection and limited treatment options, Expert Rev. Anti Infect. Ther. 21 (6) (2023) 565–570.
[67] R.J. Landovitz, et al., Cabotegravir for HIV prevention in cisgender men and transgender women, N. Engl. J. Med. 385 (7) (2021) 595–608.
[68] E. Moyo, et al., Long-Acting Injectable Drugs for HIV-1 Pre-Exposure Prophylaxis: Considerations for Africa, Trop Med Infect. Dis. 7 (8) (2022).
[69] S. Delany-Moretlwe, et al., Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial, Lancet 399 (10337) (2022) 1779–1789.
[70] M.I. Murray, et al., Satisfaction and acceptability of cabotegravir long-acting injectable suspension for prevention of HIV: patient perspectives from the ECLAIR trial, HIV Clin. Trials 19 (4) (2018) 129–138.
[71] E.E. Tolley, et al., Acceptability of a long-acting injectable HIV prevention product among US and African women: findings from a phase 2 clinical Trial (HPTN 076), J. Int. AIDS Soc. 22 (10) (2019) e25408.
[72] R. Schaefer, et al., Adoption of guidelines on and use of oral pre-exposure prophylaxis: a global summary and forecasting study, Lancet HIV 8 (8) (2021) e502–e510.
[73] A.Y. Liu, et al., Phase 1 pharmacokinetics and safety study of extended duration dapivirine vaginal rings in the United States, J. Int. AIDS Soc. 24 (6) (2021) e25747.
[74] E.T. Montgomery, et al., Vaginal ring adherence in sub-Saharan Africa: expulsion, removal, and perfect use, AIDS Behav. 16 (7) (2012) 1787–1798.
[75] A. van der Straten, et al., High acceptability of a vaginal ring intended as a microbicide delivery method for HIV prevention in African women, AIDS Behav. 16 (7) (2012) 1775–1786.
[76] B.A. Chen, et al., Phase 2a safety, pharmacokinetics, and acceptability of dapivirine vaginal rings in US postmenopausal women, Clin. Infect. Dis. 68 (7) (2018) 1144–1151.

[77] A. Nel, et al., Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women, N. Engl. J. Med. 375 (22) (2016) 2133–2143.
[78] A. Nel, et al., Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study, Lancet HIV 8 (2) (2021) e77–e86.
[79] J.M. Baeten, 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 8 (2) (2021) e87–e95.
[80] A. Nel, et al., Safety, acceptability and adherence of dapivirine vaginal ring in a microbicide clinical trial conducted in multiple countries in Sub-saharan Africa, PLoS One 11 (3) (2016) e0147743.
[81] K.K. Scarsi, Chasing the cabotegravir tail: implications for prevention, Lancet HIV 7 (7) (2020) e451–e453.
[82] R.J. Landovitz, et al., Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial, Lancet HIV 7 (7) (2020) e472–e481.
[83] Health, C.f.D.C.a.P.U.P. and Service, Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. 2021.
[84] K. Meyers, et al., The long-acting cabotegravir tail as an implementation challenge: planning for safe discontinuation, AIDS Behav. (2022).
[85] K. Ngure, et al., Pills, injections, rings, or implants? Prep formulation preferences of PrEP-experienced african women for HIV prevention, J. Acquir. Immune Defic. Syndr. 88 (4) (2021) e30–e32.
[86] E.A. Krogstad, et al., Perspectives of South African youth in the development of an implant for HIV prevention, J. Int. AIDS Soc. 21 (8) (2018) e25170.
[87] J.P. Freeling, et al., Anti-HIV drug-combination nanoparticles enhance plasma drug exposure duration as well as triple-drug combination levels in cells within lymph nodes and blood in primates, AIDS Res. Hum. Retroviruses 31 (1) (2015) 107–114.
[88] J.P. Freeling, et al., Long-acting three-drug combination anti-HIV nanoparticles enhance drug exposure in primate plasma and cells within lymph nodes and blood, AIDS 28 (17) (2014) 2625–2627.
[89] C.A. Lipinski, et al., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv. Drug Deliv. Rev. 46 (1–3) (2001) 3–26.
[90] S. Swindells, et al., Long-acting formulations for the treatment of latent tuberculous infection: opportunities and challenges, Int. J. Tuberc. Lung Dis. 22 (2) (2018) 125–132.
