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HIV-1 Entry Inhibitors: Recent Development and Clinical Use

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Abstract

Purpose of review—This review provides an overview of HIV-1 entry inhibitors, with a focus on drugs in the later stages of clinical development.

Recent findings—Entry of HIV-1 into target cells involves viral attachment, co-receptor binding and fusion. Antiretroviral drugs that interact with each step in the entry process have been developed, but only two are currently approved for clinical use. The small molecule attachment inhibitor BMS-663068 has shown potent antiviral activity in early phase studies, and phase 2b trials are currently underway. The post-attachment inhibitor ibalizumab has shown antiviral activity in phase 1 and 2 trials; further studies, including subcutaneous delivery of drug to healthy individuals, are anticipated. The CCR5 antagonist maraviroc is approved for use in treatment-naïve and treatment-experienced patients. Cenicriviroc, a small-molecule CCR5 antagonist that also has activity as a CCR2 antagonist, has entered phase 2b studies. No CXCR4 antagonists are currently in clinical trials, but once daily, next-generation injectable peptide fusion inhibitors have entered human trials. Both maraviroc and ibalizumab are being studied for prevention of HIV-1 transmission and/or for use in nucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens.

Summary—Inhibition of HIV-1 entry continues to be a promising target for antiretroviral drug development.

Keywords

attachment inhibitors; chemokine receptor antagonist; fusion inhibitor; HIV-1 envelope

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Introduction

The entry of HIV-1 into susceptible target cells is a multi-step process that leads to the fusion of viral and cell membranes. Antiretroviral drugs that interact with each step in the entry process have been developed, but only two are currently approved for clinical use (maraviroc and enfuvirtide). Four investigational drugs have reached phase 2 and 3 clinical trials. Given the potential for these agents to block viral entry, there has been renewed interest in using them to prevent acquisition of HIV-1 infection. This review summarizes progress in the development of HIV-1 entry inhibitors, with an emphasis on molecules in later stages of clinical development.

HIV-1 entry

Binding of the viral envelope to its primary receptor, CD4, on the surface of macrophages or T-helper lymphocytes is the first step in virus entry. Binding to CD4 is mediated by gp120, the surface subunit of the envelope. In its native form, the envelope glycoprotein is a heterotrimer of three gp120 molecules and three molecules of gp41, the transmembrane subunit, which remain attached through non-covalent interactions [1,2]. Conformational changes in gp120 triggered by CD4 binding exposes structural elements that engage one of two chemokine receptors, either CCR5 or CXCR4. Co-receptor binding allows the hydrophobic N-terminus, or fusion peptide, of the gp41 ectodomain to insert into the target cell membrane. The anti-parallel association of two helically coiled heptad repeats (HR-1 and HR-2) in the gp41 ectodomain to form a six-helix bundle leads to the close approximation of the cell and virus membranes, resulting in fusion [3].

Attachment inhibitors

Early attempts to develop specific inhibitors of HIV-1 entry focused on the design and testing of recombinant soluble CD4 molecules. These molecules lack the transmembrane and cytoplasmic domains of CD4, but retain the ability to bind gp120, thereby functioning as molecular decoys. Although these molecules showed good in vitro activity against tissue culture-adapted strains of HIV-1, activity in early phase clinical trials was disappointing [4–7]. More promising data were generated in preliminary studies of PRO 542, a tetravalent CD4-immunoglobulin fusion protein [8,9], but no additional studies of PRO 542 are ongoing at this time (www.clinicaltrials.gov).

