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Review

Long-Acting Antiretroviral Therapies for HIV: From Approved Strategies to the Next Generation of Treatment and Prevention

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Abstract

Background/Objectives: Long-acting antiretroviral therapies (LA-ART) represent a major evolution in HIV treatment and prevention, addressing key limitations of lifelong daily oral medication. This narrative review summarizes current evidence on approved and investigational long-acting antiretroviral strategies, focusing on efficacy, pharmacology, resistance, clinical implementation and future perspectives. **Methods:** A structured narrative literature search was performed in PubMed/MEDLINE and the Cochrane Library for records published between January 2005 and October 2026, complemented by major conference proceedings (CROI, IAS, EACS) and regulatory and public-health sources (FDA, EMA, WHO, CDC, DHHS, IAS-USA). Findings were synthesized narratively and organized by drug class and clinical indication (treatment versus prevention), given substantial heterogeneity across study designs, agents and outcomes that precluded quantitative meta-analysis. **Results:** Injectable cabotegravir plus rilpivirine has become established as the first long-acting maintenance regimen for virologically suppressed individuals, with expanding evidence in adherence-challenged and adolescent populations. Long-acting cabotegravir has demonstrated superiority over oral tenofovir-based pre-exposure prophylaxis (PrEP) in the HPTN 083 and HPTN 084 trials. Lenacapavir, the first-in-class capsid inhibitor, has shown activity against multidrug-resistant HIV and, in the PURPOSE 1 and PURPOSE 2 trials, high efficacy as twice-yearly PrEP, with durable results on long-term follow-up. Investigational strategies, including islatravir plus lenacapavir and broadly neutralizing antibodies, may further extend dosing intervals, although resistance, implementation and equitable-access challenges remain across all approaches. **Conclusions:** Long-acting antiretroviral strategies have established a new therapeutic paradigm for HIV treatment and prevention. Their future impact will depend on resistance management, healthcare-delivery capacity and equitable global access, alongside continued clinical innovation.

Keywords: long-acting antiretroviral therapy; HIV treatment; cabotegravir; rilpivirine; lenacapavir; pre-exposure prophylaxis; broadly neutralizing antibodies; islatravir

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1. Introduction

UNAIDS estimated that 40.9 million people were living with HIV in 2025, of whom 32.1 million were accessing antiretroviral therapy, while approximately 1.2 million people acquired HIV during that year; progress towards the 95-95-95 targets has been threatened by abrupt reductions in international HIV funding in 2025 [1,2]. Against this backdrop, long-acting formulations that reduce dosing frequency and dependence on daily pill-taking are increasingly viewed as central to sustaining both treatment success and prevention gains.

The introduction of combination antiretroviral therapy (ART) transformed HIV infection from a progressive, fatal disease into a chronic, manageable condition. Current oral ART regimens achieve durable viral suppression in most treated individuals and prevent HIV transmission when viral suppression is maintained. However, lifelong daily medication remains associated with several challenges, including adherence difficulties, treatment fatigue, stigma, confidentiality concerns and inequalities in access to care [3].

The development of long-acting antiretroviral (LA-ART) formulations represents a fundamental change in the therapeutic approach to HIV. Rather than requiring daily self-administered medication, these strategies maintain effective drug exposure through periodic administration, which may improve adherence, patient satisfaction and treatment persistence.

The first clinically successful long-acting regimen was the combination of cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI). Phase 3 studies demonstrated that injectable CAB/RPV administered monthly or every two months was non-inferior to standard oral ART in maintaining virological suppression among appropriately selected individuals with HIV-1 infection [4–7].

The concept of long-acting therapy has subsequently expanded beyond treatment simplification. Long-acting cabotegravir (CAB-LA) has demonstrated high efficacy as HIV pre-exposure prophylaxis (PrEP), providing an alternative to daily oral tenofovir/emtricitabine-based prevention. In the HIV Prevention Trials Network (HPTN) 083 and 084 trials, CAB-LA was superior to oral PrEP in different populations, supporting a paradigm shift in HIV prevention [8,9].

More recently, lenacapavir (LEN), the first approved capsid inhibitor, has introduced a novel mechanism of action and the possibility of extended dosing intervals. Lenacapavir has demonstrated substantial activity both in heavily treatment-experienced individuals with multidrug-resistant HIV and as part of initial therapy, and has generated considerable interest as a prevention option because of its twice-yearly administration schedule [10,11].

Beyond currently available therapies, several investigational approaches are being developed, including combinations of long-acting small molecules such as islatravir plus lenacapavir and antibody-based strategies using broadly neutralizing antibodies (bNAbs). These approaches aim to reduce dosing frequency further, increase treatment flexibility and potentially integrate antiviral therapy with immune-based interventions. This review provides an updated overview of approved and investigational long-acting antiretroviral therapies and discusses the current clinical evidence, its limitations, resistance issues and future perspectives.

2. Search Methods

This narrative review was prepared and reported in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) [12].

2.1. Search Strategy

PubMed/MEDLINE and the Cochrane Library (Cochrane Database of Systematic Reviews and CENTRAL) were searched for records published between 1 January 2005 and 1 October 2026; the last search was performed on 21 October 2026. The search strategy combined controlled vocabulary (MeSH terms and Supplementary Concepts) and free-text terms for three concepts: HIV infection; individual long-acting agents (cabotegravir, rilpivirine, lenacapavir, islatravir, GS-3242) and broadly neutralizing antibodies; and long-acting formulations. The PubMed search was limited to English-language publications and to the following publication types: clinical trials, randomized controlled trials, meta-analyses, systematic reviews and reviews. Records indexed exclusively as animal studies were excluded, whereas records not yet indexed for MEDLINE were retained irrespective of publication type, to capture recently published studies. The Cochrane Library was searched with an equivalent strategy adapted to its syntax. The full search strategies are reported in Supplementary Table S1.

Because publication-type filters do not reliably capture observational, pharmacokinetic and economic studies, the database search was complemented by (i) hand-searching of the reference lists of retrieved articles and recent reviews; (ii) screening of abstracts presented at major conferences (Conference on Retroviruses and Opportunistic Infections [CROI], International AIDS Society [IAS] conferences, European AIDS Clinical Society [EACS] conference); (iii) consultation of documents issued by regulatory and public-health bodies (US Food and Drug Administration, European Medicines Agency, World Health Organization, Centers for Disease Control and Prevention, US Department of Health and Human Services, IAS-USA) up to October 2026; and (iv) inclusion of relevant studies known to the authors.

2.2. Eligibility Criteria

Studies were considered eligible if they reported clinical, pharmacological, virological, safety, implementation or economic data on approved or investigational long-acting antiretroviral agents or broadly neutralizing antibodies used for HIV-1 treatment or prevention in humans. Eligible designs included randomized controlled trials, systematic reviews and meta-analyses, observational cohorts, pharmacokinetic and drug-resistance analyses, case series and reports, cost-effectiveness analyses and guideline documents. Studies conducted exclusively in vitro or in animal models were not included, except where needed to describe mechanisms of action or to contextualize clinical safety findings. Conference abstracts were considered when they reported sufficient methodological and outcome information. The review focused on:

- Cabotegravir/rilpivirine long-acting therapy for HIV treatment;
- Long-acting cabotegravir for HIV prevention;
- Lenacapavir for treatment and prevention;
- Islatravir-based long-acting strategies;
- Broadly neutralizing antibodies as long-acting antiviral approaches.

2.3. Study Selection

The PubMed search yielded 1465 records; records retrieved from the Cochrane Library were checked against these and duplicates were removed. Titles and abstracts were reviewed for relevance, and potentially relevant records were assessed in full text; uncertainties regarding inclusion were resolved by discussion among the authors. Studies were selected on the basis of their clinical relevance to the scope of the review, with the following order of priority: (i) peer-reviewed randomized controlled trials; (ii) systematic reviews and meta-analyses; (iii) observational cohorts and real-world studies;

and (iv) pharmacokinetic, resistance and cost-effectiveness analyses and case series/reports, included where they addressed questions not covered by randomized evidence (e.g., drug–drug interactions, special populations, virological failure). Studies identified through the Supplementary Sources described in Section 2.1 were assessed using the same criteria.

2.4. Data Extraction and Synthesis

For each selected study, information was recorded on design, population, intervention and comparator, dosing regimen, and main efficacy, safety and resistance outcomes. Given the substantial heterogeneity in study designs, populations, agents, dosing regimens and outcome definitions, a quantitative synthesis was not considered appropriate; findings were synthesized narratively and organized by drug class and clinical indication (treatment versus prevention). Consistent with the narrative design, no formal risk-of-bias assessment or evidence-grading framework was applied; instead, the type of evidence underlying key statements is indicated in the text, and data derived from conference abstracts or other non-peer-reviewed sources are identified as such and interpreted as provisional. The design, population and key efficacy outcomes of the pivotal trials of approved long-acting agents are summarized in Table 1, the comparison between long-acting cabotegravir and lenacapavir for prevention in Table 2, and the overall long-acting antiretroviral landscape, including investigational strategies, in Figure 1.

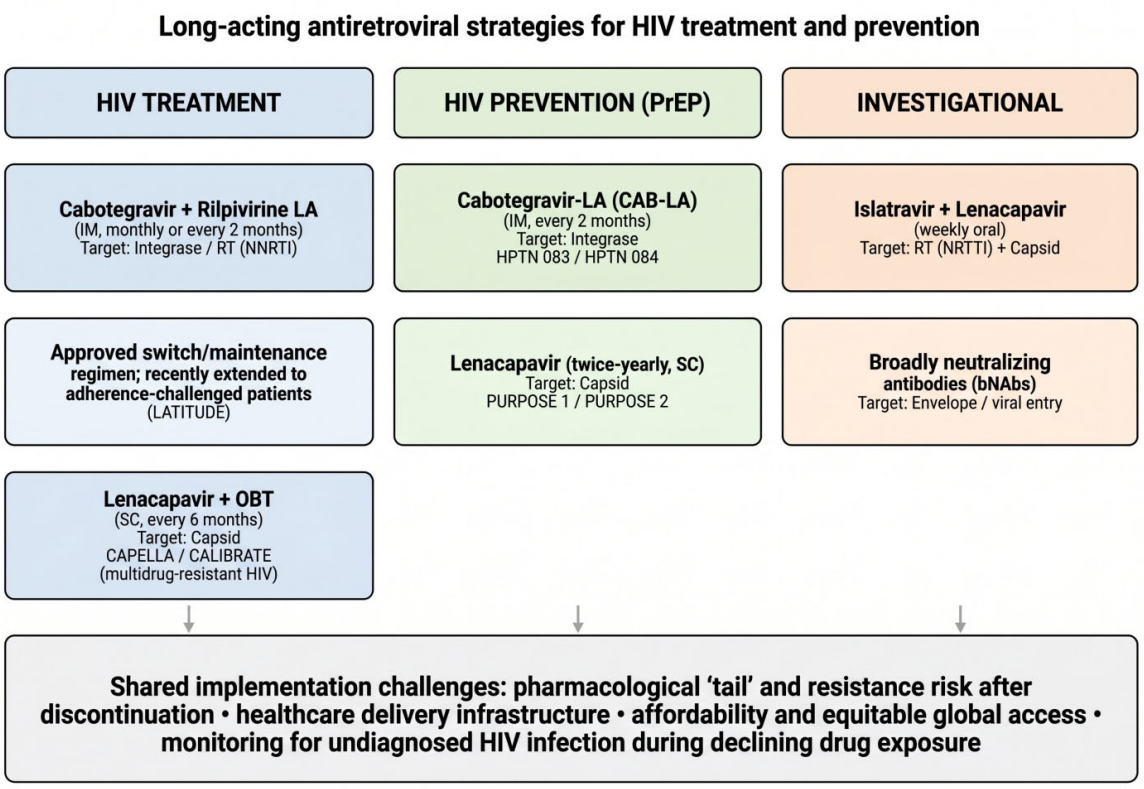


Figure 1. Overview of approved and investigational long-acting antiretroviral strategies for HIV treatment and prevention.

