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# Lenacapavir: A capsid inhibitor for HIV-1 treatment and prevention

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ABSTRACT

Lenacapavir (GS-6207) is a capsid inhibitor approved for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced people with multidrug-resistant HIV-1. Here, this study provides a comprehensive overview of lenacapavir, with a particular focus on its long-acting properties, pharmacodynamics, pharmacokinetics, clinical efficacy and safety, and resistance profile. Clinical trials have demonstrated that long-acting lenacapavir is highly effective not only for treating HIV-1 infection but also as a pre-exposure prophylactic agent. The future development of fixed-dose, long-acting combination regimens incorporating lenacapavir and other long-acting antiretroviral agents offers significant potential for durable and effective HIV-1 management in clinical settings.

## 1. Introduction

Many antiretroviral therapies have been approved over the past decades [1–6]. More recently, the development of HIV-1 capsid inhibitors has been actively pursued in both preclinical and clinical studies. Of note, HIV-1 capsid plays a pivotal role in the viral life cycle [7–9]. Each HIV-1 virion contains approximately 1000 to 1500 capsid proteins, along with various other viral components [10]. As illustrated in Fig. 1**a**, upon viral entry, capsids are released into the cytoplasm in host cells, facilitating the transport of the HIV-1 genome to the nucleus for integration into the host genome [11]. Due to its highly conserved nature [9], the capsid demonstrates minimal drug resistance, making it an attractive and promising target for antiviral drug development [12].

Lenacapavir (GS-6207), the first-in-class HIV-1 capsid inhibitor [13], binds at the interface between subunits of capsid hexamers (Fig. 1**b**) — a site critical for both the orderly assembly of new virions and the interaction with host cell factors that mediate nuclear import of the viral genome [11]. Notably, intact capsids can traverse the nuclear pore complex to enter the nucleoplasm [14]. Lenacapavir is a long-acting capsid inhibitor that enables biannual subcutaneous administration

*Abbreviations:* ART, antiretroviral therapy; BCRP, breast cancer resistance protein; BIC, bictegravir; $CC_{50}$, half maximal cytotoxic concentration; CCR5, C-C chemokine receptor 5; CD4, cluster of differentiation 4; CPSF6, cleavage/polyadenylation specificity factor 6; CYP3A, cytochrome P450 3A; $EC_{50}$, half maximum effective concentrations; FDA, Food and Drug Administration; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; IAS–USA, International Antiviral Society–USA; $IC_{50}$, half inhibitory concentration; INSTI, integrase strand transfer inhibitor; ISL, islatravir; LEN, lenacapavir; NUP153, nucleoporin 153; OBT, optimized background therapy; PBMC, peripheral blood mononuclear cell; P-gp, P-glycoprotein; PrEP, pre-exposure prophylaxis; SHIV, simian-human immunodeficiency virus; $T_{1/2}$, elimination half-life; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; $T_{max}$, time to maximum concentration.

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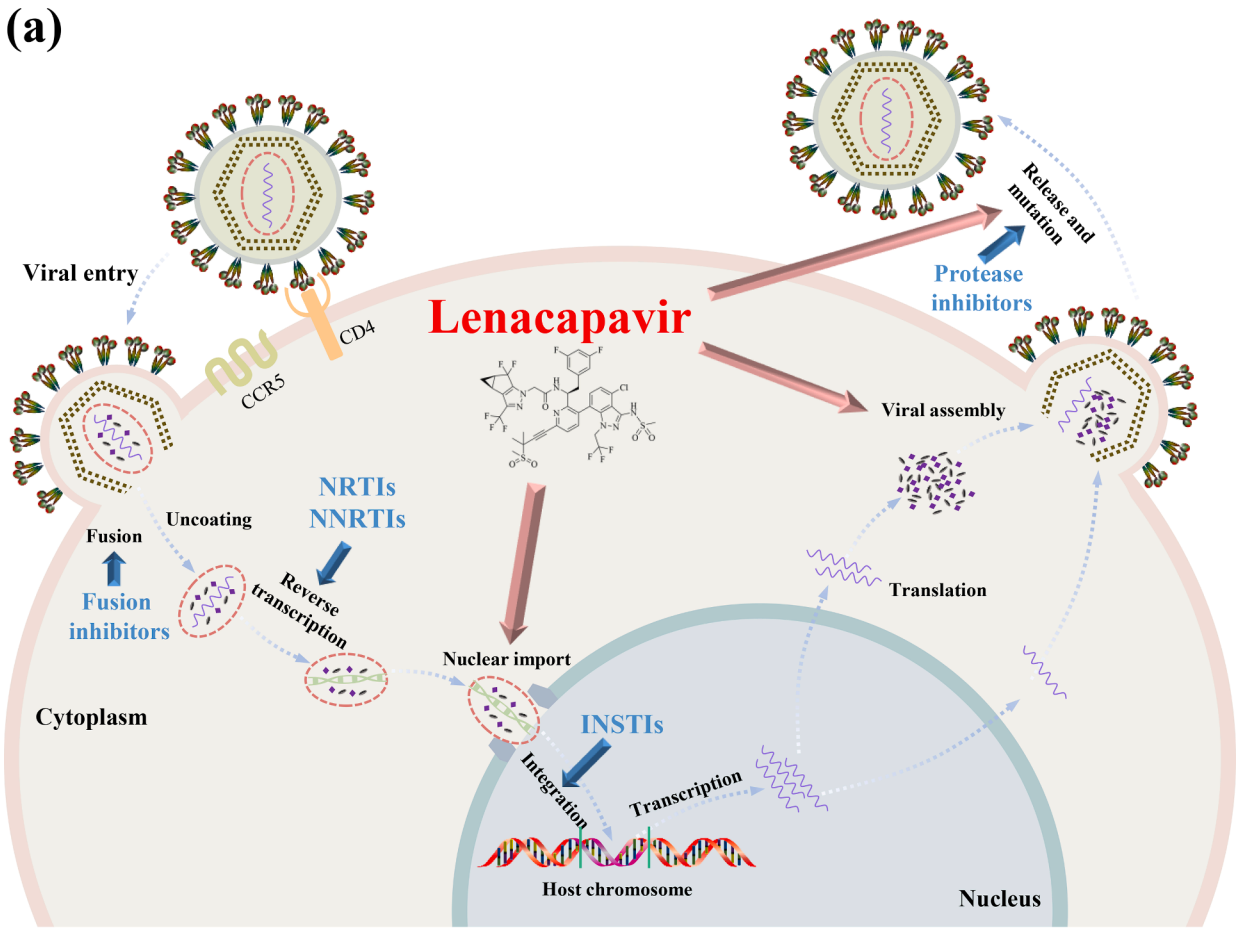



