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SPECIAL ARTICLE

Consensus recommendations for use of long-acting antiretroviral medications in the treatment and prevention of HIV-1: Endorsed by the American Academy of HIV Medicine, American College of Clinical Pharmacy, Canadian HIV and Viral Hepatitis Pharmacists Network, European AIDS Clinical Society, and Society of Infectious Diseases Pharmacists

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Abstract

Five long-acting (LA) antiretrovirals (ARVs) are currently available in a limited number of countries worldwide for HIV-1 prevention or treatment—cabotegravir, rilpivirine, lenacapavir, ibalizumab, and dapivirine. Implementing use of LA ARVs into routine clinical practice requires significant changes to the current framework of HIV-1 prevention, treatment, and service provision. Given the novelty, complexity, and interdisciplinary requirements needed to safely and optimally utilize LA ARVs, consensus recommendations on the use of LA ARVs will assist clinicians in optimizing use of these agents. The purpose of these recommendations is to provide guidance for the clinical use of LA ARVs for HIV-1 treatment and prevention. In addition, future areas of research are also identified and discussed.

KEYWORDS
antiretrovirals, HIV, long acting, pre-exposure prophylaxis, prevention, treatment

For affiliations refer to page 529.

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1 | BACKGROUND

Long-acting (LA) antiretrovirals (ARVs) recently received approval for the treatment and prevention of HIV-1, representing a significant advancement in the delivery of antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP). The introduction of these LA agents provides an alternative to the requirement for daily oral medication for preventing and treating HIV-1. In this context, and in accordance with US Department of Health and Human Services (HHS) HIV guidelines, the term LA refers to any ARV that is dosed once weekly or less frequently.[1] LA medications may be delivered orally, topically, intravaginally, or parenterally. Medications may be LA because of their inherent pharmacokinetic properties (e.g., long elimination half-life), modified medication formulations (e.g., nanoformulations), or because of a sustained delivery device (e.g., vaginal rings, implants). Five ARVs are currently available as LA options for HIV-1 prevention or treatment and are available in a limited number of countries worldwide. Individual characteristics and availability of these LA ARVs are summarized in Table 1.

The first approved complete LA ART for maintenance HIV-1 treatment includes the integrase strand transfer inhibitor (INSTI) cabotegravir (CAB) and non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV). LA CAB administered alone is indicated for PrEP. While both medications are also available as oral once-daily tablets, the intramuscular (IM) injection of each product is LA due to a characteristic known as flip-flop kinetics.[5] In flip-flop kinetics, the slow absorption of the drug from the depot injection site determines its elimination half-life rather than the drug's metabolism and elimination. This change in product formulation allows for every 4 weeks or every 8 weeks IM injection compared with daily oral administration. LA CAB and RPV are both administered via ventro- or dorsogluteal injections. However, alternative routes of administration (e.g., thigh muscle) and formulations to reduce the injection volume are being investigated.[6–8]

Lenacapavir (LEN) is a first-in-class capsid inhibitor with high picomolar potency against all subtypes of HIV-1 and no known cross-resistance to existing ARV classes. It is administered via subcutaneous (SC) injection every 6 months. LEN is approved for use in combination with an optimized background regimen (OBR) of other ARVs in heavily treatment-experienced adults with multidrug-resistant HIV-1, for whom it is otherwise not possible to construct a suppressive regimen.[9] LEN has low systemic clearance, resulting in a half-life longer than 1 week for the oral product, and greater than 2 months for the SC injection due to slow-release kinetics. Oral LEN is being studied in combination with other oral ARVs for the treatment of naïve patients,[10] while injectable LEN is being studied as a single agent administered subcutaneously every 6 months for PrEP.[11–14]

Ibalizumab (IBA) is a CD4 post-attachment inhibitor, administered intravenously (IV) every 2 weeks. IBA use is limited to heavily treatment-experienced adults with multidrug-resistant HIV-1 failing their current ARV regimen, and therefore must be combined with an OBR of other ARVs to form a complete treatment regimen. IBA is a monoclonal antibody of immunoglobulin G and is LA due to pharmacokinetics and pharmacodynamics of the drug without modification of the formulation. While IBA is currently only approved for IV administration, a Phase 1/2 study demonstrated comparable pharmacokinetic profiles between IM and IV administration of IBA.[15] A Phase 3 study for IM injection has been initiated; upon trial completion, the manufacturer is planning to apply for label extension to allow for IM administration.[16] Data on other modes of IBA administration including IV push,[17] which was recently approved, and SC injection[18] are promising because they may offer greater patient convenience.

Dapivirine (DPV), an NNRTI, is indicated for use alone as PrEP. DPV is available in a sustained release vaginal ring delivery system that delivers DPV over 1 month. The DPV vaginal ring is not available in the United States and Europe and is unlikely to be approved in these regions in the future. However, DPV has received a positive opinion from the European Medicines Agency,[19] a World Health Organization recommendation,[20] and has been approved in several countries in eastern and southern Africa. A 3-month ring and a ring co-formulated with hormonal contraception are currently in development.[21,22]

Implementing use of LA ARVs into routine clinical practice requires significant changes to the current framework of HIV-1 prevention, treatment, and service provision. Aside from new clinical challenges including unique pharmacokinetics, drug interactions, toxicities, and resistance profiles, there are many complex implementation challenges to consider. An interdisciplinary team of trained individuals is required to ensure patient eligibility and medication affordability as well as the acquisition, delivery, storage, and administration of the LA agents. Procedures for transitions of care, missed, or delayed doses, conversions to oral ART, use in special populations including pregnancy, children and adolescents, populations with adherence challenges, and the management of treatment failure will also be required.

Implementing LA ARVs in low- and middle-income countries may be limited by several challenges including cost and infrastructure. Furthermore, implementation strategies must carefully consider unique contextual issues such as health system strengthening and adaptability for innovative service delivery models; policy climates, inclusion in national guidelines and reimbursement systems; long-term sustainability amid limited availability of human and financial resources; and harnessing, creating, and sustaining demand for the product.[23–25] Low- and middle-income nations are highly diverse and therefore to facilitate the success of LA ARV availability and uptake, it is important to involve communities in the planning and implementation of LA ARV programs. This will help to ensure that programs are locally tailored, culturally appropriate, and that people with HIV or at risk of HIV acquisition have a voice in designing programs intended to advance clinical care of HIV treatment or prevention. Despite high-income countries having more readily available resources and infrastructure to support LA ARV implementation than low- and middle-income countries, there are still challenges to overcome, particularly in geographic hotspots, to ensure equitable access to LA ARVs for people with HIV or at risk of HIV acquisition.[26]

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TABLE 1 Characteristics of long-acting antiretrovirals for HIV-1 treatment and prevention.

	Cabotegravir	Rilpivirine	Lenacapavir	Ibalizumab	Dapivirine
Class	INSTI	NNRTI	Capsid inhibitor	Entry inhibitor	NNRTI
Formulation (s)	Oral tablet, suspension for injection	Oral tablet, suspension for injection	Oral tablet, solution for injection	Solution for injection	Vaginal ring
Half-life (t1/2)	Oral: 41 h IM: 5.6–11.5 weeks	Oral: 45 h IM: 13–28 weeks	Oral: 10–12 days SC: 8–12 weeks	IV: 72–84 h[2]	13 h (vaginal fluid), 82 h (plasma)
Indication	*CAB/RPV*: As a complete regimen for treatment of HIV-1 in virologically suppressed adults/adolescents 12 years of age and older and weighing ≥35 kg		Treatment of multidrug-resistant HIV-1 in combination with other antiretrovirals in adults who cannot otherwise construct a suppressive regimen	Treatment of multidrug-resistant HIV-1 in combination with other antiretrovirals in adults failing their current antiretroviral regimen	To reduce risk of HIV-1 via vaginal intercourse in females without HIV-1 who are 18 years and older
	To reduce the risk of sexually acquired HIV-1 in adults/adolescents weighing ≥35 kg	N/A—only for use in combination with CAB as described above			
Dose (HIV-1 treatment)	*Oral lead-in (optional)*: 30 mg CAB +25 mg RPV once daily with a meal for ≥28 days *Q4 Week Dosing*: *Initiation injection*: 600 mg CAB/900 mg RPV IM × 1 *Continuation injections*: 400 mg CAB/600 mg RPV IM q4 weeks *Q8 Week Dosing*: *Initiation injections*: 600 mg CAB/900 mg RPV IM q4 weeks × 2 *Continuation injections*: 600 mg CAB/900 mg RPV IM q8 weeks		Step-by-step initiation: 600 mg orally (Days 1 and 2), 300 mg orally (Day 8), 927 mg SC (Day 15) Same-day initiation: 600 mg orally plus 927 mcg SC (Day 1), 600 mg orally (Day 2) Maintenance: 927 mg SC every 6 months (26 weeks)	Single loading dose of 2000 mg IV, followed by maintenance dosing of 800 mg IV every 2 weeks	N/A
Dose (PrEP)	*Oral lead-in (optional)*: 30 mg CAB once daily for ≥28 days *Initiation injections*: 600 mg (3 mL) IM q4 weeks × 2 *Continuation injections*: 600 mg IM q8 weeks	N/A	Investigational: Day 1: 600 mg orally and 927 mg SC Day 2: 600 mg orally Every 26 weeks: 927 mg SC	N/A	Vaginal ring containing 25 mg and replaced once monthly
Adjustment in renal/hepatic dysfunction	Mild/moderate renal or hepatic dysfunction: none Child-Pugh C: use with caution CrCl<30 mL/min or ESRD: increased monitoring for adverse events		Mild, moderate, severe renal impairment, or mild/moderate hepatic impairment: none Child-Pugh C: use with caution CrCl<15 mL/min or ESRD: use with caution	None	None
Missed maintenance doses[a]	Patients on q4 weeks CAB/RPV ≤2 months since last injection: Resume with continuation dosing schedule >2 months since last injection: Resume with initiation dosing schedule Patients on q8 weeks CAB/RPV (starting at month 4, 3rd injection) ≤3 months since last injection: Resume with continuation dosing schedule >3 months: Resume with Initiation dosing schedule		If more than 28 weeks have elapsed since the last injection, restart at Day 1 of initiation schedule.	If a maintenance dose is missed by 3 days or longer, a loading dose should be administered as soon as possible. Maintenance dosing can be resumed thereafter.	If ring accidentally falls out/is removed: Rinse ring in clean water and re-insert; if ring has touched something unhygienic, discard and insert new ring immediately.
	≤3 months since last injection: Resume Continuation dosing schedule >3 months: Resume with Initiation dosing schedule	N/A			

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TABLE 1 (Continued)

	Cabotegravir	Rilpivirine	Lenacapavir	Ibalizumab	Dapivirine
Administration	Bring vials to room temperature (~15 minutes) before drawing into syringe. Drug may be kept outside of the refrigerator for 6 h in the original packaging, or for 2 h once drawn into a syringe. Administer each injection at separate gluteal injection sites (on opposite sides or at least 2 centimeters apart) using a z-track technique during the same visit. The ventrogluteal site is recommended. A dorsogluteal approach (upper outer quadrant) is acceptable, if preferred. Although a 1.5-inch needle is provided in the product packaging, a 2-inch needle may be required to reach the gluteus muscle in individuals with BMI ≥30 kg/m^2.		Administer as two 1.5 mL SC injections at separate sites in the abdomen at least 5 cm from navel. Use of a vial access device (provided in the injection kit) is required.	Dilution in 250 mL 0.9% normal saline. Infuse loading dose over at least 30 min, observe patient for 1 h after completion. If no infusion-associated reactions have occurred, subsequent maintenance doses can be infused over 15 min. The maintenance dose can also be administered as an undiluted IV push over 30 s.	Insert ring into vagina and keep in place for 1 month. Remove ring and immediately insert new ring each month. Do not remove during menses.
Metabolism	Substrate of UGT1A1 (major), UGT1A9 (minor)	Substrate of CYP3A	Substrate of UGT1A1, P-gp and CYP3A4 (minor)	Broken down into small peptides and amino acids	Substrate of CYP3A4, UGT1A1.
Drug–drug Interactions (DDIs)	IM and PO: Contraindicated with strong inducers of UGT1A1 or 1A9. PO: dose apart from polyvalent cation products (e.g., antacids)	IM and PO: Contraindicated with strong inducers of CYP3A4. Caution with drugs with a known risk of Torsade de Pointes. PO: contraindicated with proton pump inhibitors	Contraindicated with strong inducers of CYP3A4/P-gp/UGT1A1. Not recommended with moderate inducers of CYP3A4 and P-gp, and with strong inhibitors of CYP3A4, P-gp, and UGT1A1 together.	Not anticipated	Low risk of systemic drug–drug interactions; may inhibit CYP enzymes in the vaginal tissues. Use additional HIV preventative measures when co-treated with vaginal miconazole
Side effects (>1% in clinical trials)	Injection site reactions (38–82%), diarrhea (4%), headache (4%–12%), pyrexia (<1%–4%), fatigue (3%–4%), sleep disorders (1%–3%), nausea (3%–4%), dizziness (2%–4%)	Injection site reactions (83%), pyrexia (8%), fatigue (5%), headache (4%), musculoskeletal pain (3%), nausea (3%), sleep disorders (2%), dizziness (2%), rash (2%)	Injection site reactions (63%), nausea (4%)	Diarrhea (8%), dizziness (8%), nausea (5%), rash (5%)	Urinary tract infection (15%), vaginal discharge (7%), vulvovaginal pruritus (7%), vulvovaginitis (6%), pelvic pain (6%)
Lab abnormalities	Increased ALT (<1%)	Increased CK, AST, ALT, lipase	Increased creatinine (13%), AST, ALT, bilirubin. Glucosuria, hyperglycemia, proteinuria.	Increased creatinine (10%), bilirubin, lipase. Leukopenia, neutropenia (each 5%).	Minimal; Limited data regarding treatment-emergent lab abnormalities reported in clinical trials

(Continues)

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TABLE 1 (Continued)

	Cabotegravir	Rilpivirine	Lenacapavir	Ibalizumab	Dapivirine
Availability	CAB/RPV (HIV-1 treatment): Licensed in the US, Canada, Australia, EU, UK, China, Japan, Switzerland, Norway CAB (PrEP): Licensed in the US, Australia, EU, Botswana, Brazil, Malawi, South Africa, and Zimbabwe. Submitted for approval in other countries including Kenya, Uganda[3]		Licensed in the US, Canada, UK, EU, and Canada, Australia, Israel, Japan, Switzerland, and the United Arab Emirates	Licensed in the US. Previously approved in the EU but later withdrawn from market; available via a named patient program.	Approved in several African countries including Botswana, Kenya, Rwanda, South Africa, Uganda, Zambia, Zimbabwe[4]

Abbreviations: ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate transaminase; CAB, cabotegravir; CK, creatine kinase; CrCl, creatinine clearance; CYP450, cytochrome P450; ESRD, end stage renal disease; EU, European Union; IM, intramuscular; INSTI, integrase strand transfer inhibitor; IV, intravenous; N/A, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gp, P glycoprotein; PrEP, pre-exposure prophylaxis; q, every; RPV, rilpivirine; SC, subcutaneous; UGT, uridine diphosphate glucuronosyltransferase; UK, United Kingdom; US, United States.

[a]Management of missed doses of CAB for PrEP or CAB/RPV for ART vary when the missed dose occurs during the induction period. Refer to product labeling for guidance.

Overall, the implementation of LA ARVs for HIV treatment and prevention in low- and middle-income countries will require a concerted effort from governments, donors, and civil society organizations. However, the potential benefits of LA ARVs are significant, and with appropriate planning and safeguarding of resources and personnel, low- and middle-income countries may overcome the challenges of LA ARV program implementation to support better health outcomes among people with HIV or at risk of HIV acquisition.

Given the novelty, complexity, and interdisciplinary requirements needed to safely and optimally consider and procure drug (including variable pay or coverage) for diverse patient groups in different practice settings, along with supporting and scaling caseloads and programs, consensus recommendations on the use of LA ARVs will assist the clinician in optimizing use of these agents. This practice guideline provides consensus recommendations pertaining to the clinical use of LA ARV agents for HIV-1 prevention and treatment.

2 | METHODS

2.1 | Consensus panel composition

The Consensus Panel consisted of 18 multidisciplinary members from North America and Europe with diverse expertise in clinical practice and research including physicians, advanced practice providers, and pharmacists. The authors were diverse in geographic location, practice settings, race, ethnicity, and gender. They represent membership in the endorsing organizations (the American Academy of HIV Medicine [AAHIVM], the American College of Clinical Pharmacy [ACCP], the Canadian HIV/Viral Hepatitis Pharmacists Network [CHAP], European AIDS Clinical Society [EACS], and the Society of Infectious Disease Pharmacists [SIDP]). We acknowledge that all contributors to this manuscript reside in high-income countries, which may limit the applicability of these recommendations to low- and middle-income countries that face unique challenges to LA ARV program development and implementation such as limited access to specialized equipment and trained personnel. However, we believe that these recommendations have the potential to be adapted for use in countries with limited resources.

2.2 | Consensus development based on evidence

Consensus Panel members developed the list of clinical questions included in the review and were assigned key topics contributing to current knowledge and optimal utilization of LA ARVs. A draft document addressing these specific areas including recommendations was developed, written, reviewed, and approved by all panel members through a series of meetings. After review by members of AAHIVM, ACCP, CHAP, EACS, and SIDP, the panel met to review and revise the document based on the submitted comments, suggestions, and recommendations. After careful discussion and consideration, the

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document was revised and circulated among panel members and supporting societies for final approval and publication.

2.3 | Literature review and analysis

The recommendations in this guideline were developed following a review of English language literature published before March 1, 2023. Data available after the concluding date of the literature search were considered for inclusion if they were deemed to be of sufficient significance to either alter the strength of evidence or provide a recommendation for an otherwise unanswered question due to insufficient or contradictory evidence. Studies were identified through PubMed and Embase database, clinicaltrials.gov database, and HIV conference abstract searches using the search terms listed in Table S1. All study types (primary reports and systematic reviews) were included within the searches. Priority was given to evidence from randomized controlled trials or meta-analyses. However, lower level evidence, including abstracts, was reviewed in absence of higher quality data or published manuscripts. Members independently evaluated published articles retrieved from the literature search, secondary article citations, and abstracts from recent professional meetings before coming to consensus for all summary statements.

2.4 | Process overview

To evaluate evidence, the panel employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for both quality of evidence and strength of recommendation.[27] The GRADE system classifies the quality of evidence in one of four levels (high [A], moderate [B], low [C], and very low [D]) and offers two strengths of recommendations (strong and weak). Additional details on the GRADE criteria appear in Table 2. Panel members were divided into groups consisting of a primary lead author and coauthors for each section. Authors reviewed the literature, evaluated the evidence, determined the strength of the recommendation, and supplied an evidence summary for each recommendation. The panel reviewed all recommendations, strength of recommendations, and quality of evidence. Discrepancies were discussed and resolved.

