Review Article

New Antiretroviral Drugs in the Pandemic

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Abstract

The pandemic of coronavirus disease-19 (COVID-19) has impacted the care of people living with human immunodeficiency virus (HIV) and HIV prevention in several ways. Locking down and limiting transportation to slow down COVID-19 transmission can cause difficulty accessing and non-compliance to daily-dosing antiretroviral drugs (ARVs). The new formu-lations of ARVs, including long-acting ones administered as injections and implants are being approved and developed for HIV treatment and prevention. Intramuscular cabotegravir and rilpivirine co-formulation is approved by the US Food and Drug Administration for HIV treatment in virologically suppressed adults on a stable regimen, while intramuscular cabotegravir is approved for HIV pre-exposure prophylaxis. Other long-acting drugs, such as lenacapavir and islatravir have currently been developed and studied for HIV treatment and/or prevention. This present article concisely reviews the current knowledge on these new ARVs and their implications, which may serve as novel regimens for use during the current and future pandemics.

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Introduction

The emerging severe acute respiratory syndrome coronavirus-2 has caused global pandemics of coronavirus disease-19 (COVID-19) since early 2020. The disease has significant impact on the world population's health, especially among those with comorbidities and at-risk for disease progression. Among people living with human immunodeficiency virus (PLHIV), 17.7 million receiving antiretroviral drugs (ARV) were at-risk for ARV interruption, 11.5 million were from countries reporting disruption in provision of ARV services and 8.3 million were from countries having a critical low stock of ARVs.[1] The impact of ARV access, services and stock was mainly due to strict quarantine measures and transportation lock downs, unplanned stocking of ARVs and diversion of HIV care to COVID-19 care among healthcare professionals.[2] In addition, the burden and difficulties in life during the pandemics may interfere the routine daily activities including taking a standard oral ARV regimen and lead to medication non-compliance.

With the advance in HIV Medicine, ARV regimens have been improved significantly for the past decades for better efficacy and tolerability, less toxicity, and more convenience to use. The latest international guidelines have recommended oral daily-dosing three-drug regimens, preferably single-tablet regimens for treatment of ARV-naïve PLHIV.[3,4] Nonetheless, daily taking of the ARVs could still be problematic in some PLHIV since the required threshold of adherence to achieve HIV virologic suppression is at least 80% for recommended oral daily regimens.[5] For prevention of HIV infection, the approved oral regimens are emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) taking daily or before and after risk exposure (FTC/TDF only).[3,4] Although, the threshold of ARV adherence for HIV prevention is lower than for treatment,[6] these oral regimens require administering of the drugs regularly and at the appropriate time. One of the promising strategies to overcome the adherence problems of daily taking ARVs is the use of long-acting (LA) ARV regimens. The LA formulations could provide benefits of reduced social stigma associated with HIV and improve PLHIV's privacy, freedom and adherence.[7,8] Given the recent development of LA ARVs and more information from clinical trials, this present narrative review provides concise updates on the current knowledge of the new LA ARVs and their potential use as novel regimens for HIV treatment and prevention during pandemics.

Cabotegravir (CAB) and Rilpivirine (RPV)

Cabotegravir is one of the new ARVs and belongs to the integrase stand transfer inhibitor class. It prevents HIV integrase from incorporating proviral DNA into the human host cell, thus inhibiting the HIV-catalyzed strand transfer step. The drug has a great potency for HIV suppression and a high genetic barrier. Cabotegravir comes in two forms and strengths: 30-mg tablet and 600 mg/3 mL single-dose vial of extended-release injectable suspension (LA-CAB). Adequate drug level for sustained inhibition of HIV was demonstrated for the dose of 600 mg given intramuscularly every 2 months after two initiation injections administered one month apart.[9] Two multicenter randomized controlled trials demonstrated that intramuscular LA-CAB 600 mg every 2 months after 1-month oral CAB induction was superior to FTC/TDF in preventing HIV infection in at least 18 year-old cisgender men and transgender women who have sex with men and 18 - 45 year-old female (Table 1). These results have led to the recent United States Food and Drug Administration (US FDA) approval of LA-CAB for use in at-risk adults and adolescents weighing at least 35 kilograms for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV. The LA-CAB can be given either as two initiation injections given one month apart, and then every two months thereafter or following 4-week daily oral CAB.[10] The most common adverse reaction of LA-CAB is local pain and reaction at the injection site. Compared to FTC/TDF, nasopharyngitis, hyperglycemia and weight gain are more common for LA-CAB but serious adverse events are rare and not different from FTC/TDF. Cabotegravir interacts with UDP-glucuronosyltransferases (UGT)1A1, UGT1A9, organic anion transporter (OAT)1 and OAT3 systems. However, the significance of these interactions is currently unknown and needs to be updated when the drug is widely used in clinical practice.