HIV-1 life cycle and drug targets

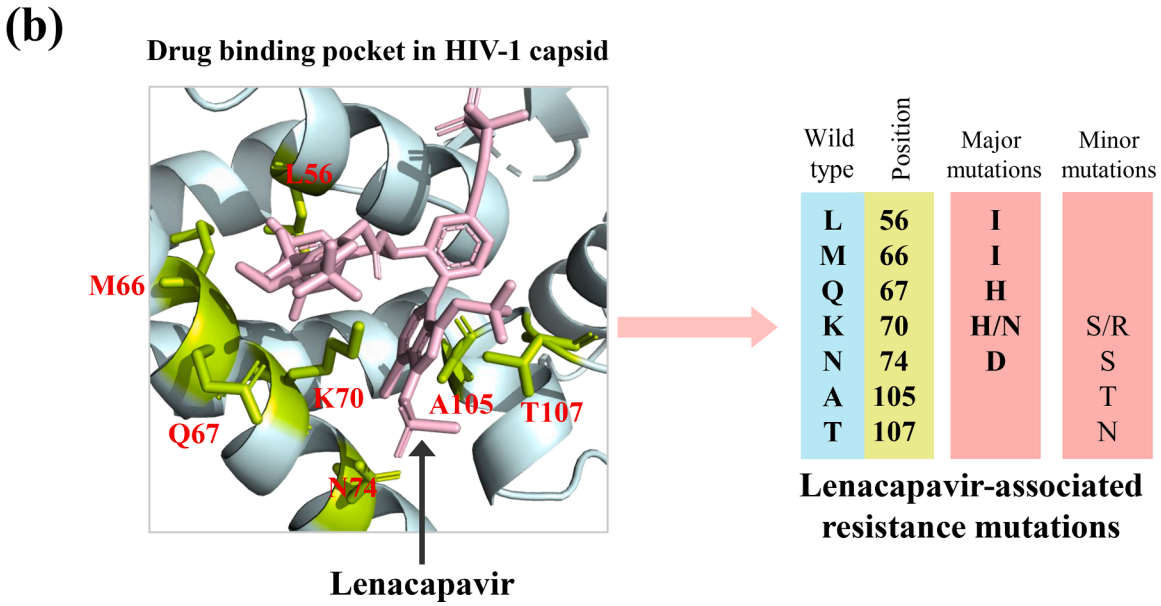



**Fig. 1.** HIV-1 life cycle and the drug targets of lenacapavir. (a) The HIV-1 life cycle. This figure was adapted from reference [33]. CCR5, C-C chemokine receptor 5; CD4, cluster of differentiation 4; INSTIs, integrase strand transfer inhibitors. (b) The structure of lenacapavir bound to the HIV-1 capsid hexamer, along with associated drug resistance mutations. The capsid structure was visualized using PyMOL V2.5 (https://www.pymol.org/) based on the PDB entry 6V2F. Key amino acid residues associated with lenacapavir resistance are highlighted. Resistance-associated substitutions were retrieved from the 2025 edition of the International

Antiviral Society–USA (IAS–USA) drug resistance mutations ( https://www.iasusa.org/).

and has shown effectiveness in managing treatment-experienced individuals with multidrug-resistant HIV-1 infection [15,16]. Its high potency, slow release kinetics, and low systemic clearance support its potential as a long-acting therapeutic option [17,18]. Lenacapavir received its first regulatory approval in the European Union on August 22, 2022, followed by approval from the U.S. Food and Drug Administration (FDA) on December 22, 2022 [19]. According to the drug label, two initiation regimens at the oral lead-in phase are available before transitioning to the maintenance phase: (i) a subcutaneous injection of lenacapavir 927 mg (2 × 1.5 mL) on Day 1, along with oral dosing of lenacapavir 600 mg (2 × 300 mg) on both Day 1 and Day 2; (ii) initiation option 2: oral dosing of lenacapavir 600 mg (2 × 300 mg) on Days 1 and 2, followed by 300 mg on Day 8, and a subcutaneous injection of 927 mg on Day 15. Both regimens are followed by a maintenance phase, consisting of a subcutaneous injection of lenacapavir 927 mg every 26 weeks, with a window of ± 2 weeks from the date of the last injection. The clinical use of lenacapavir as pre-exposure prophylaxis (PrEP) for HIV-1 was approved by the U.S. FDA on June 18, 2025.

Based on accumulated evidence over the past five years, this study provides a comprehensive overview of lenacapavir, focusing on its long-acting properties, mechanisms of action, pharmacodynamics, pharmacokinetics, clinical efficacy, safety, and drug resistance. Other potent capsid inhibitors are also summarized.

## 2. Development of lenacapavir and capsid inhibitors

The development of lenacapavir originated from a high-throughput screening campaign identifying the lead capsid inhibitor PF-3450074 (Fig. 2**a**), which exhibited half-maximal effective concentration ($EC_{50}$) values ranging from 0.113 to 0.362 μM in HIV-1-infected peripheral blood mononuclear cells (PBMCs) [20]. A subsequent optimization effort led to the identification of GS-CA1 (Fig. 2**b**), a prototype compound with the enhanced antiviral activity ($EC_{50}$: 240 ± 40 pM), reduced cytotoxicity (half-maximal cytotoxic concentration [$CC_{50}$] > 50 μM), and a high selectivity index ($CC_{50}/EC_{50}$ > 208300) across various HIV-1 strains [21]. Through further structural refinement aimed at improving both potency and pharmacokinetic properties, lenacapavir was ultimately synthesized (Fig. 2**c**). It exhibits superior antiviral potency ($EC_{50}$: 20 to 160 pM) and favorable metabolic stability, with a median apparent terminal half-life of approximately 38 days [17]. Lenacapavir is a highly potent inhibitor capable of overcoming mass action and the high abundance of capsid subunits [22]. Structurally, it exists as a mixture of two interconvertible atropisomers, arising from restricted rotation around a biaryl carbon–carbon bond [23]. Lenacapavir provides robust protection in a rectal simian-human immunodeficiency virus (SHIV) challenge macaque model [24] and has also been shown to protect pigtail macaques against intravenous challenge with a simian-tropic HIV-1 clone (stHIV-A19) [25]. Although several analogues of lenacapavir were subsequently developed, they did not demonstrate significant improvements in antiviral activity [26].