3 | CLINICAL QUESTIONS AND RECOMMENDATIONS

1. What is the evidence for using LA ARVs for the treatment of HIV-1?

Consensus recommendations

1.1 We recommend HIV-1 treatment using LA CAB/RPV as an alternative to oral ART among individuals who are virologically suppressed and otherwise clinically eligible.

Quality of evidence	A
Strength of recommendation	1

1.2 We recommend LA IBA and/or LEN may be added to an optimized background regimen for heavily treatment-experienced adults with multidrug-resistant HIV-1 with limited anticipated activity from oral ART agents alone.

Quality of evidence	B
Strength of recommendation	1

Evidence summary

Evidence for using CAB/RPV for HIV-1 treatment in adults is supported by the Phase 3 ATLAS and FLAIR studies. In ATLAS (an open-label trial of ART-experienced people 18 years of age or older with HIV-1 who were virologically suppressed for at least 6 months on standard oral therapy including INSTIs, protease inhibitors (PIs) or NNRTI regimens, all with nucleoside reverse transcriptase inhibitor (NRTI) backbones), participants were randomized to either continue daily oral ART, or switch to LA injectable CAB/RPV IM after receiving a 30-day oral lead-in (OLI) to assess tolerability. Following the OLI phase, loading dose injections of CAB and RPV were administered, followed by every 4-week injections.[28] 93% of patients completed the

TABLE 2 GRADE criteria.[27]

Level of evidence	Quality certainty	Meaning
A	High	The true effect is close to the estimated effect
B	Moderate	The true effect is probably close to the estimated effect
C	Low	The true effect may be markedly different from estimated effect
D	Very low	The true effect is probably markedly different from estimated effect
Recommendation level	**Strength of recommendation**	**Meaning**
1	Strong	Panel confident recommendation benefit outweighs risk
2	Weak	Panel uncertain, consider individual patient factors

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maintenance phase of the study. At week 48 of this non-inferiority study, HIV-1 RNA ≥50 copies/mL was observed in five participants (1.6%) in the LA injectable group compared with three (1%) in the daily oral therapy group, meeting the non-inferiority criterion of the study. A follow-up study, ATLAS-2 M,[29] demonstrated non-inferiority at 48 weeks between dosing LA injectable CAB/RPV every 8 weeks compared with every 4 weeks.[29] Of note, there were eight (2%) versus two (<1%) confirmed virologic failures (two sequential HIV-1 RNA measurements ≥200 copies/mL) in the every 8- versus every 4-week groups, with 63% (5/8) of patients in the former group found to have archived RPV-associated resistance mutations at baseline.

FLAIR was designed similarly to ATLAS, that is, as a randomized, open-label multicenter study of LA CAB/RPV designed as a non-inferiority trial. However, FLAIR enrolled people 18 years of age or older with HIV-1 who were ARV treatment-naïve. Participants who achieved virologic suppression after 20 weeks of oral daily dolutegravir/abacavir/lamivudine were randomized 1:1 to continued oral standard of care or LA CAB/RPV every 4 weeks; the latter was shown to be non-inferior to daily oral ART.[30]

Durable efficacy of LA CAB/RPV through 96 weeks was demonstrated in ATLAS, ATLAS-2 M, and FLAIR.[30–32] Furthermore, initiating LA CAB/RPV without an OLI (also known as direct-to-injection, DTI) has been shown to be safe, tolerable, and efficacious. Accordingly, the CAB/RPV OLI is deemed optional.[33] Of note, data from use of LA CAB/RPV in real-world settings, administered to patients with high levels of substance use and marginal housing, resulted in viral suppression among those undetectable and among those with viremia at baseline.[34,35] At this time, guidelines recommend LA CAB/RPV as an HIV treatment switch strategy in individuals with virologic suppression[1]; however, AIDS Clinical Trials Group 5359 is an ongoing Phase 3 clinical trial evaluating the effectiveness of LA CAB/RPV versus daily oral ART in persons with HIV-1 and a history of suboptimal treatment adherence and virologic control.[36]

Overall, LA CAB/RPV for HIV-1 treatment has been shown to be safe, tolerable, and acceptable among clinical trial participants. Across trials, adverse events were experienced more commonly among those who received LA injectable versus daily oral ART, and this was primarily related to injection site reactions (ISRs). Among ATLAS participants, 83% in the LA therapy group reported ISRs at 48 weeks with the majority of reactions (99%) being mild or moderate. ISRs consisted of pain (75% of participants), nodules (12%), induration (10%), and swelling (7%); and 88% of ISRs resolved within seven days (median three days). The frequency of ISRs significantly decreased over time (e.g., in FLAIR, from 72% to 23% to 18% of participants at Weeks 4, 48, and 96, respectively). In the pooled 48-week results from ATLAS and FLAIR, a total of six participants in the long-acting ART group (1%) withdrew from the study due to ISRs, all reporting injection site pain.[37] Other than ISRs, the most severe adverse events reported as being related to the LA therapy were pyrexia, nausea, diarrhea, headache, and grade 4 lipase increase. The incidence of serious adverse events was similar in the LA and daily oral therapy groups, occurring in 4%–5% and 8% of participants in ATLAS and FLAIR, respectively. Rates of adverse events in the LA injectable arm, as well as frequency of ISRs, at 48 weeks were similar between females and males (sex at birth) in a pooled 48-week analysis of ATLAS and FLAIR results.[37] No new safety signals were identified through 96 weeks. In ATLAS and FLAIR, participants who received LA injectable therapy had substantially higher treatment satisfaction scores compared with those receiving oral ART.

With respect to body weight change, a pooled analysis of 48-week results from ATLAS and FLAIR found that mean (standard deviation) weight increased from baseline by 2.34 (5.67) kg and by 1.17 (5.22) kg in the LA injectable and daily oral ART arms, respectively.[37] Among FLAIR participants at 96 weeks, median weight change from baseline was similar between both treatment groups and consistent with those reported previously in clinical trials of oral ART.[38] Of note, the weight gain observed among ATLAS and FLAIR participants was not associated with significant changes in lipid levels or other metabolic parameters. Additionally, there was no evidence that the weight gain was associated with other adverse clinical outcomes.

Furthermore, SOLAR was a randomized, open-label, Phase 3 multicenter non-inferiority trial that compared use of LA CAB/RPV every 8 weeks with continued daily oral bictegravir/tenofovir alafenamide/emtricitabine for the maintenance of virologic suppression.[39] At 12 months, HIV-1 RNA ≥50 copies/mL was observed in five participants (1%) in the LA injectable arm and one participant (<1%) in the daily oral therapy arm, thus meeting the non-inferiority criterion of the study. There were two confirmed virologic failures with on-time injections in the LA injectable arm of the modified intention-to-treat population, both with on-treatment RPV or INSTI resistance-associated mutations. LA CAB/RPV was well tolerated with the most common adverse events being ISRs (grade 1 or 2) and mild headache. Treatment satisfaction was greater among participants in the LA injectable arm compared with those continuing daily oral therapy.

Evidence for using LEN in highly treatment-experienced people with multidrug-resistant HIV-1 is supported by the Phase 3 CAPELLA trial. The population included persons ≥12 years old. Participants had a median age of 52 years, were 25% female, 38% Black race, and 21% Hispanic/Latinx. Persons with documented resistance to at least two ARVs from at least three of the four main ARV classes were enrolled in a two-cohort design during which participants' OBR was continued throughout. Cohort 1 included 36 participants with HIV-1 RNA >400 copies/mL and stable viremia between screening and cohort selection visits (<0.50 $\log_{10}$ copies/mL change in HIV-1 RNA) who were randomized to receive oral LEN or placebo for 14 days followed by SC LEN every 6 months on Days 15 or 29, respectively. Cohort 2 included 36 participants who all received open-label oral LEN beginning on Day 1 followed by SC LEN every 6 months beginning on day 15.

In Cohort 1, 88% (21/24) in the LEN group and 17% (2/12) in the placebo group met the primary endpoint of a reduction in HIV-1 RNA by ≥0.5 $\log_{10}$ copies/mL by Day 15. At week 26, HIV-1 RNA <50 copies/mL was observed among 81% and 83% of Cohorts 1 and 2 participants, respectively, with a least-squares mean increase in the $CD4^+$ T-cell count of 75 and 104 cells/mm^3, respectively. No serious adverse events related to LEN were identified, though ISRs were

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reported in 63% of participants. Finally, resistance to LEN was noted in 8 out of 72 participants (mainly in those with the M66I mutation), which mostly occurred among participants who had poor adherence to the OBR.

Evidence for using IBA in highly treatment-experienced people with multidrug-resistant HIV-1 is supported by a single-group, open-label, Phase 3 study.[40] IBA was evaluated in 40 adults (≥18 years of age) with multidrug-resistant HIV-1, defined as documented genotypic or phenotypic resistance to at least one drug in at least three classes of ARV medications. At study entry, mean $CD4^+$ T-cell count was 150 cells/mm^3 and mean HIV-1 RNA was 4.5 $\log_{10}$ copies/mL. Participants were required to have HIV-1 RNA >1000 copies/mL and to continue their previous oral ART regimen (Days 0–13) before initiating an OBR (Day 14 onward). A loading dose of IBA was administered IV on Day 7 and then maintenance dosing initiated on Day 21 and given IV every 14 days until Week 25. Of the 40 participants, 33 (83%) had a reduction in HIV-1 RNA by ≥0.5 $\log_{10}$ copies/mL from baseline. At Week 25, 43%, and 50% of participants had HIV-1 RNA <50 copies/mL and <200 copies/mL, respectively. Among 10 participants with virologic failure or rebound, nine had viruses with lower IBA susceptibility per *in vitro* testing. The most common adverse event was diarrhea (reported in 20% of participants). Five patients (13%) experienced adverse events that resulted in discontinuation of IBA, including four patient deaths, though none were considered related to IBA therapy. Finally, one participant developed immune reconstitution syndrome in the context of a clinical diagnosis of progressive multifocal leukoencephalopathy presenting on Day 57, considered related to IBA use and resulting in discontinuation.

2. What is the evidence for using LA pre-exposure prophylaxis (PrEP)?

Consensus recommendations

2.1 We recommend LA CAB as a PrEP option for all persons clinically eligible.

Quality of evidence	A
Strength of recommendation	1

2.2 We recommend the DPV vaginal ring as an alternative PrEP option when more effective oral or injectable PrEP strategies are not available or if the vaginal ring is the individual's preferred method.

Quality of evidence	A
Strength of recommendation	2

Evidence summary

Evidence for using CAB as PrEP is supported by the HIV Prevention Trial Network (HPTN) 083 and HPTN 084 studies, both randomized, double-blind, non-inferiority trials. HPTN 083 showed superiority of LA CAB over daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for prevention of HIV-1 acquisition in cisgender men who have sex with men (MSM) and in transgender women who have sex with men. The trial enrolled 4570 cisgender men who have sex with men and transgender women who have sex with men at 43 sites in Argentina, Brazil, Peru, the United States, South Africa, Thailand, and Vietnam.[41] Participants were randomized to either the LA CAB or daily oral TDF/FTC group, and participants in each group received both injections and oral tablets in order to maintain the blinded design. The study included three phases: 5 weeks of daily oral CAB and a daily TDF/FTC placebo pill or 5 weeks of daily oral TDF/FTC and a daily oral CAB placebo; 148 weeks of LA CAB administered IM every 8 weeks plus daily oral TDF/FTC placebo or 148 weeks of daily oral TDF/FTC plus a LA CAB placebo administered IM every 8 weeks; and an open-label daily oral TDF/FTC for 48 weeks after participants completed phase 2. A data and safety monitoring board (DSMB) recommended that the blinded part of the study be stopped early for successfully meeting its specified objectives, and the decision was approved by the study sponsor (The US National Institute of Allergy and Infectious Diseases). LA CAB was found to be superior to daily oral TDF/FTC for HIV-1 prevention. A total of 52 incident HIV-1 acquisitions occurred, with 13 incident acquisitions in the LA CAB arm (incidence rate 0.41 per 100 person-years) and 39 incident acquisitions in the TDF/FTC arm (incidence rate 1.22 per 100 person-years). The hazard ratio for LA CAB versus TDF/FTC was 0.34 (95% CI 0.18–0.62), corresponding to a 66% reduction in incident HIV-1. ISRs were reported in 81.4% of the participants in the LA CAB group and in 31.3% of those in the daily oral TDF/FTC group.[41] After unblinding, the clinical efficacy of LA CAB for PrEP persisted during an additional 1 year of study follow-up; no new safety concerns emerged.[42]

The HPTN 084 trial showed superiority of LA CAB as HIV-1 prevention over daily oral PrEP with TDF/FTC in cisgender women. This Phase 3 trial followed the same design of HPTN 083 (same phases and similar duration of each phase) and enrolled 3224 women 18–45 years of age in sub-Saharan Africa who were at risk of acquiring HIV-1.[43] Data from HPTN 084 showed LA CAB injections once every 8 weeks were safe and superior to daily oral TDF/FTC for HIV-1 prevention. Forty incident HIV-1 acquisitions were observed over 3898 person-years (incidence 1.0% [95% CI 0.73–1.40]): four in the CAB group (incidence 0.2 cases per 100 person-years [0.06–0.52]) and 36 in the TDF/FTC group (1.85 cases per 100 person-years [1.3–2.57]), resulting in a hazard ratio of 0.12 [0.05–0.31] and risk difference of −1.6% [−1.0% to −2.3%]. ISRs were reported in 38% of the participants in the LA CAB group and in 10.7% of those in the daily oral TDF/FTC group. Given findings of superiority, the independent DSMB recommended the study sponsor (The US National Institute of Allergy and Infectious Diseases) stop the blinded phase of the trial. The unblinded continuation phase of HPTN 084 confirmed the

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superiority of LA CAB over oral TDF/FTC for HIV prevention with no new safety concerns identified.[44]

While ISRs were more frequent in the LA CAB arms in both HPTN 083 and 084 when compared to participants receiving placebo injections, most were mild and did not lead to drug discontinuation. No other relevant safety issue emerged in these trials. Considering the results of HPTN 083 and 084, the World Health Organization (WHO) launched guidelines in July 2022, recommending that LA injectable CAB may be offered as an additional option for HIV-1 PrEP for people at substantial risk of HIV-1 acquisition, as part of combination prevention approaches.[45]

Evidence for using DPV as HIV-1 prevention is supported by two large Phase 3 trials in African cisgender women: A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) trial and the Ring Study.[46,47] Both trials demonstrated approximately 30% protection against HIV-1 acquisition in cisgender women using the DPV ring compared with placebo. Imperfect adherence to the ring likely contributed to the modest HIV-1 risk reduction seen in these trials. In both trials, the ring was not associated with any safety concerns.

ASPIRE (MTN-020), was a double-blind, placebo-controlled trial of sexually active, non-pregnant, non-lactating women between 18 and 45 years of age in Malawi, South Africa, Uganda, and Zimbabwe.[46] Among the 2629 women enrolled, 71 HIV-1 acquisitions occurred in the DPV group and 97 in the placebo group (incidence 3.3 and 4.5 per 100 person-years, respectively). Overall, the incidence of HIV-1 acquisition in the DPV group was 27% lower (95% CI 0.01–0.46; $p=0.046$) than in the placebo group. Higher adherence rates, as measured by plasma DPV levels, correlated with greater protection. The rates of adverse events and ARV resistance among women who acquired HIV-1 were similar in the two groups.

The Ring Study (IPM 027) evaluated the DPV vaginal ring in 1959 sexually active, non-pregnant, non-lactating women between 18 and 45 years of age in South Africa and Uganda in a randomized, double-blind, placebo-controlled trial.[47] A total of 77 HIV-1 acquisitions occurred in the DPV group and 56 in the placebo group (incidence 4.1 and 6.1 per 100 person-years, respectively). Overall, the incidence of HIV-1 acquisition was 31% lower in the DPV group than in the placebo group (95% CI 0.49–0.99; $p=0.04$). The cumulative incidence of adverse events during the trial was similar in both groups and none were assessed by the investigators as being product related. However, serious adverse events occurred more often in the DPV group than in the placebo group (2.9% vs. 0.9% of participants, respectively, $p=0.01$). Among those who acquired HIV-1 during the trial, resistance mutations to NNRTIs were observed with similar frequency in both groups, with the exception of E138A, which was observed more frequently in the DPV group. Two subsequent open-label extension studies to the ASPIRE and Ring studies, DREAM and HOPE, respectively, demonstrated increased ring adherence compared with the Phase 3 trials and suggested greater risk reduction by over 50% across both studies.[48,49]

In July, 2020, the European Medicines Agency, in cooperation with WHO, adopted a positive scientific opinion for the DPV vaginal ring, on the public benefits for women outside of the European Union.[19] In January 2021, WHO released new clinical recommendations on HIV prevention that included detailed guidance for DPV ring as an additional choice for women at substantial HIV risk as part of combination prevention approaches.[20] In December 2021, the International Partnership for Microbicides voluntarily withdrew its new drug application submitted to the US FDA. The decision was made following feedback during the agency's review that current data were unlikely to support US approval, given the current HIV epidemiology and the prevention landscape in the United States.[50]

3. For whom are LA ARVs for HIV-1 treatment or PrEP indicated?

Consensus recommendations

3.1 LA CAB/RPV for HIV-1 treatment is indicated for individuals who are virologically suppressed on oral ART without known or suspected resistance to either component, without other known contraindications, and who agree to receive timely injections and undergo recommended laboratory testing

Quality of evidence	A
Strength of recommendation	1

3.2 IBA or LEN for HIV-1 treatment is indicated for heavily treatment-experienced adults with multidrug-resistant HIV-1 failing their current antiretroviral regimen.

Quality of evidence	A
Strength of recommendation	1

3.3 Initiation of LA CAB for PrEP is indicated for individuals without evidence of HIV-1 (i.e., HIV Ag/Ab negative ± HIV-1 RNA not detected) who agree to receive timely injections and undergo recommended laboratory testing.

Quality of evidence	A
Strength of recommendation	1

3.4 DPV is recommended for cisgender women to reduce risk of HIV-1 acquisition via vaginal intercourse when oral or injectable PrEP is not being used or is not available or based on user preference.