Table 1. Design, population and key efficacy outcomes of pivotal trials of approved long-acting antiretroviral agents.

Trial (Ref.)	Agent(s)/Design	Population	Comparator	Key Outcome
LATTE-2	CAB + RPV (IM); Phase 2b RCT	ART-naive adults, suppressed after oral induction	Continued oral CAB + ABC/3TC	Proof of concept for injectable maintenance; suppression sustained to week 96
FLAIR	CAB + RPV (IM, monthly); Phase 3 RCT	ART-naive adults, suppressed after oral induction	Continued oral DTG/ABC/3TC	Non-inferior virological suppression at weeks 48 and 96
ATLAS	CAB + RPV (IM, monthly); Phase 3 RCT	Adults already suppressed on oral ART	Continued oral ART	Non-inferior suppression; high patient satisfaction
ATLAS-2M	CAB + RPV (IM, Q2M); Phase 3b RCT	Adults suppressed (from ATLAS/FLAIR)	CAB + RPV every month	Non-inferior suppression with extended dosing interval
LATITUDE	CAB + RPV (IM, monthly); Phase 3 RCT	PWH with adherence challenges and viraemia	Continued oral ART	Significantly reduced regimen failure after adherence support
HPTN 083	CAB-LA (PrEP); Phase 2b/3 RCT	Cisgender MSM and transgender women	Daily oral TDF/FTC	~66% reduction in HIV incidence vs. oral PrEP
HPTN 084	CAB-LA (PrEP); Phase 3 RCT	Cisgender women, sub-Saharan Africa	Daily oral TDF/FTC	Superior efficacy; trial stopped early for benefit
CAPELLA	Lenacapavir + OBT (SC); Phase 2/3, partially randomized	Heavily treatment-experienced, multidrug-resistant HIV	OBT alone (functional monotherapy phase)	Rapid HIV-RNA decline; high suppression with active OBT
CALIBRATE	Lenacapavir-based regimens; Phase 2 RCT	ART-naive adults	Standard oral ART (BIC/FTC/TAF)	Potent antiviral activity; resistance risk without adequate companion drugs
PURPOSE 1	Lenacapavir (twice-yearly, SC); Phase 3 RCT (PrEP)	Cisgender adolescent girls/women, sub-Saharan Africa	Daily oral TAF/FTC or TDF/FTC	No incident infections in LEN arm; superior to background incidence and oral PrEP
PURPOSE 2	Lenacapavir (twice-yearly, SC); Phase 3 RCT (PrEP)	Cisgender men, transgender men/women, gender-diverse MSM	Daily oral TDF/FTC	Superior efficacy vs. background incidence and oral PrEP

Abbreviations: ABC/3TC: abacavir/lamivudine; ART: antiretroviral therapy; BIC/FTC/TAF: bictegravir/emtricitabine/tenofovir alafenamide; CAB: cabotegravir; CAB-LA: long-acting cabotegravir; DTG: dolutegravir; IM: intramuscular; LEN: lenacapavir; MSM: men who have sex with men; OBT: optimized background therapy; PrEP: pre-exposure prophylaxis; PWH: people with HIV; Q2M: every 2 months; RCT: randomized controlled trial; RPV: rilpivirine; SC:

subcutaneous; TAF/FTC: tenofovir alafenamide/emtricitabine; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine. Sample sizes and full results are reported in the primary publications cited.

Table 2. Comparison between long-acting cabotegravir and lenacapavir as HIV prevention strategies.

Characteristic	Cabotegravir LA	Lenacapavir
Target	Integrase	Capsid
Administration	Every 2 months	Every 6 months
Development status	Approved for PrEP	Approved/under development for prevention
Mechanism	Viral integration inhibition	Capsid assembly/disassembly inhibition
Main challenge	INSTI resistance during pharmacological tail	Capsid resistance during pharmacological tail

3. Approved Long-Acting Antiretroviral Therapy for HIVTreatment

3.1. Long-Acting Cabotegravir Plus Rilpivirine for Hiv Treatment

The combination of long-acting cabotegravir and rilpivirine (CAB/RPV LA) is the first approved injectable ART regimen designed for the maintenance of HIV suppression without daily oral therapy [13]. Cabotegravir is a potent INSTI derived from dolutegravir, with high antiviral activity and prolonged pharmacokinetic persistence when formulated as a nanosuspension for intramuscular administration. Rilpivirine provides complementary activity through inhibition of HIV-1 reverse transcriptase. The rationale for combining these agents is based on complementary mechanisms of action, absence of overlapping resistance pathways and favourable pharmacokinetic properties allowing extended dosing intervals.

The LATTE-2 (Long-Acting Antiretroviral Treatment Enabling) study provided early proof of concept, demonstrating that injectable cabotegravir combined with rilpivirine could maintain virological suppression after oral induction therapy [14].

The phase 3 FLAIR (First Long-Acting Injectable Regimen) trial evaluated switching from oral dolutegravir/abacavir/lamivudine-based therapy to injectable CAB/RPV in individuals who were treatment-naive at enrolment and had achieved viral suppression after induction therapy. At week 48, monthly injectable therapy was non-inferior to continued oral therapy, with comparable rates of viral suppression. Injection-site reactions were frequent but generally mild or moderate, and patient satisfaction was high [4].

The ATLAS (Antiretroviral Therapy as Long-Acting Suppression) trial confirmed these findings in individuals already virologically suppressed on conventional ART. Monthly CAB/RPV maintained suppression rates comparable to standard oral regimens, supporting its role as a maintenance strategy for selected patients [5]. The ATLAS-2M study subsequently demonstrated that administration every 2 months was non-inferior to monthly dosing, allowing a further reduction in treatment frequency and improving convenience for patients and healthcare systems [6].

Extending this evidence to a younger population, 96-week results from the LATA (Long-Acting Treatment in Adolescents) study, presented as a late-breaker at AIDS 2026 (26th International AIDS Conference) and since published [15], showed that injectable cabotegravir and rilpivirine given every 8 weeks was superior to daily oral tenofovir

disoproxil fumarate/lamivudine/dolutegravir in virologically suppressed adolescents living with HIV across sub-Saharan Africa, extending the CAB/RPV LA evidence base to a group historically underrepresented in long-acting ART trials.

Overall, CAB/RPV LA has established a new treatment paradigm, demonstrating that effective HIV therapy does not necessarily require daily oral medication.

3.2. Real-World Effectiveness, Drug–Drug Interactions and Special Populations

Beyond the registrational trials, a growing body of real-world evidence supports the effectiveness of injectable CAB/RPV outside trial populations. Cohort data from the US Veterans Health Administration and from office-based infectious disease programmes describe durable virological suppression with long-term use in routine clinical practice [16,17].

New data presented at AIDS 2026 extend this real-world picture. In the US-based OPERA (Observational Pharmaco-Epidemiology Research and Analysis) cohort, CAB/RPV LA showed virological effectiveness comparable to that of daily oral bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) [18]. A further OPERA analysis showed high rates of viral suppression among individuals with viral loads ≥ 50 copies/mL, regardless of body mass index [19]; among women with confirmed virological failure, resuppression was frequently achieved, although resistance was detected in a subset of cases [20]. In sub-Saharan Africa, 96-week results from the IMPALA (IMProving HIV-1 Control in Africa using Long-Acting Antiretrovirals) trial similarly demonstrated the efficacy and safety of long-acting cabotegravir and rilpivirine in adults with prior adherence or engagement challenges, reinforcing the applicability of long-acting therapy in this higher-risk population [21].

CAB/RPV LA has also been successfully implemented in populations with substantial adherence barriers, including people experiencing homelessness and people with opioid use disorder engaged through low-barrier, street-medicine or syringe-exchange-based delivery models. These results have prompted updates to the DHHS and IAS-USA guidelines, which now endorse its use in people with adherence challenges, including some with detectable viraemia, although virological failure has been observed more often than in the registrational trials of virologically suppressed patients [22].

This observational picture has since been confirmed prospectively: the phase 3 LATITUDE (Long-Acting Therapy to Improve Treatment Success in Daily Life) trial randomized 453 people with HIV and documented adherence challenges. Among those who first achieved viral suppression with adherence support, switching to monthly long-acting cabotegravir/rilpivirine significantly reduced regimen failure compared with continued standard oral ART, providing randomized-trial-level evidence for a population previously studied mainly through observational cohorts [23]. A second randomized trial tested direct initiation of CAB/RPV LA, given every 8 weeks without an oral lead-in, in people with HIV-1 RNA ≥ 200 copies/mL and no known resistance to cabotegravir or rilpivirine. This open-label phase 3b trial, conducted at four hospitals in Taiwan, randomized 61 participants, of whom 45 were included in the modified intention-to-treat analysis (median baseline HIV-1 RNA 35,000 copies/mL; 91% male; 60% with past or current substance use). At week 24, HIV-1 RNA < 200 copies/mL was achieved by 88.0% (22/25) of participants who started long-acting therapy immediately and by 55.0% (11/20) of those who continued oral ART ($p = 0.026$), and HIV-1 RNA < 50 copies/mL by 76.0% and 40.0%, respectively ($p = 0.022$). The effect was sustained through week 52 (84.0% [21/25] with HIV-1 RNA < 200 copies/mL in the mITT analysis). No emergent cabotegravir or rilpivirine resistance mutations were detected, and adverse events were grade 1–2. In contrast to LATITUDE, which required viral suppression on

oral ART before randomization and used monthly injections, this study initiated long-acting therapy during viraemia. However, it was a small trial conducted with enhanced study coordination, and the per-protocol difference at week 24 did not reach statistical significance ($p = 0.055$) [24].