Other capsid-targeting compounds have also been explored. For instance, GSK878 (Fig. 2**d**), which contains a quinazoline-4(3H)-one ring [27], has demonstrated potent antiviral activity against a panel of 48 chimeric viruses with diverse capsid sequences [28]. GSK878 alters the stability of the HIV-1 capsid and inhibits both nuclear import and proviral integration of HIV-1 [28]. A phenotypic cell-based viral replication assay identified BI-1 (Fig. 2**e**) and BI-2 (Fig. 2**f**) as capsid inhibitors featuring a 4,5-dihydro-1H-pyrrolo[3,4-c]pyrazol-6-one (pyrrolopyrazolone) scaffold [29]. Both compounds bind to and stabilize the HIV-1 capsid, exhibiting potent anti-HIV activities ($EC_{50}$: 1.4 to 8.2 μM in 23 clinical isolates) [29]. Another compound, H27 (Fig. 2**g**), selectively targets the HIV-1 capsid to block nuclear import, showing low micromolar potency (50 % inhibitory concentration [$IC_{50}$]: 1.6 to 10.2 μM) [30]. Other capsid inhibitors, such as the MKN-1 (Fig. 2**h**) derivatives, have also demonstrated anti-HIV activity [31].

## 3. Mechanisms of action

As illustrated in Fig. 1, lenacapavir targets the HIV-1 capsid core and interferes with several critical stages of the viral life cycle, including capsid trafficking, viral assembly, and virion release [32]. Its antiviral activity is primarily mediated through three distinct mechanisms [33]. **(i)** Disruption of capsid assembly: lenacapavir binds at the interface between adjacent capsid protein subunits, engaging in coordinated hydrophobic and electrostatic interactions. This binding stabilizes non-native hexameric interfaces and promotes premature capsid oligomerization [34], resulting in malformed capsid structures and the production of defective, non-infectious virions [33]. During normal viral assembly, approximately 200–250 capsid hexamers and 12 pentamers organize into a fullerene cone-shaped core [35]. Both lenacapavir and its predecessor GS-CA2 disrupt this process to suppress viral replication [34,36]. **(ii)** Inhibition of nuclear translocation: lenacapavir exerts competitive antagonism against the nuclear transport mediators such as nucleoporin 153 (NUP153) and cleavage/polyadenylation specificity factor 6 (CPSF6), effectively impeding HIV-1 DNA nuclear import and subsequent genomic integration [33]. Cellular HIV-1 cofactors such as NUP153 and CPSF6 are essential for viral nuclear import and viral integration [34]. **(iii)** Interference with viral maturation: lenacapavir disrupts the conformational dynamics of the Gag and Gag-Pol polyproteins, destabilizing the HIV-1 maturation process [33]. This results in the defective assembly of virion components and the release of immature, non-infectious viral particles [33].

## 4. Pharmacodynamics and pharmacokinetics

Following oral administration, lenacapavir reaches the maximum plasma concentration ($T_{max}$) in approximately 4 h, whereas subcutaneous injection results in a delayed $T_{max}$ of approximately 77 to 84 h. The estimated elimination half-life ($T_{1/2}$) ranges from 10 to 12 days after oral dosing, and extends significantly to 8 to 12 weeks following subcutaneous administration, supporting the long-acting profile of lenacapavir. Lenacapavir demonstrates potent antiviral activity against HIV-1 strains, with a mean $IC_{50}$ of 200 pM (range: 140 to 310 pM) in single-cycle assays and 170 pM (range: 70 to 340 pM) in multicycle assays [37]. Moreover, *in vitro* experiments demonstrated that lenacapavir inhibited HIV-1 in MT-4 cells with a mean $EC_{50}$ of 105 pM [17]. It also maintained picomolar potency in primary human cells with mean $EC_{50}$ values of 32 pM in CD4 + T cells and 56 pM in macrophages [17]. Lenacapavir also demonstrated a high potency against 23 HIV-1 isolates (mean $EC_{50}$: 50 pM; range: 20 to 160 pM) in PBMCs [17]. Yet, compared with results in HIV-1, human immunodeficiency virus type 2 (HIV-2) exhibited more than 10-fold reduction in lenacapavir susceptibility with a mean $IC_{50}$ of 2.2 nM (range: 1.1 to 3.2 nM) in single-cycle HIV-2 assays and a mean $IC_{50}$ value of 2.4 nM (range: 0.94 to 5.4 nM) in multicycle HIV-2 assays [37]. Moreover, the French ANRS-MIE CO5 HIV-2 study reported the virological suppression (HIV-2 RNA < 50 copies/mL) in only one of eight participants with multidrug-resistant HIV-2 after 6 months of treatment with lenacapavir-containing regimens [38].

Following the subcutaneous injection in both animal models and humans, lenacapavir exhibits biphasic absorption kinetics—characterized by an initial rapid absorption phase followed by a prolonged, slow-release phase [18]. After a single 10 mg intravenous dose, the median $T_{max}$ was approximately 1 h [39]. Lenacapavir demonstrates high plasma protein binding, with a free fraction of 1.46 % in human