Small molecule inhibitors that bind to a specific region within the CD4 binding pocket of gp120 and block the gp120-CD4 interaction are more promising [10,11]. A proof-of-concept study with the compound, BMS-488043 resulted in 1-$\log_{10}$ reduction in plasma HIV-1 RNA in treatment-naive subjects [12]. Further development of this molecule was discontinued due to suboptimal pharmacokinetics. However, BMS-663068 (a prodrug of the attachment inhibitor BMS-626529) demonstrated improved pharmacokinetics and increased potency against a greater range of HIV-1 subtypes [13]. A recent randomized, open-label, phase 2a study of BMS-663068 with or without ritonavir boosting showed that the medication was well tolerated and resulted in up to a 1.7-$\log_{10}$ reduction in plasma HIV-1 RNA levels after 8 days of treatment [14]. The twice-daily dosing regimen without ritonavir boosting was the least potent, but a phase 2b study to investigate safety, efficacy and dose-response in

treatment-experienced individuals of this attachment inhibitor without ritonavir is underway. This study examines the use of once- or twice-daily dosing of BMS-663068 plus raltegravir and tenofovir versus a regimen containing ritonavir-boosted atazanavir, raltegravir and tenofovir (www.clinicaltrials.gov).

Post-attachment inhibitors (ibalizumab)

The monoclonal antibody (mAb) ibalizumab (formerly TNX-355) is a humanized IgG4 mAb that binds to the second (C2) domain of CD4 [15]. In contrast to attachment inhibitors, ibalizumab does not prevent gp120 binding to CD4, but is thought to decrease the flexibility of CD4, thereby hindering access of CD4-bound gp120 to CCR5 and CXCR4. The mAb is a potent inhibitor of HIV-1 in vitro, shows synergy when combined with gp120 antibodies or the fusion inhibitor enfuvirtide, and does not appear to interfere with immunological functions that involve antigen presentation [16–19].

Phase 1 studies of intravenous ibalizumab showed up to a 1.5-$\log_{10}$ reduction in plasma HIV-1 RNA levels 14–21 days after a single dose [20], but resistance emerged after repeated dosing over 9 weeks [21]. A phase 2 study of ibalizumab in highly treatment-experienced patients showed that this mAb plus an optimized background regimen resulted in significantly greater reductions in plasma HIV-1 RNA compared to the background regimen alone [22]. A subsequent phase 2 study showed that intravenous infusions given either every 2 or 4 weeks, in addition to an optimized background regimen, led to significant viral load reductions over 24 weeks [23]. Ibalizumab reduced virus load by 4-$\log_{10}$ in a patient with high-level five-class antiretroviral drug resistance, but the virologic response was lost rapidly after a single missed infusion [24].

Viruses with reduced susceptibility to ibalizumab from phase 1b trials have higher levels of infectivity compared to paired, baseline viruses, but remain susceptible to the small-molecule CCR5 antagonist maraviroc and the fusion inhibitor enfuvirtide [25]. In vitro resistance experiments suggested that reduced susceptibility to ibalizumab is correlated with fewer potential asparagine-linked glycosylation sites in the gp120 variable region 5 (V5), especially at the V5 N-terminus [25,26].

A phase 1, randomized, placebo-controlled sequential dose escalation study of ibalizumab given by weekly subcutaneous injection in healthy volunteers is currently underway (www.clinicaltrials.gov). The long-acting subcutaneous injection has been proposed to improve drug adherence in patients who have difficulty taking daily oral regimens, and is an attractive candidate for HIV-1 pre-exposure prophylaxis (PrEP).

Chemokine receptors and HIV-1 co-receptor usage

Viruses that use CCR5 exclusively as co-receptor for entry (termed R5 viruses) predominate in early HIV-1 disease and are primarily responsible for transmission of infection. Viruses that use CXCR4 (X4) or both CCR5 and CXCR4 are rare in early disease, but emerge over time. Mixtures of R5 and X4 viruses can also be found, but because commonly used tropism assays cannot distinguish between dual tropic and a mixture of R5 and X4 viruses, such samples are referred to as having “dual-mixed" (D/M) co-receptor usage. The prevalence of

X4 variants increases with decreasing CD4+ cell count, and several studies show a significantly increased risk of disease progression among patients with D/M or X4 (SI) virus [27–29].