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Quality of evidence	A
Strength of recommendation	1

Evidence summary

LA CAB/RPV injectable therapy is currently only approved for use as maintenance HIV-1 treatment in adults or in adolescents ≥12 years of age and weighing at least 35 kilograms.[1,51] Patients who might be considered for this regimen include those who express interest in less frequent dosing of ART; have pill aversion, intolerance, or malabsorption; struggle with HIV-related stigma and/or have disclosure concerns of taking a daily medication for HIV-1. For HIV-1 treatment, appropriate candidates should be virologically suppressed (HIV-1 RNA < 50 copies/mL), with no known or suspected resistance to either CAB or RPV, or taking any medications contraindicated with either CAB or RPV. Reflecting exclusion criteria from the clinical trial designs, patients with any known INSTI or NNRTI resistance mutations, excluding K103N, should not receive CAB/RPV.[51] In real-world settings, previous genotypic information may be unavailable for some patients. It is therefore important to carefully review patients' prior ART regimens, corresponding trends in virologic data, and reasons regimens may have been switched to learn of any clinical evidence suggestive of possible drug resistance. While proviral DNA genotypic resistance testing may be ordered, there is insufficient evidence to support this as a standard practice, and detection of archived resistance has unknown clinical implications. Additionally, there may be discordance between proviral DNA genotypic testing and standard HIV-1 RNA genotypic drug resistance testing, suggesting that proviral DNA genotypic testing may not be reliable for predicting resistance to ART.[1] Additional excluding factors for use of LA CAB/RPV are the presence of hepatitis B virus coinfection, unless the patient is also receiving an oral antiviral active against hepatitis B virus, hypersensitivity to CAB or RPV, coadministration with other drugs that significantly reduce CAB or RPV plasma concentrations, and individuals who are pregnant or breast/chest-feeding. If an individual is exposed to CAB/RPV during pregnancy or while breast/chest-feeding, the clinician should report outcomes to the ARV pregnancy registry database, found at www.apregistry.com.[52] Individuals initiated on LA CAB/RPV should be counseled on the importance of timely appointments for injections and the potential ramifications of missed injection appointments including the development of resistant HIV-1 or onward HIV-1 transmission to others if virologic suppression is not maintained. Garnering an understanding of an individual's lifestyle, commitments, and obligations can help delineate if an individual will be able to adhere to the dosing strategy so that shared decision-making can be used to determine whether LA ART is a viable option for them.

Patients who might be considered for an IBA- or LEN-containing regimen are those who are heavily treatment-experienced who are not able to achieve viral suppression with other broadly used classes of ARVs.[1] IBA or LEN should be used in combination with an OBR and should not be added as single agents to a failing regimen, as this will increase the likelihood for development of resistance to the new agent.[1] Patients should be amenable to regularly receiving IBA or LEN in healthcare settings, while maintaining continued adherence to the OBR.

Clinicians should offer PrEP to anyone who asks for it, including sexually active individuals who do not report behaviors that put them at risk of getting HIV-1 or persons who inject drugs.[53] LA CAB for PrEP is approved for adults and adolescents weighing 35 kg or more to reduce the risk of sexually acquired HIV-1. A negative HIV-1 test must be completed prior to starting CAB for PrEP. Patients should be counseled on the dosing schedule comprising every 4-week injections for 2 months, followed by every 8 weeks thereafter, additionally noting that LA CAB remains detectable in tissues for a year or longer. Systemic CAB levels will decline without ongoing medication administration and, for people who discontinue CAB, levels may become subtherapeutic if an exposure to HIV-1 were to occur.

DPV vaginal ring has been recommended for use by the WHO to reduce the risk for HIV acquisition via vaginal intercourse when oral PrEP is not being used or is not available or based on user preference.[20] Prospective patients should be counseled on the need for insertion of a new ring every 28 days.

4. What is the process for customizing LA ARVs for HIV-1 treatment or PrEP?

Consensus recommendations

4.1 We recommend that the choice of ART or PrEP agent(s) be based on shared clinical decision-making and patient preference to support adherence

Quality of evidence	C
Strength of recommendation	1

4.2 We recommend LA CAB/RPV as an HIV-1 treatment option, particularly for scenarios where there are concerns regarding safety, effectiveness, convenience, or access of oral ART or based on user preference.

Quality of evidence	B
Strength of recommendation	1

4.3 Clinicians should reserve IBA for individuals in whom a suppressive ART regimen cannot be constructed based on available alternatives, have access to the medication, and who are able to receive intravenous administration every 2 weeks.

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Quality of evidence	B
Strength of recommendation	1

4.4 Clinicians should reserve LEN for individuals in whom a suppressive ART regimen cannot be constructed based on available alternatives, have access to the medication, and are able to receive subcutaneous administration every 6 months.

Quality of evidence	B
Strength of recommendation	1

4.5 We recommend LA CAB as a PrEP option for scenarios where there are concerns regarding safety, effectiveness, convenience, or access of oral PrEP or based on user preference.

Quality of evidence	B
Strength of recommendation	1

4.6 We recommend DPV as a PrEP option for scenarios where there are concerns regarding safety, effectiveness, convenience, or access to oral or injectable PrEP or based on user preference.

Quality of evidence	C
Strength of recommendation	1

Evidence summary

We suggest that choice of ART or PrEP agent(s) be based on shared clinical decision-making and patient preference to support adherence. LA ARVs may be preferred for persons who have difficulty taking pills daily and, furthermore, may represent a convenient and potentially discreet option to overcome barriers to daily oral ARVs such as difficulties with pill swallowing, HIV-related stigma, intimate partner violence, and, in the case of HIV treatment, fear of HIV disclosure.

We recommend LA CAB/RPV as an HIV-1 treatment option, particularly for scenarios where there are concerns regarding safety, effectiveness, convenience, or access of oral ART or based on user preference. LA CAB/RPV for HIV-1 treatment is recommended for people with undetectable HIV-1 RNA and without resistance to either agent.[28,31,33,54] LA CAB/RPV is approved as an optimization option for patients who are virologically suppressed on oral ART for 3–6 months and who agree to adhere to the frequency of injection visits and do not have contraindications.[1]

IBA and LEN are currently reserved for persons with HIV-1 who have extensive resistance to existing ARV classes with limited therapeutic options and in whom it is not otherwise possible to construct a fully suppressive ART regimen.[40,55] As with other ARV drugs approved for persons with multidrug-resistant HIV-1, combination with a carefully selected OBR containing fully or partially active drugs based on a complete resistance profile is necessary. Patients should agree to receive on-time administration of LA agents. The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options. Thus, functional monotherapy should be avoided whenever possible.

The use of LA CAB as PrEP may be particularly compelling when low adherence to oral PrEP is expected. LA CAB is well suited for women who prefer a LA injectable agent for PrEP, particularly in sub-Saharan Africa where it demonstrated protective benefit across age groups, and in populations where other PrEP delivery formulations provided less protection.[41,43] LA DPV as PrEP may be offered in scenarios where there are concerns regarding safety, effectiveness, convenience, or access to oral or injectable PrEP or based on user preference.[46,47]

5. What is the process for facilitating access to LA ARVs?

Consensus recommendations

5.1 Clinicians should inform eligible patients about LA ARV options, and healthcare systems should facilitate access to the regimen.

Quality of evidence	C
Strength of recommendation	1

Evidence summary

Facilitating access to LA ARVs and securing medication coverage requires dedicated staff and resources. For all LA ARVs, clinicians should consider drug benefits coverage and medication procurement early in the evaluation process because ARV formularies and criteria for select treatment options vary by payor. Procuring initial and continuous medication coverage and access is an integral part of the operational plan for healthcare systems and community-based organizations that wish to deliver LA ART or PrEP.

In addition to the cost of the medication, it is important to consider the cost of the laboratory testing required for monitoring with LA ARV use. The cost of these laboratory tests can vary depending on payor and laboratory used and is an important consideration for patients and providers when considering LA ARVs. Stakeholders should work together to ensure that patients have access to the affordable laboratory monitoring needed to safely and effectively use LA ARVs.

Key implementation issues for providing LA ARV access include workflow, communication, and monitoring strategies among interdisciplinary members of the healthcare team, healthcare provider

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training on administering the medications, adequate clinic space for medication storage and administration, and maintaining supply chains. In addition, access to LA PrEP may be dependent on global and national public health priority strategies and capacity of local healthcare delivery systems. Given the substantial acquisition costs of LA ARVs, access to the regimen should be facilitated by stakeholders.

6. What is the process for initiating LA ARVs?

Consensus recommendations

6.1 For patients initiating LA CAB/RPV, we recommend that the 1-month OLI with CAB and RPV be optional and based on shared decision-making between the patient and provider.

Quality of evidence	B
Strength of recommendation	1

6.2 We recommend individuals who are eligible for LA CAB and RPV and have a body mass index greater than or equal to 30 kg/m^2 receive CAB and RPV injections with a 2-inch needle, rather than the 1.5-inch needle provided in the injection kits, to optimize drug pharmacokinetics.

Quality of evidence	B
Strength of recommendation	1

6.3 We recommend initiation of IBA or LEN with an OBR.

Quality of evidence	A
Strength of recommendation	1

6.4 Clinicians providing the DPV vaginal ring should provide information to patients regarding appropriate techniques for self-insertion and removal of the vaginal ring.

Quality of evidence	B
Strength of recommendation	1

Evidence summary

At least a 4-week OLI was used prior to LA injections in clinical trials leading to the approval of both LA CAB/RPV for ART and LA CAB for PrEP. Pooled data from FLAIR, ATLAS, and ATLAS-2M studies were analyzed to assess the frequency and severity of adverse events during the OLI. Of 1245 total participants, 396 (32%) reported any adverse event during the OLI, most were Grade 1 or 2, and <1% led to drug discontinuation.[56] The only adverse events occurring in ≥2% of participants during the OLI were headache (3%), nasopharyngitis (2%), and diarrhea (2%); no drug-related adverse events occurred in ≥2% of participants. Grade 3 or greater adverse events were reported in 15 participants (1%), of which only five (<1%) were drug-related. Based on these data, the open-label extension phase of the FLAIR trial allowed participants who were transitioning from oral ART to LA injectable CAB/RPV to choose an OLI, or to proceed directly to injectable LA CAB/RPV (i.e, DTI).[33] Of the 232 participants who transitioned from daily oral ART to LA CAB/RPV, 111 (48%) chose the DTI option. After 24 weeks on LA CAB/RPV, adverse event rates were similar between those with and without the OLI, and no hypersensitivity reactions were observed in the DTI group. In the CAB PrEP registrational trials, adverse events during the OLI were rare, and similar to the comparator group (TDF/FTC).[42–44] Overall, these data support the current labeling for both PrEP and HIV-1 treatment, which designates a minimum 28-day lead-in of CAB or CAB/RPV as optional.

We recommend that use of the OLI with CAB and RPV is based on shared decision-making between the patient and provider, as there are advantages and disadvantages when considering OLI initiation. Given that once an injection is administered, there is no way to remove the agent in the event of an adverse reaction, some patients and providers may be more comfortable with an OLI to assess tolerability. Alternatively, it may be more convenient for some patients to start the injectable sooner and not be required to take daily pills for a month. Also, DTI is more advantageous for patients taking concomitant medications that interfere with oral, but not injectable, absorption of CAB or RPV (e.g., proton pump inhibitors or polyvalent cations). Lastly, while an OLI was given for 4 weeks in clinical trials to assess tolerability, some providers and patients may elect to use the OLI for a shorter duration.

LA CAB/RPV for ART or LA CAB for PrEP are administered as IM gluteal injections. The product package includes a 1.5-inch needle; however, a longer needle length (e.g., a 2-inch needle) is suggested for use in patients with a BMI ≥30 kg/m^2 to optimize medication delivery into the muscle rather than fat tissue, which improves drug exposure over the dosing interval.[51,57]

LA CAB/RPV for ART is provided as a co-packaged kit.[51] If the OLI is administered, the first injection should occur on the last day, or within three days, of the final dose of the OLI. Patients should be observed for approximately 10 min after CAB/RPV injections for adverse reactions.

Unlike LA CAB/RPV, IBA and LEN should be initiated in combination with an OBR based on the patient's current and former ART regimens and the results of resistance testing history. Therefore, access to the OBR should be confirmed before the LA product is initiated.

The IBA loading dose infusion should be administered in the cephalic vein over 30 min.[58] After the first dose, patients should be observed for at least 1 h for infusion-related adverse events. If no

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adverse events are observed, subsequent maintenance doses are administered via IV infusion over 15 min or IV push over 30 s.

There are two options for LEN initiation. The induction phase of option 1 includes LEN by SC injection plus LEN orally on Days 1 and 2. The induction phase of option 2 includes LEN orally on Days 1, 2, and 8, followed by SC LEN on Day 15.[9,59] Thereafter, the subcutaneous dose is administered every 26 weeks ±2 weeks.

The DPV ring is inserted into the vagina with the intention to remain in place for 1 month.[60] After 1 month, the ring should be immediately replaced with a new DPV ring to maintain efficacy if continued HIV prevention is desired. Product labeling includes detailed instructions on administration and removal techniques, which may be used to educate the patient on appropriate insertion and increase their comfort level with ring insertion. Once in place, the ring should not cause discomfort. If the patient experiences discomfort, the ring may not be placed far enough into the vagina, which may be corrected by pushing the ring further into the vagina or reinserting the ring. If the ring is removed or expelled accidentally, it may be rinsed with clean water and reinserted if it occurs in a clean environment but should be discarded and replaced with a new ring if it touches an unhygienic surface. The ring should not be removed during menses.

To increase the ease of injection availability and access, and potentially alleviate burden of LA ARV administration within healthcare settings, alternative anatomic sites of injection such as the thigh, and alternate delivery settings for injection administration, such as in community pharmacies, are being investigated for LA CAB and RPV.[6–8] There are ongoing clinical trials to investigate LEN for PrEP. Further evaluation of other LA ARVs to pair with LEN to create a fully suppressive LA ART regimen is critical. Finally, product development is ongoing to generate a vaginal ring providing both HIV-1 prevention and contraception by co-formulating DPV plus contraceptive hormones in a multipurpose vaginal ring.

7. What is the process for promoting and supporting patient adherence to LA ARVs for HIV-1 treatment or PrEP?

Consensus recommendations

7.1 We recommend adherence strategies center around maintaining good communication with individuals accessing LA ARVs about the dosing window, providing education about potential side effects including injection site reactions, and reinforcing the importance of adherence to medications, clinic appointments, and injection visits.

Quality of evidence	B
Strength of recommendation	1

7.2 We recommend supplemental strategies to optimize LA ARV adherence including appointment reminders such as text messaging, automated electronic alerts, or phone reminders as well as interdisciplinary health care or community team support.

Quality of evidence	C
Strength of recommendation	1

7.3 We recommend that patients who are started on LA ARVs be closely monitored to identify potential adherence challenges and to provide individualized adherence support, as needed

Quality of evidence	C
Strength of recommendation	1

Evidence summary

ARV adherence has traditionally meant taking the dose and frequency of an ARV as prescribed, with an emphasis on patients limiting missed doses. However, most currently available LA ARVs require administration by a healthcare provider (CAB/RPV, IBA, LEN, and CAB) while only one allows for self-administration (DPV). Therefore, for those LA ARVs requiring administration by a healthcare provider, treatment adherence can additionally be defined as attending visits for medication administration within dosing windows as prescribed.[61] We recommend that patients who are started on LA ARVs be closely monitored to identify potential adherence challenges and to provide individualized adherence support, as needed.

There are several strategies to optimize treatment adherence to LA ARVs described in recent participant and provider studies (Table 3).[62–64] Education should be provided by multidisciplinary team members to ease concerns patients may have over dosing and administration, adverse events, and efficacy of LA ARVs. Furthermore, counseling regarding potential side effects and proactive management of adverse reactions may minimize discontinuation of LA ARVs prematurely. Providing details around the dosing window is critical, informing patients about the dosing interval for effective maintenance therapy and the importance of contacting clinic staff for planned or unplanned missed injection visits. Appointment reminders via individual-specified preferred methods of communication (e.g., telephone call, text message, email) can minimize the number of missed visits and clinic inefficiency.[62,63] Automated system reminders, such as web- or app-based technology, can reduce the burden on staff and likelihood of human error. Timely tracking, contacting, and rescheduling of patients after missed visits is an important component of any LA ARV program protocol.

Another aspect to optimize patient adherence to LA ARVs includes training staff on proper administration techniques, leading to increased staff confidence. This training is particularly helpful if the LA ARV administration necessitates deviation from standard practice, such as ventrogluteal versus dorsogluteal IM injections of CAB/

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TABLE 3 Strategies to optimize and support adherence to LA ARVs for HIV-1 treatment and pre-exposure prophylaxis.

Strategy categories	Strategy examples
Patient education	• Discuss benefits and risks of LA ARVs • Provide information about LA ARVs: • Dosage and dosing schedule/window • Administration technique • Strategy if missed or delayed dose intervals • Potential adverse reactions; advise on how to mitigate and/or manage reactions, when to contact provider • Explain importance of adherence, and relation to risk for HIV-1 treatment or PrEP failure • Discuss importance of timely communication and rescheduling missed appointments • Answer questions, ease patient concerns regarding LA ARVs
Appointment logistics	• Schedule appointment reminders for injections, infusions, or prescription refills based on individual communication preferences (e.g., mail, email, text reminders) • Consider reminders via automated, web-based methods • Track missed appointments and maintain rescheduling flexibility; facilitate access to bridge therapy, if appropriate • Coordinate transportation assistance
Patient outreach and engagement	• Facilitate social support (e.g., peer support groups or adherence clubs) • Educate PrEP patients' sexual partners as appropriate • Consider text messages and social media platform utilization for targeted and general reinforcement • Differentiated outreach for populations traditionally difficult to engage in care (e.g., younger age, unstably housed)
Miscellaneous	• Optimize workflow and throughput time throughout a multistep process (e.g., for LA ARVs administered at the clinic: dose preparation time, time to exam room, post-dose monitoring) • Anticipated necessary capacity building • Hire (and train) additional staff • Adjust hours of operation • Designate exam rooms for injection visits • Cold chain supply (e.g., LA CAB/RPV) • Address medication access concerns • Identify additional and/or alternative care sites to receive injection or infusion • Assist with management during pandemic-related or catastrophic events

Abbreviations: ARV, antiretroviral; LA, long-acting; PrEP, pre-exposure prophylaxis.

RPV or CAB. Additional workflow considerations include expanding or adjusting clinic hours of operation, if resource allocation allows, and establishing operational processes to address expected and unanticipated challenges, such as the need to scale-up services and medication procurement issues.

DPV is unique among currently available LA ARVs in that it is the only LA ARV that is self-administered. In clinical trials, DPV vaginal ring effectiveness was strongly associated with adherence. DPV adherence rates were influenced by patient perceptions around wearing the vaginal ring, such as unfamiliarity with an intravaginal ring device or how the ring might impact sexual intercourse or be perceived by their sexual partner, and uncertainty regarding removing the ring for sex, bathing, or menses.[22,65] In ASPIRE, improved adherence over the course of the study was attributed to participants becoming more comfortable with the ring through practice, self-experimentation, education, counseling, and peer support from other trial participants.[66] Another strategy to reduce barriers to DPV adherence is addressing intimate partner dynamics via lay counselors, as introduced in a substudy of HOPE.[67,68] HIV-1 self-testing may be an additional strategy that can be incorporated into implementation of DPV vaginal ring use, to reduce the number of required in-person clinic visits, especially if travel to and from clinic is a challenge.[69] Thus, similar to other LA ARVs, education, counseling, and peer support may serve as important tools for improving DPV adherence.