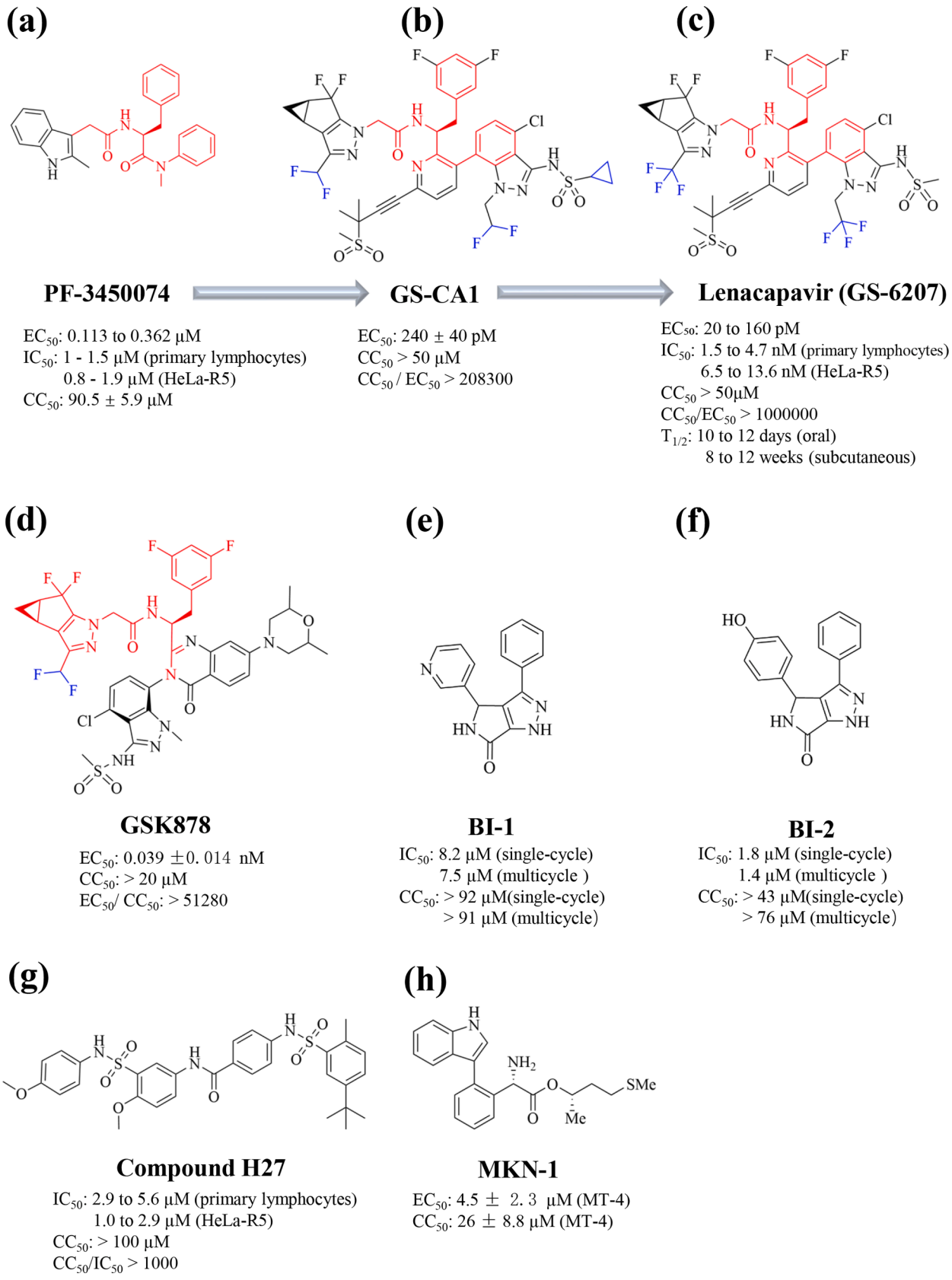
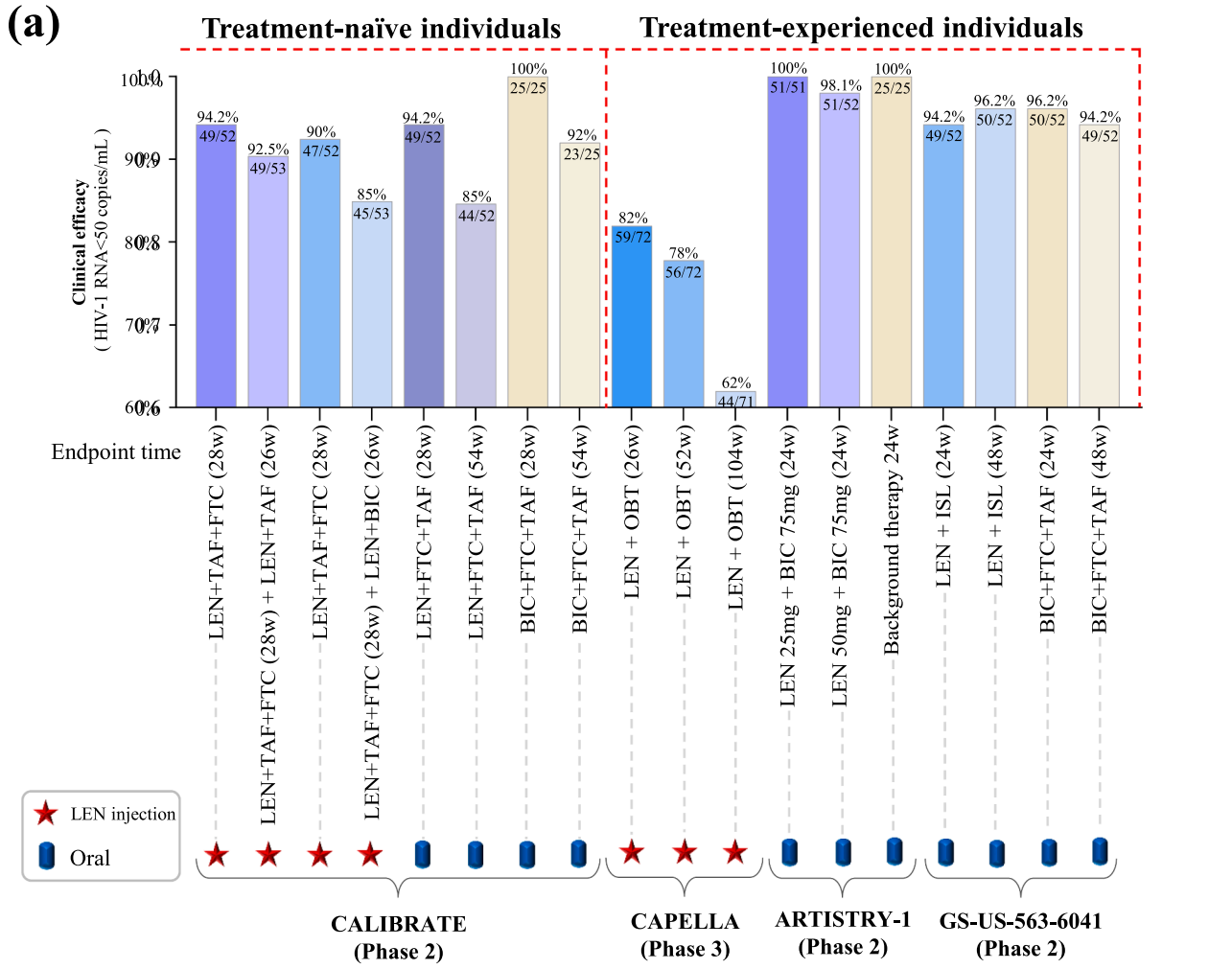



**Fig. 2.** Structural formulas of HIV-1 capsid inhibitors. Chemical structures of PF-3450074 (a), GS-CA1 (b), lenacapavir (c), GSK878 (d), BI-1 (e), BI-2 (f), compound H27 (g), and MKN-1 (h). Antiviral parameters of these inhibitors were collected from the literature: PF-3450074 [20], GS-CA1 [21], lenacapavir[17], GSK878 [27,28], BI-1 and BI-2[29], H27 [30], and MKN-1[31].

plasma, 1.45 % in rhesus monkeys, and 0.83 % in beagle dogs [23]. No major circulating metabolites in plasma or feces were found, indicating a minimal metabolism of lenacapavir [39]. Lenacapavir is primarily eliminated by intestinal excretion [23], and is eliminated mainly via the feces, while the renal pathway plays a minor role in lenacapavir elimination [39].