CCR5 antagonists

Several approaches have been developed to block interactions between HIV-1 and CCR5, including small molecule antagonists, mAbs and covalently modified natural CCR5 ligands (e.g., AOP-RANTES). However, only small-molecule CCR5 antagonists are currently approved for use or in later-stages of clinical development. Several orally available compounds—aplaviroc, maraviroc, vicriviroc, cenicriviroc and INCB009471—have progressed to phase 2 or 3 clinical trials. These compounds demonstrate potent inhibition of HIV-1 replication in vitro against laboratory-adapted and primary isolates across all clades of group M HIV-1.

Aplaviroc treatment resulted in significant reduction in plasma HIV-1 RNA levels during 10 days of treatment [30], but development was terminated after non-fatal, reversible drug-induced hepatitis occurred in 5 subjects in phase 2b and 3 trials [31]. Vicriviroc demonstrated potent suppression of HIV-1 in combination with an optimized background regimen in placebo-controlled phase 2b studies in antiretroviral experienced individuals, but increased rates of virologic failure in treatment-naive patients compared with an efavirenz control arm led to the discontinuation of a preceding phase 2b study [32–34]. Development was terminated after data from a phase 3 trial showed that when combined with an optimized background regimen, vicriviroc failed to demonstrate superiority to the background regimen alone [35*].

Maraviroc is a spirodiketopiperazine CCR5 antagonist with potent in vitro and in vivo anti-HIV-1 activity, and is the only chemokine receptor agonist currently in clinical use. The molecule is a pure CCR5 antagonist that blocks MIP-1- α and RANTES-mediated signaling at nanomolar concentrations [36]. The efficacy of maraviroc was confirmed in a pair of phase 3 randomized, placebo-controlled trials (MOTIVATE 1 and 2) [37,38]. Eligible subjects were highly treatment-experienced, had plasma HIV-1 RNA levels >5,000 copies/mL, and had exclusively R5 virus at screening by the Trofile assay (Monogram Biosciences, South San Francisco, CA). In both studies, subjects in the maraviroc arms experienced plasma HIV-1 RNA reductions that were more than twice as great as those in the control arms using optimized background regimens alone (−1.7 to −1.9 log10 copies/mL versus 0.8 log10 copies/mL, respectively) [37,38]. More than twice as many maraviroc recipients achieved a plasma HIV-1 RNA level below 50 copies/mL compared to placebo recipients (42–47% versus 16%, respectively). Increases in CD4 cell counts were also higher in the maraviroc arms, and the frequency of adverse events was similar in all groups. Virologic response to maraviroc remained durable through 96 weeks of therapy [39].

The possibility that treatment with CCR5 antagonists would promote emergence of X4 viruses, thereby accelerating disease progression, was a significant concern during early clinical trials with these agents. Virologic failure to maraviroc was associated with emergence of CXCR4-using virus in 57% of subjects in whom a repeat tropism test was

obtained at the failure time-point [37]. Although CD4 count increases were smaller in this subgroup than among those with R5 virus at failure, a greater increase in CD4 counts was nevertheless observed among maraviroc recipients with D/M or X4 virus at failure when compared to the placebo group overall. Although all subjects had R5 virus at screening, 8% were found to have dual/mixed virus at baseline (day 0) [37]. Subjects with D/M virus at baseline who received maraviroc had a lower rate of virologic response, shorter time to virologic failure, and smaller CD4 increases as compared to those with R5 virus [37].

Subjects found to be ineligible for the MOTIVATE trials due to presence of D/M, X4 or non-typable virus at screening were offered entry into a parallel phase 2 study that tested the effect of maraviroc versus placebo in subjects with CXCR4-using virus. Overall, this study found no significant virologic or immunologic benefit of maraviroc as compared to placebo, although CD4 counts increased from baseline to weeks 24 and 48 in all treatment groups [40]. These results and those of the MOTIVATE trials suggest that the presence or emergence of CXCR4-using virus was not associated with rapid CD4 decline or disease progression.

