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Recent advances in the development of integrase inhibitors for HIV treatment

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Abstract

Purpose of the review—The complex multistep life-cycle of HIV allows it to proliferate within the host and integrate its genome in to the host chromosomal DNA. This provirus can remain dormant for an indefinite period. The process of integration, governed by integrase (IN), is highly conserved across the *Retroviridae* family. Hence, targeting integration is not only expected to block HIV replication but may also reveal new therapeutic strategies to treat HIV as well as other retrovirus infections.

Recent findings—HIV integrase (IN) has gained attention as the most promising therapeutic target as there are no equivalent homologues of IN that has been discovered in humans. Although current nano-formulated long-acting IN inhibitors have demonstrated the phenomenal ability to block HIV integration and replication with extraordinary half-life, they also have certain limitations.

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Summary—In this review, we have summarized the current literature on clinically established IN inhibitors, their mechanism of action, the advantages and disadvantages associated with their therapeutic application, and finally current HIV cure strategies using these inhibitors.

Keywords

HIV Integration; Integrase inhibitors; Latent provirus; Retroviridae; Therapeutic application

Introduction

Human Immunodeficiency Virus (HIV) is an etiological agent of the Acquired Immunodeficiency Syndrome (AIDS)(1–3), which has caused major devastation across the globe from past 4 decades. After the introduction of combination antiretroviral therapy (cART), HIV-1 induced AIDS-related morbidity and mortality has dropped significantly. However, HIV infected long-lived CD4⁺ T-cells and macrophages in different anatomical sanctuaries represent a major obstacle for a cure since cART fails to completely eliminate the virus from immunologically privileged tissues and organs(4). There are more than 20 antiretroviral drug formulations approved by the USFDA that are in clinical use for the treatment of HIV exploiting different modes of action as summarized in Fig. 1. HIV RT (reverse transcriptase) enzyme governs the conversion of viral ssRNA genome to dsDNA and lacks 3'–5' exonuclease proofreading activity. Additionally, selective drug pressure, suboptimal penetrance of the cART drug candidates in anatomical sanctuaries, limited ability to cross blood brain barrier and accumulation of accrued mutations confer resistance to different classes of anti-retroviral drugs. In certain scenarios, the resistant mutations are observed even in cART naïve individuals due to horizontal transmission of drug resistance viral strains(5, 6). Moreover, a lifelong cART regimen comes with various undesired effects such as drug fatigue, chronic systemic toxicity, persistent immune inflammation, and premature ageing. These side effects can accelerate non-AIDS related complications like chronic obstructive pulmonary disease (COPD), and cardiovascular diseases. Therefore, more effective strategies are of the urgent need to combat these drawbacks of the current anti-HIV therapeutic arsenal and to eventually eradicate HIV.

With limited resources of its own, HIV is inefficient to complete its life-cycle without exploiting the host. Furthermore, to escape from the host anti-viral immune response, HIV-1 hijacks the host's cellular machinery, thus proliferating throughout the host while simultaneously seizing the means of propagation. (7, 8•). One key step in the HIV-1 replication cycle involves the conversion of ssRNA genome into cDNA which further associates with multiple hosts as well as viral factors and the formation of the pre-integration complex (PIC). PIC is transported into the nucleus, and cDNA gets integrated into the host genome(9•, 10•). Once integrated, the virus establishes latent reservoirs in the host cells and persists there forever through clonal expansion. With present therapeutic interventions, it is virtually impossible to eliminate the entire pool of latent reservoirs. Hence, it is important to develop therapeutic strategies to block HIV-1 before integration.

RT, IN, and Protease (PR) enzymes of HIV-1 participate in three rate-limiting steps of the HIV-1 replication cycle, including reverse transcription, integration, and maturation,

respectively. For this reason, these enzymes are major targets for the development of anti-retroviral drugs. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) block HIV-1 replication during the reverse transcription. Unfortunately, HIV-1 tends to develop resistance to both NRTIs and NNRTIs faster than any other class of inhibitors due to the extremely fast error prone kinetics(11, 12). As nucleotide analogues, NRTIs also pose a disadvantage by causing mitochondrial toxicity; these inhibitors get incorporated into the host mitochondrial DNA, thus hampering cellular metabolism(12) and causing toxicity. In comparison to RT inhibitors, PR inhibitors are less desirable because PR inhibitors hamper viral replication at the very late stage of the viral life-cycle. This means that PR inhibitors cannot prevent the death of infected cells as reviewed by Eron 2017(13). Also, due to poor specificity, PR inhibitors also act against host cell proteases resulting in cellular toxicity of the host(14, 15). Targeting IN for anti-HIV drug development is both advantageous and important because IN plays a pivotal role in the integration of the viral genome in the host cell chromosome(16, 17). Due to the absence of any HIV-1 IN ortholog in host cells, the off-target effects of IN inhibitors are relatively limited when compared to RT and PR inhibitors.