## (b) Adverse events in clinical studies

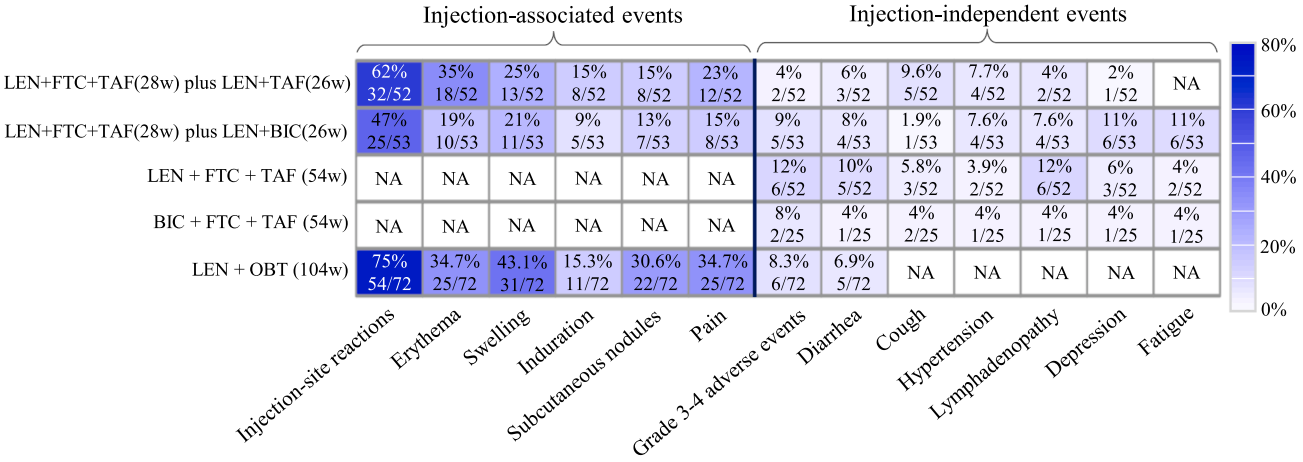



**Fig. 3.** Clinical efficacy and safety of lenacapavir in HIV-1 treatment. **(a)** Clinical efficacy (defined as HIV-1 RNA < 50 copies/ml) of lenacapavir in treatment-naïve and treatment-experienced individuals living with HIV-1 infection. **(b)** Incidence of adverse events reported in clinical trials of lenacapavir-treated participants. OBT: optimized background therapy. NA: not available.

## 5. Clinical efficacy of lenacapavir for the treatment of HIV-1 infection

Randomized clinical trials have evaluated the clinical efficacy and safety of lenacapavir among treatment-naïve and virologically-suppressed individuals with HIV-1 infection (Fig. 3**a**). The virological suppression was defined by HIV-1 RNA < 50 copies/mL. Below, we summarize the efficacy results of lenacapavir in four phase 2 or 3 clinical trials. Other lenacapavir trials are still ongoing, including CALENDULA (NCT06657885), ARTISTRY-2 (NCT06333808), ISLEND-1 (NCT06630286), LENAddON (NCT06799338), and HOME-1 (NCT04979728). Their results have not been released at the time of manuscript preparation.

The ARTISTRY-1 trial was a randomized, open-label, multicenter phase 2 study that evaluated bictegravir (BIC) plus lenacapavir in virologically suppressed adults [40]. Patients were randomized at the ratio of 2:2:1 to receive oral lenacapavir 25 mg plus bictegravir 75 mg once-daily (n = 51), oral lenacapavir 50 mg plus bictegravir 75 mg once-daily (n = 52), or baseline antiretroviral therapy (n = 25). At week 24, the virological suppression of HIV-1 RNA < 50 copies/mL was maintained in participants who received lenacapavir 25 mg plus bictegravir 75 mg (96.1 %, 49/51), lenacapavir 50 mg plus bictegravir 75 mg (96.2 %, 50/52), and the baseline antiretroviral therapy (25/25, 100 %). The ARTISTRY-2 trial continues to evaluate the clinical efficacy and safety of lenacapavir 50 mg plus bictegravir 75 mg at week 48 (NCT06333808).

The CALIBRATE trial was a phase 2, randomized, open-label study that evaluated lenacapavir-based regimens in treatment-naïve adults with HIV-1 RNA ≥ 200 copies/mL and CD4 + counts ≥ 200 cells/μL, and without HBV/HCV coinfection [41]. Participants (N = 182) were randomized to four arms: (i) Group 1: subcutaneous lenacapavir + (FTC + TAF → TAF), (ii) Group 2: subcutaneous lenacapavir + (FTC/TAF → BIC), (iii) Group 3: oral lenacapavir + FTC + TAF, and (iv) Group 4: oral bictegravir + emtricitabine (FTC) + tenofovir alafenamide (TAF) [41]. At week 28, the virological suppression of HIV-1 RNA < 50 copies/mL was observed among 94 % (49/52) participants for Group 1, 93 % (49/53) in Group 2, 94 % (49/52) for Group 3, and 100 % (25/25) for Group 4 [41]. At week 54, the virological suppression was found in 90 % (47/52) for Group 1, 85 % (45/53) for Group 2, 85 % (44/52) for Group 3, and 92 % (23/25) for Group 4 [41].

A phase 2, randomized, open-label, active-controlled study evaluated the oral regimen of lenacapavir + islatravir (ISL) versus BIC + FTC + TAF as the maintenance therapy for virologically-suppressed adults (NCT05052996). Participants were randomized to receive either once-daily BIC + FTC + TAF for ≥ 48 weeks or oral lenacapavir 600 mg + islatravir 40 mg on Day 1 and 2 followed by Day 8 and weekly use of lenacapavir 300 mg + islatravir 20 mg thereafter. Virological suppression in the lenacapavir + islatravir group was 98.1 % (51/52) at week 12, 94.2 % (49/52) at week 24, and 96.2 % (50/52) at week 48. Comparable efficacy was observed in the BIC + FTC + TAF group with the virological suppression of 96.2 % (50/52) at week 12, 96.2 % (50/52) at week 24, and 94.2 % (49/52) at week 48.

The phase 3 CAPELLA trial evaluated the efficacy and safety of lenacapavir in participants (≥12 years old) with multidrug-resistant HIV-1 infection [42]. In cohort 1, 36 participants randomly received either oral lenacapavir or placebo plus their failing therapy for 14 days and subsequently subcutaneous or oral lenacapavir [42]. By day 15, the virological suppression rate was higher in the lenacapavir-treated participants (88 %, 21/24) than in the placebo (17 %, 2/12) [42]. In cohort 2, 36 participants with HIV-1 RNA < 400 copies/mL at baseline or after the completion of cohort 1, all participants received oral lenacapavir plus optimized background therapy for 14 days, followed by subcutaneous lenacapavir every 6 months plus optimized background therapy. At week 26, virological suppression was found in 81 % (29/36) of cohort 1 and 83 % (30/36) of cohort 2 [42]. At week 52, virological suppression was reported in 83 % (30/36) of cohort 1 versus 72 % (26/36) of cohort 2 [43]. At week 104, virological suppression was found in 69 % (24/35) of participants in cohort 1 and 56 % (20/36) of participants in cohort 2 [44]. Except for injection site reactions, no Grade 4 or serious adverse events were observed over 104 weeks of lenacapavir treatment.