Another phase 3 study compared maraviroc (300 mg once or twice daily) to efavirenz in treatment-naïve patients; both drugs were given together with zidouvdine plus lamivudine. The once-daily maraviroc arm was closed due to inferior efficacy that became apparent at an interim analysis. Final study results showed that the twice-daily maraviroc arm failed to demonstrate non-inferiority to the efavirenz-based regimen. However, a post hoc analysis including only individuals with R5 virus by an enhanced phenotypic coreceptor-usage assay, demonstrated that maraviroc did meet criteria for non-inferiority (68.5% versus 68.3% of maraviroc and efavirenz recipients reached viral loads <50 copies/mL by week 48) [41*,42].

Given the clinical efficacy of maraviroc, its relatively low toxicity profile, and its ability to antagonize viral entry, there has been much interest in using the drug for antiretroviral treatment intensification and as a component in nucleoside/nucleotide reverse transcriptase inhibitor (NNRTI)-sparing regimens; several trials are currently ongoing (www.clinicaltrials.gov). In a small study of 34 patients on suppressive antiviral therapy, the addition of maraviroc did not lead to a target increase of 20 CD4+ T cells/μL, but was associated with decreased markers of inflammation [43]. Maraviroc intensification also led to a decrease in the proviral latent HIV-1 reservoir size in memory T cells in four patients, but there was no change in residual, low-level viremia [44]. Larger studies are needed in order to clarify the effects of maraviroc intensification on immunologic response and viral reservoirs.

R5 virus is primarily responsible for establishing acute and early HIV-1 infection, and as a result, there has been interest in using maraviroc as PrEP, either in oral form or as a topical virustatic agent. Maraviroc has showed some promise in protecting macaques from R5 simian-human immunodeficiency virus challenge [45], but further investigation of maraviroc to prevent HIV-1 infection is needed.

Cenicriviroc (TBR-652, formerly TAK-652) is an investigational small-molecule CCR5 antagonist currently in clinical development. Cenicriviroc has a longer half-life than

maraviroc and is dosed once daily. It also inhibits CCR2, a receptor for monocyte chemoattractant protein-1 that has been associated with various inflammatory diseases. In phase 1–2a studies, cenicriviroc treatment resulted in up to a 1.8-$\log_{10}$ reduction in plasma HIV-1 RNA levels and was generally safe and well tolerated without significant adverse events [46*,47*]. A phase 2b study of cenicriviroc in combination with tenofovir/emtricitabine or efavirenz plus tenofovir/emtricitabine in HIV 1-infected, treatment-naïve patients with only R5 virus is underway (www.clinicaltrials.gov). The long-term effects of CCR2 antagonism and subsequent modulation of inflammation are not known and are the subject of ongoing investigation.

CXCR4 antagonists

In contrast to CCR5, there are no known naturally occurring mutations that lead to absence of CXCR4. As a result, the development of CXCR4 inhibitors has been more challenging. One problem unique to CXCR4 inhibitors is that whereas R5 viruses are found on their own in 50% or more of patients, X4 viruses usually are present as mixtures together with R5 viruses [43,48]. Inhibition of just the X4 component of the virus population may not lead to measurable declines in overall plasma viremia, thereby complicating assessment of drug activity. Co-administration of CCR5 and CXCR4 antagonists may be effective, but development of CXCR4 antagonists has stalled.

Preliminary studies with AMD3100 showed inhibition of the X4 component of the virus population, but development of this parenterally administered drug as an antiretroviral agent was discontinued due to QTc prolongation [49]. Interestingly, early studies revealed that CXCR4 blockade releases myeloid and plurioptent (CD34+) stem cells from the bone marrow into the blood [50]. This observation led to the subsequent development of AMD3100 (now called plerixafor) as an adjunct to G-CSF stimulation of the bone marrow, resulting in substantially increased stem cell yields [50]. The safety of long-term CXCR4 blockade is unknown.