Because cabotegravir is metabolized via UGT1A1 and rilpivirine via CYP3A4, both agents remain susceptible to interactions with strong enzyme inducers, even though intramuscular administration bypasses first-pass intestinal metabolism. Physiologically based pharmacokinetic modelling predicts that co-administration with rifampicin reduces cabotegravir and rilpivirine exposure to potentially subtherapeutic concentrations, a concern corroborated by a case report documenting concentrations below the protein-adjusted target during concurrent intravenous rifampicin therapy; rifabutin is likewise not recommended with the injectable regimen [25,26]. This interaction profile is clinically relevant given the substantial overlap between the HIV and tuberculosis burdens in many high-prevalence settings.

Data in special populations are more limited. Current DHHS guidance does not endorse CAB/RPV LA in pregnancy because of lower drug concentrations, although the open-label extension of the HPTN 084 prevention study and an accompanying pharmacokinetic substudy, presented in 2024, reported pregnancy outcomes similar to background rates among participants who continued cabotegravir after conception, indicating that the evidence base is evolving [27]. In adolescents, the FDA has extended approval of the co-packaged cabotegravir/rilpivirine regimen to adolescents aged at least 12 years and weighing at least 35 kg who are virologically suppressed and have no history of treatment failure, and the paediatric antiretroviral guidelines have been revised accordingly [28].

Viral hepatitis coinfection adds a further layer of complexity. Because cabotegravir and rilpivirine lack activity against hepatitis B virus (HBV), they are not recommended in people with active HBV coinfection. Cases of low-level HBV reactivation after switching in patients with resolved past infection have also been reported, prompting calls for closer monitoring of HBV markers in this setting [29]. Hepatitis C virus (HCV) coinfection appears less problematic: in the ATLAS-2M trial, participants with HIV/HCV coinfection maintained rates of virological suppression comparable to those of participants with HIV monoinfection through week 48, with no excess of hepatic adverse events [30].

3.3. Synthesis from Systematic Reviews and Meta-Analyses

Several independent systematic reviews and meta-analyses published between 2023 and 2025 corroborate the individual trial findings summarized above. A meta-analysis of six randomized controlled trials (2829 participants) found long-acting cabotegravir/rilpivirine to be non-inferior to standard oral therapy for virological suppression, although participants receiving long-acting therapy had a higher risk of drug resistance, cross-resistance and treatment-related adverse events [31]. A separate meta-analysis, the first to focus specifically on viraemic populations, concluded that the use of CAB/RPV LA in viraemic patients without alternative oral options could be justified [32]. A broader systematic review spanning multiple long-acting agents and patient-reported outcomes also showed consistent improvements in treatment satisfaction scores with comparable safety, indicating that the efficacy and tolerability signals observed in registrational trials generalize across the accumulating evidence base [33].

3.4. Virological Failure and Resistance in Real-World Practice

In the registrational trials, virological failure on CAB/RPV LA was associated with three baseline factors: rilpivirine resistance-associated mutations, HIV-1 subtype A6/A1, and body mass index above 30 kg/m^2, although the original multivariable analysis was based on only 23 failure cases [34].

As the regimen has moved into wider clinical use, larger case series have refined this picture. A pooled analysis of the first approximately 100 reported real-world failure cases found that only 4.4% of individuals met the high-risk threshold of two or more baseline risk factors, yet 87.2% of failures showed predicted reduced susceptibility to cabotegravir, rilpivirine or both; cross-resistance to other INSTIs and NNRTIs was common, although susceptibility to dolutegravir, bictegravir, doravirine or etravirine was preserved in a substantial proportion of cases [35,36].

A systematic review of observational cohorts similarly concluded that, although trial-level failure rates are reassuring, INSTI and NNRTI resistance after failure can constrain future treatment options in the individuals affected [37]. The review identified 79 cohorts comprising 13,899 individuals, 172 of whom experienced virological failure (VF); definitions of VF varied considerably across studies.

Genotypic data at the time of failure were available for 80 VF events: NNRTI-associated mutations were detected in 45 cases, INSTI mutations in 40, and dual-class resistance in 33, while 28 VF events occurred without any detectable resistance. Among the 92 VF events for which post-failure regimens were reported, approaches included protease inhibitor–based regimens, oral INSTI-based regimens and, in some cases, continuation of CAB/RPV LA itself. Resuppression was achieved in 87.8% (65/74) of the VF events with reported outcomes.

The authors concluded that, in real-world clinical practice, VF with CAB/RPV LA remains uncommon and broadly consistent with rates observed in randomized controlled trials; however, when VF does occur, it is frequently accompanied by resistance, particularly dual-class resistance. Post-failure management strategies were heterogeneous but generally successful in restoring viral suppression, including, in some cases, continued use of CAB/RPV LA.

Subtype distribution adds a geographically variable dimension to this risk: in a Polish multicentre cohort, HIV-1 subtype A6 carrying the L74I polymorphism accounted for half of the infections, and roughly 40% of patients carried either a resistance-associated mutation or the A6 subtype polymorphism, reinforcing calls for genotypic and subtype assessment before initiating long-acting therapy in regions with a substantial subtype A burden [38].

Further real-world evidence on virological failure comes from the French Dat'AIDS cohort, which followed 2196 virologically suppressed adults who switched to CAB/RPV LA between December 2021 and December 2023 (median follow-up 13 months) [39]. Virological failure occurred in 42 participants (1.9%) after a median of 103 days, and 90.5% of events occurred within the first year. Among the 26 failures with a genotype, emergent resistance-associated mutations were found in 13 (50%; 0.6% of the whole cohort), mostly involving INSTI mutations (Q148H/R/K, E138K, G140R, N155H) and, in eight cases, both INSTI and NNRTI mutations [39]. The clinical consequences were asymmetric: once-daily dolutegravir or bictegravir remained fully active in 58–65% of genotyped failures (depending on the ANRS or Stanford algorithm), whereas doravirine remained active in 92–96% [39]. Resistance also emerged in 7 of the 13 cases during low-level viraemia or transient rebound followed by resuppression, which would not always satisfy consensus definitions of failure [39]. In multivariable analysis, higher body mass index (BMI; adjusted hazard ratio [aHR] 1.07 per kg/m^2), a nadir CD4 count < 200 cells/mm^3 (aHR 2.44) and a duration of prior suppression < 12 months (aHR 2.39) were

independently associated with failure, and historical cabotegravir resistance mutations increased the risk further (aHR 6.3) [39]. These observational findings, limited by the availability of genotypes for only a subset of failures and by the lack of data on injection delays, support individualized candidate selection and early resistance testing, even during low-level viraemia.

4. Long-Acting Cabotegravir for Hiv Prevention

CAB-LA has been a major advance in HIV prevention, overcoming some of the limitations of daily oral PrEP. Although oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and tenofovir alafenamide/emtricitabine (TAF/FTC) are highly effective when taken consistently, adherence remains a critical determinant of effectiveness, particularly among populations facing social, behavioural and structural barriers [40].

4.1. Hptn 083: Cabotegravir Prevention in Cisgender Men and Transgender Women

The HPTN 083 trial evaluated the efficacy and safety of CAB-LA compared with daily oral TDF/FTC in cisgender men and transgender women who have sex with men [8]. In this double-blind, double-dummy trial, participants were randomized to receive either injectable cabotegravir every eight weeks or daily oral TDF/FTC. The intention-to-treat population comprised 4566 participants (2282 randomized to CAB-LA and 2284 to TDF/FTC), 12.5% of whom identified as transgender women; the median age was 26 years. A total of 52 incident HIV infections occurred during follow-up: 13 in the cabotegravir group (incidence rate, 0.41 per 100 person-years) versus 39 in the TDF/FTC group (incidence rate, 1.22 per 100 person-years), corresponding to a hazard ratio of 0.34 (95% CI, 0.18–0.62). This result indicated a 66% relative reduction in HIV incidence with CAB-LA compared with TDF/FTC, and the effect was consistent across prespecified subgroups. Injection-site reactions were common and more frequent in the cabotegravir arm than in the TDF/FTC arm (81.4% vs. 31.3%). Among participants who acquired HIV infection despite exposure to CAB-LA, INSTI resistance and delayed detection of infection were observed. No new safety signals emerged over the course of the trial.

CAB-LA was therefore superior to oral PrEP, representing a major improvement over the existing prevention standard: it reduced HIV acquisition by approximately two-thirds compared with TDF/FTC, its efficacy was maintained across demographic subgroups, injection-site reactions were common but generally acceptable, and adherence to scheduled injections was high. The superior efficacy observed with CAB-LA was attributed primarily to improved adherence compared with daily oral medication rather than to intrinsic differences in antiviral potency. The HPTN 083 results established injectable cabotegravir as the first long-acting HIV prevention strategy with demonstrated superiority over oral PrEP [8].

4.2. Hptn 084: Cabotegravir Prevention in Cisgender Women

The HPTN 084 trial evaluated CAB-LA among cisgender women in sub-Saharan Africa, a population with a substantial burden of HIV infection and historically lower uptake of oral PrEP [9]. Participants were randomized to receive CAB-LA every eight weeks or daily oral TDF/FTC. The trial was stopped early after an interim analysis demonstrated the superiority of injectable cabotegravir, with a marked reduction in HIV incidence among participants receiving CAB-LA. These results were particularly important because they showed that long-acting prevention could overcome the adherence challenges observed with daily oral PrEP in some women. The findings from HPTN 084 expanded the applicability of long-acting prevention strategies and supported regulatory approval of CAB-LA for HIV prevention [9].

Real-world data presented at AIDS 2026 reinforce these findings outside the controlled trial setting. In the US-based OPERA cohort, no HIV acquisitions were observed among cisgender and transgender women receiving CAB-LA PrEP despite injection delays, which were mostly short [41]. Complementary evidence from the CAPTIVATE study, which combined cross-sectional surveys with retrospective chart review, and from the PrEPFACTS study, which used healthcare administrative claims data, describes real-world use, acceptability and adherence patterns of CAB-LA PrEP in routine US clinical practice [42,43]. Looking ahead, baseline data from the phase 2b registrational EXTEND 4M trial describe the population enrolled in the first study of a novel long-acting cabotegravir formulation dosed three times yearly, which builds on the established six-times-yearly regimen with the aim of further extending the dosing interval for HIV prevention [44].