## 6. Clinical efficacy of lenacapavir for HIV-1 pre-exposure prophylaxis (PrEP)

Application of lenacapavir for HIV-1 PrEP has been evaluated in different populations: **(i)** adolescent girls and young women in the PURPOSE 1 study (NCT04994509), **(ii)** cisgender men, transgender women/men, and gender non-binary individuals who have sex with partners assigned male at birth in the PURPOSE 2 study (NCT04925752), **(iii)** cisgender adult women in the PURPOSE 3 study (NCT06101329), **(iv)** participants who inject drugs in the PURPOSE 4 study (NCT06101342), and **(v)** participants who would benefit from PrEP in the PURPOSE 5 study (NCT06513312). Lenacapavir was administered as a twice-yearly subcutaneous injection in the five studies above. To date, results have been reported from the PURPOSE 1 and PURPOSE 2 studies (Fig. 4), while the remaining three trials are ongoing. Recently, a phase 1 open-label study demonstrated favorable pharmacokinetics and tolerability of once-yearly intramuscular lenacapavir in 20 healthy participants [45]. Median lenacapavir concentrations remained higher with the once-yearly intramuscular lenacapavir compared to the twice-yearly subcutaneous lenacapvir for at least 56 weeks [45]. Beyond pre-exposure prophylaxis, lenacapavir has also been explored in a case report for prevention of mother-to-child HIV transmission, highlighting its potential in broader preventive applications [46]. Below, we summarize the key findings from the PURPOSE 1 and 2 trials.

The PURPOSE 1 trial was a phase 3, multicenter, double-blind, randomized controlled study that evaluated the PrEP use of lenacapavir among sexually-active HIV-negative adolescent girls and young women (aged 16–25 years) who were not currently using any PrEP [47]. A total of 5,338 eligible participants were randomized to receive one of the following regimens: **(i)** subcutaneous lenacapavir every 26 weeks, **(ii)** oral TAF 25 mg plus FTC 200 mg, or **(iii)** oral TDF 300 mg plus FTC 200 mg. During the 52-week follow-up, 55 cases were identified as positive HIV in three arms: (i) the lenacapavir arm: 0 HIV-1 case among 2134 participants (0.0 per 100 person-years), (ii) the TAF + FTC arm: 39 HIV-1 cases among 2136 participants (2.02 per 100 person-years); and (iii) the TDF + FTC arm: 16 HIV-1 cases among 1068 participants (1.69 per 100 person-years) [47]. Comparative analyses revealed lower HIV-1 incidences in the lenacapavir arm than in the TAF + FTC arm and the TDF + FTC arm (p-value < 0.001). However, the injection-site reactions were frequently observed in the lenacapavir arm (68.8 %) and 4 (0.2 %) participants discontinued lenacapavir owning to injection-site reactions [47].

The PURPOSE 2 trial was a phase 3, double-blind, randomized controlled study that evaluated the PrEP use of lenacapavir in cisgender men and gender-diverse individuals (aged ≥ 16 years) recruited from seven countries: United States, Brazil, Thailand, South Africa, Peru, Argentina, and Mexico [48]. A total of 3265 HIV-negative participants with the history of condomless receptive anal intercourse with male or transgender partners were randomized to receive either subcutaneous lenacapavir every 26 weeks or once-daily oral TDF + FTC [48]. After the 52-week follow-up, 11 HIV-1 cases were found among 3265 participants in the modified intention-to-treat analysis, including 2 in the lenacapavir arm (0.1 per 100 person-years, 95 %CI: 0.01 to 0.37) and 9 in the TDF + FTC arm (0.93 per 100 person-years, 95 %CI: 0.43 to 1.77) [48]. The incidence rate ratio of HIV-1 infection was significantly lower in the lenacapavir arm compared with the TDF + FTC arm (rate ratio: 0.11, P = 0.002) and the background (rate ratio: 0.04, p-value < 0.001) [48].