[91] D.H. Surve, A.B. Jindal, Recent advances in long-acting nanoformulations for delivery of antiretroviral drugs, J. Control. Release 324 (2020) 379–404.
[92] G. van 't Klooster, et al., Pharmacokinetics and disposition of rilpivirine (TMC278) nanosuspension as a long-acting injectable antiretroviral formulation, Antimicrob. Agents Chemother. 54 (5) (2010) 2042–2050.
[93] L.M. Tatham, et al., Towards a Maraviroc long-acting injectable nanoformulation, Eur. J. Pharm. Biopharm. 138 (2019) 92–98.
[94] Sezer, A.D., *Recent advances in novel drug carrier systems.* 2012.
[95] A.M. Grumezescu, Design of nanostructures for versatile therapeutic applications, William Andrew, 2018.
[96] E. Fernandes, et al., Spectroscopic studies as a toolbox for biophysical and chemical characterization of lipid-based nanotherapeutics, Front. Chem. 6 (2018) 323.
[97] J.C. Kraft, et al., Mechanism-based pharmacokinetic (MBPK) models describe the complex plasma kinetics of three antiretrovirals delivered by a long-acting anti-HIV drug combination nanoparticle formulation, J. Control. Release 275 (2018) 229–241.
[98] S. Perazzolo, et al., Three HIV drugs, atazanavir, ritonavir, and tenofovir, coformulated in drug-combination nanoparticles exhibit long-acting and lymphocyte-targeting properties in nonhuman primates, J. Pharm. Sci. 107 (12) (2018) 3153–3162.
[99] L. Kinman, et al., Optimization of lipid-indinavir complexes for localization in lymphoid tissues of HIV-infected macaques, JAIDS J. Acquired Immune Deficiency Syndromes 42 (2) (2006) 155–161.
[100] L. Kinman, et al., Lipid–drug association enhanced HIV-1 protease inhibitor indinavir localization in lymphoid tissues and viral load reduction: a proof of concept study in HIV-2287-infected macaques, JAIDS J. Acquired Immune Deficiency Syndromes 34 (4) (2003) 387–397.
[101] D. Alukda, T. Sturgis, B.B.C. Youan, Formulation of tenofovir-loaded functionalized solid lipid nanoparticles intended for HIV prevention, J. Pharm. Sci. 100 (8) (2011) 3345–3356.
[102] S.N. Kudalkar, et al., Structural and pharmacological evaluation of a novel non-nucleoside reverse transcriptase inhibitor as a promising long acting nanoformulation for treating HIV, Antiviral Res. 167 (2019) 110–116.
[103] S. Mandal, et al., An enhanced emtricitabine-loaded long-acting nanoformulation for prevention or treatment of HIV infection, Antimicrob. Agents Chemother. 61 (1) (2017).
[104] C. Hansch, J.P. Björkroth, A. Leo, Hydrophobicity and central nervous system agents: on the principle of minimal hydrophobicity in drug design, J. Pharm. Sci. 76 (9) (1987) 663–687.
[105] S. Mandal, et al., Long-acting parenteral combination antiretroviral loaded nano-drug delivery system to treat chronic HIV-1 infection: a humanized mouse model study, Antiviral Res. 156 (2018) 85–91.
[106] P.K. Prathipati, et al., Pharmacokinetic and tissue distribution profile of long acting tenofovir alafenamide and elvitegravir loaded nanoparticles in humanized mice model, Pharm. Res. 34 (2017) 2749–2755.
[107] S. Mandal, et al., Nanoencapsulation introduces long-acting phenomenon to tenofovir alafenamide and emtricitabine drug combination: a comparative pre-exposure prophylaxis efficacy study against HIV-1 vaginal transmission, J. Control. Release 294 (2019) 216–225.
[108] S. Mandal, et al., A concept evaluation study of a new combination bictegravir plus tenofovir alafenamide nanoformulation with prolonged sustained-drug-release potency for HIV-1 preexposure prophylaxis, Antimicrob. Agents Chemother. 65 (4) (2021).
[109] S. Mandal, et al., Tenofovir alafenamide and elvitegravir loaded nanoparticles for long-acting prevention of HIV-1 vaginal transmission, AIDS (London, England) 31 (4) (2017) 469.
[110] A. Hill, et al., Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J. Virus Erad. 4 (2) (2018) 72–79.