Current combination therapy uses formulations that contain two or more classes of anti-retroviral drugs that include NRTIs, NNRTIs, PIs, INIs, and entry inhibitors. A list of US FDA approved fixed-dose combinational anti-retroviral drug formulations is described in Table 1.

In the next section, we will discuss USFDA approved IN inhibitors (INIs) that are used to treat HIV infection as well as the INIs drug candidates at various stages of development. We will also highlight the mechanistic details of these inhibitors, as well as their advantages and disadvantages as anti-HIV therapeutic agents.

HIV-1 Integrase

Integration, like reverse transcription, is conserved and unique to retroviruses. Both integration and transcription, collectively govern mutagenic activities, oncogenic activities, and the establishment of latent reservoirs of retroviruses(18). Once the provirus is established in the host genome, it would pass to any progeny cell as a Mendelian locus. As a result, removing the hidden provirus from host cell is virtually impossible using current anti-HIV drugs(19, 20).

Structurally, HIV-1 IN is a 288-amino acid long, 32 kDa protein composed of three domains: the *N-terminal* HH-CC zinc-binding domain, the RNaseH fold containing *catalytic core* domain, and the DNA binding *C-terminal* domain(21). IN forms a tetramer of two dimers(22), which binds to both 3' ends of viral DNA and uses the same active site for catalytic activity. This active site contains a triad of carboxylates comprising the canonical D, DX35E active site motif. These carboxylates coordinate Mg^{+2} or Mn^{+2} , a pair of divalent cations, which are critical for catalytic activity(23–25). Notably, although IN can function with either of these cations, it is largely dependent on Mg^{+2} over Mn^{+2} for *in vivo* functioning. These findings were supported by the study in which pharmacological inhibitors for Mn^{+2} -based carboxylates failed to inhibit HIV-1 integration *in vivo* (26•).

Once assembled with viral DNA, IN immediately cleaves the conserved sequences of two nucleotides. Removal of two nucleotides from both 3' ends generates pre-integration substrates with 3' *sticky* ends. This is followed by strand transfer reaction that occurs inside the nucleus where IN governs the cleavage of host DNA and 3' *sticky* ends are joined to the 5' overhangs of host DNA. Finally, the cellular repair machinery fills the gaps leading to the completion of the integration process(27, 28).

Integrase inhibitors (INIs)

Since INIs likely have reduced off-target effects compared to other classes of anti-retrovirals, HIV-1 IN emerged as a high-value therapeutic target. INIs belong to two major categories: **i)** IN strand transfer inhibitors (INSTIs) that bind to the catalytic core domain of the enzyme to block the binding of the enzyme to dsDNA, and **ii)** IN binding inhibitors (INBIs) that bind to the allosteric pocket of the IN and hamper the conformational changes required for strand transfer reaction. Currently, all USFDA-approved INIs belong to the group of INSTIs; whereas, therapeutic use of INBIs is still under the developmental phase (Table 2).

FDA approved INIs

Raltegravir (RAL)

RAL (MK-0518; Table 2) was the first IN inhibitor approved by USFDA in 2007 following the evidence of rapid, potent, and sustained anti-HIV activity in clinical trials(29). While it was initially approved for salvage therapy of patients who had developed resistance to first- and second-line cART, it has since been promoted to be a first-line drug(30, 31). RAL demonstrates significant anti-HIV activity *in vitro*, with an IC₅₀ value of 2 to 7 nM; whereas, the IC₉₀ value is 19 to 31 nM. Notably, RAL is reported to be active against multidrug-resistant isolates of HIV(32–34). In a randomised, double-blind, 156-week STARTMRK trial, RAL revealed significant durability in combination with Tenofovir disoproxil fumarate (TDF) in treatment naïve patients. RAL is also reported to alter the kinetics of HIV-1 decay and reduce the second phase viral load remarkably(35, 36).