To optimize LA PrEP adherence, outreach efforts should be tailored to the individual's and the community's needs. Optimizing the healthcare delivery system's operational plans and the visit experiences can also improve treatment adherence. Social determinants of health (e.g., health literacy, access to transportation, housing, and health care), healthcare provider bias, and community mistrust continue to impact adherence. Practice of cultural competence and neutralizing communication with patients by interdisciplinary members of the LA ART or PrEP program team may improve perceived stigma and discrimination, as well as begin to augment patient trust.[70] Building trust and acknowledging concerns among marginalized communities is imperative.[71]

Studies validating strategies and tools to improve adherence to LA ARVs specifically are needed to support evidence-based methods for practice implementation in the novel landscape of LA modalities for HIV-1 treatment and prevention, particularly to reduce inequities in uptake and persistence.

8. What is the process for monitoring efficacy of LA ARVs for HIV-1 treatment or PrEP?

Consensus recommendations

8.1 More research is needed to determine the optimal timing and frequency of efficacy monitoring for people with HIV-1 receiving

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LA ART treatment with CAB/RPV, IBA, or LEN. However, we recommend that these individuals undergo regular plasma HIV-1 RNA testing to ensure that they are achieving or maintaining viral suppression as indicated by existing local- or country-specific guidance; though adjustments may be made based on individual circumstances, patient and provider comfort level/preference, response to therapy, and/or monitoring/testing capacity.

Quality of evidence	A
Strength of recommendation	1

8.2 More research is needed to determine the optimal timing and frequency of efficacy monitoring for people initiating LA CAB as PrEP, including the potential role of HIV-1 plasma RNA testing. However, we recommend that these individuals undergo regular efficacy monitoring with standard approved HIV-1 screening/testing assays, following local- or country-specific guidance as appropriate.

Quality of evidence	A
Strength of recommendation	1

8.3 Until further data are available on specific HIV-1 screening/testing strategies for people using DPV vaginal ring for PrEP, we suggest HIV-1 screening at least once every 3 months. Since optimal follow-up HIV-1 testing intervals and approaches have not yet been clearly established, more frequent testing may be warranted in specific situations such as suboptimal medication adherence or vaginal ring damage/loss, or concern for HIV-1 exposure.

Quality of evidence	B
Strength of recommendation	1

Evidence summary

HIV treatment guidelines generally recommend HIV-1 plasma RNA viral load testing as the preferred approach to monitor initial and sustained ART response and to recognize treatment failure.[1,72–74] The timing and frequency of such testing should generally follow local or country-specific guidance, but may be adjusted based on individual clinical circumstances, patient and provider comfort level and preference, response to therapy, and testing capacity. For persons switching to LA CAB/RPV from a suppressive oral ART regimen, US guidelines recommend performing HIV-1 RNA testing 4–8 weeks following the switch.[1] HIV-1 RNA should also be checked in the event of unplanned missed visits and/or delayed doses of LA CAB/RPV. US guidelines do not currently specify how frequently to monitor HIV-1 RNA among virologically suppressed people with HIV-1 maintained on LA CAB/RPV. In general, they indicate that persons with HIV-1 on a stable, suppressive regimen should generally undergo HIV-1 RNA testing every 3–4 months, and no more than every 6 months, or as clinically indicated to confirm continuous viral suppression.[1] By contrast, the 2022 British HIV Association guidelines recommend checking HIV-1 RNA every 2 months for people receiving LA CAB/RPV, which follows the HIV-1 RNA testing intervals utilized during initial registrational trials.[72] For patients experiencing viral rebound, prompt repeat HIV-1 RNA and genotype resistance testing are recommended. Because real-world use of LA CAB/RPV remains relatively limited, and no single universal approach has been endorsed by multiple guidelines regarding key practices (e.g., determination of whether/when to offer every 4 weeks versus every 8 weeks injections for continuation therapy or LA CAB/RPV initiation in people with HIV-1 with baseline viremia) some providers may opt to adapt HIV-1 RNA testing protocols and practices based on initial clinical assessment and individualize thereafter according to virologic response. Decisions regarding treatment efficacy monitoring should include careful consideration of factors that have been associated with LA CAB/RPV virologic failure based on clinical trials data (i.e., certain proviral RPV resistance-associated mutations, BMI ≥30 kg/m^2, HIV-1 subtype A6/A1).[75] Of note, Phase 3 clinical trials of LA CAB/RPV included a limited number of participants with BMI ≥40 kg/m^2. Predictors of LA CAB/RPV virologic failure may be incompletely characterized at this time, and additional real-world data are urgently needed. Laboratory monitoring may also depend on resource availability and practice workflows as well as patient preference/availability. Table 4 describes the rationale for HIV-1 RNA testing at various time points with LA CAB/RPV use.

As described previously, LA IBA and LEN are typically reserved for use in adults with multidrug-resistant HIV-1. As with any ART modification, efficacy monitoring should include a repeat plasma HIV-1 RNA within 4–8 weeks after IBA or LEN initiation. Subsequent HIV-1 RNA testing should be repeated at 4–8-week intervals until the HIV-1 RNA falls below the assay's limit of detection, to ensure desired treatment response.[1] Of note, in the initial IBA Phase 3 trial, HIV-1 RNA was measured 7 days after loading dose administration, then 7 days later, and every 4 weeks thereafter through Week 25.[40] For the LEN Phase 3 trial, HIV-1 RNA testing occurred approximately every 7 days for the first 4 weeks, and then every 6 weeks thereafter through 22 weeks.[55]

As for persons receiving oral PrEP, efficacy monitoring of LA PrEP is centered on ensuring the person remains negative for HIV-1 for the duration of PrEP use. Table 5 outlines recommendations for laboratory monitoring/testing for persons receiving LA CAB for PrEP. Although most HIV-1 screening/testing guidelines recommend that laboratory assessment for HIV-1 be conducted with an HIV-1 antibody (Ab)-inclusive assay (preferentially, 4th generation antigen–antibody combination immunoassays), nucleic acid amplification tests (NAATs) for HIV-1 RNA are increasingly being incorporated into PrEP initiation and monitoring guidelines. This is because ARV exposure

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TABLE 4 Treatment efficacy monitoring for people with HIV-1 receiving long-acting cabotegravir/rilpivirine: rationale and timepoints for HIV-1 RNA testing.[a]

Timepoint for HIV-1 RNA testing	Rationale
Before [optional] oral lead-in	Switch: To ensure patient is virologically suppressed on oral ART, prior to starting LA CAB/RPV "Off label" use in patients with baseline viremia: To serve as pre-LA CAB/RPV baseline
After [optional] oral lead-in, and/or at first LA CAB/RPV injection—INITIATION PHASE	Switch: To ensure patient remains suppressed on oral CAB+RPV, prior to first LA CAB/RPV injection "Off label" use in patients with baseline viremia: To provide information on early virologic response on oral CAB+RPV. For patients with viremia who transition directly to LA CAB/RPV (i.e., direct-to-injection), HIV-1 RNA at first initiation injection will serve as pre-LA CAB/RPV baseline.
At second LA CAB/RPV injection—INITIATION PHASE	Switch: To evaluate whether patient remains suppressed after first initiation injection, prior to transitioning to continuation phase "Off label" use in patients with baseline viremia: To confirm adequate initial virologic response to LA CAB/RPV
Subsequent LA CAB/RPV injections (as clinically indicated)—CONTINUATION PHASE	Switch: To evaluate whether patient remains suppressed on LA CAB/RPV "Off label" use in patients with baseline viremia: To monitor virologic response[b]
• At first visit after missed dose and/or at time of injection if delayed doses (planned or unplanned)	To assess for early virologic rebound potentially attributable to missed/delayed dose
• Repeat testing for recent viremia above the lower limit of quantification (will vary depending on HIV-1 RNA assay utilized) but <200 copies/mL[c,d]	To follow-up on previous viremia and ascertain whether patient is experiencing a "blip," low-level viremia[d], or virologic rebound/potential virologic failure
• Repeat testing for recent viremia ≥200 copies/mL[c]	To confirm previous viremia and determine whether confirmed virologic failure

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; RPV, rilpivirine.

[a]HIV-1 RNA testing may be performed at other time points, as guided by clinical assessment.

[b]Two studies have examined LA CAB/RPV initiation among people with HIV-1 with baseline viremia: in one, median time to virologic suppression as reflected in quarterly clinical updates was 5 months,[76] and in the second, people with HIV-1 who began injections with detectable viremia achieved virologic suppression or had a 2-log decline in HIV-1 RNA within 1 month of first injection.[34]

[c]Although various guidelines offer general recommendations regarding management of viremia for people with HIV-1 on treatment, the specific approach to individuals receiving LA CAB/RPV should be tailored to their antiretroviral exposure and drug resistance history, level and duration of viremia (or virologic failure), and treatment preferences. For persons with previous virologic suppression on oral ART who develop new viremia after switching to LA CAB/RPV (or persons with baseline viremia and suboptimal virologic response after LA CAB/RPV initiation), timely HIV-1 RNA re-testing should be pursued first. Clinical assessment of confirmed viremia—and subsequent management—may be informed by review of recent LA CAB/RPV administration timing and injection technique, and consideration of medication absorption/systemic drug exposure including verification of oral bridge therapy adherence if relevant.

[d]For people with HIV-1 receiving LA CAB/RPV who develop low-level viremia, that is, HIV-1 RNA between the lower limit of detection and 200 copies/mL, little evidence is currently available to guide clinical management. In initial LA CAB/RPV trials, cases of transient HIV-1 RNA increases (defined per study protocols as "blips" < 200 copies/mL) outside of the predetermined analytic timepoints were not considered suspected virologic failures and therefore did not lead to changes in study therapy. Participants with persistent low-level viremia (RNA level ≥ 50 copies/mL and <200 copies/mL) were reviewed on an individual basis; investigators then determined whether to perform additional testing in between study visits to inform appropriate disposition.

can modify or mask the virologic, immunologic, and clinical features of HIV-1 among people who acquire HIV-1 in the setting of PrEP use.[78] Regular HIV-1 screening/testing also ensures that persons on, or requesting, LA PrEP who have undiagnosed HIV-1 are not inadvertently treated with a suboptimal ARV regimen. Recommended HIV-1 testing approaches for individuals receiving LA PrEP vary between guidelines[45,53,77] and may also depend on testing/resource availability at the care setting or location. Although NAATs may provide the earliest detection of HIV-1,[79–81] limited availability of these tests in certain settings, such as low- and middle-income countries, as well as potentially long turnaround times may not make them a feasible option for LA PrEP monitoring. Thus, WHO does not currently recommend NAAT as a standalone test for HIV-1 diagnosis[45]; however, US-based guidelines recommend their use as a component of routine PrEP monitoring.[53,77] Continued interest in PrEP should be assessed at least yearly. For persons who discontinue CAB for PrEP, US guidelines recommend follow-up every 3 months with HIV-1 testing and reassessment of PrEP needs.[53] Given the long pharmacokinetic "tail" of LA CAB after medication discontinuation, it is important to monitor for potential HIV-1 acquisition as well as residual drug effects during the post-injection period. Discussion and implementation of other HIV-1 prevention methods, such as oral PrEP or condoms, during the "tail" period should be prioritized to minimize the potential for HIV-1 acquisition and subsequent development of HIV-1 drug resistance should a person acquire HIV-1 during the time that CAB remains systemically detectable.

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For providers caring for cisgender women using the DPV intravaginal ring as PrEP, efficacy monitoring is less standardized at this time. Open-label extension trials of the DPV vaginal ring employed monitoring approaches aligned with "real-world" practices. In the HOPE trial, participants were evaluated monthly for the first 3 months of medication use and then quarterly with rapid HIV-1 serologic tests performed at each follow-up.[49] In the DREAM study, screening for HIV-1 seroconversion using rapid HIV-1 tests occurred at participants' 1-month visit, monthly up to Month 3 for those participants who opted for more frequent initial visits, and then at quarterly visits.[48] Of note, HIV-1 RNA testing was only performed on stored plasma samples to determine timing of HIV-1 seroconversion and not as a prospective screening tool to detect incident HIV-1. Results from these extension studies suggest that quarterly HIV-1 testing is feasible for persons using DPV vaginal ring. Until further data are available on specific HIV-1 screening/testing strategies for people using DPV vaginal ring for PrEP, screening at least once every three months is suggested. Since optimal follow-up HIV-1 testing intervals and approaches have not been clearly established, more frequent testing may be warranted in specific situations such as suboptimal medication adherence or vaginal ring damage/loss, or concern for HIV-1 exposure.

Studies are needed to establish the optimal efficacy monitoring approach for people with HIV-1 on LA ART, given the unique properties and indications among individual LA ART options. Studies are also needed to further evaluate the prevalence and optimal management strategy for people with HIV-1 on LA ART who develop low-level viremia. For people receiving LA ARVs as PrEP, the optimal approach for CAB and DPV efficacy monitoring should be established. Data are also needed regarding time from LA PrEP initiation to level of maximal protection, given individual pharmacokinetic variability which may affect pharmacokinetic-dynamic considerations. This information could influence whether more frequent monitoring may be warranted during the therapy initiation phase. Because of varying levels of resources/capacity and health systems infrastructure globally, studies are needed to identify universally cost-effective LA ARV efficacy monitoring strategies.

9. What is the process for monitoring and managing adverse drug reactions to LA ARVs?

Consensus recommendations

9.1 We recommend individuals receiving LA ARVs for HIV-1 treatment or prevention receive clinical monitoring for adverse events according to local standard of care and clinical treatment guidelines.

Quality of evidence	B
Strength of recommendation	1

9.2 We recommend the duration of monitoring for adverse events in patients receiving LA therapies should take into consideration the half-life of the product.

Quality of evidence	C
Strength of recommendation	1

9.3 In patients who experience an adverse event to LA ARVs for HIV-1 treatment or prevention and require a therapy switch, we recommend the revised ARV(s) are initiated no later than the date of the next scheduled dose of the LA product(s).

Quality of evidence	C
Strength of recommendation	1

Evidence summary

Overall, patients receiving LA ARVs should follow the same laboratory and clinical monitoring schedules as outlined by national treatment guidelines for people with HIV-1, or national PrEP guidelines for people at risk for HIV-1.[45,53,72–74,82] In the setting of an adverse event related to LA ARVs, providers should consider the potential prolonged period of exposure after drug discontinuation (also known as the pharmacokinetic "tail") and monitor adverse events until they are resolved. In some situations, enzyme inducing agents have been prescribed to accelerate the elimination of a non-ARV drug causing an adverse event, for example, with kidney injury related to tacrolimus.[83–85] This may not be a feasible strategy with drugs that undergo flip-flop kinetics, such as CAB and RPV as the drug will persist in the depot site. Furthermore, for IBA, which is catabolized, there is no way to speed up its elimination from the body. Specific adverse events and monitoring suggestions for LA ARVs are discussed below.

If LA CAB/RPV for HIV-1 treatment or LA CAB for HIV-1 prevention must be discontinued due to an adverse event, alternative ART or PrEP should be prescribed to begin on the date of the next scheduled injection. If discontinuation is needed due to an adverse event, it should be noted that residual concentrations of both CAB and RPV may remain in the systemic circulation for prolonged periods (up to 12 months or longer). When selecting alternative ARVs, providers should consider overlapping toxicities between the new ARVs and CAB or RPV.[1] The most common adverse event observed in clinical trials of LA CAB/RPV for HIV-1 treatment and CAB for HIV-1 prevention, compared with oral ART were ISRs, which rarely resulted in treatment discontinuation, indicating the reactions were tolerated by trial participants. Most ISRs can be managed through measures to counteract symptoms, including use of cold compresses at the injection site, and over-the-counter analgesics, antipyretics, and/or antihistamines.[37]

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TABLE 5 Prevention efficacy monitoring for persons receiving long-acting cabotegravir for pre-exposure prophylaxis: recommended laboratory testing [adapted from[53,77]].

Test	Baseline or CAB initiation (1st injection) visit* (Completed within 1 week prior to PrEP initiation)	At Month 1 visit (2nd injection)	At Month 3 visit (3rd injection) and every 8 weeks LA CAB injection visits (subsequent injections)	At the time of LA CAB discontinuation
HIV-1 RNA	X	X	X	Monitor every 3 months for 1 year after discontinuation
HIV-1/2 Ag/Ab**	X	X	X	Monitor every 3 months for 1 year after discontinuation
Serum creatinine	X		At least annually	As clinically indicated
Syphilis screening	X		Every 2–4 months, depending on reported risks***	As clinically indicated
Gonorrhea and Chlamydia screening	X		Every 2–4 months, depending on reported risks***	As clinically indicated

Note: Individuals of childbearing potential should receive a pregnancy test at baseline and discussion of benefits and risks of PrEP should pregnancy occur. Assessing the possibility of pregnancy should occur at each PrEP follow-up visit and a pregnancy test performed as appropriate. Routine monitoring of renal and liver function tests and lipid profile with CAB used as PrEP are not currently recommended. Hepatitis B serology screening and monitoring is also not needed for persons initiating LA CAB as PrEP (unlike with oral tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine), although all persons on PrEP may benefit from hepatitis B virus status assessment due to potential exposures. The NYSDOH PrEP guidelines[77] recommend renal function testing (i.e., serum creatinine and calculated creatinine clearance) at baseline and at least annually, as increased monitoring for potential adverse events may be warranted for persons with creatinine clearance <30 mL/min.

Abbreviations: Ag/Ab, antigen/antibody; CAB, cabotegravir; LA, long-acting; PrEP, pre-exposure prophylaxis.

* If 1 month of oral CAB lead-in is used, then HIV-1 RNA and HIV-1/2 Ag/Ab tests should be completed at the end of the oral CAB period/prior to first LA CAB injection. ** A rapid HIV-1/2 Ag/Ab test can be used, but blood should be drawn for confirmatory testing (e.g., HIV-1 RNA). *** US PrEP Guidelines[53] make a distinction between timing of sexually transmitted infection screening for men who have sex with men and transgender women who have sex with men versus heterosexually active men and women (i.e., Collect pharyngeal, rectal, and urine specimens in men who have sex with men. Collect vaginal, rectal, urine—as indicated, and blood specimens in heterosexually active women and men. Vaginal specimens preferred for gonorrhea testing in women, but rectal specimens should be collected in women who report anal sex.)