[111] G. Birkus, et al., Intracellular activation of tenofovir alafenamide and the effect of viral and host protease inhibitors, Antimicrob. Agents Chemother. 60 (1) (2016) 316–322.
[112] D.A. Cobb, et al., Transformation of tenofovir into stable ProTide nanocrystals with long-acting pharmacokinetic profiles, Nat. Commun. 12 (1) (2021) 5458.
[113] S. Das et al. An ultralong-acting tenofovir ProTide nanoformulation achieves monthslong HBV suppression Sci Adv 8 51 2022 p. eade9582.
[114] I.M. Ibrahim, et al., Synthesis and characterization of a long-acting emtricitabine prodrug nanoformulation, Int. J. Nanomed. 14 (2019) 6231–6247.
[115] D. Singh, et al., Development and characterization of a long-acting nanoformulated abacavir prodrug, Nanomedicine (Lond.) 11 (15) (2016) 1913–1927.
[116] D. Guo, et al., Creation of a long-acting nanoformulated 2',3'-dideoxy-3'-thiacytidine, J. Acquir. Immune Defic. Syndr. 74 (3) (2017) e75–e83.
[117] N. Smith, et al., A long acting nanoformulated lamivudine ProTide, Biomaterials 223 (2019), 119476.
[118] T. Zhou, et al., Creation of a nanoformulated cabotegravir prodrug with improved antiretroviral profiles, Biomaterials 151 (2018) 53–65.
[119] B. Sillman, et al., Creation of a long-acting nanoformulated dolutegravir, Nat. Commun. 9 (1) (2018) 443.
[120] T.A. Kulkarni, et al., A year-long extended release nanoformulated cabotegravir prodrug, Nat. Mater. 19 (8) (2020) 910–920.
[121] T. Khuroo, et al., Ultra-long acting prodrug of dolutegravir and delivery system - Physicochemical, pharmacokinetic and formulation characterizations, Int. J. Pharm. 607 (2021), 120889.
[122] J.J. Hobson, et al., Semi-solid prodrug nanoparticles for long-acting delivery of water-soluble antiretroviral drugs within combination HIV therapies, Nat. Commun. 10 (1) (2019) 1413.
[123] A. Shakil, et al., Linear and branched polymer prodrugs of the water-soluble nucleoside reverse-transcriptase inhibitor emtricitabine as structural materials for long-acting implants, J. Mater. Chem. B 10 (23) (2022) 4395–4404.
[124] J.T. Su, et al., A subcutaneous implant of tenofovir alafenamide fumarate causes local inflammation and tissue necrosis in rabbits and macaques, Antimicrob. Agents Chemother. 64 (3) (2020).
[125] R. Jacobstein, Liftoff: the blossoming of contraceptive implant use in Africa, Glob Health Sci Pract 6 (1) (2018) 17–39.
[126] A. Puri, et al., Development of a transdermal delivery system for tenofovir alafenamide, a prodrug of tenofovir with potent antiviral activity against HIV and HBV, Pharmaceutics 11 (4) (2019).
[127] D. Mansour, et al., The effects of Implanon on menstrual bleeding patterns, Eur. J. Contracept. Reprod. Health Care 13 (Suppl 1) (2008) 13–28.
[128] X. Wang, D.J. Burgess, Drug release from in situ forming implants and advances in release testing, Adv. Drug Deliv. Rev. 178 (2021), 113912.
[129] M. Markowitz, J.A. Grobler, Islatravir for the treatment and prevention of infection with the human immunodeficiency virus type 1, Curr. Opin. HIV AIDS 15 (1) (2020) 27–32.
[130] D. Schürmann, et al., Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naive adults infected with HIV-1: an open-label, phase 1b, consecutive-panel trial, Lancet HIV 7 (3) (2020) e164–e172.
[131] S.E. Barrett, et al., Extended-duration MK-8591-eluting implant as a candidate for HIV treatment and prevention, Antimicrob. Agents Chemother. 62 (10) (2018).
[132] M. Gunawardana, et al., Pharmacokinetics of long-acting tenofovir alafenamide (GS-7340) subdermal implant for HIV prophylaxis, Antimicrob. Agents Chemother. 59 (7) (2015) 3913–3919.