Rilpivirine in one of the ARVs in the class of non-nucleoside reverse transcriptase inhibitor (NNRTI). The HIV characteristics of drug-resistant

mutations for RPV are different from the two older NNRTIs, nevirapine and efavirenz. Oral RPV 25 mg is used in combination with FTC or lamivudine and TDF or TAF for initial treatment in ARV-naïve individuals. Long-acting RPV has been developed for intramuscular use with the results from phase I studies showing that dosing between 600 and 1200 mg, was effective in maintaining adequate drug concentrations in plasma, vaginal secretion and rectal tissue compartments for at least 4 weeks.[11] Common adverse reactions of RPV include elevated liver enzymes, rashes, headache, and insomnia, while depression, suicidality and hypersensitivity reactions are rarely observed. The drug is a cytochrome P450 (CYP) 3A substrate and its concentrations may be affected when administered with other CYP3A-modulating medications.

Long-acting CAB and RPV have been studied the most among LA-ARV. For HIV initial treatment, LA-CAB/LA-RPV 400/600 mg given intramuscularly every month after oral daily ARV induction for 20 weeks was shown to be as effective as the recommended oral daily ARV regimens in ARV-naïve individuals who were at least 18 years of age (Table 1). As a continuing treatment regimen in those with virologic suppression on previous ARV regimens for at least 6 months, LA-CAB/LA-RPV was effective in maintaining virologic suppression at 48 weeks as continuing the previous oral daily ARV regimens (Table 1). With these results, the US FDA has approved LA-CAB/LA-RPV as a complete regimen for HIV treatment in adults to replace a current ARV regimen in those who are virologically suppressed on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.[12] This is the first FDA-approved injectable, complete regimen for HIV-infected adults that is administered once a month. The recommended oral lead-in regimen is CAB 30 mg and RPV 25 mg once daily with a meal for at least 28 days, then loading dose to be given on last day of the oral therapy is CAB 600 mg and RPV 900 mg given intramuscularly, followed by continuation therapy to begin 1 month after the loading dose with CAB 400 mg and RPV 600 mg given intramuscularly once a month with allowance for a ±7-day administration window. The purpose of oral induction therapy is to ensure the ARV tolerability before switching to the LA injectable formulation. Adverse reactions and drug-drug interactions should be considered as the use of CAB and RPV individually. The use of carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, and systemic dexamethasone with LA-CAB/LA-RPV is contraindicated due to the significant drug-drug interactions.

Lenacapavir (LEN)

Lenacapavir is a first-in-class, investigational long-acting HIV-1 capsid inhibitor. It interferes several capsid-dependent functions, which are essential for HIV replication, including capsid assembly and disassembly, nuclear transport and virus production.[13] In addition, the drug showed high synergy and no cross-resistance with currently-approved ARVs. Lenacapavir is metabolized via glucuronidation by UGT1A1, and to a lesser extent, CYP3A.

The drug is currently in phase II/III development for HIV treatment. In the study of heavily treatment-experienced individuals with multidrug-resistant HIV infection and failing current ARV regimens, additional of oral LEN induction during the first 2 weeks, followed by subcutaneous LEN every 6 months to the optimal background regimens (OBRs) resulted in improved virologic suppression (Table 2). The drug has also been evaluated for treatment in ARV-naïve HIV-infected persons. The preliminary results demonstrated that the rate of virologic suppression at 16 weeks among individuals who were treated with oral LEN induction during the first 2 weeks, followed by subcutaneous LEN every 6 months in combination with FTC/TAF was 92 - 94% (Table 2). This rate was comparable to the rates among those treated with daily oral LEN/FTC/TAF and bictegravir/FTC/TAF. Resistance analysis of these ongoing phase II/III trials revealed that two participants developed treatment-emergent capsid mutations (M66I and N74D in one participant and M66I in another participant). Both participants had viral rebound above detectable levels and both re-suppressed while on LEN, but one with a change in the OBR and one with no change in the OBR. Although the current ongoing trials are assessing the effectiveness of subcutaneous injection of LEN in combination with once-daily oral ARV drugs, which is not considered