Docking studies provided a better insight into INSTI's mechanism of action by revealing a crucial binding site in the active IN site. Specifically, RAL directly interacts with the catalytic residues D64, D116, E152, T66, E92, Y143, Q148, and N155 of HIV-1 IN. Additionally, sequencing data from clinical studies confirmed that mutations in E92 and Y143 led to reduced RAL susceptibility(37). The plasma half-life of RAL is approximately 9 hours in adults, with a rapid elimination stage lasting approximately 1 hour, thus making it possible to administer this drug twice a day(38, 39). RAL also demonstrated a relatively minimal level of interaction with NNRTIs and PR inhibitors (PIs), meaning that these drugs could potentially be used in combination(40). The phase-III ONCEMRK trial reported a higher bioavailability of the 600 mg tablet over the 400 mg RAL formulation twice daily post 48 and 96 hours of treatment(29). Currently, RAL is administered as a once daily 1200 mg dose with emtricitabine and TDF.

A major drawback associated with RAL based therapy is the development of drug associated resistance mutations. RAL associated minor INI-resistance mutations are frequently observed in drug naïve patients due to horizontal transfer of HIV-1 strains harbouring the mutations(41). Over 40 mutations are currently associated with INSTI inhibitors, with 14 associated with RAL resistance(42, 43). In particular, N155H and Q148K/R/H mutations are associated with almost complete resistance to RAL in infected individuals(31, 44). Phenotypic analysis of viral isolates from patients revealed that Q148K/R/Hs confer greater resistance than N155H mutation. However, none of the transmitted viral isolates carried both these mutations simultaneously. This indicates that resistance to INSTIs may be developed through two or more independent pathways(45). Importantly, some mutations, such as E92, E157, and Y143, have a debated role in resistance against RAL due to the fact that they reduce INSTI susceptibility to the IN enzyme that occur significantly less frequently than the other mutations(46). RAL has a relatively shorter half-life compared to other INSTIs. Development of rapid INI resistance mutations against RAL makes it a less effective therapeutic option in salvage therapy for patients failing second-line cART. For this reason, nowadays RAL is best used as a component of the first-line cART for treatment naïve individuals.

Elvitegravir (EVG)

EVG (GS-9137) was the first anti-HIV drug developed by Gilead and Japan Tobacco Company in early 2008 and received FDA approval in late 2012(47). EVG demonstrated significant anti-HIV activity in *in vitro* assays on various laboratory strains of both HIV-1 and HIV-2, with an IC₅₀ value ranging from 0.7 to 1.5 nM. EVG also inhibited the IN strand transfer reaction *in vitro* with an EC₅₀ value of 54 nM. Compared to RAL, EVG demonstrated superior therapeutic efficacy due to its blocking ability against multidrug-resistant strains of HIV, Murine Leukaemia Virus (MLV), and Simian Immunodeficiency Virus (SIV)(48). Moreover, EVG absorption increases if taken with food and interestingly, ritonavir booster can increase its elimination half-life from 3 hours to a maximum of 9 hours(49, 50). Mechanistically, EVG recognises the IN-DNA complex and binds to the interface between the 3' end of the viral DNA and the IN enzyme. EVG interacts strongly with D64 and E152 amino acids in the catalytic core domains that contain β-hydroxy carboxylates, chelates metal ions, and hydroxylic oxygen(51) leading to the inhibition of strand transfer reaction as well as the integration of viral dsDNA into the host genome.

A series of clinical trials and cohort studies have identified multiple mutations that govern EVG treatment failure. Five different substitution mutations were reported, and among these, E92Q alone was found to be capable of reducing EVG susceptibility by 33-fold(52). The other substitution mutations T66I/A/K, T124A, P145S, Q148K/R can reduce EVG susceptibility by a range of 3 to 30 folds(53). EVG has a low barrier to resistance compared to other INIs as it overlaps with some of RAL's resistance mutations including Q148K(54, 55) which limits its therapeutic efficiencies.

Dolutegravir (DTG)

DTG (GSK-1349572) belongs to the World Health Organisation's (WHO) List of Essential Medicines and is currently thought to be the single most promising long-term anti-HIV

medication available. In 2013, DTG received USFDA approval for third-line cART in patients who developed resistance to first- and second-line cART. However, DTG is now preferred in combination with abacavir and lamivudine, collectively known as Triumeq(56). Mechanistically, DTG binds to the active site of HIV-1 IN which brings the β 4- α 2 loop of the enzyme into close contact with the extended linker region. This interaction leads to conformational changes that disengage IN from the deoxyadenosine present at the 3' end of the virus. As a result, DTG chelates the divalent cations that are required for the enzyme function leading to inhibition of strand transfer reaction. The presence of a halobenzyl group in the structure allows DTG to reach even farther in the active site, resulting in more stable interaction with the enzyme than RAL and EVG. This enables DTG to *re-adjust* to the conformational changes observed in RAL and EVG resistant mutants that make DTG capable of inhibiting IN mutant strains more effectively than other INIs(57).