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Serious post-injection reactions were reported immediately after the RPV injection in <1% of clinical trial participants. Symptoms included dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain. All symptoms resolved within minutes and were proposed to be related to accidental intravenous administration of the injection. Patients should be observed for 10 minutes after the loading or maintenance injection of LA CAB/RPV, and supportive care given for post-injection reactions, as indicated.[51]

Hypersensitivity reactions have been reported with LA CAB/RPV, including drug reaction with eosinophilia and systemic symptoms (DRESS). In clinical trials of CAB/RPV for HIV-1 treatment and CAB for HIV-1 prevention, an OLI was used to identify participants at risk for hypersensitivity reaction. Providers should discontinue LA CAB/RPV for HIV-1 treatment or CAB for HIV-1 prevention if signs or symptoms of hypersensitivity develop, including severe rash or rash with fever, other constitutional symptoms, or organ dysfunction. In these situations, clinical monitoring, including hepatic transaminases, should be performed and appropriate supportive therapy provided. Providers should be aware that depression, hepatotoxicity, and weight gain have been reported with CAB/RPV for HIV-1 treatment and CAB for HIV-1 prevention; additional monitoring for these adverse effects is not currently recommended.[51,57]

In the CAPELLA study of LEN in treatment-experienced participants, 63% of participants reported at least one ISR (generally mild to moderate), including pain, swelling, or erythema. Most ISRs were grade 1 and resolved within days.[55] If LEN needs to be discontinued due to adverse events, it should be noted that LEN may remain detectable in the systemic circulation for a prolonged period of up to nine months after discontinuation. To minimize risk of developing viral resistance, an alternative ARV should replace LEN in the fully suppressive regimen no later than 28 weeks after the final injection of LEN.[59]

Monoclonal antibodies, including IBA, may be associated with hypersensitivity reactions, including infusion-related adverse events and anaphylaxis. Symptoms of hypersensitivity reactions can include dyspnea, angioedema, wheezing, chest pain or tightness, nausea, vomiting, and flushing. IBA is generally well tolerated, with common adverse events of diarrhea, dizziness, nausea, and rash. Rashes can appear within 1–3 weeks after the first dose of IBA with varying presentations, including macular and/or papular, erythematous, pruritic, and generalized. Most rashes are mild to moderate and resolve in 1–3 weeks despite continued IBA administration. Patients initiating IBA therapy should be monitored for the development of rash, particularly within the first few weeks of therapy. Usually, rashes can be managed symptomatically with antihistamine or corticosteroid therapy, without interruption of IBA treatment.[86] Immune reconstitution inflammatory syndrome (IRIS) related to IBA therapy has been reported. Severely immunocompromised patients starting ART, including use of IBA, should be closely monitored for development of immune reconstitution inflammatory syndrome[40] If IBA treatment needs to be discontinued due to adverse events, an alternate ARV, if available, should be started no later than the date that the next IBA infusion was scheduled.

In the RING and ASPIRE studies, there was no difference in primary safety endpoints related to the study product between the groups who received the DPV ring versus those who received placebo.[47,87] In open-label extension studies, no serious treatment-related adverse events were reported.[48,49] Treatment-related adverse events were mild, and included urinary tract infection, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain. The DPV ring does not protect against other sexually transmitted infections. Patients should be advised to let their healthcare provider know if they experience symptoms such as itching, severe lower abdominal pain, or vaginal discharge, discomfort, or pain. If the DPV ring is removed, protection against HIV-1 is immediately no longer provided, and alternate methods of protection should be used.[60]

10. What procedures should be implemented for LA ARV missed doses, self-discontinuations, and loss to follow-up?

Consensus recommendations

10.1 We recommend oral therapy bridging in cases of planned absence more than seven days beyond the scheduled injection for LA CAB/RPV or LA CAB.

Quality of evidence	B
Strength of recommendation	1

10.2 We recommend resistance testing, including the integrase region, if available, in cases of self-discontinued LA CAB/RPV, or in individuals lost to follow-up, as soon as possible to ensure future ART remains optimized.

Quality of evidence	B
Strength of recommendation	1

10.3 After discontinuation of LA CAB/RPV, we recommend initiation of an alternative, fully suppressive ART regimen no later than 4 weeks following the last LA CAB/RPV injection when dosed every 4 weeks or no later than 8 weeks after the last LA CAB/RPV injection when dosed every 8 weeks.

Quality of evidence	B
Strength of recommendation	1

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10.4 We recommend resistance testing, if available, in cases of self-discontinued LA IBA or LEN, or among individuals lost to follow-up, to evaluate susceptibility to the background ART regimen.

Quality of evidence	B
Strength of recommendation	1

10.5 After discontinuation of LA IBA, we recommend initiation of a new potentially suppressive ART regimen, based on resistance testing, if available, no later than 2 weeks following the last IBA infusion.

Quality of evidence	B
Strength of recommendation	1

10.6 After discontinuation of LA LEN, we recommend initiation of a new potentially suppressive ART regimen, based on resistance testing, if available, no later than 28 weeks following the last LEN injection.

Quality of evidence	B
Strength of recommendation	1

10.7 We recommend patients who self-discontinue the DPV vaginal ring be tested for HIV-1 and, if negative, counseled regarding the potential benefits and risks of the DPV vaginal ring and alternative PrEP and post-exposure prophylaxis (PEP) options.

Quality of evidence	B
Strength of recommendation	1

10.8 We recommend transition to oral PrEP, if continued PrEP is desired, no later than 8 weeks after the last CAB injection if the patient or provider determines LA CAB continuation is not feasible, safe, or desired.

Quality of evidence	B
Strength of recommendation	1

Evidence summary

The prolonged pharmacokinetic tail of LA CAB and LA CAB/RPV has critical impact on the clinical consequences of their use for HIV-1 treatment and PrEP. Failure to receive ongoing or timely injections poses a serious threat to therapeutic or preventive effectiveness. The HIV-1 prophylactic or therapeutic efficacy diminishes once drug concentrations wane after a final injection, and it is important to note that non-protective or subtherapeutic CAB and RPV concentrations may persist for several months. This has implications for both delayed dosing and discontinuation. Based on data from the post-injection tail phase of HPTN 077, it is estimated that the concentration of CAB may persist above the limit of quantification for as long as 4.3 years for cisgender females and 2.9 years for cisgender males; furthermore, longer durations may occur in individuals with higher BMI.[88] These drug concentrations, which may be inadequate to suppress viral replication but sufficient to apply selective pressure to select for existing or de novo INSTI- or NNRTI-resistant viral variants, can lead to an increased risk for HIV-1 acquisition (in the case of LA ARVs for HIV-1 prevention) or viral rebound (in the case of LA ARVs for HIV-1 treatment). Resistance testing including the integrase region should be done as soon as possible for people who acquire HIV after discontinuation of LA CAB for PrEP without addition of oral PrEP; for people who discontinue LA CAB/RPV for HIV treatment without initiating oral ART; and, for people who are lost to follow-up.

To date, the majority of data around how to address missing doses from LA CAB or LA CAB/RPV are derived from pharmacokinetic modeling.[89] These simulations demonstrated that the proportion of individuals with CAB trough concentrations below 0.65 μg/mL (the 5th percentile of trough concentrations after the first injection in Phase 3 trials) was highly influenced by both the length of the delay and how many injections had been previously received. By the third injection, delays of less than one week resulted in more than 80% of individuals maintaining troughs above 0.65 μg/mL; however, only 61% of individuals maintained troughs above 0.65 μg/mL with delayed second injections. Therefore, with planned injection delays of less than or equal to 7 days, clinicians may resume injections as per normal, but planned injection delays of more than 7 days warrant oral bridging with daily CAB and RPV or any other fully suppressive ART regimen for HIV-1 treatment, or an alternative PrEP option for HIV-1 prevention.[51,57] Of note, oral CAB may not be available in community pharmacies[61] and may require special ordering from the manufacturer. Therefore, patients and providers must plan for any disruption in the LA dosing administration schedule. Bridging should continue until the day of their next injection. If LA CAB/RPV injections for HIV-1 treatment have been delayed by more than 8 weeks, regardless if the dosing schedule is every 4 or 8 weeks, it is recommended that the next injection administered is the initiation dose of IM LA CAB/RPV. Additional information on the recommended dosing schedule for missed LA CAB/RPV injections appears in Table 1. If being used for PrEP and the LA CAB injection has been delayed by more than 8 weeks, it is recommended to reload the patient with the initiation doses and then resume with every 8-week dosing.

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Recently presented data from HPTN 084 preliminarily suggest there may be up to 6 weeks of forgiveness with delayed CAB maintenance injections in women.[90] CAB concentrations were analyzed in participants randomized to the LA CAB arm who experienced at least one injection delay during the blinded phase of the trial. There were 205 instances where maintenance injections were administered outside of the visit schedule at 12–18 weeks. When injections were administered 12–14 weeks apart (representing a 6-week delay), 98% of participants maintained CAB concentrations 4 times above the protein-adjusted 90% inhibitory concentration (PA-IC90). Even with 16–18 weeks between these injections, 90% maintained concentrations four times above the PA-IC90 target. Collectively, these initial data may suggest some forgiveness with late CAB injections in women. However, before these data can be considered in making recommendations, clinical trials must address several concerns. First, these data only represent persons assigned female at birth. The absorption rate constant of intramuscular CAB is higher in men and, therefore, there is likely less injection forgiveness in men. Additionally, these data largely describe women who experienced one delayed injection event and not women who were on a delayed injection schedule. The presented data, while promising, highlight the need for additional evidence to ensure target CAB concentrations are achieved if alternative dosing regimens are pursued in women.

To minimize the risk of developing drug resistance following discontinuation of LA CAB/RPV, it is essential to ensure an alternative, fully suppressive ART regimen no later than four weeks after the final injection of LA CAB/RPV when dosed every 4 weeks or no later than 8 weeks after the final injection of LA CAB/RPV when dosed every 8 weeks. Individuals at risk for HIV-1 who discontinue LA CAB as PrEP could transition to alternative PrEP options, as desired, to provide protection against HIV-1.

If IBA is discontinued, the remaining ARV regimen should be reevaluated to avoid novel or further resistance mutation accumulation against drugs of the OBR. It may be valuable to repeat resistance testing depending on the duration of IBA discontinuation to decide on the composition of a regimen for treatment continuation. After discontinuation of LA IBA, we recommend initiation of a new potentially suppressive ART regimen, based on resistance testing, if available, no later than 2 weeks following the last IBA infusion.

If LEN is discontinued, or in individuals lost to follow-up, we recommend resistance testing to evaluate susceptibility to the OBR. Table 6 reviews recommended approaches to missed LEN oral loading doses. During the LEN maintenance phase, if more than 28 weeks have passed since the last injection, the oral loading dose regimen should be reinitiated or switched to another fully suppressive ART regimen, based on history and resistance testing, immediately.[59] Emerging data demonstrate that bridging with LEN 300 mg orally every week during planned delays of the LEN injectable maintenance phase, results in maintenance of virologic suppression.[91]

Unlike other LA formulations, the DPV vaginal ring delivers drug at a constant rate for the duration of its insertion and concentrations fall rapidly upon removal; therefore, there is little concern for coverage of a pharmacokinetic tail or need for bridging therapy upon removal. Patients should be counseled that their protection from HIV-1 is only while the product is accurately in place. To maintain protection from incident HIV-1, a new ring should be inserted immediately upon removal of the previous ring.[60] Additionally, patients who discontinue the DPV vaginal ring should be tested for HIV-1 and, if negative, counseled regarding the potential benefits and risks of the DPV vaginal ring and alternative PrEP as well as post-exposure prophylaxis options.

There is a paucity of data on the prevalence of missed doses and discontinuation of LA ARVs, including switch back to oral ARVs, outside of controlled trial settings. Future research should address these knowledge gaps.

11. What is the process for identifying and assessing HIV-1 drug resistance and breakthrough infections for patients receiving LA ARVs for HIV-1 treatment or PrEP?

Consensus recommendations

11.1 We recommend that any abnormal or indeterminate HIV-1 screening or testing result (HIV-1 Ab, p24 Ag, and HIV-1 RNA) among people receiving LA PrEP should be further evaluated since it may suggest evidence of HIV-1 acquisition

Quality of evidence	B
Strength of recommendation	1

11.2 HIV-1 RNA may be detected in low levels or even undetectable in persons who acquire HIV-1 in the context of LA CAB for PrEP. Therefore, if a clinician encounters ambiguous or indeterminate HIV-1 test results for a patient receiving LA PrEP, we suggest additional testing, such as repeat HIV-1 RNA or qualitative proviral HIV-1 DNA polymerase chain reaction testing

Quality of evidence	C
Strength of recommendation	2

11.3 For persons who acquire HIV-1 in the context of LA CAB for PrEP, we recommend immediate initiation of non-INSTI-based ART, such as a boosted PI-based ART regimen, while awaiting resistance testing results

Quality of evidence	B
Strength of recommendation	1

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11.4 For persons who acquire HIV-1 in the context of DPV vaginal ring for PrEP, we recommend immediate removal of the ring and initiation of a first-line regimen for HIV-1 treatment following local guidelines

Quality of evidence	A
Strength of recommendation	1

11.5 We suggest NNRTI-based ART, if INSTI- or boosted PI-based regimens are not available, for persons who acquire HIV-1 in the context of using DPV vaginal ring for PrEP

Quality of evidence	C
Strength of recommendation	2

11.6 We recommend genotype resistance testing, where available, in people who experience virologic breakthrough (i.e., two consecutive HIV-1 RNA ≥200 copies/mL) while on LA CAB/RPV to evaluate for potential emergence of resistance to INSTI and/or NNRTI drug classes

Quality of evidence	A
Strength of recommendation	1

TABLE 6 Approach to missed lenacapavir oral loading dose scenarios.

Missed loading dose	Missed dose scenario	Recommended replacement dosing
Day 2 (600 mg oral dose)	Missed by <6 days	• Oral LEN 600 mg as soon as possible • Oral LEN 300 mg on day 8
	Missed by ≥6 days	• Oral LEN 600 mg as soon as possible • Oral LEN 300 mg on day 15 + regularly scheduled subcutaneous LEN
Day 8 (300 mg oral dose)	Missed by <6 days	• Oral LEN 300 mg as soon as possible
	Missed by ≥6 days	• Oral LEN 300 mg on day 15 + regularly scheduled subcutaneous LEN

Abbreviations: LEN, lenacapavir.

11.7 In people with HIV-1 who experience low-level viremia (i.e., confirmed detectable HIV-1 RNA <200 copies/mL) while on LA ART, clinicians should consult with a provider experienced in HIV medicine, as there is currently a lack of evidence on optimal evaluation and management strategies

Quality of evidence	D
Strength of recommendation	2

11.8 For people with HIV-1 receiving LA CAB/RPV with confirmed virologic failure and evidence or concern for emergent CAB- or RPV-associated resistance, we recommend HIV-1 treatment modification as soon as possible to avoid mutation selection and accumulation; given concern for potential INSTI and NNRTI resistance, we recommend PI-based combination ART be considered while awaiting resistance testing results

Quality of evidence	A
Strength of recommendation	1

11.9 For people with HIV-1 receiving IBA or LEN who experience confirmed virologic failure (i.e., two consecutive HIV-1 RNA > 200 copies/mL), we suggest consultation with a provider experienced in HIV medicine, as resistance testing for IBA or LEN is not currently available

Quality of evidence	B
Strength of recommendation	1

Evidence summary

As with oral PrEP, LA CAB exposure modifies virologic, immunologic, and clinical features of HIV-1 among people who acquire HIV-1 in the setting of PrEP.[78,92] Observations from clinical trials among persons who acquire HIV-1 on LA CAB suggest that initial viremia is lower or may even be undetectable by commercially available assays. Seroconversion may also be delayed (median delay of 62 days for baseline cases and 98 days for incident cases).[93] Additionally, clinical presentation of primary HIV-1, traditionally observed as an influenza-like syndrome, is almost always absent. Therefore, timely recognition and HIV-1 diagnosis may be challenging with LA CAB use.[92] Retrospective analysis of participants failing LA CAB in HPTN 083 suggests efficacy monitoring with HIV-1 RNA performed simultaneously with combination HIV Ag/Ab testing may detect cases of PrEP failure earlier and help prevent development of viral resistance.[93,94]

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For people who acquire HIV-1 in the setting of LA CAB use, timely resistance testing should be pursued to select an appropriate treatment regimen, as selection of INSTI resistance was observed in several incident HIV-1 cases among study participants despite on-time injections or during the OLI; emergent resistance during the CAB "PK tail" may also be of concern.[45,93–95] Feasibility of such testing may be challenging; furthermore, if plasma HIV-1 RNA is too low for resistance testing via traditional Sanger sequencing methods, proviral genotype resistance testing may be considered. No systematic data are currently available on virologic outcomes using second-generation INSTI-based treatment, such as dolutegravir or bictegravir, after LA CAB failure. Therefore, if HIV-1 acquisition is suspected, a prudent approach would be to modify therapy immediately to non-INSTI-based ART, such as a boosted PI-based regimen, while awaiting resistance testing results.

In DPV trials, HIV-1 screening was typically performed at study visits using rapid tests as an initial step, with follow-up/confirmatory testing with an instrument-based assay (or Western Blot) as indicated. Real-world screening and laboratory monitoring/testing practices will likely be guided by available platforms and workflows, in addition to program experience and preferences. To date, no cases of delayed seroconversion have been described among DPV trial participants. For persons who acquire HIV-1 while using DPV vaginal ring for PrEP, we recommend immediate removal of the ring and initiation of a first-line regimen for HIV-1 treatment following local guidelines. Resistance analyses from the Phase 3 trials and open-label extension studies suggest no increased risk for NNRTI-resistant HIV-1 among seroconverting participants; although the E138A polymorphism was observed more frequently in the DPV group, this difference was not statistically significant.[95–97] Among trial participants who acquired HIV-1 and subsequently initiated NNRTI-containing ART, DPV and placebo participants had similar virologic outcomes after ART initiation suggesting that NNRTI-based regimens may still be effective.[98,99] Therefore, clinicians may consider NNRTI-based ART, if INSTI- or boosted PI-based regimens are not available, for persons who acquire HIV-1 in the context of using DPV vaginal ring for PrEP. As with LA CAB breakthrough infections, standard best clinical practices regarding initial resistance evaluation and subsequent HIV-1 treatment selection should generally be employed.

For providers considering LA CAB/RPV for HIV-1 treatment, key features related to HIV-1 drug resistance should be noted. Most ATLAS-2 M participants who had virologic failure with LA CAB/RPV had retrospectively identified, archived resistance substitutions for RPV.[29] Additionally, many cases of RPV resistance-associated virologic failure will also demonstrate resistance to other NNRTI agents,[100] potentially impacting future therapy options. Among trial participants who had virologic failure with LA CAB/RPV and developed HIV-1 drug resistance, as well as people with HIV-1 receiving LA CAB/RPV in "real-world" settings, resistance was observed for both the NNRTI and INSTI classes.[37,75,76]

Genotype resistance testing is therefore recommended for all people with HIV-1 receiving LA CAB/RPV who develop virologic breakthrough, defined as two consecutive HIV-1 RNA ≥200 copies/mL, to evaluate for potential emergence of resistance to INSTI and/or NNRTI ARVs. Similar to people with HIV-1 failing oral ART, timely resistance evaluation should be pursued. For persons with viremia between 200 and 500 copies/mL, plasma-based Sanger sequencing may be unsuccessful but should still be considered. There is currently little evidence to guide management of low-level viremia with a confirmed detectable HIV-1 RNA <200 copies/mL with LA CAB/RPV use. Clinicians may consider consultation with a provider experienced in HIV medicine, as there is currently a lack of evidence on optimal evaluation and management strategies. Evaluation should include assessment of potential drug–drug interactions as well as confirmation that the LA ARVs were administered correctly (e.g., on-time and proper gluteal IM technique). If a potentially modifiable cause is identified, such as a drug–drug interaction, appropriate interventions should be implemented.