Table 1 Summarized results from clinical trials of long-acting cabotegravir (LA-CAB) and rilpivirine (RPV) for HIV treatment and prevention

Clinical trials [Reference]	Phase	Indication	Sample size	Study population	Country	Study arms	Results/Comments
LATTE-2 [24]	IIb	Treatment	286	18+ year-old, all sexes, ARV naïve, after 20-week CAB/ABC/3TC oral induction	Multicenter: North America and Europe	LA-CAB (400 mg) + LA-RPV (600 mg) IM q 4 weeks LA-CAB (600 mg) + LA-RPV (900 mg) IM q 8 weeks CAB/ABC/3TC (50/600/300 mg) oral q 24 hours	Rate of virologic suppression at 96 weeks LA q 4wk - 87% LA q 8wk - 94% Oral - 84% (NS)
FLAIR [25]	III	Treatment	566	18+ year-old, all sexes, ARV naïve, after 20-week DTG/ABC/3TC oral induction	Multicenter: North America, Europe, Africa, and Asia	LA-CAB (400 mg) + LA-RPV (600 mg) IM q 4 weeks DTG/ABC/3TC (50/600/300 mg) oral q 24 hours	Rate of virologic suppression at 48 weeks LA - 93.6% Oral - 93.3% (NS)
ATLAS [26]	III	Treatment	616	18+ year-old, all sexes, previously on stable ARV regimen ≥ 6 months	Multicenter: North America, Europe, Africa, and Asia	LA-CAB (400 mg) + LA-RPV (600 mg) IM q 4 weeks 2NRTIs + 1NNRTI or boosted PI or unboosted ATV (orally)	Rate of virologic suppression at 48 weeks LA - 92.5% Oral - 95.5% (NS)
ATLAS-2M [27]	IIIb	Treatment	1,045	18+ year-old, all sexes, previously on stable ARV regimen ≥ 6 months	Multicenter: North America, Europe, Africa, and Asia	LA-CAB (400 mg) + LA-RPV (600 mg) IM q 4 weeks LA-CAB (600 mg) + LA-RPV (900 mg) IM q 8 weeks	Rate of virologic suppression at 48 weeks LA q 4wk - 93% LA q 8wk - 94% (NS)

Table 1 Summarized results from clinical trials of long-acting cabotergavir (LA-CAB) and rilpivirine (RPV) for HIV treatment and prevention (Cont.)

Clinical trials [Reference]	Phase	Indication	Sample size	Study population	Country	Study arms	Results/Comments
HPTN 083 [28]	IIb/III	PrEP	4,566	18+ year-old cisgender men and transgender women who have sex with men	Multicenter: North America, Europe, Africa, and Asia	LA-CAB (600 mg) IM q 8 weeks FTC/TDF (200/300 mg) oral q 24 hours	HIV incidence rate LA - 0.41% Oral - 1.22% (The LA regimen was superior than the oral regimen)
HPTN 084 [29]	III	PrEP	3,224	18 - 45 year-old female	Muticenter: Africa	LA-CAB (600 mg) IM q 8 weeks FTC/TDF (200/300 mg) oral q 24 hours	HIV incidence rate LA - 0.21% Oral - 1.79% (The LA regimen was superior than the oral regimen)

Note: 3TC = lamivudine; ABC = abacavir; ARV= antiretroviral drug; ATV = atazanavir; CAB = cabotegravir; DTG = dolutegravir; FTC = emtricitabine; HIV = human immunodeficiency virus; LA = long acting; NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTIs = nucleoside reverse transcriptase inhibitors; NS = non-statistically significant difference; PI = protease inhibitor; PrEP = pre-exposure prophylaxis; TDF = tenofovir disoproxil fumarate.

as a true LA-ARV regimen, the LA formulation of LEN has a potential to be studied and used with other LA-ARV formulations in the future. For HIV prevention, further clinical trials evaluating use of LEN as injectable PrEP are currently planned.