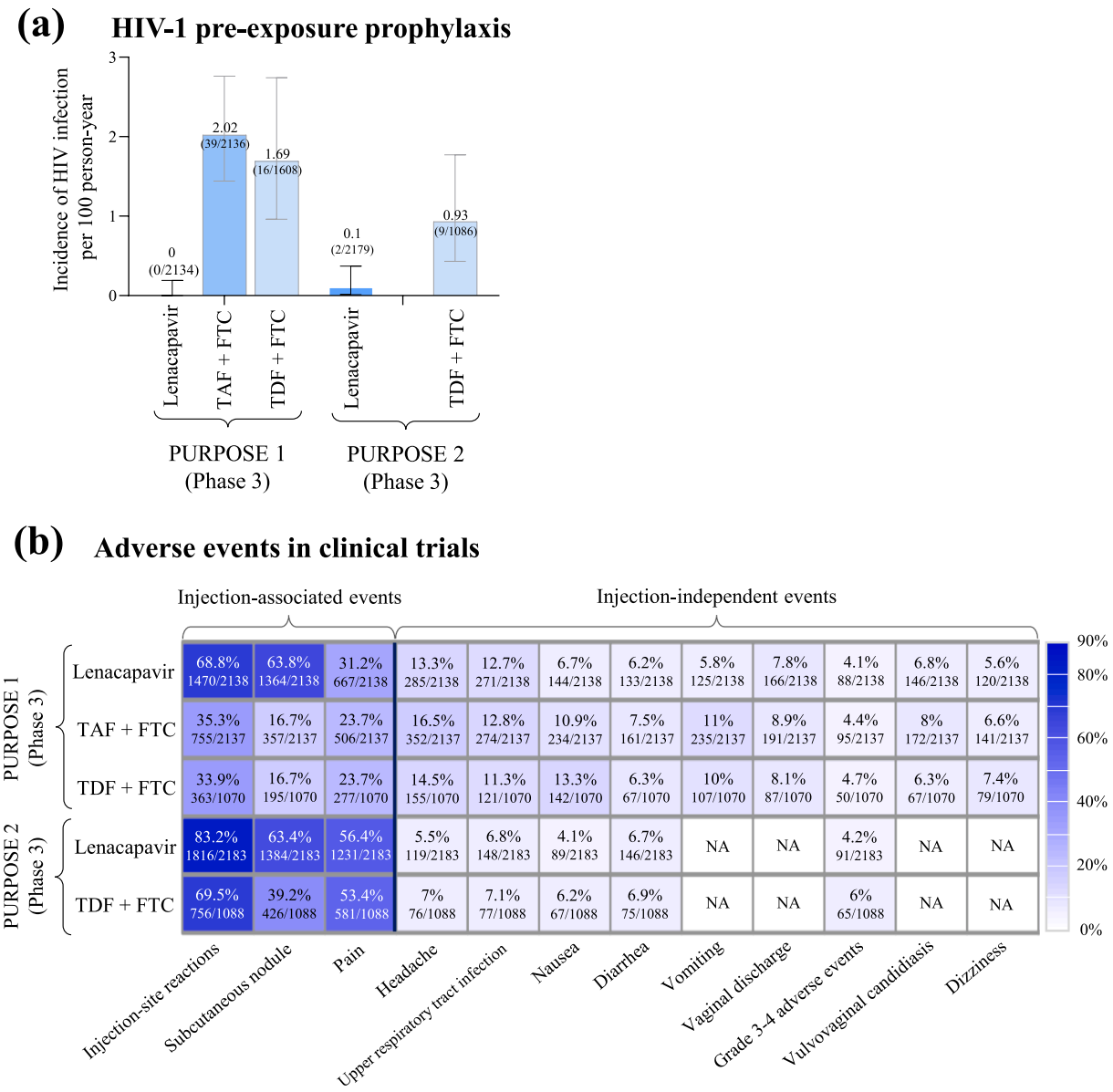



**Fig. 4.** Clinical efficacy and safety of lenacapavir for HIV-1 pre-exposure prophylaxis. (a) Clinical efficacy of lenacapavir for pre-exposure prophylaxis, measured as the incidence of HIV-1 infection per 100 person-year in clinical trials. (b) Incidence of adverse events reported in the studies of PURPOSE 1 [47] and PURPOSE 2 [48]. NA: not available.

## 7. Clinical safety of lenacapavir

We pooled the data of clinical symptoms in lenacapavir-treated participants from randomized clinical trials such as ARTISTRY-1 [40], CALIBRATE [41] and GS-US-563–6041 (NCT05052996). As shown in Fig. 3**b**, the most frequent side effects include injection site reactions, nausea, diarrhea, and others. Injection-related adverse events were predominantly localized reactions, including subcutaneous nodules, pain, and erythema, which were primarily observed as grade 1–2 in severity [41,42]. In the PrEP studies of PURPOSE 1 [47] and PURPOSE 2 [48], comparable safety profiles were observed between the lenacapavir arm and the control arm (Fig. 4**b**). Lenacapavir has been considered as safe and well tolerated in patients with hepatic or renal impairment [49]. Pharmacologically, lenacapavir is a moderate inhibitor of cytochrome P450 3A (CYP3A) and a weak inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore, concomitant use with drugs that are substrates of CYP3A, P-gp, or BCRP is not recommended, due to the potential for increased systemic exposure and heightened risk of adverse drug reactions [50].

## 8. Viral resistance to lenacapavir

The resistance-associated mutations are located near the drug-binding pocket of lenacapavir within the HIV-1 capsid (Fig. 1**b**). Lenacapavir maintains robust antiviral activity across a broad range of HIV-1 strains, including those with naturally occurring polymorphisms in the *gag* gene or known resistance mutations to other antiretroviral classes [50]. A study in France found that viral strains isolated from 85 participants with HIV-1 infection were all lenacapavir-sensitive [51]. Among drug-naïve individuals across HIV-1 clades, lenacapavir resistance-associated mutations were found at low frequencies (<1%) [52]. However, in highly treatment-experienced participants, lenacapavir added to an optimized background regimen led to high efficacy (viral suppression in 81 % of participants) but could select for resistance when used unintentionally as functional monotherapy [53] due to either nonadherence or resistance-driven non-susceptibility to an optimized

background regimen [54]. Therefore, to optimize efficacy and minimize the risk of lenacapavir-associated resistance, it is recommended to use lenacapavir in combination with at least one or two fully active antiretroviral agents, ensuring good adherence [55].

The 2025 edition of the International Antiviral Society–USA (IAS–USA) drug resistance mutations summarized the major mutations (L56I, M66I, Q67H, K70H/N, N74D) and minor mutations (K70S/R, N74S, A105T, T107N) associated with resistance to lenacapavir (https://www.iasusa.org/). Lenacapavir-associated substitutions such as Q67H and K70R were reported in the CALIBRATE study [41]. At week 26, M66I mutation (6/8) appeared most frequently in the CAPELLA study, while only one case of Q67H, N74D, K70H and K70R resistance was observed [42]. After lenacapavir treatment for 104 weeks, 14 participants developed capsid amino acid substitutions associated with resistance to lenacapavir, including 6 participants with M66I, 8 participants with Q67H/K/N, 7 participants with K70H/N/R/S, 5 participants with N74D/H/K, 5 participants with A105S/T, and 6 participants with T107A/C/N [44]. Notably, the N74D mutation would result in the loss of a direct hydrogen bond and electrostatic repulsions between lenacapavir and HIV-1 capsid [56]. Consequently, a decreased binding affinity of lenacapavir to HIV-1 capsid was observed by 20-fold and a decreased virus susceptibility by 10-fold [56]. Similar to the N74D mutation in HIV-1, the N73D mutation in HIV-2 confers resistance to lenacapavir, resulting in viral load rebound [57]. In the French ANRS-MIE CO5 HIV-2 cohort, rapid selection of capsid mutations (N73D, N73D + A76V, Q66H + R69K, Q66H) was observed in 5 out of 8 participants with multidrug-resistant HIV-2 who received lenacapavir-containing regimens [38]. Due to the emergence of lenacapavir-associated mutations, a rapid and simple method to amplify capsid fragments and to determine their sequence may help in identifying the resistance-associated mutations when treatment failure occurs [58].

## 9. Antiretroviral combinations

Lenacapavir is not indicated for monotherapy; rather, it is approved for use in combination with other FDA-approved antiretrovirals for the treatment of HIV-1 infection in heavily treatment-experienced adults harboring multidrug-resistant HIV-1. Table 1 summarizes the development of lenacapavir-based combination regimens in clinical studies. Viral suppression for up to 52 weeks could be achieved if lenacapavir was administered in combination with an optimized background regimen in participants with multidrug-resistant HIV-1 infection [43]. A high rate of virological suppression would even be extended to 104 weeks if lenacapavir was combined with an optimized background regimen [44].

### 9.1. *Lenacapavir + cabotegravir*

Another combination that could be pursued is lenacapavir plus cabotegravir – an FDA-approved integrase inhibitor [59]. A case study analyzed 34 treatment-experienced participants who switched their background therapy to lenacapavir plus cabotegravir (with or without rilpivirine). This study reported that 90 % (32/34) of participants achieved virologic suppression, defined as HIV-1 RNA < 75 copies/mL, at a median of 8 weeks (range: 4 to 16 weeks)[59]. The combination of lenacapavir plus cabotegravir was also reported to achieve virological re-suppression after the failure of cabotegravir plus rilpivirine [60]. The ongoing phase 2 CALENDULA study in France will evaluate the clinical efficacy and safety of lenacapavir plus cabotegravir (NCT06657885).