4.3. Implementation Challenges of Cab-La Prep

4.3.1. Healthcare Delivery Requirements

Unlike oral PrEP, CAB-LA requires trained healthcare personnel, scheduled clinic attendance, injection capacity, and management of missed appointments. These requirements may represent barriers in settings where healthcare infrastructure is limited [45].

4.3.2. Pharmacological Tail and Resistance

A major concern with CAB-LA prevention is the prolonged pharmacological tail after discontinuation. Detectable concentrations of cabotegravir may persist for many months after the last injection. If HIV infection occurs during this period, suboptimal drug exposure may promote the selection of INSTI resistance mutations, including Q148 pathway mutations, N155H, R263K and G118R. Implementation programmes therefore require HIV testing before each injection, careful evaluation of symptoms suggestive of acute HIV infection and strategies for managing missed injections.

5. Lenacapavir: A New Generation of Long-Acting Antiretroviral Therapy

Lenacapavir represents a major innovation in HIV therapeutics: it is the first clinically available capsid inhibitor and interferes with multiple capsid-dependent stages of the viral life cycle.

5.1. Mechanism of Action

The HIV capsid plays essential roles during both early and late stages of viral replication. Lenacapavir binds to conserved regions between capsid protein monomers, resulting in inhibition of capsid disassembly after viral entry, disruption of nuclear transport, interference with capsid assembly, and production of structurally abnormal viral particles. Because of this novel mechanism, lenacapavir retains activity against HIV strains resistant to multiple existing antiretroviral classes [46].

5.2. Lenacapavir for Multidrug-Resistant Hiv Infection: The Capella Trial

The CAPELLA trial evaluated lenacapavir in heavily treatment-experienced individuals with HIV resistant to multiple antiretroviral classes [10]. Participants had extensive previous ART exposure, multidrug-resistant HIV and limited remaining treatment options.

This phase 2/3 trial (randomized, double-blind and placebo-controlled in cohort 1) enrolled heavily treatment-experienced adults with HIV-1 resistant to at least three of

the four main antiretroviral classes and a failing regimen. A total of 72 patients were enrolled, 36 in each cohort. In cohort 1 (randomized 2:1), participants received oral lenacapavir or placebo added to their failing regimen for a 14-day functional monotherapy period, followed in both arms by open-label subcutaneous lenacapavir (927 mg every 6 months) plus optimized background therapy (OBT); in cohort 2 (non-randomized), participants received open-label oral lenacapavir plus OBT from day 1, followed by the same subcutaneous regimen.

The primary endpoint, assessed in cohort 1 during functional monotherapy, was a decrease in viral load of at least 0.5 log10 copies/mL by day 15; it was met by 21 of 24 patients (88%) in the lenacapavir group and by 2 of 12 patients (17%) in the placebo group. At week 26 (key secondary endpoint), a viral load below 50 copies/mL was reported in 81% of patients in cohort 1 and 83% of those in cohort 2, with a concurrent increase in CD4+ cell count.

Overall, 19 patients (11 in cohort 1 and 8 in cohort 2) met the criteria for resistance analysis and were evaluated for the emergence of capsid inhibitor resistance. Lenacapavir-associated capsid substitutions developed in 8 patients (4 in cohort 1 [1 in the lenacapavir group and 3 in the placebo group] and 4 in cohort 2) during the maintenance period. Of these, 5 had M66I alone, 1 had M66I + N74D, 1 had Q67H + K70R and 1 had K70H alone. The median fold decrease in lenacapavir susceptibility was 234 in patients with M66I, 15 in the patient with Q67H + K70R and 265 in the patient with K70H. These substitutions map to the capsid hexamer interface targeted by lenacapavir and confer substantial to very high phenotypic resistance.

Notably, 4 of the 8 participants with emergent resistance mutations still achieved virological suppression, possibly because these mutations carry a high fitness cost in vivo; this suggests that the clinical impact of capsid resistance may be tempered by reduced viral replicative capacity, which distinguishes it to some extent from resistance patterns seen with other drug classes.

In summary, lenacapavir produced a rapid and clinically meaningful reduction in plasma HIV RNA during the monotherapy phase, and high rates of virological suppression were achieved when it was combined with active background agents. These findings demonstrated that capsid inhibition is a valuable therapeutic option for people with multidrug-resistant HIV. However, resistance may emerge when lenacapavir is used without sufficient companion activity; appropriate background therapy therefore remains essential.

5.3. Calibrate Study: Exploring Lenacapavir Earlier in Treatment

The CALIBRATE study evaluated lenacapavir in treatment-naive individuals initiating ART [11]. Lenacapavir-containing regimens were compared with standard oral therapy, providing important information on antiviral activity, pharmacokinetics, safety and resistance. This phase 2, randomized, open-label, active-controlled trial in antiretroviral-naive adults with HIV-1 was conducted at 41 sites in the USA and the Dominican Republic. A total of 182 participants were randomized (2:2:2:1) to four groups: Group 1—subcutaneous lenacapavir (927 mg every 26 weeks, after oral loading) + oral TAF/FTC for the first 28 weeks, then subcutaneous lenacapavir + oral TAF alone; Group 2—the same lenacapavir induction, then subcutaneous lenacapavir + oral bictegravir; Group 3—daily oral lenacapavir + TAF/FTC; Group 4 (control)—oral B/F/TAF. At week 54, viral suppression (HIV-1 RNA < 50 copies/mL) was achieved by 90% of participants in Group 1, 85% in Group 2, 85% in Group 3, and 92% in the B/F/TAF control group, with no significant differences between groups. Suppression rates were maintained through week 80 (87%, 76%, 87%, and 92%, respectively) and were nearly universal (98–100%) among participants remaining on treatment at week 132. CD4+ cell

counts increased substantially and comparably across all arms (median increase > 200 cells/μL).

Six participants met the criteria for resistance testing (1, 1, 3, and 1 in Groups 1–4, respectively), of whom 2 developed lenacapavir resistance. One participant in Group 2 developed Q67H + K70R in capsid at week 10 (20-fold reduced susceptibility); one participant in Group 3 developed isolated Q67H at week 54 (7-fold reduced susceptibility). Both resistance cases occurred in the context of documented low adherence to the oral companion drugs, effectively exposing the virus to functional lenacapavir monotherapy—the same mechanism implicated in CAPELLA. Both participants achieved resuppression after switching to an INSTI-based regimen with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), again suggesting a fitness cost of these capsid substitutions rather than irreversible treatment failure. Although lenacapavir demonstrated potent antiviral activity, the emergence of resistance when it was combined with insufficient companion therapy highlighted the importance of using agents with complementary activity. The CALIBRATE study provided the foundation for future investigations of long-acting lenacapavir-based combinations [11].

6. Lenacapavir for Hiv Prevention

The prolonged half-life of subcutaneous lenacapavir, together with its high antiviral potency, made a twice-yearly HIV prevention strategy possible. This approach has the potential to address one of the main limitations of oral PrEP: the need for consistent daily adherence. The PURPOSE clinical development programme evaluated the efficacy and safety of lenacapavir for HIV prevention in different populations.

6.1. Purpose 1: Twice-Yearly Lenacapavir for Hiv Prevention in Cisgender Women

PURPOSE 1 was a landmark phase 3 trial comparing twice-yearly subcutaneous lenacapavir with daily oral tenofovir-based PrEP for HIV prevention in cisgender adolescent girls and young women [47].

The trial was conducted in South Africa and Uganda; participants were randomized in a 2:2:1 ratio to receive twice-yearly subcutaneous lenacapavir, daily oral TAF/FTC or daily oral TDF/FTC, with matching oral or subcutaneous placebos in each arm. Efficacy was assessed against both the estimated background HIV incidence in the screened population and TDF/FTC. Among 5338 initially HIV-negative participants included in the modified intention-to-treat analysis, 55 incident HIV infections occurred overall:

- Lenacapavir: 0 infections among 2134 participants (incidence 0 per 100 person-years; 95% CI, 0.00–0.19)
- TAF/FTC: 39 infections among 2136 participants (incidence 2.02 per 100 person-years; 95% CI, 1.44–2.76)
- TDF/FTC: 16 infections among 1068 participants (incidence 1.69 per 100 person-years; 95% CI, 0.96–2.74)
- Background incidence (screened population, n = 8094): 2.41 per 100 person-years (95% CI, 1.82–3.19)

HIV incidence with lenacapavir was significantly lower than both the background incidence and the incidence with TDF/FTC, with no infections at all in the lenacapavir group. In contrast, HIV incidence with TAF/FTC did not differ significantly from background incidence, and no meaningful difference was observed between TAF/FTC and TDF/FTC (incidence rate ratio, 1.20; 95% CI, 0.67–2.14); these findings were largely attributable to low adherence to the daily oral regimens. As no breakthrough infections occurred in the lenacapavir group, there was no lenacapavir resistance to analyse in this trial. The poor effectiveness of TAF/FTC in this trial, driven by adherence rather than

drug potency, underscores by contrast the adherence-independent advantage of a twice-yearly injectable. No safety concerns were identified. Injection-site reactions were more common in the lenacapavir group (68.8%) than in the pooled placebo-injection group (34.9%), but only 4 participants (0.2%) discontinued lenacapavir because of them. This trial demonstrated that twice-yearly lenacapavir provided extremely high protection against HIV acquisition.

The implications of PURPOSE 1 extend beyond efficacy: improved acceptability, reduced stigma associated with daily medication, increased privacy, and potential benefit for individuals unable to maintain daily adherence [47].