The most common adverse reaction of LA-LEN is injection site reactions (ISRs), including swelling, erythema, nodule, and pain. The majority of these ISRs were grade I and resolved spontaneously within days. Other common adverse reactions occurring in at least 5% of participants in the clinical trials included headache, nausea, cough, diarrhea, back pain, pyrexia, rash, and urinary tract infection. Co-administering LEN with strong CYP3A and P-gp inhibitors, resulted in increased LEN area under the curve (AUC). These interactions, however, are not considered clinically significant. Until further data is available, co-administration of LEN with strong UGT1A1 inhibitors or potent inducers of CYP3A/P-gp/UGT, such as rifampicin, is currently not recommended.[14]

Islatravir (ISL)

Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor. It uniquely inhibits reverse transcriptase of the HIV to suppress viral replication by multiple mechanisms of action, including inhibition of translocation. The drug has potent activity against HIV-1 and is also active against HIV-2 and multidrug-resistant HIV strains. The 4′-ethynyl group of ISL blocks primer translocation and causes chain termination during the viral RNA transcription, while the 2-fluoro group protects ISL from being metabolized by adenosine deaminase, contributing to its long half-life.[15] The plasma half-life of ISL after oral administration is 50 - 60 hours, while the intracellular half-life of ISL triphosphate is 130 - 210 hours. In an open-label phase Ib trial, a single dose of ISL 0.5 mg could suppress plasma HIV-1 RNA for at least 7 days.[16] Based on this result, the extended period of viral suppression is most-likely achievable by administration higher doses of ISL.

Oral ISL has been evaluated in the phase II and III studies for use as monthly PrEP (Table 2). The phase II study mainly assesses adverse events of ISL given at the dose of 60 mg and 120 mg monthly, while the phase III studies are conducted to determine effectiveness in HIV prevention of ISL 60 mg in comparison with FTC/TDF and FTC/TAF in cisgender female, and cisgender male and transgender women who have sex with men. All of these studies are ongoing and their results have not been reported. The IMAGINE-DR clinical trial (MK-8591-013) is a phase II, randomized, controlled, double-blind, dose-ranging study, designed to evaluate a switch to MK-8507 and ISL in combination as a once-weekly oral treatment in adults with HIV who have been virologically suppressed for greater than or equal to six months on bictegravir (BIC)/FTC/TAF once-daily.[17] Decreases in total lymphocyte and CD4+ T-cell counts were observed in study participants randomized to receive combined ISL and MK-8507. After a review by the external Data Monitoring Committee, this effect was related to treatment with the combination regimen and the greatest decreases were seen in the arms of the study receiving the highest doses of MK-8507 (200 mg and 400 mg). The trial was then stopped prematurely, however, given the overall profile of ISL, this drug still has a potential to be further studied for its use in combination with other LA-ARV drugs for HIV treatment.

Based on the successful use and drug delivery of implantable contraceptives, ISL has been developed in a form of a non-degradable subcutaneous polymer implant that slowly releases the drug from a biodegradable matrix. The half-live of this ISL implant was approximately 100 days in a study of rat models.[18] A phase I study of radiopaque ISL eluting implants suggests adequate drug release for HIV prevention for at least one year.[19] The drug is currently evaluated for adverse events in a phase II study comparing ISL 47 mg, 52 mg, or 57 mg implantable rods with placebo (Table 2).

Most ISL-related AEs preliminarily reported in the phase II study were mild in intensity, with the most common AEs overall being headache, diarrhea, and nausea. Islatravir does not interact with renal or hepatic drug transporters or major enzymes involved in drug metabolism, including CYP enzymes and UGT1A1.