### 9.2. *Lenacapavir + bictegravir*

The combination of lenacapavir with bictegravir in both treatment-experienced and −naïve patients was recommended for treatment of HIV-1 infections [61]. The switching regimen of oral daily lenacapavir 50 mg plus bictegravir 75 mg exhibited 96.2 % (50/52) of virological suppression by 24 weeks in treatment-experienced adults with HIV-1 RNA < 50 copies/mL [40]. In addition, a case report described successful HIV-2 viral load suppression following administration of oral lenacapavir in combination with BIC + FTC + TAF [57].

**Table 1**
Summary of lenacapavir-based combination therapies in clinical studies.

| Lenacapavir-based combination regimens | Dosing schedule | Clinical efficacy* | Ref. |
|---|---|---|---|
| Lenacapavir + emtricitabine + tenofovir alafenamide | An oral loading dose of lenacapavir 600 mg on days 1 and 2 and 300 mg on Day 8, followed by subcutaneous lenacapavir 927 mg every 26 weeks from Day 15. Oral emtricitabine 200 mg plus tenofovir alafenamide 25 mg daily starting on Day 1. | 93.3 %(98/105) at 28 weeks | [41] |
| Lenacapavir + emtricitabine + tenofovir disoproxil fumarate | An oral loading dose of lenacapavir 600 mg on Day 1 and Day 2. Oral lenacapavir 50 mg + emtricitabine 200 mg + TAF 25 mg daily starting on Day 3 | 85 % (44/52) at 54 weeks | [41] |
| Lenacapavir + bictegravir | An oral loading dose of lenacapavir 600 mg on Day 1 and Day 2, in addition to the daily tablets of lenacapavir 50 mg and bictegravir 75 mg starting on Day 1 | 96.2 % (50/52) at 24 weeks | [40] |
| Lenacapavir + islatravir | Lenacapavir 600 mg and islatravir 2 mg orally on Day 1 and 2. Oral lenacapavir 300 mg and islatravir 2 mg weekly starting on Day 8 | 96.2 % (50/52) at 48 weeks | NCT05052996 |
| Lenacapavir + teropavimab + zinlirvimab | An oral loading dose of lenacapavir 600 mg on Day 1 and 2. Subcutaneous lenacapavir 927 mg plus intravenous teropavimab and zinlirvimab 10 or 30 mg/kg on Day 1 | 90 % (18/20) at 26 weeks | [63] |
| Lenacapavir + cabotegravir | An oral loading dose of lenacapavir 600 mg on Day 1 and 2. Subcutaneous lenacapavir 927 mg every 26 weeks, plus intramuscular injection of cabotegravir 30 mg (with or without rilpivirine) every 4 or 8 weeks | 90 % (32/34) at a median of 8 (4 to 16) weeks | [59] |

*: Efficacy was generally defined as HIV-1 RNA < 50 copies/mL, except in study [59] where the virological suppression was defined as HIV-1 RNA < 75 copies/mL. Efficacy results from the intention-to-treat analysis were collected. Results across different trials may not be directly comparable due to variations in clinical settings, including differences in participant characteristics, treatment history, and background therapies.

### 9.3. *Lenacapavir + islatravir*

Although the feasibility of pairing lenacapavir with islatravir remains under study [62], a phase 2 trial (NCT05052996) demonstrated that a regimen of oral islatravir (2 mg) plus oral lenacapavir (600 mg on days 1 and 2, followed by weekly doses of islatravir and 300 mg lenacapavir from day 8) achieved virological suppression in 96.2 % (50/52)

of participants at week 48.

### 9.4. Lenacapavir + other options

Other innovative therapeutic strategies are also emerging. For instance, a combination of subcutaneous lenacapavir (927 mg plus oral loading) with broadly neutralizing antibodies—including teropavimab (30 mg/kg) or zinlirvimab (10 or 30 mg/kg)—achieved HIV-1 suppression lasting at least 26 weeks [63]. Furthermore, in a participant with multidrug-resistant HIV-1, lenacapavir combined with UB-421, an anti-CD4 domain 1 monoclonal antibody, resulted in sustained viral suppression [64].

Last but not least, due to its pharmacokinetic profile, lenacapavir requires a long-acting companion drug to fully realize its potential as part of a complete long-acting antiretroviral therapy regimen.

## 10. Conclusions

Lenacapavir, as a first-in-class capsid inhibitor, holds a promise in both therapeutic and prophylactic settings for the management of HIV-1 infection. Given its unique mechanism and long-acting properties, it is important to evaluate the efficacy and safety of lenacapavir in larger and more diverse populations, especially since many clinical trials to date have enrolled fewer than 100 participants (Table 1**,** Fig. 3**a**). To further reduce dosing frequency and minimize outpatient visits, strategies such as eliminating the oral lead-in phase and exploring once-yearly injections could be considered; however, additional clinical evidence is required. The remarkable efficacy of lenacapavir has been demonstrated in clinical trials (Fig. 3**a,** Fig. 4**a**); however, its effectiveness in real-world studies and treatment efficacy in large populations remains to be validated by future studies [65]. In PURPOSE 1 [47] and PURPOSE 2 [48], subcutaneous injections of lenacapavir once every 6 months achieved promising results for the prophylaxis of HIV-1 infection. Moreover, once-yearly intramuscular injection of lenacapavir [45] may serve as a promising alternative. Whether the dosing interval can be extended beyond one year remains to be determined.

For the treatment of HIV-1 infection, current protocols often involve an oral lead-in phase followed by every-6-month injections, recent studies have shown that long-term oral administration of lenacapavir in combination with other antiretrovirals also produces favorable outcomes [40,41]. Although oral adherence may be less consistent than long-acting injections, it still presents a viable alternative due to its convenience and flexibility. Despite its clinical potential, the high cost of lenacapavir remains a significant barrier to access, particularly in resource-limited settings [66]. As of today, lenacapavir has not been recommended as first-line anti-HIV therapy [67,68]. To achieve global health impact, lenacapavir requires substantial price reduction strategies to ensure equitable access. Nevertheless, the advent of lenacapavir represents a paradigm shift in HIV-1 treatment and prevention, with the potential to improve outcomes for both high-risk populations and those with multidrug-resistant HIV-1 infections.

## CRediT authorship contribution statement

**Erik De Clercq:** Writing – review & editing, Writing – original draft, Conceptualization. **Yuya Zhang:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Guangdi Li:** Writing – review & editing, Writing – original draft, Conceptualization. **Yelin Deng:** Visualization. **Ricardo Khouri:** Writing – review & editing. **Daniel Růžek:** Writing – review & editing. **Ewelina Król:** Writing – review & editing. **Li Tan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

## Declaration of competing interest

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

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