In people with HIV-1 with confirmed virologic failure and evidence of, or concern for, emergent CAB or RPV-associated resistance, HIV-1 treatment should be modified as soon as possible to avoid selection and accumulation of drug resistance mutations. Given concern for potential INSTI and/or NNRTI resistance, an ART regimen avoiding INSTIs and NNRTIs, such as a boosted PI regimen should be considered while awaiting resistance test results. ART selection should be guided by careful review of the entire ARV history, recent and prior resistance test results, and consideration of comorbidities and concurrently administered medications. If resistance testing subsequently demonstrates evidence of susceptibility to CAB/RPV, then resumption may be considered.

Decreased susceptibility to IBA is associated with genotypic changes in the coding sequence of the HIV-1 envelope causing loss of potential N-linked glycosylation sites in the V5 loop of gp120. In the Phase 3 IBA study, decreased sensitivity to IBA was detected in most participants who experienced virologic failure through Week 24.[40] IBA is not expected to have clinically relevant residual effects in cases where resistance has developed, and thus should be discontinued in most patients. However, consultation with a provider experienced in HIV medicine is highly recommended for clinicians treating people with HIV-1 who do not experience a favorable treatment response, since persons on IBA will have multidrug-resistant HIV-1 and IBA resistance testing is not currently commercially available for use in clinical practice. Importantly, decreased susceptibility to IBA does not alter susceptibility to other currently approved ARVs and cross-resistance has not been described[101]; it also does not result in the selection of CD4-independent viral strains.

In vitro studies have identified specific resistance-associated mutations conferring reduced LEN susceptibility. Resistance to LEN results in a decreased replication capacity of mutant viruses.[102] Eight heavily treatment-experienced participants in CAPELLA developed substitutions associated with decreased drug susceptibility.[102] Given limited clinical experience with LEN at this time, consultation with a provider experienced in HIV medicine is highly recommended for clinicians managing people with HIV-1 who do not have a favorable response, especially if the patient is heavily treatment-experienced. Although LEN is highly potent, it appears to have a low genetic

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barrier to resistance. As with IBA, decreased susceptibility to LEN is not expected to alter susceptibility to other currently approved ARVs, since it is a "first in class" capsid inhibitor.[103,104] There is currently no commercially available resistance test for LEN.

Future research needs include the clinical management of persons who acquire HIV-1 in the setting of LA PrEP with CAB or DPV and of persons who fail LA CAB/RPV for HIV-1 treatment. For people with HIV-1 receiving IBA or LEN experiencing confirmed virologic failure, subsequent ART strategies need to be developed and evaluated. Use of proviral resistance testing needs to be prospectively evaluated and clinically validated for use in persons with low-level viremia in the setting of any LA ARV exposure.

12. What are the notable drug interactions involving LA ARVs?

Consensus recommendations

12.1 We recommend LA injectable CAB and LA injectable RPV (as well as oral CAB and oral RPV, if used for OLI) be avoided with potent inducers of drug metabolizing enzymes.

Quality of evidence	B
Strength of recommendation	1

12.2 If oral RPV is used as part of the optional OLI therapy with oral CAB, we recommend proton pump inhibitors be avoided. Proper dose separation from oral RPV is warranted with other acid suppressants (e.g., antacids, H2 receptor antagonists).

Quality of evidence	B
Strength of recommendation	1

12.3 Although no drug–drug interactions are expected with IBA, we recommend clinicians evaluate drug interactions with the other components of the OBR.

Quality of evidence	B
Strength of recommendation	1

12.4 Although clinically significant drug–drug interactions with DPV vaginal ring are not expected, clinicians should monitor for potential interactions involving co-administered intravaginally applied products.

Quality of evidence	C
Strength of recommendation	2

12.5 We recommend that LEN should not be used with strong inducers of CYP3A4, P-gp, or UGT1A1.

Quality of evidence	B
Strength of recommendation	1

12.6 We recommend LEN be used with caution in individuals taking CYP3A4 substrate agents with a narrow therapeutic index during or within 9 months after the last LEN subcutaneous injection due to LEN's potential inhibitory effects on the substrates' metabolism and increased substrate drug exposure

Quality of evidence	C
Strength of recommendation	1

Evidence summary

CAB and RPV undergo minimal renal clearance; however, both are hepatically metabolized and are therefore susceptible to drug–drug interactions[105,106] Both CAB and RPV should be avoided with concomitant medications that are potent inducers of drug metabolizing enzymes. Both drugs have minimal inhibitory or induction effects on metabolism enzymes or drug transporters and are therefore unlikely to have clinically significant effects on concentrations of any concomitant medications.[107] At high exposures, RPV can enhance the QTc interval and therefore there is increased concern for pharmacodynamic interactions with other QTc-prolonging drugs. Drugs administered systemically that bypass absorption and first-pass metabolism may also see less impact on metabolism-mediated interactions as they are no longer exposed to CYP3A4 or other enzymes in the gastrointestinal tract.[108] Table 7 summarizes recommendations on management of common drug–drug interactions with oral and intramuscular formulations of CAB and RPV with acid-reducing agents, polyvalent cations, rifamycin antibiotics, anti-epileptics, potent CYP3A inhibitors, dexamethasone, methadone, and some other agents.

LEN is contraindicated with strong inducers of CYP3A4, P-gp, or UGT1A1, and should be administered with caution when co-administered with sensitive CYP3A4 substrate agents that have a narrow therapeutic index during or within 9 months after the last LEN SC injection. LEN may be co-administered with most ARVs except for boosted atazanavir, efavirenz, nevirapine, and tipranavir due to potential for altered LEN exposure. Common agents to avoid with concurrent LEN use are summarized in Table 7.

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Drug–drug interactions with IBA are not expected due to its mechanism of action and target-mediated drug disposition. Therefore, no formal drug interaction studies have been conducted with IBA.[58] IBA is a protein which is degraded into small peptides and amino acids.[109] In the IBA clinical trials, all patients received standardized IBA dosing regardless of their OBR containing CYP inhibitors (e.g., boosted PIs) and/or CYP inducers (e.g., etravirine).[40,110] Thus, IBA concentrations are not expected to be affected by ARV drugs interacting with metabolizing enzymes. While pharmacokinetic drug interactions with IBA are not anticipated, patients should still be monitored for possible pharmacodynamic interactions between IBA and other medications, such as overlapping toxicities. Additionally, clinicians should evaluate drug interactions with the other components of the OBR.

Drug interaction studies with DPV vaginal ring are limited. Data from *in vitro* studies suggest DPV is metabolized by CYP1A1 and CYP3A4[111] with some metabolism by CYP2B6, CYP2C19, as well as glucuronidation via UGT enzymes[60] but is not affected by P-gp inhibitors.[112] Of note, UGT enzymes are not present in vaginal tissues, therefore local concentrations of DPV delivered via vaginal ring are not expected to be affected by glucuronidation.[113] Concurrently administered vaginal miconazole appears to increase DPV concentrations via inhibition of CYP1A1 and CYP3A4,[111] resulting in approximately 20% higher systemic DPV maximum concentration and area under the concentration–time curve; however, these changes are unlikely to be clinically significant due to the overall very low systemic concentrations of DPV (<1 ng/mL) from vaginal ring delivery.[114] The low plasma concentrations of DPV are not expected to lead to clinically significant systemic pharmacokinetic drug–drug interactions; however, there is potential for drug–drug interactions involving co-administered vaginal products.[60,111] Increases in local and/or systemic antifungal concentrations were observed when DPV vaginal ring was co-administered with a single-dose vaginal miconazole suppository[114] and repeated daily administration of clotrimazole vaginal cream. In a secondary analysis of the ASPIRE trial, rates of pregnancy among women using various forms of hormonal contraceptives (injectable, implantable, and oral) and DPV vaginal ring versus placebo were not significantly different, suggesting that DPV does not reduce the effectiveness of hormonal contraceptives.[115] Based on these data, concentrations of vaginally administered DPV may be affected by co-administered vaginal products which are strong CYP1A1 and CYP3A4 inhibitors and inducers, while DPV vaginal ring may also affect drug levels of other vaginally applied products which are CYP or UGT substrates, although the clinical significance of such interactions are not yet well defined. Therefore, while clinically significant drug–drug interactions with DPV vaginal ring are not expected, clinicians should monitor for potential interactions involving co-administered intravaginally applied products.

13. What is the process for facilitating transitions of care for patients receiving LA ARVs for HIV-1 treatment or PrEP?

Consensus recommendations

13.1 Providers involved in care transitions should be familiar with use of LA ARVs—especially dosing and administration intervals—and coordinate patient care closely to avoid treatment interruptions

Quality of evidence	C
Strength of recommendation	2

Evidence summary

As LA ARVs are implemented more broadly, care transitions and other health system concerns will inevitably arise for patients accessing these novel therapies. Transitions of care refers to "the movement patients make between healthcare practitioners and settings as their condition and care needs change during the course of a chronic or acute illness."[116,117] This includes geographic changes related to relocation as well as transfers between acute hospital- and community-based facilities, ambulatory care practices, short-term rehabilitation, long-term care facilities, and changes in institutionalization status, such as incarceration. Additionally, patients may change from one provider or care team to another as new health-related needs arise, such as during and after pregnancy, or when youth and adolescents transition into adulthood. For people with HIV-1, some transitions may be especially consequential,[118–120] as these scenarios occasionally involve disruptions in health payor coverage, continuous ART access and/or loss to follow-up.

Given that LA ARVs are not yet universally available, systematic understanding of important service delivery factors to anticipate and address is lacking. Therefore, at this time, pragmatic considerations and general principles to facilitate successful care transitions for people on LA ARVs may be most useful until more evidence and real-world experience emerges. Providers involved in care transitions should be familiar with the use of LA ARVs—especially dosing and administration intervals—and coordinate patient care closely to avoid treatment interruptions. Ideally, transitions should involve a comprehensive, up-to-date care plan which includes the patient's goals, preferences, and clinical status.

Prior to the care transition, the patient's desire and eligibility to continue LA ARVs as maintenance therapy for either HIV-1 treatment or PrEP should be confirmed, as well as whether the LA ARVs will be available via the new care provider and setting. LA ARV procurement may require advanced planning and coordination for medication procurement. The LA ARV dosing schedule, including the date and dose of the last—and anticipated next—medication administration should be communicated clearly. For providers with less LA ARV experience, it may be helpful to clarify the allowable window for the next dose, if applicable. Care teams should also confirm recommended medication storage and handling practices, administration technique, medication monitoring guidelines, and procurement-related issues. For patients who are hospitalized or individuals in

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TABLE 7 Select clinically significant drug–drug interactions with cabotegravir, rilpivirine, and lenacapavir formulations.

		Oral RPV	Oral CAB	LA CAB/RPV	LA CAB	LEN
Absorption-related	Proton pump inhibitors	Contraindicated	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
	H2 antagonists	Give H2 antagonists at least 12 h before or at least 4 h after oral RPV	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
	Antacids containing aluminum, calcium, magnesium	Give antacids at least 2 h before or at least 4 h after oral RPV	Give antacids at least 2 h before or at least 4 h after oral CAB	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Rifamycins	Rifabutin	Increase oral RPV to 50 mg daily	Decreased CAB exposure expected but no dose adjustment needed	Contraindicated	When rifabutin is started before or concomitantly with the first CAB injection, the recommended dosing of CAB is one 600-mg injection, followed 2 weeks later by a second 600-mg initiation injection, and then every 4 weeks thereafter while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended CAB dosing is 600 mg every 4 weeks while on rifabutin. After stopping rifabutin, the recommended dosing of CAB is 600 mg every 8 weeks.	Do not coadminister
	Rifampin	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Rifapentine	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Do not coadminister
Anti-seizure	Carbamazepine	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Phenobarbital	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Do not coadminister
	Phenytoin	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Oxcarbazepine	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Do not coadminister
Potent CYP 3A4 inhibitors	Azole antifungals, macrolide antibiotics	Monitor QTc	No dose adjustment needed	Monitor QTc	No dose adjustment needed	No dose adjustment needed
Other agents	Bosentan	Consider alternative to bosentan	No dose adjustment needed	Consider alternative to bosentan	No dose adjustment needed	Do not coadminister
	Dexamethasone (more than one dose)	Contraindicated	No dose adjustment needed	Contraindicated	No dose adjustment needed	Initiate with lowest dexamethasone starting dose and titrate carefully while monitoring for safety; do not coadminister with dexamethasone >16 mg/day
	Methadone	No dose adjustment needed, but monitor for withdrawal symptoms	No dose adjustment needed	No dose adjustment needed, but monitor for withdrawal symptoms	No dose adjustment needed	No dose adjustment needed
	Ergot derivatives	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed	Do not coadminister

Abbreviations: CAB, cabotegravir; CYP, cytochrome P450; IM, intramuscular; LEN, lenacapavir; RPV, rilpivirine.

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custody in a jail or prison, LA ARVs may not be on the institutional formulary; therefore, special arrangements may need to be made to ensure timely receipt of the next LA ARV dose or to coordinate oral medication bridging until LA ARVs are resumed.

Implementation science research is needed to identify clinical and practice/systems-level factors that influence LA ARV service delivery during transitions of care.

14. What is the process for minimizing HIV-1 treatment and prevention disparities and optimizing equitable access to LA ARVs for HIV-1 treatment or PrEP?

Consensus recommendations

14.1 Development of LA ART and PrEP programs should consider patient preference for medication administration, such as community-based delivery, to optimize equitable access and minimize disparities in uptake of LA ART and PrEP options.

Quality of evidence	C
Strength of recommendation	2

Evidence summary

The need for repeat medical visits for injection delivery of specific LA ARVs may particularly affect persons with individual, social, or structural barriers to treatment access, as well as cause additional strain on traditional service delivery settings (e.g., clinical offices) to adapt/create processes for a new type of demand.[121] Furthermore, increased need for clinic visits (compared to infrequent clinic visits among stable, virologically suppressed patients) have been reported among patients to result in increased stigma and may increase personal costs due to medical visits and travel.[122] Development of LA ART and PrEP programs that consider patient preference for medication administration, such as innovative community-based delivery models, may optimize equitable access and minimize disparities in uptake of LA ART and PrEP options. This concept has been proven with nurses and other health professionals delivering ART in non-traditional healthcare settings which led to improved uptake, retention, and viral suppression among persons with HIV-1.[123]

Furthermore, addressing disparities in the implementation of LA ARVs requires equitable access through formulary availability, affordable pricing, support programs, education for patients and providers to decrease stigma and bias, simplified medication procurement, improved choice and access (pharmacy or home administration), and development of novel delivery and monitoring strategies such as mobile delivery, de-medicalized PrEP, or combining PrEP and long-acting contraceptive modalities.[124]

Significant disparities in oral PrEP access persist, including disparities in race/ethnicity, gender, age, socioeconomic status, and locale. These disparities remain concentrated in populations already disparately impacted by HIV-1.[121] Strategies to reduce PrEP uptake disparities include addressing provider and patient knowledge and acceptability, decreasing HIV stigma, improving access, implementing self-testing for HIV-1 and sexually transmitted infections, decreasing monitoring requirements, and addressing financial limitations.[125,126] Lessons learned from the slow uptake and rollout of oral PrEP should inform strategies for more equitable rollout of LA ARVs to avert repeating the challenges and minimizing the disparities in access and delivery.

15. What resources and personnel are involved in the provision of LA ARVs to patients and what are their roles?

Consensus recommendations

15.1 We recommend organizational and workflow policy development to build, sustain, and grow programmatic LA ARV infrastructure whereby a dedicated multidisciplinary team is at the core of program implementation

Quality of evidence	B
Strength of recommendation	1

15.2 We recommend dedicated resources for successful LA ARV program implementation including physical space, cold chain supply (if applicable), medication administration supplies and storage, and electronic prescription and data management capacity

Quality of evidence	B
Strength of recommendation	1

Evidence summary

The advent of LA ARVs requires newfound, intensive efforts and capital investment of health systems and personnel. At the core of successful implementation of LA ARV use is a multidisciplinary team dedicated to building the programmatic infrastructure needed to initiate, sustain, and scale-up delivery of these novel HIV-1 therapeutic and preventive agents. This team would ideally be comprised of clinical and non-clinical personnel who are appropriately supported to do this work and collaborate on designing innovative and accessible LA ARV programs; secure necessary resources including electronic prescription and data management capacity, physical space for appropriate drug storage and administration, and supplies; and recruit, train, and retain staff to facilitate drug procurement and storage, medication counseling and administration, patient tracking and monitoring, maintenance of drug and supplies inventory, and appropriate billing and reimbursement. Close communication among interprofessional team members is essential for optimizing medication safety in LA ARV programs. Program design,

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multidisciplinary team structure, and patient enrollment capacity will depend on health system- and/or clinic-specific resource and staffing availability and investment from health systems leadership and/or public health programming. Involving colleagues with diverse training, skills, and perspectives including from medicine, pharmacy, nursing, scheduling, billing, social work, case management, and patient navigation services as part of the multidisciplinary team is paramount. Incorporating administration and management personnel is essential for smooth integration of an LA ART workflow from programmatic vision and design to day-to-day operations. In descriptions of early experiences implementing LA ART with injectable CAB/RPV,[34,127] programs have used a centralized approach whereby providers refer patients to a multidisciplinary team for review of clinical and program eligibility.

For eligible patients, drug procurement is typically led by medication access specialists, community pharmacists, and clinical pharmacists who have the expertise needed to navigate this potentially complex process. Coordination is often needed between the LA ARV team and health insurance programs and/or payors integrated with pharmaceutical companies, drug wholesalers, specialty pharmacies, and distributors. The process for LA ARV acquisition may be cumbersome, involving deciphering drug benefits coverage based on payor source; completing documentation for prior authorization, appeal, and patient assistance programs; and ordering and storing the medication and supplies for administration. Once the drug is procured, pharmacy and nursing staff team members, including community and clinical pharmacists, pharmacy technicians, registered nurses, licensed practical nurses, and medical assistants, should work collaboratively to appropriately store the drug, contact patients for medication counseling, schedule drug administration visits, conduct the drug administration visit which may involve patient observation after first dose and drawing laboratories for monitoring as indicated, schedule follow-up drug administration visits, and then documenting and billing for the encounters.