In *in vitro* studies, DTG demonstrated superiority compared to RAL and EVG, with an IC₅₀ value of 2.7 nM, EC₅₀ value of 0.51 nM, and a Therapeutic Index of > 9400 in human peripheral blood mononuclear cells (PBMCs); all of which are remarkably higher than in either RAL or EVG(58). Randomised double-blind phase-II and phase-III trials were conducted on 208 patients as a part of the SPRING study. In this study, patients received DTG in combination with Abacavir (ABC) and Lamivudine (3TC) for 96 weeks. DTG maintained significant bioavailability without any dose-related clinical adverse effect. The subjects were also found to maintain CD4⁺ cell counts with an average of 301 cells/ μ L after 96 weeks of therapy(59). Additionally, treatment of DTG in combination of TDF and emtricitabine (FTC) did not significantly alter the time of virologic failure as compared to the patients treated with TDF/3TC. These results collectively indicate that the difference in the events of viral failure upon different regimen is not due to the intrinsic difference in the anti-HIV activity of these drugs(60, 61). FLAMINGO, SINGLE and VIKING trials suggest that DTG is the best available INSTI, and the WHO's current guideline recommends the addition of DTG in combination with 3TC/FTC and ABC in first-line drug therapy for cART naïve patients(62–64). DTG has a plasma half-life of ~ 14 days, and recent reports suggest that DTG may persist for up to 72 hours after the last dose with 90% protein binding concentration(65). DTG is administered without any pharmacokinetic boosters such as cobicistat (66); its consistent efficacy, excellent tolerability, and lack of reported drug-drug interactions make it an excellent option and the preferred choice to couple with two NNRTIs/NRTIs for cART.

Although DTG has demonstrated promising results over other INI regimens, DTG-resistance mutations have been observed in the viruses isolated from DTG treated individuals. Surprisingly, these mutations are different from the resistance mutations that are frequently associated with RAL and EVG, thus implying that DTG may be inhibited through a unique pathway of its own. R263K substitution, for example, was the first documented DTG-resistance mutation (67). Pham *et al.* recently reported that mutation at S230R of IN impaired HIV-1 IN function as well as reduced DTG susceptibility by approximately 4 fold (68). In the DOMONO trial, due to its high genetic barrier, DTG was used as an HIV maintenance monotherapy in patients who attained complete virologic control with cART (69). In this study, several individuals reported virologic failure who carried HIV-1 strains without any mutations in the integrase gene. A comprehensive analysis of the viral genome

revealed that mutations in the 3'-polypurine tract (3'-PPT) confer high-level resistance to DTG(69, 70). This finding further validates one previous report where Malet *et.al.*, showed *in vitro* that high concentrations of prolonged DTG exposure confers mutations in 3'-PPT of wildtype HIV-1 strains(71••). This mutant strain of HIV-1 selected by high DTG exposure were also highly resistant to RAL and EVG. These reports reveal cautionary signals for a shift to DTG based monotherapy as well as DTG based combination therapy. An *in vitro* study reported that *de novo* selection of Env mutations confer resistance to DTG(72). These findings suggest that in order to evaluate virologic failure and drug resistance mutation, the complete IN gene needs to be screened to detect genetic alterations that may be responsible for therapeutic failure of INIs. Furthermore, the TSEPAMO study from Botswana reported a greater risk for development of infant neural tube defects in women receiving DTG at the time of conception compared to other classes of anti-retrovirals(73). Based on these findings, WHO revised its guideline of use of DTG in women of childbearing age (<https://www.who.int/hiv/mediacentre/news/dtg-qa/en/>).

Bictegravir (BIC)

Bictegravir (BIC), also known as GS-9883, was developed by Gilead in 2016(74). BIC is one of the latest INIs to receive US FDA-approval and is being used in clinic as a single tablet fixed-dose combination with bictegravir 50mg, emtricitabine 200mg and tenofovir alafenamide 25 mg (Biktarvy). Clinical data and pharmacokinetic studies revealed that BIC is a more efficient INSTI compared to RAL or EVG(74). A rapid absorption rate and an elimination half-life of 18 hours mean that BIC is supportive of a once-daily administration plan without a pharmacokinetic booster(76). Notably, BIC also possesses the longest integrase/DNA dissociation half-life of approximately ~ 35 hours which is best among this class(77).

In vitro, BIC demonstrated the strong, specific, anti-HIV activity with an IC₅₀ value ranging between 1.5 – 2.4 nM in both T-cell lines and primary cells. BIC inhibits IN strand transfer activity with an EC₉₀ of ~ 8.3 nM in the cell-free assay system. Additionally, BIC demonstrated improved anti-HIV potential against various INSTIs resistant clinical isolates of HIV-1 compared to DTG. BIC also demonstrated a slower rate of resistance mutations' accumulation compared to DTG and EVG, even after 150 days in culture(75–77).