6.2. Purpose 2: Lenacapavir Prevention in Populations Including Cisgender Men and Gender-Diverse Individuals

PURPOSE 2 evaluated twice-yearly lenacapavir for HIV prevention in a diverse population of cisgender men, transgender women, transgender men and gender-nonbinary individuals who have condomless sex with partners assigned male at birth [48]. In this phase 3, double-blind, randomized, active-controlled trial, conducted at 92 sites in 7 countries, participants were randomly assigned in a 2:1 ratio to receive subcutaneous lenacapavir every 26 weeks or daily oral TDF/FTC (active control), with matching placebos. Efficacy was assessed against both the estimated background HIV incidence in the screened population and TDF/FTC. Among the 3265 participants included in the modified intention-to-treat analysis (2179 in the lenacapavir group and 1086 in the TDF/FTC group), 11 incident HIV infections occurred overall:

- Lenacapavir: 2 infections (incidence 0.10 per 100 person-years)
- TDF/FTC: 9 infections (incidence 0.93 per 100 person-years)
- Background incidence (screened population, n = 4634): 2.37 per 100 person-years (95% CI, 1.65–3.42)

HIV incidence with lenacapavir was significantly lower than both the background incidence and the incidence with TDF/FTC. Unlike in PURPOSE 1, two breakthrough infections occurred in the lenacapavir group. As in the treatment trials, the clinically relevant question was whether these were associated with emergent capsid resistance. Case-level resistance analyses attributed such breakthroughs to inadequate lenacapavir exposure (missed or delayed injections) rather than to selection of high-level resistance mutations. No safety concerns were identified. Discontinuation of the trial regimen because of injection-site reactions occurred in 26 of 2183 participants (1.2%) in the lenacapavir group versus 3 of 1088 (0.3%) in the TDF/FTC group. The study demonstrated the superior efficacy of lenacapavir compared with both background HIV incidence and oral PrEP. The results confirmed that capsid inhibition can provide effective prevention across multiple populations and supported the concept that PrEP strategies may move away from daily medication towards intermittent, long-acting biomedical prevention [48].

6.3. Long-Term Follow-Up: Purpose 1 and Purpose 2 Open-Label Extension

Long-term follow-up data from the 52-week open-label extension (OLE) phases of PURPOSE 1 and PURPOSE 2, presented at AIDS 2026, indicate that these results are durable [49,50]. More than 95% of eligible participants across the two trials chose to continue lenacapavir or to switch to lenacapavir from once-daily oral PrEP. With more than 7178 person-years of follow-up in PURPOSE 1 and 5295 in PURPOSE 2, no HIV infections occurred during the PURPOSE 1 OLE phase, including among participants who switched from oral PrEP, and a single infection was observed among participants continuing lenacapavir in PURPOSE 2. Adherence to scheduled twice-yearly injections

remained high through 52 weeks (96% in PURPOSE 1 and 92% in PURPOSE 2), and the safety profile remained consistent with that of the randomized blinded phases of both studies, with no new safety signals [49,50].

6.4. Clinical Implications of Lenacapavir Prep

6.4.1. Reduced Adherence Burden

The requirement for only two administrations per year represents a fundamental change compared with daily oral PrEP.

6.4.2. Improved Privacy

Some individuals avoid oral PrEP because of concerns related to disclosure, stigma or fear of being identified as at risk for HIV. An injectable option may reduce these barriers.

6.4.3. Expanded Prevention Choices

The availability of different PrEP modalities allows prevention to become more individualized. Future HIV prevention programmes may include daily oral PrEP, injectable CAB-LA, twice-yearly LEN and, eventually, implantable technologies.

6.5. Challenges Associated with Lenacapavir Prevention

Despite its remarkable efficacy, lenacapavir PrEP raises several issues that require consideration.

6.5.1. Resistance During Undiagnosed Hiv Infection

As with other long-acting agents, the prolonged pharmacological persistence of lenacapavir creates a potential risk of resistance if HIV is acquired while drug concentrations are declining. Capsid resistance mutations associated with lenacapavir exposure include M66I, Q67H, K70R, N74D and A105T. Overall, single mutations (Q67H, K70R, N74D, A105T) typically produce modest reductions in susceptibility with limited fitness cost, whereas M66I, K70H and multi-mutation combinations (e.g., Q67H + K70R or M66I-containing patterns) confer progressively greater phenotypic resistance, sometimes at the expense of replicative capacity unless compensated by accessory substitutions. This gradient underscores why early detection of infection—before declining, subtherapeutic drug concentrations allow the sequential accumulation of mutations—is critical to preventing the emergence of higher-level resistance genotypes. Prevention programmes must therefore incorporate sensitive HIV diagnostic strategies, rapid confirmation of infection and timely transition to fully suppressive combination ART.

6.5.2. Access and Implementation

The greatest challenge may lie not in biological efficacy but in global implementation. Key considerations include affordability, manufacturing capacity, regulatory approval and healthcare delivery models. The history of HIV treatment demonstrates that innovative therapies achieve their greatest public health impact only when access is equitable.

6.6. Comparison Between Cabotegravir and Lenacapavir Prevention Strategies

CAB-LA and LEN represent complementary approaches to long-acting HIV prevention (Table 2). Lenacapavir does not replace cabotegravir but rather expands the prevention landscape. The availability of multiple long-acting options may allow

prevention strategies to be tailored to individual preferences, healthcare infrastructure and epidemiological context.

Direct participant-level comparisons between the two long-acting prevention options are now emerging. In the phase 1 CLARITY randomized crossover study, a single dose of long-acting cabotegravir was more acceptable than a single dose of lenacapavir, with fewer and less bothersome injection-site reactions [51]. Six-month follow-up data from CLARITY in participants without HIV, presented at AIDS 2026, extend these findings to provider experience and to injection acceptability over time, providing further evidence to inform shared decision-making when initiating long-acting injectable PrEP [52].

CLARITY, the first head-to-head comparison of injection-site reaction (ISR) acceptability and tolerability between CAB-LA and LEN, enrolled 63 HIV-negative adults, who were randomized to receive one agent on day 1 (a single intramuscular CAB-LA injection or two subcutaneous LEN injections) followed by the other agent on day 15, allowing within-participant comparison. It was not an efficacy trial: no virological outcomes were reported, and the focus was entirely on participant- and provider-reported tolerability and preference.

The primary endpoint (local-reaction acceptability, assessed 7 days after each injection) favoured cabotegravir: 69% (42/61) of participants rated CAB-LA injections as "totally or very acceptable" versus 48% (29/60) for LEN (post hoc $p = 0.019$). Overall, 90% of participants and 86% of healthcare providers preferred CAB-LA to LEN after a single dose of each. ISRs were more frequent and more visible with LEN than with CAB-LA. About 80% of participants reported injection-site pain with both agents, indicating that pain itself was common regardless of the drug, whereas the acceptability and visibility of reactions differed. Six-month follow-up data reinforced the initial findings: in the updated analysis, 70% (42/60) of participants rated the CAB-LA injection experience as "very acceptable" or "totally acceptable", compared with 37% (22/60) for LEN. ISRs remained less visible with CAB-LA than with LEN through 6 months of follow-up, consistent with the earlier day 22 data. Findings were consistent across participant-reported and provider-reported measures, indicating that the acceptability gap between the two agents persisted over a longer observation window and not only after a single dose. Overall, despite lenacapavir's markedly longer dosing interval (every 6 months vs. every 2 months for CAB-LA), its subcutaneous, larger-volume, two-injection administration was associated with less favourable local-reaction acceptability and lower participant and provider preference than intramuscular cabotegravir, at least after limited (single-dose or early) exposure [52].

7. Islatravir and Lenacapavir: Towards Weekly Oral Long-Acting Therapy

Although injectable therapies are the most visible form of long-acting ART, an alternative strategy is the development of oral agents with prolonged intracellular activity. The combination of islatravir (ISL) and lenacapavir represents one of the most innovative investigational approaches currently under evaluation.

7.1. Islatravir: Pharmacological Characteristics

Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI). Unlike conventional nucleoside analogues, islatravir combines a distinctive mechanism of action, involving incorporation into viral DNA and inhibition of reverse transcriptase translocation, with prolonged intracellular persistence of its active

metabolite. The exceptionally long intracellular half-life of islatravir triphosphate provides the pharmacological rationale for reduced dosing frequency [53].

7.2. Rationale for Combining Islatravir and Lenacapavir

The combination of ISL and LEN is based on complementary mechanisms: islatravir inhibits reverse transcription, while lenacapavir inhibits capsid function. This dual mechanism may provide potent antiviral activity, a higher genetic barrier than single-agent strategies and reduced dosing frequency. A weekly oral regimen combining agents with prolonged intracellular or plasma persistence could be an attractive alternative to injectable approaches, particularly for individuals who prefer oral administration but desire reduced dosing frequency.

Early clinical studies demonstrated potent antiviral activity and favourable pharmacokinetic properties. However, the development of islatravir has been complicated by safety concerns identified during clinical trials. In earlier studies, dose-dependent reductions in total lymphocyte and CD4+ T-cell counts were observed in some participants receiving islatravir-containing regimens. These findings led to the temporary interruption of several clinical development programmes and prompted a reassessment of dosing strategies [54–56]. Subsequent investigations explored lower doses and alternative combinations to preserve antiviral efficacy while improving safety. This experience highlights an important principle in long-acting antiviral development: prolonged drug exposure provides therapeutic advantages but also requires careful evaluation of long-term safety, because adverse effects may persist beyond conventional dosing intervals. A weekly oral regimen would represent a different model of long-acting therapy, combining the convenience of oral administration with extended pharmacological activity.

7.3. Clinical Development and Safety Considerations

Updated data reported in 2025–2026 refine this picture. In a phase 2 study, once-weekly oral islatravir 2 mg plus lenacapavir 300 mg maintained high rates of virological suppression through week 48 in participants switching from B/F/TAF, with no clinically relevant decline in CD4+ T-cell or lymphocyte counts at the lower islatravir dose [57].

This phase 2, randomized, open-label, active-controlled trial was conducted at 44 sites in the United States and enrolled 104 adults with HIV-1 who were virologically suppressed (HIV-1 RNA < 50 copies/mL for at least 24 weeks) on B/F/TAF. Participants were randomized 1:1 to switch to once-weekly oral ISL 2 mg plus LEN 300 mg or to continue daily B/F/TAF. Weekly oral ISL 2 mg + LEN 300 mg was well tolerated and maintained high rates of viral suppression (HIV-1 RNA < 50 copies/mL) at week 24, which were sustained through week 48.

In contrast to earlier trials with higher islatravir doses, no clinically relevant decreases in CD4+ T-cell or lymphocyte counts were observed, and changes in these counts did not differ significantly between groups. This finding supports the hypothesis that islatravir lymphocyte toxicity is dose-dependent and that the lower weekly dose (2 mg, in combination with lenacapavir) does not reproduce the adverse effect seen at the higher doses (0.75 mg daily or 20 mg weekly) used in earlier clinical programmes.

Building on these findings, the phase 3 ISLEND-1 and ISLEND-2 trials of once-weekly oral islatravir/lenacapavir met their primary efficacy endpoints at week 48, with a safety profile broadly comparable to that of standard-of-care regimens and no new safety signals, positioning this combination as a candidate for the first complete once-weekly oral antiretroviral regimen [58,59].