Patient, provider, and staff education on the process of eligibility, access, coverage, procurement, and administration will help to facilitate optimal uptake and sustainability of LA ART programs. This is important to meet the potential challenges of non-adherence, virologic failure and patients lost to follow-up.[23] Finally, LA ART programmatic development should include building electronic medical record capacity for tracking patient adherence to drug administration visits, medication tolerability/acceptability, clinical outcomes, and contacting patients who have missed or delayed drug administration visits to re-engage them in care and discuss appropriateness of continued LA ARVs on a case-by-case basis.

In addition to building and supporting a multidisciplinary LA ARV team, investment in and provision of clinic resources such as physical space, cold chain supply, equipment, and additional personnel are critical to the implementation of a successful LA ARV program. Physical space for LA ARV administration and equipment storage should be allocated. In comparison to accessing oral ART from a pharmacy and daily administration outside of the clinic (usually in a home setting), patient visits to the clinic for administration of LA ARVs (which would ideally occur in a private space) will substantially increase the need for additional clinic space and resources.[128]

Further, for some LA ARV options, cold chain management is needed. In particular, optimal storage temperature for vials of LA CAB/RPV and IBA is between 2 and 8 degrees Celsius. Depending on clinic volume and LA ARV packaging, smaller clinic refrigerators may not be sufficient to store anticipated LA ARV inventory stock and larger, more costly equipment may be needed to accommodate anticipated clinic needs.[129] For LA ARVs requiring an injection or infusion, equipment required for injection administration such as gloves, syringes, needles, and a biohazard sharps container should be appropriately procured.[130]

High priority areas for future research include assessment of LA ARV programmatic design and staffing needs; development of best practices for LA ARV accessibility, procurement, and administration; and documentation of successful LA ARV programs across a diversity of clinical and non-clinical settings.

16. What is the process for discontinuing LA ARVs or transitioning to an alternative regimen for HIV-1 treatment or PrEP?

Consensus recommendations

16.1 We recommend initiation of oral ARV coverage when LA ARVs, for HIV-1 treatment or prevention, are discontinued to minimize development of drug resistance or HIV-1 acquisition.

Quality of evidence	B
Strength of recommendation	1

Evidence summary

Careful counseling on adherence to drug administration windows should be done with individuals initiating LA ARVs for HIV-1 prevention or treatment. Decisions to discontinue LA agents may be made by the patient or the provider. If discontinuation of LA ART is in the setting of HIV-1 RNA suppression, it is recommended that HIV-1 RNA testing be done at the time of ART switch and then in the subsequent weeks to assure sustained viral suppression. If discontinuation of LA ART is due to confirmed virologic failure/rebound, ARV resistance testing should be performed immediately and ideally at the time of discontinuation.[1] In the setting of PrEP, the recommendation after LA CAB discontinuation is that alternative PrEP is initiated within 8 weeks after the last injection to cover the pharmacokinetic tail, subsequently avoiding resistance development should HIV-1 acquisition occur.

Concerns in the setting of transitioning from LA CAB/RPV to oral ART include the potential for there being residual systemic drug concentrations, albeit below protective thresholds, which have the potential to cause drug–drug interactions and adverse events. However, to date, adverse events related to dual INSTI exposure (e.g., residual LA CAB plus new oral INSTI) have not been observed

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in trials and limited real-world studies. In LA CAB/RPV clinical trial participants who were restarted on other INSTI-based regimens after experiencing virologic failure on LA CAB/RPV, the new INSTI-based regimen was well tolerated without incident.[28,30,31,54]

Future research should include evaluation of patient clinical outcomes in which LA ARVs have been discontinued, in addition to evaluation of toxicities with transitions to alternative ARVs for HIV-1 treatment and prevention.

17. What evidence is available for using LA ARVs in key patient populations including children, or adolescents, people planning to become pregnant, persons who are pregnant and persons who are breast/chest-feeding?

Consensus recommendations

17.1 We recommend inclusive research to evaluate the optimal safety and efficacy of LA ART and PrEP among pregnant and lactating individuals, children, adolescents, and persons of trans experience, as these populations have been underrepresented in clinical trials.

Quality of evidence	B
Strength of recommendation	1

17.2 We recommend development of safe, accessible, non-discriminatory, gender-affirming guidelines and prescribing protocols for use of LA ART and PrEP.

Quality of evidence	C
Strength of recommendation	1

Evidence summary

Unique developmental (physiologic, cognitive, and psychosocial) and pharmacokinetic changes occur across the life course from infancy to adolescence underscoring the importance of specific and intentional study of LA ARV agents in this population.[1] Data on LA ART for HIV-1 treatment among virologically suppressed individuals 12–18 years of age are being obtained from IMPAACT 2017 (NCT03497676). Preliminary data demonstrated that the pharmacokinetic targets of LA CAB/RPV were similar to those in the adult population, prompting expanded approval of LA CAB/RPV down to 12 years of age and weighing at least 35 kg.[51,131] Additional data are being collected in the adolescent population including pharmacokinetics of the DTI approach compared to the OLI approach as well as quality of life indicators. Other relevant adolescent studies in development include the safety, tolerability, pharmacokinetics, and antiviral activity of LA CAB/RPV down to two years of age.[132] Given the unique circumstances of children and adolescents with HIV-1, it is critically important to examine issues such as the optimal site of LA ARV administration, pharmacokinetic changes with evolving development, as well as the impact of LA ART on HIV-1 disclosure, quality of life, and psychosocial well-being.

Approximately half of all pregnancies worldwide are unintended, and most pregnancies are recognized between 5 and 6 weeks' gestation.[133,134] Given the potential for transplacental transfer of ARV agents during critical fetal development, it is important to examine the impact of LA ARVs on the developing fetus. For individuals utilizing any medication, including LA ARVs for either HIV-1 prevention or treatment, clinicians should understand an individual's pregnancy intentions and optimize sexual reproductive health access and care for persons with childbearing potential. There is currently no evidence that LA ARVs impact pregnancy potential or have harmful effects on fetal development or outcomes. It is, therefore, imperative to evaluate the improved adherence observed with LA ARVs with improvements in quality-of-life indicators as to not eliminate or artificially preclude access for individuals with pregnancy potential.

Current US guidelines recommend clinicians and pregnant individuals should reach a shared decision about continuing LA CAB/RPV during pregnancy or switching to preferred or alternative three-drug ART due to limited pharmacokinetic, efficacy, and safety data during pregnancy.[135] Physiologic and pharmacokinetic changes that occur during pregnancy include changes in weight, alterations in fat and water distribution, expansion of maternal blood volume and volume of distribution, delayed gastric emptying and motility, altered hepatic drug metabolizing enzymes, and decreased plasma protein concentrations.[136] Data on ARV agents in pregnancy have been obtained through pharmacokinetic studies and inform selection and management of ART during pregnancy.[135] Pharmacokinetic and pregnancy outcome data for persons with HIV-1 who become pregnant while on LA ARVs are critical to inform use of these agents. Out of 26 individuals between ages 18 and 49 years who became pregnant while receiving LA CAB/RPV in clinical trials, there were 11 live births with 10 having no congenital abnormalities. In one individual, congenital ptosis in the setting of intrauterine growth restriction was observed. Plasma CAB/RPV drug concentrations were within the range of non-pregnant women for all pregnant individuals.[137]

Currently, there are no studies on individuals who have breastfed while on LA ARVs. When administered to lactating rats, LA CAB/RPV was present in breastmilk; however, it is unknown whether it is present in human breastmilk and how its presence affects milk production or adverse events in the infant. However, decreased ARV adherence may be observed in the post-partum period, leading to increases in the risk of breastmilk transmission of HIV-1.[138] LA ARVs could be a strategy that decreases risk of HIV-1 transmission due to the potential for improved adherence, underscoring the importance of careful and inclusive, well-designed studies during lactation.

Few studies have explored use of LA ARVs in persons of trans experience. The 2015 Trans Survey found that 61% of transgender women and 85.7% of transgender men with HIV-1 reported

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adequate adherence to ART.[139] Known barriers to adherence in this population are the result of a combination of personal, social, and socioeconomic factors and the added challenges of managing hormone therapy and financial concerns.

Reproductive health among transgender individuals with HIV-1 encompasses a variety of challenges: hormonal therapy, fertility preservation, contraception, pregnancy, and lactation.[140] Thoughtful consideration should be made for lactating individuals who decide to breastfeed, chestfeed or incorporate human milk feeding.[141] The Academy of Breastfeeding Medicine position statement recommends clinicians caring for breast/chest-feeding patients who are transgender consider broader definitions of lactation and collect information on hormone therapy and surgeries for transgender individuals.[142] Studies using LA ART for viral suppression in persons who are transgender are limited and there are currently no studies on pregnancy and lactation in individuals who are transgender taking LA ARVs.[143,144] Appropriate and gender-affirming guidelines and prescribing protocols are critical for safe, effective care of this population.[142]

Future research is needed examining the use of LA ARVs for HIV-1 treatment and prevention in key patient populations including children, adolescents, those planning to become pregnant or who are pregnant, persons of trans experience, and individuals who are breast/chest-feeding.

18. What is the cost effectiveness of LA ARVs?

Consensus recommendations

18.1 Based on currently available cost-effectiveness models, we suggest CAB/RPV as a cost-effective ART option, but real-world analyses are needed.

Quality of evidence	B
Strength of recommendation	2

18.2 We suggest IBA to improve survival for people with multidrug-resistant HIV-1, although cost-effectiveness has not consistently been demonstrated.

Quality of evidence	B
Strength of recommendation	2

18.3 We suggest LA CAB or DPV for PrEP to decrease HIV-1 acquisition and, because universal cost effectiveness has not been demonstrated, we recommend additional focused cost effectiveness studies.

Quality of evidence	C
Strength of recommendation	2

Evidence summary

Cost-effectiveness analyses and cost comparisons have been conducted for most available LA ARV agents, including LA CAB and DPV for PrEP, and LA CAB/RPV and IBA for HIV-1 treatment. These analyses demonstrate that LA ARVs are not universally cost-effective for all populations at risk for and with HIV-1, but there may be instances where cost savings is demonstrated. Currently, no data exist evaluating cost effectiveness of LEN for HIV-1 treatment.

Despite LA CAB demonstrating superiority to oral TDF/FTC in the HPTN 083 and HPTN 084 studies,[41,43] a major concern remains the cost of LA CAB compared with oral TDF/FTC for PrEP. One study[145] employed a cost comparison simulation between oral and LA injectable PrEP evaluating cost effectiveness while another separate simulation study evaluated cost utility.[146] The former cost-effectiveness model evaluated men who have sex with men and transgender women in the United States while the latter cost-utility analysis evaluated oral versus LA injectable PrEP in men who have sex with men in Southeast Asia. Findings from these studies are summarized below with costs listed in US dollars.

An analysis by Neilan, et al.,[145] evaluated LA CAB compared to oral tenofovir-based PrEP in self-identified very high-risk MSM and transgender women living in the US. Evaluable drug costs included generic oral daily TDF/FTC ($360 USD/year), brand tenofovir alafenamide/emtricitabine (TAF/FTC) ($16,800 USD/year), and LA CAB ($25,850 USD/year). Additional costs included office visits, lab monitoring and HIV-1 testing. Annual costs for care associated with HIV-1 ranged between $3280 and $32,580 while annual treatment costs for ART ranged between $31,560 and $68,680. The 10-year estimated cost for LA CAB far exceeded that of branded TAF/FTC when compared to generic TDF/FTC and no PrEP. Although drug costs for PrEP exceeded that of ART for year 1, by year 10, ART exceeded PrEP costs. Specifically, estimated cost for generic TDF/FTC compared to ART was $17.57 million and $4.09 billion, respectively. Branded TAF/FTC was $862.24 million compared with ART being $4.09 billion. LA CAB was $1.44 billion while ART was $3.64 billion. LA CAB increased life expectancy in self-identified very high-risk individuals by 28,000 quality-adjusted life-years (QALYs) compared with generic or branded tenofovir-based PrEP (26,000 QALYs). At 10 years, LA CAB could achieve incremental cost-effectiveness ratios (ICERs) at most $100,000 per QALY compared with generic TDF/FTC. Based on this analysis, LA CAB for PrEP in this population would be cost effective if it were priced no more than $3000–$6600 above the cost of generic TDF/FTC per year. This is substantially less than the current price of branded tenofovir options. LA CAB is superior to oral PrEP in terms of QALYs gained and HIV-1 transmissions averted. However, oral PrEP is still a viable option given its current cost.

A cost-utility analysis[146] evaluating PrEP in men who have sex with men compared oral daily TDF/FTC with LA CAB in Southeast

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Asia and found LA CAB was 4.2 times higher in cost compared with oral TDF/FTC. Based on these initial findings, the authors concluded that oral PrEP was more appropriate in men who have sex with men living in Southeast Asia compared with LA CAB.

Two studies[147,148] employed cost comparisons for the DPV vaginal ring for PrEP in resource-limited countries. These analyses demonstrate the cost effectiveness of the ring in high-risk women living in high-incidence areas.

An analysis by Reidy, et al. estimated potential cost savings of the DPV vaginal ring compared to oral PrEP with TDF/FTC in different implementation scenarios among women, including female sex workers, in Kenya, South Africa, Uganda, and Zimbabwe—countries where the DPV clinical trials were held.[148] For ring unit cost, a cost of $7 per ring and 12 rings per year was used. The cost per HIV-1 acquisition averted ranged from $13,000 to $121,000 in the highest and lowest-impact scenarios. While the cost may seem excessive, the authors employed scenarios assuming scale-up of both oral PrEP and ART. As such, HIV-1 incidence in the population would expectedly decrease, causing smaller incremental impact of an additional prevention intervention.

An analysis by Glaubius, et al. estimated cost effectiveness of DPV among women in KwaZulu-Natal, South Africa—the province with the highest HIV-1 incidence—compared with a reference scenario without PrEP using various implementation strategies.[147] Cost for the ring ranged from $72 to $96 per person-year. Compared with the reference scenario without PrEP, implementation of DPV, assuming 56% effectiveness and covering 50% of 22- to 29-year-old or high-incidence women, prevented 10% or 11% of acquisitions by 2030, respectively. DPV implementation among female sex workers was cost-effective in nearly 100% of simulations over both intervention and lifetime horizons. The authors concluded that DPV PrEP could make a substantial contribution to HIV-1 prevention in South Africa if scaled-up among women at high risk of HIV-1 and reduce costs if prioritized to female sex workers.

When evaluating cost effectiveness of LA CAB/RPV for HIV-1 treatment in Canada, an adapted, previously validated hybrid decision tree and Markov model estimated incremental costs and health outcomes based on improvement of treatment adherence and virologic suppression. When compared to oral ART, per 1000 patients treated, a lifetime cost savings of $1.5 million was predicted where QALY and life-year increases were 107 and 138, respectively, with three new cases of HIV-1 averted.[149]

Another analysis conducted in sub-Saharan Africa evaluated cost-effectiveness of LA CAB/RPV every 4 weeks in a health system setting over a 10-year period with a 3% discount of disability-adjusted life-years (DALYs) along with costs. A cost-effectiveness threshold of $500 per DALY averted was utilized to establish whether implementing the use of CAB/RPV was cost-effective. By assuming a cost of $120 per person per year, LA CAB/RPV in people with an HIV-1 RNA greater than 1000 copies/mL was borderline cost-effective whereas median cost per DALY averted was $404. Based on this analysis, the authors concluded that for LA CAB/RPV to be cost-effective, the maximum benefit would be in individuals with suboptimal ART adherence.[150]

Within the United States, data presented at a conference evaluated costs and QALYs with LA CAB/RPV dosed every 8 weeks compared with daily oral bictegravir/TAF/FTC or pooled daily oral ART that was considered standard of care. The analysis adapted a Markov model based on data derived from pooled ATLAS, FLAIR, and ALTAS-2 M studies. Current wholesale acquisition costs were used for ART costs, administration costs associated with LA CAB/RPV, along with an annual discount and utility advantage. The dominant treatment strategy was LA CAB/RPV every 8 weeks producing QALY gain of 0.177 and cost savings of $45,792 when compared to oral ART. LA CAB/RPV was deemed cost-effective and below the willingness-to-pay threshold of $100,000 per QALY. Factors associated with cost-effectiveness included cost of ART, $CD4^+$ progression, discontinuations, adherence, and onward disease transmission.[151]

Two cost-effectiveness analyses using independent simulation models demonstrated that IBA-containing ARV regimens would substantially improve survival for people with multidrug-resistant HIV-1 but at a higher cost, yielding a cost per QALY that is not cost-effective.[152,153] The overall budget impact of such regimens is expected to be relatively small, given the limited number of people who qualify for IBA use. Both analyses compared two treatment strategies for multidrug-resistant HIV-1: OBR + IBA and OBR alone. ICERs were calculated using discounted QALYs.

In a cost-effectiveness analysis by Millham, et al., IBA loading dose costs were estimated at $10,500 and IBA maintenance dose costs at $8400 per month.[153] By comparison, the estimated cost of the OBR was $4500 per month. Cost-effectiveness ratios of less than $100,000/QALY were considered cost-effective. In the base case, adding IBA to an OBR increased 5-year survival by 9% compared with OBR alone. The ICER for IBA + OBR compared with OBR was $260,900/QALY. Using a willingness-to-pay ratio of $100,000 per QALY, the authors concluded that for persons with multidrug-resistant HIV-1 who lack other treatment options, IBA will substantially increase survival, but adding this drug to an OBR is not cost-effective.

In a second cost-effectiveness analysis by Brogan, et al., IBA loading dose costs were estimated at $11,350 and IBA maintenance dose costs at $9080 per month.[152] The estimated cost of the OBR was $4404 per month. In the base case, the lifetime cost-effectiveness analysis estimated that individuals who receive IBA + OBR lived 1.47 years longer and accrued 1.45 more QALYs than individuals receiving OBR alone. The ICER for IBA + OBR compared with OBR was $133,040/QALY. The study concluded that IBA can provide significant health benefits and may be cost effective if using willingness-to-pay thresholds for rare diseases (e.g., $50,000 to $500,000 per QALY gained).

Additional research is needed to determine the cost-effectiveness of LA CAB and DPV for PrEP in key populations, particularly in resource-limited settings, if drug costs decrease, or if more HIV-1 acquisitions are averted in real-world settings. Cost effectiveness of LA CAB/RPV, IBA, and LEN for HIV-1 treatment should be further explored utilizing real-world data, varying life expectancy estimates, and varying costs based on low- and high-income countries.

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19. What considerations should be taken for using LA ART for HIV-1 treatment in patients with a history of treatment failure, challenges with medication adherence, or other barriers to oral ART?

Consensus recommendations

19.1 We recommend consultation with a provider experienced in HIV medicine when contemplating LA ART in patients with a history of treatment failure and/or prior challenges with medication adherence.