Despite these advantages, a Q148 substitution mutation was reported to reduce the efficiency of BIC by ~ 63 folds, while an R263L single mutation or R263K/M50I dual mutation have also been reported to reduced BIC efficiency by 2.5 – 3.0 folds *in vitro*(78). Notably, no other mutations have yet been reported in patients, and further studies on viral resistance to BIC are urgently needed.

Drugs in various stages of development

Cabotegravir (CAB)

CAB (GSK744), with its carbamoyl pyridone backbone, is structurally and mechanistically similar to DTG(79) also demonstrating very promising results in Phase-IIa trials(80). *In vitro*, CAB displayed significant anti-HIV activity with an IC₅₀ value of 3 nM and an IC₉₀

value of ~ 400 nM(81). Due to its extremely high efficacy, rapid absorption rate upon intramuscular injection, and elimination half-life of ~ 40 days, CAB has attracted significant attention as an ideal candidate for monthly or even quarterly administration(82). CAB's unique properties allow it to be administered as either an oral tablet or a long-acting nano-formulated injectable. Currently, CAB combined with rilpivirine is being investigated through phase-IIb trials in antiviral naïve patients by the ÉCLAIR, LATTE, and LATTE-2 studies(83–85). Recently, preliminary outcomes of ATLAS (Antiretroviral Therapy as Long-Acting Suppression: NCT02951052) and FLAIR (First Long-Acting Injectable Regimen: NCT02938520) trials were reported. The ATLAS and FLAIR were Phase III randomized, open-label trials involving 616 and 566 active participants, respectively. In both trials, during viral suppression, study participants were given oral CAB 30 mg + RPV 25 mg once daily for 4 weeks followed by intramuscular (IM) injections of a loading dose of CAB LA (600 mg) and RPV LA (900 mg). From week eight, the participants received IM injection of CAB LA 400 mg and RPV LA 600 mg every four weeks up to 48 weeks. The other arm received daily oral dose of 2 NRTIs plus an INI, NNRTI, or PI for 48 weeks (ATLAS) and daily oral dose of ABC / DTG / 3TC (600 mg/50mg/300mg) once daily for 48 weeks (FLAIR). In the ATLAS trial, at the end of 48 weeks, the CAB LA and RPV LA was non-inferior in maintaining viral suppression in treated participants (5 [1.6%] out of 313 had plasma viral loads above 50 copies/ml) when compared with the arm receiving conventional oral daily ART regimen (3 [1.0%] participants out of 313 had plasma viral loads above 50 copies/ml) (adjusted difference: 0.6%, 95% confidence interval [CI]: -1.2, 2.5). The CAB LA and RPV LA arm of the FLAIR trial was also non-inferior in maintaining viral suppression (6 [2.1%] out of 283 participants had plasma viral loads above 50 copies/ml) when compared with the arm receiving conventional oral daily ART regimen (7 [2.5%] out of 283 participants had plasma viral loads above 50 copies/ml) (adjusted difference: -0.4%, 95% CI: -2.8, 2.1). Overall the long acting formulation is well-tolerated, with low rates of serious adverse events (SAEs) of (13/308 [4.2%]) and (18/283 [6.4%]) in ATLAS and FLAIR trials, respectively. These results demonstrated a proof-of-principle that a once monthly dose of a long acting CAB+RPV formulation can achieve long-term virologic control. Furthermore, a recent study using a SHIV infected macaque model of HIV infection showed a risk of drug resistance to CAB-LA when used as a post-exposure prophylaxis. Radzio-Basu *et al.*, found selection of multiple mutations in integrase gene conferring resistance to CAB, several of which also have cross-resistance to all other INIs(86); and these mutations potentially reduce the option of using INSTIs in follow-up therapy. This study warrants detailed sequencing and use of frequent serological tests while using CAB LA for post-exposure prophylaxis therapy. In *in vitro* studies, CAB shows a high genetic barrier. To better predict the clinical efficacy of CAB in *in vivo* studies, long term follow up of the patients in the above-mentioned trials is required to monitor development of virologic failure due to the emergence of drug-associated mutations.

Due to longer biological half-life and sustained release that is achieved by nano-formulations, CAB has the potential to reduce the daily anti-retroviral pill burden to just once a month administration. Also, both CAB, as well as nano-formulated CAB, does not show any major drug-drug interactions in the short term as well as long term usage. CAB is

also administered without pharmacokinetic boosters. These characteristics collectively make CAB a potential candidate for both pre- and post-exposure prophylaxis (PrEP/PEP).