ISLEND-1 compared once-weekly islatravir/lenacapavir with daily B/F/TAF in virologically suppressed adults. Participants had a viral load below 50 copies/mL for at

least six months, no history of virological failure, and a high median baseline CD4 count of approximately 740 cells/μL. At week 48, islatravir/lenacapavir was non-inferior to B/F/TAF, meeting the primary endpoint; 93.4% of those who switched and 92.4% of those who stayed on B/F/TAF maintained viral suppression, with no emergent resistance detected in either arm. Treatment was generally safe and well tolerated, with adverse events occurring in 13% of participants in both groups; the most frequent side effects (nausea and headache) were uncommon (3%), only 2% of participants in either group discontinued because of adverse events, and there were no clinically meaningful changes in body weight. Participants receiving islatravir/lenacapavir did not experience the decreases in white blood cell counts seen in earlier, discontinued trials of higher islatravir doses: CD4 counts remained stable, and total lymphocyte counts showed a similar small increase in both arms.

ISLEND-2 was an open-label trial that enrolled 626 people virologically suppressed on various standard-of-care daily oral regimens across 13 countries and compared switching to ISL/LEN with remaining on the existing regimen. At baseline, most participants were receiving INSTI-based regimens, had no history of virological failure and had a mean CD4 count of 778 cells/μL. Islatravir/lenacapavir was again non-inferior to standard therapy: at week 48, 95.2% of those who switched and 95.5% of those who remained on their prior regimen maintained viral suppression, with no emergent resistance. Treatment-related adverse events occurred in 18% of the islatravir/lenacapavir group versus less than 1% of the unchanged-treatment group, although none were severe; the most common were headache, diarrhoea and nausea. As in ISLEND-1, body weight and CD4 and total lymphocyte counts remained stable in both arms. The trial also collected patient-reported outcomes: nearly two-thirds of those who switched found their previous daily regimen more burdensome than the weekly pill, and more than 75% reported greater satisfaction with the weekly treatment at week 48.

In parallel, a separate strategy has paired lenacapavir with long-acting broadly neutralizing antibodies rather than a second small molecule: in a phase 1b study, lenacapavir combined with the extended-half-life antibodies teropavimab and zinlirvimab maintained viral suppression for at least 26 weeks in 18 of 20 participants after discontinuation of oral ART [60].

This was a randomized, blinded, phase 1b proof-of-concept study conducted at 11 HIV treatment centres in the USA. The study enrolled adults with HIV-1 RNA < 50 copies/mL who had been on oral ART for at least 18 months, had CD4 counts of at least 500 cells/μL, and had protocol-defined susceptibility to both bNAbs. Twenty-one participants were included; 86% (18/21) were male, ages ranged from 25 to 61 years, and the median baseline CD4 count was high, at 909 cells/μL (IQR 687–1270).

Participants discontinued oral ART and were randomly assigned 1:1 to one of two dose regimens of subcutaneous lenacapavir plus teropavimab (30 mg/kg) and zinlirvimab at either 10 mg/kg or 30 mg/kg. The primary endpoint was the incidence of serious adverse events through week 26. One participant withdrew on day 1, before completing the regimen.

The regimen was generally well tolerated, and no serious adverse events occurred. Only two grade 3 adverse events were reported (lenacapavir injection-site erythema and injection-site cellulitis), both of which resolved. The most common adverse events were injection-site reactions, which occurred in 85% (17/20) of participants receiving subcutaneous lenacapavir and were mostly grade 1 (mild; 12/20 participants, 60%). One participant (10%) in the zinlirvimab 10 mg/kg group experienced viral rebound (confirmed HIV-1 RNA ≥ 50 copies/mL) and was successfully resuppressed after

restarting ART; one participant in the zinlirvimab 30 mg/kg group withdrew at week 12 while still virologically suppressed (HIV-1 RNA < 50 copies/mL).

Results of a multicentre, open-label, randomized, active-controlled phase 2 trial conducted at 34 sites in the USA, Canada, Australia and Puerto Rico have also been published [61].

Virologically suppressed people with HIV-1 (HIV-1 RNA < 50 copies/mL) on oral ART whose virus was highly susceptible to teropavimab and zinlirvimab (IC90 ≤ 2 μg/mL) were randomized 2:1 to switch to twice-yearly subcutaneous lenacapavir 927 mg (with oral loading) plus intravenous teropavimab 2550 mg and zinlirvimab 2550 mg, or to continue their stable baseline oral regimen (SBR). Eighty participants were enrolled (53 in the lenacapavir/teropavimab/zinlirvimab [LTZ] arm and 27 in the SBR arm).

At week 26, only 1.9% (1/53) of participants in the LTZ group and none in the SBR group had HIV-1 RNA ≥ 50 copies/mL (FDA Snapshot algorithm), meeting the criterion for non-inferiority (one participant per group lacked virological data). Excluding lenacapavir injection-site reactions (n = 33, mostly grade 1), treatment-emergent adverse events occurred in 68% of participants in the LTZ group and 63% of those in the SBR group. In the LTZ group, there were no infusion-related reactions to the bNAbs, no drug-related grade ≥ 3 adverse events, no serious adverse events, no deaths and no discontinuations due to adverse events.

Week 104 outcomes from this study were also reported at AIDS 2026. At week 52, virologically suppressed participants could either continue LTZ or switch from SBR to LTZ in the extension phase. Endpoints included HIV-1 RNA < 50 copies/mL, change in CD4 cell count from baseline and adverse events through week 104. Viral suppression rates were 98% (40/41) and 100% (19/19) in the continuous and late-switch groups, respectively, and CD4 count changes differed between groups, with median changes at week 104 of +34 (−71 to +111) and −38 (−159 to +140) cells/μL in the continuous and late-switch groups, respectively [62].

The first two phase 3 trials of this combination, Daybreak 1 and Daybreak 2, which will evaluate a potential complete twice-yearly injectable regimen, were also presented at AIDS 2026 [63]. Daybreak 1 (NCT07682961) will compare switching to twice-yearly lenacapavir, teropavimab and zinlirvimab with other long-acting regimens (e.g., injectable cabotegravir and rilpivirine) in virologically suppressed adults, whereas the companion study Daybreak 2 (NCT07683000) will evaluate the twice-yearly regimen in participants switching from stable daily oral regimens, assessing long-term safety, durability and patient preference.

In a further parallel effort, lenacapavir is being paired with GS-3242, a novel investigational INSTI. GS-3242 has a high barrier to resistance and minimal cross-resistance within the INSTI class, a profile comparable to that of bictegravir. It is being tested in combination with lenacapavir in two ongoing phase 2 studies (Pulsar 1 and Pulsar 2) as an additional candidate component of a future twice-yearly injectable HIV treatment regimen [64,65].

8. Broadly Neutralizing Antibodies as Long-Acting Antiviral Strategies

Broadly neutralizing antibodies (bNAbs) represent a distinct approach within the field of long-acting HIV therapeutics. Unlike most conventional antiretroviral drugs, which inhibit viral replication after entry into target cells, bNAbs recognize conserved regions of the HIV envelope glycoprotein and block viral entry. The development of bNAbs has been driven by the observation that a small proportion of individuals living with HIV naturally develop antibodies capable of neutralizing a broad range of viral variants [66]. Major classes include CD4 binding site, V3 glycan and membrane-

proximal external region (MPER) antibodies. Clinically investigated bNAbs include VRC01, 3BNC117, 10-1074 and N6LS.

8.1. Mechanisms of Action of Bnabs

bNAbs exert antiviral activity through several mechanisms:

1. Prevention of viral entry by blocking the interaction between HIV envelope proteins and host receptors.
2. Fc-mediated immune mechanisms, including antibody-dependent cellular cytotoxicity and antibody-dependent phagocytosis.
3. Potential modulation of viral reservoirs through immune-mediated clearance of infected cells.

Because bNAbs act before cellular infection is established, they have potential applications in both prevention and treatment [67].

8.2. Broadly Neutralizing Antibodies in Hiv Treatment

Early studies demonstrated that passive administration of bNAbs could reduce plasma HIV RNA levels in untreated individuals. However, monotherapy was limited by the rapid emergence of antibody-resistant viral variants. This led to the development of combination antibody strategies.

8.2.1. 3bnc117

3BNC117 targets the CD4 binding site of the HIV envelope and showed antiviral activity in early clinical studies. A single dose reduced plasma viraemia, providing proof of concept for antibody-mediated antiviral therapy. However, resistance emerged in some participants, particularly when antibody pressure was applied without complementary antiviral activity.

8.2.2. 10-1074

10-1074 targets the V3 glycan region of gp120. Like 3BNC117, it showed potent antiviral activity, but escape variants emerged when it was used alone.

8.2.3. Combination Bnab Therapy

Combining antibodies with non-overlapping resistance profiles is the preferred strategy. The combination of 3BNC117 and 10-1074 maintained prolonged suppression in selected individuals with antibody-sensitive virus. These findings suggest that future antibody-based therapy may follow the principles of conventional ART, in which multiple active agents are required to prevent resistance [68–70].

8.2.4. Vrc01

VRC01 is a CD4 binding site antibody that was first evaluated as treatment in a phase 1 study of six ART-treated individuals with undetectable plasma viraemia and eight ART-untreated viraemic individuals. In the ART-treated group, two infusions of VRC01 did not reduce the cell-associated viral reservoir measured four weeks after the second infusion. In contrast, six of eight untreated viraemic participants who received a single infusion had a 1.1 to 1.8 log10 reduction in plasma viraemia [71]. These treatment studies are distinct from the prevention trials discussed in Section 8.3.

8.3. Hvtn 703/Hptn 081 and Hvtn 704/Hptn 085: Bnabs for Prevention

The efficacy of VRC01 for HIV prevention was evaluated in two phase 2b placebo-controlled Antibody-Mediated Prevention (AMP) trials conducted in HIV-negative

participants: HVTN 704/HPTN 085, in cisgender men and transgender people who have sex with men in the Americas and Europe, and HVTN 703/HPTN 081, in cisgender women in sub-Saharan Africa. Participants received intravenous VRC01 (10 or 30 mg/kg) or placebo every eight weeks for a total of 10 infusions [72]. VRC01 did not significantly reduce overall HIV-1 acquisition compared with placebo in either trial. However, a prespecified analysis of breakthrough infections showed an estimated prevention efficacy of approximately 75% against viruses highly sensitive to VRC01 (IC80 < 1 μg/mL), which represented only about 30% of the circulating viruses [72]. These studies suggested that antibody potency is critical, that broad coverage is required and that combinations of antibodies may be necessary. The results stimulated the development of next-generation antibodies with greater neutralization breadth and potency, extended half-life and suitability for subcutaneous administration.