Quality of evidence	B
Strength of recommendation	1

19.2 We recommend against the routine use of LA CAB/RPV in patients with a history of treatment failure or when resistance to either component is known or suspected, except the K103N mutation in isolation.

Quality of evidence	A
Strength of recommendation	1

19.3 For all people with HIV-1, including those receiving LA ART with medication adherence challenges, lack of viral suppression, or other barriers to oral ART, we recommend that the ART regimen includes at least two fully active agents with a high resistance barrier, if possible.

Quality of evidence	A
Strength of recommendation	1

Evidence summary

When composed of agents with novel mechanisms of action, LA ART should be a viable HIV-1 treatment option regardless of a person's history of treatment failure, intolerance, or non-adherence to ART. There is no concern for cross-resistance with IBA or LEN given their novel mechanisms of action. However, both IBA and LEN require coadministration with a daily OBR, limiting options for an exclusively LA ART regimen without the need for concomitant daily oral ART.

Patients with a history of ARV treatment failure were excluded from registration trials of LA CAB/RPV, except if a K103N mutation was documented in isolation.[29,30] This NNRTI mutation does not impact RPV activity.[154] Despite the exclusion from clinical trials, there are scant data on LA CAB/RPV use in patients with a history of treatment failure and/or non-adherence. In one study, LA CAB/RPV was used in patients with limited treatment options via compassionate use programs.[76] Participants had no or limited ART options, no major INSTI or NNRTI mutations (except K103N), and inability to receive effective oral ART due to malabsorption, dysphagia, other gastrointestinal conditions, or prolonged non-adherence with progressing HIV-1 disease. Although most patients (80%) were viremic at the start of LA CAB/RPV therapy, 57% (16/28) and 86% (6/7) achieved or maintained virologic suppression. Patients with incomplete virologic response developed new NNRTI mutations (6/7) not present prior to LA CAB/RPV, while two also developed INSTI mutations. Another case series described a high rate of virologic suppression among patients with barriers to oral ART adherence.[35] Despite high levels of substance use and unstable housing, all virologically suppressed patients on oral ART at baseline ($n=76$) remained virologically suppressed after initiating LA CAB/RPV. Among those initiating CAB/RPV while viremic ($n=57$), virologic failure occurred in two. The rest achieved viral suppression or were responding appropriately at the time of analysis. Both studies have shown promise in using LA CAB/RPV for HIV-1 treatment among difficult to treat patient populations.

LA ART formulations introduce an additional risk for the development of resistance: the potential for prolonged exposure to subtherapeutic concentrations particularly in the setting of treatment non-adherence (e.g., loss to follow-up or missed appointments). Identifying past HIV-1 resistance test results, periods of virologic failure, extent of ART adherence during these periods (complete non-adherence versus intermittent adherence), and duration of time on failing regimens may all inform the level of suspicion warranted for de novo development of resistance. Proviral DNA genotype sequencing can be considered, although results should be interpreted with caution.[62]

Expert consultation is recommended when considering LA ART in the setting of salvage therapy. Online resources such as the Stanford University HIV Drug Resistance Database (https://hivdb.stanford.edu) or HIV-ASSIST (https://www.hivassist.com/) can aid in interpretation and selection of therapy for individuals with multidrug-resistant HIV.[155] The risk-to-benefit ratio of LA ART may be favorable in select salvage therapy cases if there are ≥2 active ARV agents in the regimen, if select patient factors are present (e.g., low risk of missed appointments, controlled or low HIV-1 RNA), and if the patient is fully integrated into the decision-making process with a complete understanding of the risks and benefits of the approach. Investigational agents through compassionate use programs should be considered in highly treatment-experienced patients with multidrug-resistant HIV-1.

Future research may provide clarity on the efficacy and/or risks of LA CAB/RPV in patients with prior virologic failure. An ongoing randomized open-label study to evaluate LA CAB/RPV compared with oral ART in patients with a history of adherence challenges (NCT03635788) will offer additional data in this population beyond observational cohorts.[36]

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20. What is the evidence for emerging models for delivery of LA ARVs for the treatment and prevention of HIV-1?

Consensus recommendations

20.1 Implementation models should focus on unique expansion efforts to increase access to LA ARVs for the treatment and prevention of HIV-1 beyond the traditional clinic setting.

Quality of evidence	C
Strength of recommendation	1

Evidence summary

Currently, no data exist evaluating alternative models for administration of LA ARVs for the treatment and prevention of HIV-1; however, several trials are underway.[156–159] Additional administration models, beyond normal clinic hours and facilities, should be evaluated for feasibility of expanding access to LA ARVs for the treatment and prevention of HIV-1. Implementation models of LA ARVs should focus on unique expansion efforts to increase access to LA ARVs for the treatment and prevention of HIV-1 beyond the traditional clinic setting. As DPV will be uniquely provided in the community setting, we await implementation data on this agent.

21. What is the evidence for patient and consumer perspectives on LA ARVs for HIV-1 treatment and PrEP?

Consensus recommendations

21.1 We recommend shared decision-making with patients to determine if LA ARVs are an appropriate choice for the treatment or prevention of HIV-1.

Quality of evidence	C
Strength of recommendation	1

Evidence summary

It is known from the advancement of medication formulations to treat other chronic disease states that many patients prefer treatments that are administered less frequently and do not require daily oral administration.[160] Though many advancements have been made to ARVs since the late 1980s when the first ARV was approved, it was only in 2021 that a novel formulation, avoiding daily oral administration, was developed for the treatment of HIV-1 outside of salvage therapy. A study of 2389 people with HIV-1 were surveyed in 25 countries to assess their attitudes to the advancement of ART; 54.7% of participants preferred LA ART with an increased preference observed in those with medication-related privacy concerns.[161]

Clinical trial data evaluating LA CAB/RPV have shown that participants were more satisfied with their LA regimen than prior regimens requiring daily oral administration.[162–164] Murray et al.[164] assessed treatment satisfaction and acceptance for the use of LA CAB/RPV in participants in the ATLAS and FLAIR studies. Though greater improvement in patient satisfaction scores were seen compared with baseline in those using LA CAB/RPV, patients perceived no difference in their general health from baseline and throughout the study regardless of treatment type. At week 48, it was determined that over 97% of participants on LA ART preferred this treatment modality.[164] The ATLAS-2 M study also assessed patient preference of LA ART administered every four or eight weeks. In those participants who transitioned from every four to every eight weeks and those who switched from oral ART to every eight weeks, over 90% preferred every 8-week dosing due to administration frequency and convenience. Those who preferred oral daily therapy stated they preferred it due to the impact of side effects and convenience. A real-world implementation study of LA CAB/RPV also found that LA ART was acceptable and appropriate for over 91% of 105 patients surveyed across eight US sites.[165] A qualitative study on LA ART implementation interviewed clinical and non-clinical (community or government-based) stakeholders in addition to consumers. Consistent with prior studies, those interviewed shared the sentiment that LA ART minimizes treatment burden, treatment frequency, and responsibility for treatment by consumers. It was noted that persons who may find LA ART easier include those who experience challenges with oral medication adherence. Comments from this study highlight results of prior studies including medical mistrust but, overall, note that LA ART should be an individualized discussion regarding the pros and cons of treatment.[130]

Perspectives of patients with multidrug-resistant HIV-1 receiving IBA have also been positive. An online questionnaire was given to 30 patients receiving IBA to assess patient satisfaction with the treatment. In this study, the average time on IBA was 8.5 months and 87% of patients stated they were very satisfied with their treatment due to efficacy of the regimen. Additionally, 87% of participants had positive ratings toward seeing a healthcare provider every 2 weeks for medication administration.[166] The PROMISE-US study will continue to evaluate satisfaction of patients on IBA for HIV-1 treatment.[167]

Though specific studies on the use of SC LEN administered every 6 months are not available, prior studies noted monthly or bi-monthly visits to a provider's office for injections may be a barrier to LAIs in some patient populations. The use of a medication given every 6 months may be more advantageous; however, LEN was only evaluated for heavily treatment-experienced patients with multidrug-resistant HIV-1 requiring concomitant oral ART.

LA PrEP options such as CAB have also shown improved patient satisfaction compared to daily oral therapies. In a Phase 2 study of LA CAB in a population consisting predominantly of men who have sex with men, 56 patients ranked their satisfaction with LA CAB: 72% did not find it inconvenient or difficult to receive the injections and 80% would have been satisfied continuing on CAB following study completion.[168] Similarly, 68 women in HPTN 084 were interviewed

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for their perspectives on CAB for PrEP with the majority preferring IM injections over daily oral PrEP.[15] Comparable results were observed in all populations evaluated for LA CAB use for PrEP.[169]

Perspectives of patients using the DPV vaginal ring were evaluated in women where the majority found it easy to use and comfortable.[17] Similar results were seen in the ASPIRE study, where over 95% of participants reported being very likely or likely to use the DPV ring in the future.[170]

Patient and consumer preference for, and acceptability of, LA ARVs are overall high from available clinical trial and real-world data. Though convenience, confidentiality, and possible improvement in adherence have all been documented as advantageous reasons for LA ARVs, conversely medical mistrust, increased frequency of appointments, and possible adverse reactions are all barriers to LA ARV implementation.

Despite the acceptability of LA ARVs being high compared with daily oral therapies in clinical trial participants, additional research on patient acceptability and preference outside of clinical trials is necessary to identify real-world barriers to all LA ARVs.

22. Are there legislative barriers in using LA ARVs for the treatment of HIV-1 or PrEP?

Consensus recommendations

22.1 We recommend eliminating cost and coverage barriers that impact access to LA ARVs.

Quality of evidence	C
Strength of recommendation	1

Evidence summary

There is great promise for the impact LA ARVs can have on ending the global HIV epidemic. Before such promise can be realized; however, healthcare professionals and patients will have to overcome myriad legislative,[171] regulatory, and policy barriers, primarily related to access and cost. This section will only focus on the US healthcare system, which serves as a poignant example illustrating the impacts of legislative, regulatory, and policy barriers on LA ARVs for HIV-1 treatment or PrEP.

The greatest legislative barrier to accessing LA ARVs in the United States is the fractured system of coverage. The HIV healthcare system includes those who are uninsured or underinsured, those who have coverage through Medicaid or a government-subsidized plan, a marketplace plan or private insurance, those who rely on the Ryan White HIV/AIDS Program/AIDS Drug Assistance Program, and those with Medicare coverage or a combination of coverage types. Since implementation of the Affordable Care Act, the number of people with healthcare coverage has reached an all-time high, but one's ability to access affordable, comprehensive healthcare coverage varies widely from state to state and by income.[171]

When looking at how such a system impacts LA ARV access, there are a few considerations. First, new LA ARV agents are more costly than generic ARV counterparts—necessitating more comprehensive coverage options. Next, injectable LA ARVs create unique complications for access depending on whether the injection is considered a medical or pharmacy benefit, which may determine the provider type that can administer the medication, the resulting coverage determination, and the patient's out-of-pocket costs.[172] Finally, with LA ARVs for HIV-1 prevention, additional costs associated with ancillary services, such as laboratory fees, may be covered differently than the medication itself.[173]

Studies have documented PrEP accessibility barriers to many potential users.[70,174,175] The US Centers for Disease Control and Prevention provides tools for helping prospective patients locate coverage for PrEP medication, laboratories, and clinic visits; however, not all resources extend to LA ARVs.[53,176] In 2019, the US Preventive Services Task Force stated that oral PrEP and ancillary services should be covered as a "Grade A" recommendation without cost sharing.[177] In 2023, the US Preventive Services Task Force updated their recommendations to include LA CAB for PrEP.[178]

Financial concerns have been identified as common barriers to PrEP use across most populations at risk for HIV-1 and as a contributor to worse PrEP persistence.[70,179,180] Many of the coverage woes that patients and providers experience as it pertains to PrEP could be remedied by the creation of a national PrEP program, passage of legislation to improve PrEP access for people who are uninsured or receiving Medicaid coverage, and greater federal funding to support existing HIV prevention programs.[181,182] Particularly, with new opportunities presented by LA ARVs, a better system for distribution and coverage is needed.

Future research is needed to better understand the impact of legislative barriers on costs and payor coverage on LA ARV access and outcomes.

23. What is the future forecast of other investigational LA ARV options for HIV-1 treatment and PrEP?

Consensus recommendations

23.1 We suggest the availability of future LA formulations for HIV-1 treatment and PrEP should focus on pairing with other multipurpose technologies.

Quality of evidence	B
Strength of recommendation	2

Evidence summary

LA ARV agents in later stages of development include islatravir and monoclonal antibodies with mechanisms different from IBA, among others. These agents are being studied for a variety of indications, including treatment-naïve and treatment-experienced

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populations with HIV-1 as well as for PrEP. In the PrEP arena, development of multipurpose prevention technologies—such as products that combine protection against multiple risks, such as HIV-1, unintended pregnancy, and other sexually transmitted infections (STIs)—continues to be a priority. Candidates in late-stage development are summarized in Table 8.

Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI). It has enhanced potency over other NRTIs, including against resistant HIV-1 strains, as well as a prolonged plasma half-life of 48–64 h.[183] Furthermore, 10 mg once weekly (the lowest studied dose in Phase 1 study) maintained concentrations of the active metabolite, islatravir triphosphate, above the concentration predicted for efficacy for over 4 weeks.[183] Islatravir was investigated as an oral (daily, weekly, and monthly) tablet and LA implant for HIV-1 treatment and prevention. In 2021, the FDA placed a clinical hold on all islatravir formulations in development, suspending enrollment in all clinical studies. This action was in response to observations of reductions in total lymphocytes and in $CD4^+$ T cells in clinical study participants receiving islatravir.[184] In September 2022, Merck resumed development of islatravir at lower doses, and the monthly dose under investigation was discontinued. Current studies include oral islatravir 0.75 mg in combination with doravirine 100 mg once daily in previously untreated patients and as a switch option in virologically suppressed patients, and a once-weekly oral combination with oral LEN.[185] While studies are ongoing, decreases in total lymphocyte cell counts are not expected to be observed with these lower islatravir doses.[186] Other NRTTIs are still being evaluated for their potential as LA agents for both treatment and prevention of HIV-1.[185]

Leronlimab is a monoclonal antibody to C-C chemokine receptor type 5 (CCR5), being studied for HIV-1, cancer, and autoimmune disorders. It was being evaluated for the treatment of COVID-19 but the FDA halted the trials[187] due to reported cardiac events.[188] Partial hold for the HIV-1 program was placed by the FDA in March 2022.[188] Evidence of HIV-1 viral suppression has been demonstrated in both rhesus macaques and humans.[189]

Broadly neutralizing monoclonal antibodies (bNAbs) are antibodies harvested from individuals with HIV-1 with high neutralizing activity targeting various regions of the HIV-1 env protein. Various bNAbs have been investigated for their potential in both prevention and treatment of HIV-1. Current antibodies under investigation have plasma half-lives amenable for dosing every 3–6 months. Currently, there are over a dozen different bNAbs in various stages of development.[190,191]

Teropavimab (TAB) and zinlirvimab (ZAB) are bNAbs which target the CD4 binding site and the V3 loop of gp120, respectively. In a Phase 1b clinical trial, virologically suppressed adults who were sensitive to both bNAbs by HIV-1 proviral DNA phenotype were randomized to receive subcutaneous LEN 927 mg after oral dosing plus TAB 30 mg/kg IV and ZAB 10 or 30 mg/kg IV. Participants were monitored every 4 weeks to Week 26; the primary endpoint was safety and secondary endpoints included virologic outcomes by FDA snapshot analysis. Of 21 randomized subjects, 20 received the complete study regimen. One participant withdrew at week 12

TABLE 8 Long-acting investigational drugs in late-stage development.

Drug	Class/mechanism	Expected dosing for HIV-1 PrEP	Expected dosing for HIV-1 treatment	Current phase of development	Other notes
Albuvirtide	Fusion inhibitor	N/A	Once-weekly injection	Approved in China	
Islatravir	Nucleoside reverse transcriptase translocation inhibitor	*Discontinued*	Oral once daily with doravirine or oral once weekly with lenacapavir	Phase 3 for daily; Phase 2 for weekly	Implant discontinued
Leronlimab	C-C chemokine receptor type 5 monoclonal antibody	N/A	Once weekly	Phase 2/3- NCT03902522	Currently on clinical hold
Teropavimab and Zinlirvimab	Broadly neutralizing antibodies	N/A	Intravenous every six months with subcutaneous lenacapavir	Phase 2-NCT05729568	

Abbreviations: N/A, not applicable; PrEP, pre-exposure prophylaxis.

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with HIV-1 RNA <50 copies/mL, another had confirmed HIV-1 RNA of 155 copies/mL at Week 16 and resuppressed upon resumption of baseline ART, and the remaining 90% remained virologically suppressed at Week 26. There were no serious adverse events and no adverse events leading to study discontinuation. The preliminary results of this proof-of-concept study are promising and suggest that twice-yearly dosing of LA ART may be possible.[192]

Albuvirtide is a once-weekly injectable fusion inhibitor that was found in a Phase 3 study to be non-inferior to a boosted PI-based ART regimen.[193] The drug has received regulatory approval in China; it is unclear if regulatory approval will be pursued elsewhere.

Elsulfavirine is a NNRTI. It is currently approved for daily oral HIV-1 treatment in Russia, and LA formulations are currently under investigation.[194,195] A single ascending dose trial in healthy volunteers recently completed in 2022 (NCT05165550).[196]

The goal of multipurpose technologies (MPTs) is to combine different therapeutic agents in a unified distribution system to simultaneously prevent HIV-1, unintended pregnancy, and/or STIs. Early work on MPTs to prevent HIV-1 and pregnancy via administration of ARVs and hormonal contraceptive agents as subcutaneous injections, implants, and intravaginal rings is promising.[197–200] Future LA ARV formulations should focus on pairing with other MPTs.

4 | CONCLUSION

These consensus recommendations aim to represent a comprehensive list of practical recommendations for the use of long-acting ARVs in the treatment and prevention of HIV-1. While CAB, RPV, LEN, IBA, and DPV have tremendous potential for the advancement of HIV-1 treatment and/or prevention, there are both clinical and implementation challenges to consider. In the development of these recommendations, the multidisciplinary author group sought to provide guidance regarding questions that may be relevant to HIV care providers globally. Although the above recommendations represent guidance for questions which the author group found adequate evidence to address, many unanswered questions remain and opportunities for future research were identified.

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CONFLICT OF INTEREST STATEMENT

See Appendix.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 2023

COI Disclosures (8/14/2023).

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Allison L. Agwu	Johns Hopkins University School of Medicine, Baltimore, Maryland, USA	Gilead Sciences, Inc. and Merck & Co.	Merck & Co.	None	Gilead Sciences, Inc., Merck & Co., and GSK/ViiV Healthcare	None
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