BMS-707035

BMS-707035, a pyrimidinone carboxamide, is structurally similar to RAL and differs only by the substitution of an oxadiazole group for the sulphonamide group in the scaffold(87). BMS-707035 also interacts with many of the same amino acid residues in the catalytic core domain as RAL, including D64, D116, E152, T66, E92, Y143, Q148, and N155(88), displaying significant anti-HIV potential *in vitro*, with an IC₅₀ value of ~ 2–20 nM(18, 89). Although BMS-707035 displays similar efficacy as RAL, BMS-707035's efficacy can be significantly reduced by mutations in HIV-1 LTR(90). Additionally, the toxicity studies and results of a 12-month dog safety assessment study showed multiple acute as well as chronic systemic toxicities that ultimately halted the development of BMS-707035 for higher studies and further therapeutics. Recent studies by Naidu et al. revealed several structural analogues with improved specificity and anti-HIV activity(91). The EC₅₀ values of these analogues range from 2 nM to 19 nM in a cell-free assay system, while the *in vitro* IC₅₀ values range from 1 nM to 206 nM. Some of these molecules also displayed an improved toxicity profile in dogs, and additional animal studies are currently being investigated as pre-clinical trials(91).

MK-2048

MK-2048 was first developed by Merck & Co. in early 2009. The first phase of the phase-II trial of MK-2048 was completed in 2014. One advantage of MK-2048 is that it inhibits viral isolates with R263K resistant mutation more efficiently than wild type virions (IC₅₀ value of 1.5 nM and 2.6 nM, respectively) in the cell-free integrase strand transfer assay(43). A daily MK-2048 dosage of 30 mg is currently being evaluated for safety and efficacy in combination with vicriviroc in phase-I trials(92). These initial studies suggest that MK-2048 does not show cross-resistance to RAL and EVG resistance mutations, making it one of the most potent second generation INSTIs(93).

In vitro, MK-2048 demonstrates significant anti-HIV activity in both cell lines and human PBMCs with an IC₅₀ value of 0.9 nM and an IC₉₀ value of 57 nM(94). However, it has an extremely low half-life of only 1–1.5 hours, and its efficacy can be reduced more than 8 fold by the G118R and E138K mutations, which do not affect either RAL or EVG(95, 96). As a result, additional research is necessary to develop more specific, efficient, and longer lasting analogues of MK-2048.

BI224436

BI224436, a non-catalytic site integrase inhibitor, binds to the allosteric pocket of IN enzyme and blocks the conformational changes required by the strand transfer and recombination steps of integration(97). BI224436 is a 3-quinolineacetic acid derivative with a significantly higher therapeutic index (TI > 10,000) than other INIs against various laboratory strains of HIV-1, as shown by *in vitro* assay systems(97). The binding of BI224436 with IN enzyme interferes with the interaction of IN with LEDGF (Lens Epithelial Derived Growth Factor) on the allosteric pocket of the enzyme, thus preventing

the formation of PIC and its nuclear import. Initially, BI224436 was thought to be a potent inhibitor of IN as it targets the conserved non-catalytic domain of IN and is unlikely to develop resistant mutations. However, three mutations A128T, A128N and L102F in the conserved region of IN, which reduced the binding affinity of BI224436 with the IN by 2.9, 64, and 61 folds, respectively, were reported in HIV-1 infected patients(98), limiting the advancement of BI224436 to phase-I trials.

Nano-formulations

Nano-formulations have recently gained popularity for AIDS-related neurological complications due to cART's suboptimal penetrance to cross the blood-brain barrier(99–101•). The primary purpose of nano-formulations is to implement a sustained release of the drug in the host along with a target-specific delivery of the drug(s). Both of these outcomes can potentially result in a specific and long-term therapeutic effect(102). Many cART candidate drugs, as described earlier, are designed in gold and diamond-based nano-formulations in order to increase the specificity and efficacy of the drug(103). Both gold and diamond nano-formulations have a high surface area to volume ratio providing a large surface for drug binding and interaction. This property results in a more sustained release of the drug and may eventually be applied to reduce the burden of daily administration. This also assists in overcoming the issues of uneven tissue distribution and toxicity to the host(104).