8.4. Next-Generation Antibody Strategies

Future bNAb approaches aim to overcome the limitations observed with first-generation antibodies. Strategies include:

8.4.1. Fc Engineering

Modification of Fc regions can prolong antibody half-life, potentially allowing dosing intervals of several months.

8.4.2. Combination Antibody Cocktails

Using multiple antibodies targeting different envelope regions may reduce the risk of viral escape [73].

8.4.3. Combination with Antiretroviral Therapy

bNAbs can be combined with long-acting small molecules, as with lenacapavir plus teropavimab and zinlirvimab (Section 7.3), to provide suppression of active viral replication, immune-mediated targeting of infected cells and greater protection against resistance.

The clinical evidence base for bNAbs has broadened considerably. A review of the clinical trial landscape identified 154 registered bNAb studies in people with HIV, 62 of which met the inclusion criteria for adults with HIV; these spanned single agents and combination regimens and confirmed that intravenously administered bNAbs are generally safe and can sustain ART-free suppression in selected individuals, particularly when antibodies targeting non-overlapping epitopes are combined to limit resistance escape [74]. Extending viral suppression to most of an unselected population, rather than only the subset with favourable baseline sensitivity, remains the central obstacle to bNAb-based regimens competing with small-molecule long-acting antivirals for routine use.

9. Discussion

The development of long-acting antiretroviral therapies represents a major transformation in HIV medicine, comparable in clinical relevance to the introduction of combination ART in the mid-1990s (originally termed highly active antiretroviral therapy, HAART). For more than three decades, HIV treatment has relied almost exclusively on daily oral medication. Although modern oral regimens are highly effective, lifelong adherence remains a challenge for many individuals. Long-acting approaches offer a new therapeutic paradigm in which sustained antiviral activity is achieved through intermittent administration [75]. The clinical impact of long-acting

therapy extends beyond pharmacological efficacy: these strategies have the potential to address important barriers associated with daily ART, including pill fatigue, stigma, confidentiality concerns and adherence difficulties [76]. However, their implementation requires careful consideration of clinical, pharmacological and health-system challenges.

9.1. Clinical Positioning of Approved Long-Acting Therapies

Long-acting cabotegravir/rilpivirine is currently the most established long-acting maintenance regimen for HIV treatment. Randomized clinical trials have consistently demonstrated that injectable CAB/RPV maintains virological suppression at rates comparable to those of contemporary oral ART in appropriately selected individuals. The optimal candidates for CAB/RPV LA are generally individuals who are virologically suppressed, have no history of resistance to INSTIs or rilpivirine, are reliably engaged in care and prefer injectable therapy to daily oral medication [5]. However, CAB/RPV is not currently suitable for all people living with HIV. Important limitations include the limited evidence supporting its initiation in individuals with uncontrolled viraemia, although some studies have shown efficacy in this population [22,23]; the need for resistance assessment; the risk of virological failure with emergent resistance; and dependence on regular healthcare visits. Future long-acting regimens with higher barriers to resistance may expand access to populations currently excluded from injectable therapy.

9.2. Resistance Considerations in Long-Acting Therapy

Resistance is one of the central challenges in long-acting antiretroviral development. The prolonged pharmacokinetic persistence that provides convenience may also create a period of incomplete antiviral protection after discontinuation. This phenomenon, commonly described as the "pharmacological tail", may allow viral replication under suboptimal drug pressure [77]. Resistance has been reported with cabotegravir, rilpivirine and lenacapavir. Risk factors include delayed HIV diagnosis, missed injections, inadequate companion therapy and pre-existing resistance mutations [33,78]. Long-acting programmes therefore require robust monitoring systems, including HIV RNA testing when clinically indicated, rapid confirmation of suspected infection and resistance testing after virological failure. Resistance management will become increasingly important as long-acting therapies are introduced into larger and more diverse populations.

9.3. Patient-Centred Care and Treatment Preference

One of the major advantages of long-acting therapy is the possibility of individualizing HIV management. Treatment success depends not only on antiviral potency but also on patient acceptability and long-term persistence. Clinical studies evaluating CAB/RPV have consistently reported high patient satisfaction, with many participants preferring injectable therapy to daily oral ART [79]. Similarly, prevention studies with CAB-LA and LEN have shown that many individuals value reduced dosing frequency, improved privacy, decreased stigma and reduced daily treatment burden [80]. Future HIV management should therefore regard long-acting therapy not simply as a replacement for oral ART but as an additional option within a personalized treatment model.

9.4. Implementation Challenges and Global Access

The successful integration of long-acting therapies into clinical practice will depend on healthcare infrastructure. Unlike oral ART, injectable strategies require trained healthcare workers, appointment systems, drug storage and distribution networks, and

mechanisms for follow-up after missed visits. These challenges are particularly relevant in low- and middle-income countries, where the burden of HIV remains highest [81]. Although long-acting prevention strategies have enormous potential, equitable access will require affordable pricing, technology transfer, increased manufacturing capacity and integration into existing HIV programmes. Past experience in HIV medicine shows that scientific innovation must be accompanied by strategies that ensure global accessibility.

9.5. The Future of Long-Acting Hiv Treatment

The current generation of long-acting therapies is likely only the beginning of a broader transformation. Future directions include:

9.5.1. Longer Dosing Intervals

Research is moving towards six-monthly and annual regimens and implant-based drug delivery systems. The phase 2b EXTEND 4M trial is assessing a novel long-acting cabotegravir formulation dosed three times yearly for HIV prevention, building on the six-times-yearly regimen already in use [44].

9.5.2. Multi-Class Long-Acting Combinations

Combining agents with different mechanisms may raise the barrier to resistance, improve antiviral durability and increase suitability for diverse patient populations. Potential combinations include capsid inhibitors plus INSTIs, capsid inhibitors plus reverse transcriptase inhibitors and small molecules plus bNAbs; the latter two are already in phase 3 development (Section 7.3), and the first is in phase 2: GS-3242, a novel investigational INSTI, is being evaluated in combination with lenacapavir as a potential twice-yearly injectable HIV treatment regimen [64,65].

9.5.3. Integration with Hiv Cure Strategies

Long-acting antivirals may also support future cure-directed approaches by maintaining suppression during interventions targeting viral reservoirs. Possible partners include therapeutic vaccines, bNAbs, immune modulators and latency-reversing strategies.

9.5.4. Emerging Biologic and Microbial Delivery Platforms

Beyond injectable formulations and broadly neutralizing antibodies, alternative platforms for the sustained or oral delivery of biologics are under investigation and may complement future long-acting HIV therapeutics. Engineered bacteria are one example. In a preclinical study, an engineered strain of the probiotic *Escherichia coli* Nissle 1917 was used to deliver orally both antigen-bearing outer-membrane vesicles, as a vaccine, and surface-displayed nanobodies, as an antiviral treatment against SARS-CoV-2, inducing systemic and mucosal antibody responses in animals [82]. Although this proof of concept concerns SARS-CoV-2 rather than HIV, it illustrates how microbes could be programmed to deliver antiviral proteins, antibodies or vaccines. More broadly, microbial medicines are emerging as a therapeutic modality, so far mainly in oncology [83]. Advances in bacterial protein expression and secretion systems—for example, engineering of the flagellar type III secretion system of *E. coli*, which increased laboratory-scale secretion of recombinant proteins, including an scFv antibody fragment—may also support more cost-effective manufacture of biologics [84], an important consideration for antibody-based strategies. These approaches are at an early preclinical stage and have not been tested in HIV, and their safety, durability and regulatory pathway remain to be established.

9.6. Positioning Within International Clinical Practice Guidelines

Regulatory and guideline endorsement has expanded considerably since the initial approvals discussed above. Long-acting injectable cabotegravir/rilpivirine is now endorsed by DHHS and IAS-USA guidelines not only as a switch option for virologically suppressed patients but also, more recently, for selected patients with adherence challenges [85,86]. On the prevention side, the WHO issued new guidelines in July 2025 recommending twice-yearly injectable lenacapavir as an additional PrEP option within combination HIV prevention programmes, alongside updated testing strategies to support its roll-out, and CDC guidance issued shortly afterwards strongly recommended lenacapavir PrEP for eligible individuals in the United States [87,88]. The rapid succession of these policy actions illustrates how quickly the long-acting armamentarium is being incorporated into routine practice, even though implementation capacity and funding in many settings lag behind normative guidance.

9.7. Economic Considerations and Equitable Global Access

The clinical promise of long-acting antiretrovirals must be weighed against their cost and the infrastructure required for injectable delivery. A modelled economic evaluation using data from the HPTN 083 and HPTN 084 trials estimated that CAB-LA PrEP could be cost-effective in South Africa relative to generic oral TDF/FTC if priced below approximately $9–14 per injection, with a cost per infection averted comparable to or lower than that of the oral regimen at scale [89]. A similar model-based analysis in adolescent girls and young women emphasized that affordability, rather than efficacy, is the principal barrier to broad uptake in low- and middle-income countries [90].

Economic evaluations of lenacapavir highlight a marked gap between its high clinical efficacy and its financial sustainability, with the size of the gap varying by healthcare system and price. In high-income countries, current commercial pricing yields very high incremental cost-effectiveness ratios, requiring substantial price reductions, whereas in low- and middle-income settings the strategy is cost-effective only if procurement costs remain minimal [91].

UNAIDS has accordingly framed the introduction of long-acting technologies as a potential "prevention revolution" contingent on overcoming production monopolies and driving down prices, particularly following the 2025 disruption to international HIV funding, which threatens to undermine the delivery systems needed to bring these innovations to the populations most in need [2].

9.8. Integrated Overview of Resistance, Safety and Implementation Issues

Resistance, safety and implementation issues are discussed throughout this review in the sections dedicated to each agent. Because they cut across agents and settings, we summarize them here and in Table 3, with cross-references to the relevant sections.

Table 3. Integrated summary of resistance, safety and implementation issues of long-acting strategies.