[133] M. Markowitz, et al., Once-weekly oral dosing of MK-8591 protects male rhesus macaques from intrarectal challenge with SHIV109CP3, J Infect Dis 221 (9) (2020) 1398–1406.
[134] Merck Presents Early Evidence on Extended Delivery of Investigational Anti-HIV-1 Agent Islatravir (MK-8591) via Subdermal Implant. 2019.
[135] Merck Announces Clinical Holds on Studies Evaluating Islatravir for the Treatment and Prevention of HIV-1 Infection. December 2021.
[136] Merck to Initiate New Phase 3 Clinical Program with Lower Dose of Daily Oral Islatravir in Combination with Doravirine for Treatment of People with HIV-1 Infection. September 2022.
[137] J. Chen, et al., Biphasic elimination of tenofovir diphosphate and nonlinear pharmacokinetics of zidovudine triphosphate in a microdosing study, J. Acquir. Immune Defic. Syndr. 61 (5) (1999) 593.
[138] P.J. Ruane, et al., Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1–positive adults, JAIDS J. Acquired Immune Deficiency Syndromes 63 (4) (2013) 449–455.

[139] L.M. Childs-Kean, E.F. Egelund, J. Jourjy, Tenofovir alafenamide for the treatment of chronic hepatitis B monoinfection, Pharmacotherapy: J. Human Pharmacol. DrugTherapy 38 (10) (2018) 1051–1057.
[140] L.M. Johnson, et al., Characterization of a reservoir-style implant for sustained release of tenofovir alafenamide (TAF) for HIV pre-exposure prophylaxis (PrEP), Pharmaceutics 11 (7) (2019) 315.
[141] E. Schlesinger, et al., A tunable, biodegradable, thin-film polymer device as a long-acting implant delivering tenofovir alafenamide fumarate for HIV pre-exposure prophylaxis, Pharm. Res. 33 (2016) 1649–1656.
[142] M. Gunawardana, et al., Multispecies evaluation of a long-acting tenofovir alafenamide subdermal implant for HIV prophylaxis, Front. Pharmacol. 11 (2020), 569373.
[143] M. Gunawardana et al., MARY ANN LIEBERT, INC 140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, NY 10801, Multispecies, in vivo evaluation of subdermal implants delivering tenofovir alafenamide: Of mice, dogs and sheep, in: AIDS RESEARCH AND HUMAN RETROVIRUSES 2018 USA.
[144] N. Di Trani, et al., Electrostatically gated nanofluidic membrane for ultra-low power controlled drug delivery, Lab Chip 20 (9) (2020) 1562–1576.
[145] D. Fine, et al., Silicon micro-and nanofabrication for medicine, Adv. Healthc. Mater. 2 (5) (2013) 632–666.
[146] S. Ferrati, et al., Leveraging nanochannels for universal, zero-order drug delivery in vivo, J. Control. Release 172 (3) (2013) 1011–1019.
[147] F.P. Pons-Faudoa, et al., Preventive efficacy of a tenofovir alafenamide fumarate nanofluidic implant in SHIV-challenged nonhuman primates, Adv Ther (Weinh) 4 (3) (2021).
[148] J.T. Su, et al., A subcutaneous implant of tenofovir alafenamide fumarate causes local inflammation and tissue necrosis in rabbits and macaques, Antimicrob. Agents Chemother. 64 (3) (2020) e01893–e10919.
[149] C. Bagia, T. Shah, V. Sant, Development of novel accelerated stability testing models for tenofovir alafenamide (TAF) in long-acting implants for HIV prevention, in: Proceedings of the Controlled Release Society, Las Vegas, NV, USA, 2020. **27**.
[150] F.P. Pons-Faudoa, et al., 2-Hydroxypropyl-β-cyclodextrin-enhanced pharmacokinetics of cabotegravir from a nanofluidic implant for HIV pre-exposure prophylaxis, J. Control. Release 306 (2019) 89–96.
[151] D. Karunakaran, et al., Design and testing of a cabotegravir implant for HIV prevention, J. Control. Release 330 (2021) 658–668.
[152] I.C. Young, et al., Ultra-long-acting in-situ forming implants with cabotegravir protect female macaques against rectal SHIV infection, Nat. Commun. 14 (1) (2023) 708.
[153] C.Y.X. Chua, et al., Transcutaneously refillable nanofluidic implant achieves sustained level of tenofovir diphosphate for HIV pre-exposure prophylaxis, J. Control. Release 286 (2018) 315–325.