The nano-suspension of GSK1265744 with polysorbate 20 and polyethylene glycol 3350 is currently being evaluated in phase II trials, both for sustained delivery as well as reduced toxicity (NCT02076178). In these trials, GSK1265744 was detected in the plasma of seronegative donors even after 48 weeks post-exposure, thus demonstrating the drug to be a promising long-acting IN inhibitor. Additionally, recently Sillman *et al.* developed a long-acting parenteral nano-formulation of DTG prodrug by encapsulating it in a poloxamer (NMDTG). Pharmacokinetic profiling of NMDTG revealed an IC₉₀ concentration of nearly 64 ng/mL in the plasma for 56 days, with a similar concentration obtained from lymphoid tissues after 28 days(105). However, in a recent study the combination of sequential long-acting slow-effective release antiviral therapy and CRISPR-Cas 9 treatment eliminated complete HIV in few of humanized mice (106••). Recent exploitation of nano-formulated DTG and CAB, given once in two-month administration formulation, are currently under critical investigations(105, 107, 108••). These studies have opened new horizons of long-acting antiretroviral therapy and may potentially change the future of anti-HIV therapeutics.

To conclude, nano-formulations of drugs have comparatively longer half-lives, and can easily cross cellular barriers, such as the BBB and the portal systems of the body, thus serving as potential therapy for the central nervous system viral reservoir and other immune-privileged areas. Nano-formulated medicines are also metabolized slightly differently than conventional cytochrome mediated metabolism. However, additional studies are necessary to gain a better understanding of nano-formulated medicines as well as nanoparticles. Therefore, long term toxicity of nano-formulations should be understood in more detail. It is also important to examine the metabolism that is mediated by the cytochrome machinery of

nano-formulations *in vivo* because the conjugation of gold nanoparticles can potentially affect the metabolism of the prodrug in the long term.

Future considerations

Development of drug resistant mutations is a major challenge in achieving a functional cure of HIV-1. Current therapeutics has greatly reduced the lethality of the disease; but nevertheless, we are still far from the true cure. Additionally, the issue of resistance mutations increases the complexity of treatment. For this reason, current treatment strategies must be continuously updated. Integration is a *point of no return* and is of unique importance because a provirus that has been integrated into the host genome is virtually impossible to eliminate from host cells. IN inhibitors present a promising option to this end. However, since all current INSTIs bind directly to the active site of the enzyme, which is more prone to the point mutations, the development of drug resistance can occur. For this reason, other sites on the IN enzyme should be explored as well, including the allosteric pocket of enzymes that are less sensitive to mutations. Additional studies on the structural perspective of PIC formation will provide new insights regarding the HIV dependency factors (HDFs) that are required for IN function. Understanding the role of these HDFs in host cells regulating the viral life cycle can potentially assist in identifying new HDFs as well as better treatment options.

Another promising area of anti-retroviral drug discovery is the development of dual inhibitors that will simultaneously act against two different targets like IN and RT enzymes using a single drug molecule. Several small molecules that act against IN and RNase H domain of RT are at different stages of pre-clinical development(109, 110). A new class of dual inhibitors that target IN and LEDGF/p75 interaction is also in development(111).

Nano-formulations and sustained release long-acting (LA) formulations of both RT as well as IN inhibitors are at various stages of their clinical trials which are expected to improve the efficiency of anti-HIV therapeutics overcoming the drawbacks of present arsenal (112••). Nano-formulations of the current IN inhibitors and other investigational drugs require further evaluation in both treatment-naïve and ART-experienced patient populations. If a sustained release can be achieved without any significant adverse effect, these nano-formulations could potentially be considered for PrEP. Design of new INIs with pharmacological properties that consider the drug-resistant IN mutations should be a priority for anti-HIV therapeutic development. Also, designing of the INIs that can also hamper the function of RT as well as PR might revolutionize the antiretroviral therapeutic arsenal.

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Fig. 1.
Schematic representation of FDA approved anti-HIV drugs inhibiting different stages of the HIV-1 life cycle.

Table 1:

Timeline of FDA approved formulation [Information adapted from www.aidsinfo.nih.gov accession date: July 13, 2019]