Issue	Agents Mainly Concerned	Key Evidence in This Review	Implication
INSTI/NNRTI resistance and dual-class resistance	CAB/RPV; CAB-LA PrEP	Dual-class resistance in 33/80 genotyped failures; INSTI/NNRTI cross-resistance after failure; INSTI resistance in HPTN 083 breakthrough infections with delayed diagnosis	Baseline resistance and subtype assessment; resistance testing after failure; sensitive HIV RNA testing on PrEP
Capsid resistance	Lenacapavir	15–265-fold reduced susceptibility in	Active companion agents;

(M66I, Q67H + K70R, K70H)		CAPELLA; Q67H + K70R and Q67H in CALIBRATE with poor adherence to companion drugs; resistance analysis in PURPOSE	avoid functional monotherapy; diagnose HIV before and during PrEP
Pharmacological tail	CAB/RPV; CAB-LA; lenacapavir	Drug concentrations persist for months after discontinuation	Cover the tail with fully suppressive oral ART or PrEP; monitor after discontinuation
Missed or delayed injections	All injectable agents	Short delays without HIV acquisition in OPERA CAB-LA PrEP users; missed injections as a risk factor for resistance	Appointment systems and follow-up of missed visits
Injection-site reactions	All injectable agents	Frequent but mostly mild or moderate with CAB/RPV and CAB-LA; more frequent with lenacapavir, including nodules; 77% in CARES; CLARITY acceptability comparison	Patient counselling; reactions rarely lead to discontinuation
HBV coinfection and reactivation	CAB/RPV	No activity against HBV; reactivation reported after switching	HBV markers before switching; no use in active HBV
Pregnancy	CAB/RPV; CAB-LA	Lower concentrations in pregnancy; outcomes similar to background in the HPTN 084 extension	Individualized decision; evidence evolving
Drug–drug interactions (tuberculosis)	CAB/RPV	Rifampicin reduces exposure; rifabutin not recommended	Avoid strong inducers
Islatravir lymphocyte toxicity	Islatravir-based regimens	Dose-dependent lymphocyte and CD4+ decreases; no relevant decline at 2 mg weekly with lenacapavir	Lymphocyte monitoring in development programmes
Long-term metabolic, renal and bone safety	CAB/RPV (data); other agents (limited data)	Greater weight gain in women, mainly lean mass; higher eGFR with long-acting therapy; tenofovir-related withdrawals only in the oral arm; no clinically relevant weight or metabolic changes vs. BIC/FTC/TAF in SOLAR; small real-world cohort with less weight gain and no eGFR difference	Long-term pharmacovigilance and monitoring

Abbreviations: CAB: cabotegravir; CAB-LA: long-acting cabotegravir; DEXA: dual-energy X-ray absorptiometry; eGFR: estimated glomerular filtration rate; INSTI: integrase strand transfer inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PrEP: pre-exposure prophylaxis; RPV: rilpivirine.

Resistance. Virological failure on CAB/RPV is uncommon but, when it occurs, is frequently accompanied by resistance: in a systematic review of observational cohorts, among 80 failures with genotypic data, NNRTI mutations were found in 45, INSTI mutations in 40 and dual-class resistance in 33 [37] (Section 3.4), and larger case series describe predicted reduced susceptibility to cabotegravir, rilpivirine or both in the large majority of failures [35,36]. More recently, the French Dat'AIDS cohort (2196 virologically suppressed adults) confirmed that virological failure with CAB/RPV LA was uncommon (1.9%) and that resistance emerged in 0.6% of participants, mainly as INSTI mutations that compromised once-daily dolutegravir or bictegravir in 35–42% of genotyped failures, whereas doravirine remained active in 92–96%. Resistance also emerged during low-level viraemia, and failure was associated with higher BMI, nadir CD4 count < 200 cells/mm^3 and prior suppression < 12 months [39]. For lenacapavir, capsid substitutions (M66I, Q67H + K70R, K70H) emerged in CAPELLA with 15- to 265-fold reductions in susceptibility, mainly when the drug was effectively used as

functional monotherapy [10] (Section 5.2). The same mechanism (low adherence to the oral companion drugs) explained the two resistance cases in CALIBRATE [11] (Section 5.3). Resistance is also a concern in prevention: infections acquired during CAB-LA or lenacapavir PrEP may carry INSTI or capsid mutations [8,9,78]. In HPTN 083, delayed diagnosis, linked to cabotegravir-induced viral suppression and delayed antibody expression, sometimes resulted in continued cabotegravir exposure in participants with undetected infection, delayed ART initiation and drug resistance [92] (Sections 4.3 and 6.5). The pharmacological tail after discontinuation, which can last many months, creates a period of subtherapeutic drug exposure that may select for resistance [77] (Sections 4.3 and 9.2). These risks make baseline and post-failure resistance testing, sensitive HIV RNA-based diagnosis in people receiving long-acting PrEP and a plan for covering the tail essential components of long-acting programmes.

Tolerability and implementation. Injection-site reactions are the most frequent adverse events with injectable regimens. They were common but generally mild to moderate with CAB/RPV [4–6], more frequent with CAB-LA than with oral PrEP [8], and more frequent with lenacapavir than with comparators, including subcutaneous nodules [47,48]; in the CLARITY crossover study, a single dose of CAB-LA was more acceptable than a single dose of lenacapavir because of fewer and less bothersome reactions [51]. In the 96-week CARES trial in Africa, 77% of participants on CAB/RPV LA reported injection-site reactions, mostly mild pain, and one sterile abscess led to discontinuation [93]. Missed or delayed injections prolong the period of subtherapeutic exposure and are a recognized risk factor for failure and resistance [35,78], although short delays were not associated with HIV acquisition among women on CAB-LA PrEP in the OPERA cohort [41] (Sections 4.2 and 9.2). Among clinical situations requiring special attention, CAB/RPV is not active against HBV, and cases of HBV reactivation after switching have been reported [29]; guidance does not endorse CAB/RPV in pregnancy because of lower drug concentrations, although data on CAB-LA in pregnancy are accumulating [27,28]; and strong enzyme inducers, notably rifampicin and rifabutin used for tuberculosis, are not recommended because they reduce cabotegravir and rilpivirine exposure [25,26] (Section 3.2). For islatravir, dose-dependent reductions in total lymphocyte and CD4+ T-cell counts led to temporary interruption of the development programmes [54–56]; at the lower weekly dose used in combination with lenacapavir, no clinically relevant decline was observed [57–59] (Sections 7.2 and 7.3).

Long-term metabolic, renal and bone safety. Data on the long-term metabolic, renal and bone safety of long-acting regimens remain limited and come mainly from trials with two to three years of follow-up. In the 96-week CARES trial, which randomized 512 adults in Africa, women receiving CAB/RPV LA gained more weight, had a greater increase in body mass index and a higher incidence of new obesity than women on oral therapy, whereas no differences were seen in men; in a dual-energy X-ray absorptiometry (DEXA) substudy, the weight gain in women was mainly lean tissue [93]. Estimated glomerular filtration rate (eGFR) increased in the long-acting group relative to the oral group, and two participants in the oral group, which included tenofovir-based regimens, discontinued because of osteoporosis [93], consistent with the notion that tenofovir-free long-acting regimens may avoid some tenofovir-related renal and bone effects. Other data are reassuring but come from limited sources. In the randomized phase 3b SOLAR trial, presented as a conference abstract, the median change in weight at month 12 was −0.40 kg with CAB/RPV LA every 2 months and +0.05 kg with continued B/F/TAF, and changes in BMI, waist and hip circumference and the proportion of participants with metabolic syndrome or insulin resistance were not clinically relevant in either arm [94]. In a small retrospective single-centre cohort (22

people switching to CAB/RPV LA and 44 remaining on oral INSTI-based regimens), mean weight change over 12 months was +1.5 kg with oral therapy and −0.6 kg after the switch ($p = 0.05$), and eGFR did not differ significantly between groups at 12 months [95]; this study was limited by its size, retrospective design and imbalances in age and race between groups. Overall, the available findings derive from an open-label trial, a conference presentation and a small observational cohort, involving small populations with short follow-up, and equivalent data for lenacapavir-based and islatravir-based regimens are not yet available. Long-term pharmacovigilance and cohort data, including routine monitoring of weight, renal function and bone health in people on long-acting therapy, will be needed to define the long-term safety profile of these agents.

In summary, the available data show that resistance to long-acting agents is uncommon but, when it occurs, is often linked to periods of subtherapeutic drug exposure, such as missed or delayed injections, the pharmacological tail after discontinuation, low adherence to oral companion drugs, or undetected infection during long-acting PrEP. Injection-site reactions are the most frequent adverse events but are mostly mild to moderate, whereas evidence on long-term metabolic, renal and bone safety remains limited, deriving from trials and cohorts with short follow-up and restricted populations. Further long-term pharmacovigilance and real-world cohort data will be needed to better define the safety profile of these agents and the implementation requirements for their wider use.

9.9. Limitations of This Review

This review has several limitations inherent to its narrative design. First, although the literature search was structured and is fully reported, it was not conducted according to a pre-registered systematic-review protocol: study selection was based on clinical relevance and discussed among the authors, but was not performed independently in duplicate, and no formal risk-of-bias assessment or evidence grading was applied. The use of language and publication-type filters, and the inclusion of studies identified through supplementary sources, including the authors' knowledge of the field, may have introduced selection bias, and some relevant studies may not have been captured.

Second, the heterogeneity of study designs, populations and outcome definitions precluded any quantitative synthesis; the conclusions drawn are therefore qualitative and should not be interpreted as effect estimates.

Third, because the field of long-acting antiretroviral therapy is evolving rapidly, with several agents (e.g., islatravir/lenacapavir, next-generation cabotegravir formulations and antibody-based strategies) still in clinical development, some of the data discussed derive from interim analyses or conference presentations that may change following full peer-reviewed publication.

Finally, most of the pivotal efficacy and implementation data summarized here originate from well-resourced trial settings or high-income countries; their generalizability to resource-limited settings, where the global burden of HIV is greatest, remains to be fully established.

10. Conclusions

Long-acting antiretroviral therapies have ushered in a new era in HIV treatment and prevention. Cabotegravir/rilpivirine has demonstrated that durable viral suppression can be achieved without daily oral therapy, providing a valuable alternative for selected individuals living with HIV. Long-acting cabotegravir has expanded prevention options by providing highly effective HIV prophylaxis independent of daily

adherence, while lenacapavir has introduced a novel capsid-targeting mechanism with promising applications in both treatment and prevention.

Investigational strategies, including islatravir/lenacapavir combinations and broadly neutralizing antibodies, may further extend dosing intervals and broaden the therapeutic possibilities of long-acting approaches. Nevertheless, several challenges remain, including resistance management, healthcare delivery requirements and equitable global access.

The future of HIV therapy will likely involve a diversified landscape in which oral and long-acting therapies coexist, allowing treatment and prevention strategies to be tailored to individual needs. By reducing treatment burden and addressing adherence barriers, long-acting antiretroviral therapies have the potential to improve quality of life for people living with HIV and contribute substantially to global efforts towards HIV prevention and control.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines14112530/s1, Table S1: Full search strategies. Date of last search: 21 October 2026. Publication window: 1 January 2005–1 October 2026.

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