[154] J. Etima, et al., Does the ring work? Perceptions and understanding of the efficacy of a dapivirine vaginal ring for HIV prevention amongst women in a placebo-controlled trial, AIDS Behav. 26 (5) (2022) 1597–1606.
[155] K. Ngure, Choice and Adherence to Dapivirine Ring or Oral PrEP by Young African Women in REACH: 67% prefer ring vs 31% oral PrEP in Conference on Retroviruses and Opportunistic Infections. 2022: Virtual.
[156] R.K. Malcolm, et al., Advances in microbicide vaginal rings, Antiviral Res. 88 (Suppl 1) (2010) S30–S39.
[157] P.M. Mesquita, et al., Intravaginal ring delivery of tenofovir disoproxil fumarate for prevention of HIV and herpes simplex virus infection, J. Antimicrob. Chemother. 67 (7) (2012) 1730–1738.
[158] T.J. Johnson, et al., Segmented polyurethane intravaginal rings for the sustained combined delivery of antiretroviral agents dapivirine and tenofovir, Eur. J. Pharm. Sci. 39 (4) (2010) 203–212.
[159] J.T. Su, et al., A dose ranging pharmacokinetic evaluation of IQP-0528 released from intravaginal rings in non-human primates, Pharm. Res. 34 (10) (2017) 2163–2171.
[160] C.J. Hoesley, et al., Phase 1 safety and pharmacokinetics study of MK-2048/Vicriviroc (MK-4176)/MK-2048A intravaginal rings, Clin. Infect. Dis. 68 (7) (2019) 1136–1143.
[161] T.J. Johnson, et al., A 90-day tenofovir reservoir intravaginal ring for mucosal HIV prophylaxis, Antimicrob. Agents Chemother. 56 (12) (2012) 6272–6283.
[162] A.R. Thurman, et al., Randomized, placebo controlled phase I trial of safety, pharmacokinetics, pharmacodynamics and acceptability of tenofovir and tenofovir plus levonorgestrel vaginal rings in women, PLoS One 13 (6) (2018) e0199778.
[163] J.M. Smith, et al., Intravaginal ring eluting tenofovir disoproxil fumarate completely protects macaques from multiple vaginal simian-HIV challenges, PNAS 110 (40) (2013) 16145–16150.
[164] M.J. Keller, et al., Tenofovir disoproxil fumarate intravaginal ring for HIV pre-exposure prophylaxis in sexually active women: a phase 1, single-blind, randomised, controlled trial, Lancet HIV 6 (8) (2019) e498–e508.
[165] A.J. Paredes, et al., Microarray patches: Breaking down the barriers to contraceptive care and HIV prevention for women across the globe, Adv. Drug Deliv. Rev. 173 (2021) 331–348.
[166] A.J. Paredes, et al., Systemic delivery of tenofovir alafenamide using dissolving and implantable microneedle patches, Mater. Today Bio 13 (2022), 100217.
[167] E. Larrañeta, et al., Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development, Mater. Sci. Eng. R. Rep. 104 (2016) 1–32.
[168] M.T.C. Mc Crudden, et al., Design, formulation and evaluation of novel dissolving microarray patches containing a long-acting rilpivirine nanosuspension, J. Control. Release 292 (2018) 119–129.
[169] S. Rojekar, et al., Etravirine-loaded dissolving microneedle arrays for long-acting delivery, Eur. J. Pharm. Biopharm. 165 (2021) 41–51.
[170] F. Volpe-Zanutto, et al., Hydrogel-forming microarray patches with cyclodextrin drug reservoirs for long-acting delivery of poorly soluble cabotegravir sodium for HIV pre-exposure prophylaxis, J. Control. Release 348 (2022) 771–785.
[171] I.A. Tekko, et al., Novel Bilayer Microarray Patch-Assisted Long-Acting Micro-Depot Cabotegravir Intradermal Delivery for HIV Pre-Exposure Prophylaxis (Adv. Funct. Mater. 9/2022). Advanced Functional Materials, 2022. **32**(9): p. 2270059.
[172] A. Puri et al., Development of a Transdermal Delivery System for Tenofovir Alafenamide, a Prodrug of Tenofovir with Potent Antiviral Activity Against HIV and HBV Pharmaceutics 11 2019 10.3390/pharmaceutics11040173.