FDA Approved combinations	Generic Name	Dosage	Approval Date
lamivudine and zidovudine [3TC / ZDV]	Combivir	Twice a day	September 27, 1997
lopinavir and ritonavir [ritonavir-boosted lopinavir, LPV/r, LPV / RTV]	Kaletra	Twice a day	September 15, 2000
abacavir, lamivudine, and zidovudine [abacavir sulfate / lamivudine / zidovudine, ABC / 3TC / ZDV]	Trizivir	Twice a day	November 14, 2000
abacavir and lamivudine [abacavir sulfate / lamivudine, ABC / 3TC]	Epzicom	Once daily	August 2, 2004
emtricitabine and tenofovir disoproxil fumarate [emtricitabine / tenofovir DF, FTC / TDF]	Truvada	Once daily	August 2, 2004
efavirenz, emtricitabine, and tenofovir disoproxil fumarate [efavirenz / emtricitabine / tenofovir DF, EFV / FTC / TDF]	Atripla	Once daily	July 12, 2006
emtricitabine, rilpivirine, and tenofovir disoproxil fumarate [emtricitabine / rilpivirine hydrochloride / tenofovir disoproxil fumarate, emtricitabine / rilpivirine / tenofovir, FTC / RPV / TDF]	Complera	Once daily	August 10, 2011
elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate [QUAD, EVG / COBI / FTC / TDF]	Stribild	Once daily	August 27, 2012
abacavir, dolutegravir, and lamivudine [abacavir sulfate / dolutegravir sodium / lamivudine, ABC / DTG / 3TC]	Triumeq	Once daily	August 22, 2014
atazanavir and cobicistat (atazanavir sulfate / cobicistat, ATV / COBI)	Evotaz	Once daily	January 29, 2015
darunavir and cobicistat [darunavir ethanolate / cobicistat, DRV / COBI]	Prezcobix	Once daily	January 29, 2015
elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate [elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide, EVG / COBI / FTC / TAF]	Genvoya	Once daily	November 5, 2015
emtricitabine, rilpivirine, and tenofovir alafenamide [emtricitabine / rilpivirine / tenofovir AF, emtricitabine / rilpivirine / tenofovir alafenamide fumarate, emtricitabine / rilpivirine hydrochloride / tenofovir AF, emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide, emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide fumarate, FTC / RPV / TAF]	Odefsey	Once daily	March 1, 2016
emtricitabine and tenofovir alafenamide [emtricitabine / tenofovir AF, emtricitabine / tenofovir alafenamide fumarate, FTC / TAF]	Descovy	Once daily	April 4, 2016
dolutegravir and rilpivirine [dolutegravir sodium / rilpivirine hydrochloride, DTG / RPV]	Juluca	Once daily	November 21, 2017
efavirenz, lamivudine, and tenofovir disoproxil fumarate [EFV / 3TC / TDF]	Symfi Lo	Once daily	February 5, 2018
bictegravir, emtricitabine, and tenofovir alafenamide [bictegravir sodium / emtricitabine / tenofovir alafenamide fumarate, BIC / FTC / TAF]	Biktarvy	Once daily	February 7, 2018
lamivudine and tenofovir disoproxil fumarate [3TC / TDF]	Cimduo	Once daily	February 28, 2018
efavirenz, lamivudine, and tenofovir disoproxil fumarate [EFV / 3TC / TDF]	Symfi	Once daily	March 22, 2018
darunavir, cobicistat, emtricitabine, and tenofovir alafenamide [darunavir ethanolate / cobicistat / emtricitabine / tenofovir AF, darunavir ethanolate / cobicistat / emtricitabine / tenofovir alafenamide, darunavir / cobicistat / emtricitabine / tenofovir AF, darunavir / cobicistat / emtricitabine / tenofovir alafenamide fumarate]	Symtuza	Once daily	July 17, 2018
doravirine, lamivudine, and tenofovir disoproxil fumarate (doravirine / lamivudine / TDF, doravirine / lamivudine / tenofovir]	Delstrigo	Once daily	August 30, 2018

Table 2:

Summary of INIs (approved and in development)

Integrase Inhibitor	Chemical Structure	In Vitro Efficacy	In Vivo Dosage	Estimated Half-life	Resistant Mutations
BI224436		<1 nM	NA	NA	A128T, A128N, L102F
Bictegravir (BIC) (GS-9883)		1.5 – 2.4 nM	NA	~35 h	Q148-E138, Q148-G140, R263L, R263K/M50I
BMS-707035		2–20 nM	NA	NA	NR
Cabotegravir (GSK744)		3 nM	400 mg (or 200 mg split injection) once a month	~40 d	NR
Dolutegravir (DTG) (GSK-1349572)		0.51 – 2 nM	50 mg per day	~ 14 d	R263K, S230R, Q148-E138, Q148-G140
Elvitegravir (EVG) (GS-9137)		0.7 – 1.5 nM	85 mg and 150 ng twice per day	3–9 h	E92Q, T66I/A/K, T124A, P145S, Q148K/R
MK-2048		1.5–2.6 nM	30 mg once daily	1–1.5 h	G118R, E138K
Raltegravir (RAL) (MK-0518)		2–7 nM	400 mg thrice per day	9 h	N155H, Q148K/R/H

NA = Not Available NR = Not Reported