Ibalizumab

Ibalizumab is a humanized IgG4 antibody that binds to the extracellular CD4 domain and prevents HIV from entering the host cell. In a s ingle-group, open-label, phase III study conducted in adults with multidrug-resistant (MDR) HIV-1 infection in whom multiple antiretroviral therapies

Table 2 Summarized ongoing studies of lenacapavir (LEN) and islatravir (ISL) for HIV treatment and prevention

Clinical trials [Reference]	Phase	Indication	Sample size	Study population	Country	Study arms	Results/Comments
CAPELLA [30]	II/III	Treatment	36 (cohort 1)	12+ year-old, all sexes, with multidrug-resistant HIV and VL > 400 copies/ml at baseline	Multicenter: North and Central America, Europe, Africa and Asia	- Oral LEN (600, 600 and 300 mg) for 14 days then SC LEN 927 mg q 6 months with OBR - Oral placebo for 14 days then oral LEN (600, 600 and 300 mg) for 14 days then SC LEN 927 mg q 6 months with OBR	Rate of virologic suppression 81% (combined results of the two arms)
CALIBRATE [31]	II	Treatment	182	18+ year-old, all sexes, ARV-naïve	United States, Dominican Republic and Puerto Rico	- Oral LEN (600, 600 and 300 mg) for 14 days then SC LEN 927 mg q 6 months with FTC/TAF (200/25 mg) for 28 weeks then TAF (25 mg) daily - Oral LEN (600, 600 and 300 mg) for 14 days then SC LEN 927 mg q 6 months with FTC/TAF (200/25 mg) for 28 weeks then BIC (75 mg) daily - Oral LEN (600, 600, 300 and 50 mg daily) and FTC/TAF (200/25 mg) daily - Oral BIC/FTC/TAF (75/200/25 mg) daily	Rate of virologic suppression at 16 weeks LEN + FTC/TAF and TAF - 92% LEN + FTC/TAF and BIC - 94% LEN + FTC/TAF daily - 94% BIC/FTC/TAF - 100% (NS)

Table 2 Summarized ongoing studies of lenacapavir (LEN) and islatravir (ISL) for HIV treatment and prevention (Cont.)

Clinical trials [Reference]	Phase	Indication	Sample size	Study population	Country	Study arms	Results/Comments
Islatravir IMPOWER-022 [32]	III	PrEP	4,500	16 - 45 year-old cisgender female	United States, South Africa, and Uganda	- Oral ISL (60 mg) monthly + Placebo of FTC/TDF daily - Oral FTC/TDF (200/300 mg) daily + Placebo of ISL monthly	HIV incidence rate: not reported (ongoing study)
IMPOWER-024 [33]	III	PrEP	1,500	16+ year-old cisgender men and transgender women	United States, France, Japan, Peru, South Africa, Thailand, and Brazil	- Oral ISL (60 mg) monthly + Placebo of FTC/TDF or FTC/TAF daily - Oral FTC/TDF (200/300 mg) or FTC/TAF (200/25 mg) daily + Placebo of ISL monthly	HIV incidence rate: not reported (ongoing study)
MK-8591-016 [34]	II	PrEP	250	18 - 65 year-old, all sexes, low risk for HIV infection	United States, Israel, and South Africa	- Oral ISL (60 mg) + Placebo of ISL monthly - Oral ISL (120 mg) monthly - Placebo of ISL monthly	Adverse events: not reported (ongoing study)
MK-8591-043 [35]	II	PrEP	175	18 - 55 year-old, all sexes, low risk for HIV infection	No study site provided	- ISL 47 mg, 52 mg or 57 mg implantable rods placed subdermally in the upper arm - Placebo implantable rod placed subdermally on the upper arm	Adverse events: not reported (ongoing study)

Note: BIC = bictegravir; FTC = emtricitabine; HIV = human immunodeficiency virus; NS = non-statistically significant difference; OBR = optimal baseline regimen; PrEP = preexposure prophylaxis; SC = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; VL = viral load.

had failed, ibalizumab plus an optimized background regimen decreased a mean of HIV viral load of 1.6 log10 copies/ml from baseline, 43% of the patients had a viral load of less than 50 copies/ml, and 50% had a viral load of less than 200 copies/ml at week 25.[20] Ibalizumab is the first monoclonal antibody that has been approved from the US FDA to be used with other antiretroviral drugs for treatment of MDR HIV infection.[21] The recommended dosing is intravenous injection as a single loading dose of 2000 mg, followed by maintenance doses of 800 mg injected intravenously every 2 weeks. Compared to other LA-ARV drugs, ibalizumab has the disadvantage of requiring a shorter administration interval. In addition, if a maintenance dose is missed by 3 days or more, a loading dose has to be re-administered. This may lead to potential discomfort for the patients and incurs cost. However, ibalizumab could still serve as a part of novel ARV regimens for heavily treatment-experienced adults infected with MDR HIV. Most of the AEs of ibalizumab were mild to moderate and included diarrhea, nausea, fatigue, fever, rashes, and dizziness.[20] Because ibalizumab is a therapeutic protein, it has a potential to trigger immunogenicity. Nonetheless, such AE has not yet been reported.