[173] Y. Jiang, et al., Pharmacokinetics of a weekly transdermal delivery system of tenofovir alafenamide in hairless rats, Int. J. Pharm. 582 (2020), 119342.
[174] A. Pattani, et al., Microneedle mediated intradermal delivery of adjuvanted recombinant HIV-1 CN54gp140 effectively primes mucosal boost inoculations, J. Control. Release 162 (3) (2012) 529–537.
[175] M. Zaric, et al., Long-lived tissue resident HIV-1 specific memory CD8+ T cells are generated by skin immunization with live virus vectored microneedle arrays, J. Control. Release 268 (2017) 166–175.
[176] A.V. Boopathy, et al., Enhancing humoral immunity via sustained-release implantable microneedle patch vaccination, PNAS 116 (33) (2019) 16473–16478.
[177] D. Sok, D.R. Burton, Recent progress in broadly neutralizing antibodies to HIV, Nat. Immunol. 19 (11) (2018) 1179–1188.
[178] S. Kumar, S. Singh, K. Luthra, An overview of human anti-HIV-1 neutralizing antibodies against diverse epitopes of HIV-1, ACS Omega 8 (8) (2023) 7252–7261.
[179] Y. Liu, et al., Broadly neutralizing antibodies for HIV-1: efficacies, challenges and opportunities, Emerg Microbes Infect 9 (1) (2020) 194–206.
[180] L. Khan, et al., Cross-neutralizing anti-HIV-1 human single chain variable fragments(scFvs) against CD4 binding site and N332 glycan identified from a recombinant phage library, Sci. Rep. 7 (2017) 45163.
[181] S.R. Walsh, M.S. Seaman, Broadly neutralizing antibodies for HIV-1 prevention, Front. Immunol. 12 (2021), 712122.
[182] M. Caskey, et al., Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117, Nature 522 (7557) (2015) 487–491.
[183] J.E. Ledgerwood, et al., Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults, Clin. Exp. Immunol. 182 (3) (2015) 289–301.
[184] C.A. Bricault, et al., HIV-1 neutralizing antibody signatures and application to epitope-targeted vaccine design, Cell Host Microbe 25 (1) (2019) 59–72.e8.
[185] Gilead. 2023.
[186] S.H. Eshleman, et al., Characterization of Human Immunodeficiency Virus (HIV) Infections in Women Who Received Injectable Cabotegravir or Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Prevention: HPTN 084, J Infect Dis 225 (10) (2022) 1741–1749.
[187] V. Soriano, J.D. Romero, Rebound in Sexually Transmitted Infections Following the Success of Antiretrovirals for HIV/AIDS, AIDS Rev. 20 (4) (2018) 187–204.
[188] C.W. Dieffenbach, A.S. Fauci, Thirty years of HIV and AIDS: future challenges and opportunities, Ann. Intern. Med. 154 (11) (2011) 766–771.
[189] Thirty Years of HIV and AIDS: Future Challenges and Opportunities. Annals of Internal Medicine 154(11) (2011) 766-771.
[190] C.-Z.-Y. Abana, et al., HIV cure strategies: which ones are appropriate for Africa? Cell. Mol. Life Sci. 79 (8) (2022) 400.
[191] M.M. Elsheikh, et al., Deep latency: a new insight into a functional HIV cure, EBioMedicine 45 (2019) 624–629.
[192] C.P. Garris, et al., Perspectives of people living with HIV-1 on implementation of long-acting cabotegravir plus rilpivirine in US healthcare settings: results from the CUSTOMIZE hybrid III implementation-effectiveness study, J. Int. AIDS Soc. 25 (9) (2022) e26006.
[193] P.K. Dash, et al., Sequential LASER ART and CRISPR Treatments Eliminate HIV-1 in a Subset of Infected Humanized Mice, Nat. Commun. 10 (1) (2019) 2753.
[194] R.K. Gupta, et al., Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report, The Lancet HIV 7 (5) (2020) e340–e347.
[195] V. Soriano, et al., New antivirals for the treatment of chronic hepatitis B, Expert Opin. Invest. Drugs 26 (7) (2017) 843–851.
[196] M. Bessesen, et al., Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine, Clin. Infect. Dis. 28 (5) (1999) 1032–1035.