Challenges and Future Directions for LA-ARV Formulations

Although the new LA-ARV formulations seem to be promising options for HIV treatment and prevention, several challenges need to be considered along with appropriate solutions. First, the prolonged terminal decay or "PK tail" after discontinuation of the LA-ARVs can lead to non-viral suppressible level of the drugs and resistance development. It is therefore recommended to initiate a daily oral ARV regimen as soon as the LA-ARVs discontinuation is considered and PLHIV need to be informed and compliant to this practice. Second, although the overall drug-drug interaction (DDI) risk seems to be smaller than the oral ARV regimens, there are other drug transporters and metabolizing enzymes in skeletal muscles and subcutaneous adipose tissues causing DDI and require further investigations for these LA-ARVs. Third, administration of the LA-ARVs, in particular via injection or subdermal implantation, requires infrastructure resources including trained personnel who can administer the drugs, appropriate shipment and storage, and selection of appropriate PLHIV to receive the drugs. Fourth, given the LA formulations are new technologies, acceptability, worries and misconceptions of PLHIV, drug access, cost, and medical coverage will need to be assessed and resolved accordingly before implementation. Lastly, to improve satisfaction and adherence to the LA-regimens, development of newer formulations should be focused on reducing injection-induced pain and use of ARV-refillable and durable implant to obliterate the need for surgical removal or insertion of the device.

According to an analysis of the COVID-19 pandemic's impact on dosing in 6 ongoing global phase IIb and IIIb clinical trials of LA-CAB/LA-RPV with 1744 study participants, a total of 129 (7%) had injection site visits that were impacted by COVID-19.[22] Of these 129 participants, clinical closure or staffing constraints interrupted dosing for 54 (42%) participants; self-quarantine interrupted dosing for 11 (9%) participants; confirmed or suspected COVID-19 infection interrupted dosing for 11 (9%) participants; and 46 (36%) participants cited other reasons for dosing interruption. A few mitigation strategies were implemented, including short-term oral therapy with CAB and RPV for 94 participants (73%), short-term standard-of-care ART for 27 participants (21%), and rescheduling of long-acting injections for 7 participants (5%). There have been no reports of suspected or confirmed virologic failure for any of the participants impacted by COVID-19. The CUSTOMIZE study which is a phase IIIb, 12-month, hybrid III implementation-effectiveness study evaluating the implementation of LA-CAB/LA-RPV in US healthcare settings from the perspectives of healthcare providers and PLHIV demonstrated that LA-CAB/LA-RPV implementation remained highly acceptable and appropriate among healthcare staff and participants during the COVID-19 pandemic.[23] Acceptability of attending monthly clinic visits, preference for LA-ARV drugs, and treatment effectiveness remained high among the participants, including those with COVID-19 impacted visits. These findings suggest that LA-CAB/LA-RPV is an appealing treatment option from the perspective of both healthcare providers and PLHIV despite healthcare disruptions caused by the COVID-19 pandemic.

The current and ongoing development of LA formulations of ARV would potentially have

major impact on HIV treatment and prevention soon. Generally, PLHIV could benefit from these LA regimens regarding improved satisfaction and adherence and feasibility of use during pandemics. The LA-CAB/LA-RPV and LA-CAB are currently approved for HIV treatment and prevention, respectively. However, their dosing intervals are to be further studied for extension. Alternatively, implantable LA-ARVs may serve as even more convenient options, while oral LA-ARVs could become the best regimens for long term use once these drugs have been adequately evaluated and proven for their effectiveness. Further studies are warranted to evaluate effectiveness and adverse effects of LA-ARVs, address challenges and provide appropriate solutions for practical use in the real-life situation and during pandemics.

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