Fusion inhibitors

Enfuvirtide (T-20) is a 36-mer synthetic oligopeptide whose sequence corresponds to that of the HR-2 region of the HIV-1 envelope gp41 subunit. Binding of enfuvirtide to the trimeric HR-1 complex prevents the association of HR-1 with HR-2, thereby inhibiting fusion and blocking virus entry [51]. Enfuvirtide became the first entry inhibitor approved for clinical use as a result of phase 3 clinical trials that demonstrated efficacy of the drug when combined with an optimized background regimen [52,53]. Because the drug is an oligopeptide, it must be administered by subcutaneous injection. The drug has minimal systemic toxicity, but the frequent occurrence of painful injection site reactions has limited long-term use. Co-administration of enfuvirtide significantly improved response rates to newer agents such as tirapanavir, darunavir and maraviroc in clinical trials conducted in highly treatment-experienced patients [37,54,55]. When given as part of a regimen that does not succeed at fully suppressing HIV-1 replication, however, resistance to enfuvirtide emerges rapidly [56].

Sifuvirtide, a third generation fusion inhibitor than can be injected once daily, has entered early phase human clinical studies in Asia. Sifuvirtide has a longer plasma half-live and greater in vitro antiviral activity compared to enfuvirtide as a result of improved helical structure stability and high affinity for its target N-terminal HR peptide. It also demonstrated activity against HIV-1 strains resistant to enfuvirtide [57*,58,59*]. HR-1-based and small molecule fusion inhibitors are being developed, but no clinical data are available for these novel compounds. Fusion inhibitors are covered in greater detail in the review by Berkhout et al. in a previous volume of this journal [60].

Conclusion

Although a variety of inhibitors that target different steps in HIV-1 entry have been developed, only maraviroc, a small-molecule CCR5 antagonist, and enfuvirtide, an oligopeptide fusion inhibitor, are approved for clinical use. Several other drugs are currently active in the development pipeline, and entry inhibitors may play an important role in preventing acquisition of HIV-1infecton.

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Highlights

- HIV-1 entry inhibitors are promising agents as antiretroviral drugs.
- The CCR5 antagonist maraviroc and the fusion inhibitor enfuvirtide are approved for clinical use
- Novel inhibitors targeting attachment, coreceptor usage and fusion are in development.
- Entry inhibitors may play an important role in prevention of HIV-1 transmission.

Table 1

Entry inhibitors that have reached later stage clinical trials, are approved for clinical use, or are in active development

Inhibitor	Development Status	Drug Class	Action Against Entry Stage
BMS-488043	Development discontinued due to suboptimal pharmacokinetics [12]	Small molecule attachment inhibitor	Binds to region within CD4 binding pocket of gp120
BMS-663068 (BMS-626529 prodrug)	Phase 2a study resulted in up to a 1.7-$\log_{10}$ reduction in plasma VL; phase 2b study of BMS-663068 plus RAL/TDF versus RAL/TDF/ritonavir-boosted ATZ currently underway [13,14]	Small molecule attachment inhibitor	
Ibalizumab (TNX-355)	Phase 2 studies of ibalizumab plus an OBR resulted in greater reductions in VL compared to OBR alone in treatment experienced individuals; phase 1 studies of long-acting subcutaneous ibalizumab in healthy volunteers currently enrolling [22,23]	Post-attachment inhibitor (mAb)	Hinders access of CD4-bound gp120 to CCR5 and CXCR4
Aplaviroc	Significant reduction in plasma VL in early phase trials; development terminated after drug-induced hepatitis in 5 subjects in phase 2b and 3 trials [31]	Small molecule CCR5 antagonist	Binds to CCR5 preventing interaction with gp120
Vicriviroc	Development discontinued after vicriviroc failed to demonstrate superiority when combined with OBR to OBR alone in a phase 3 trial [35*]	Small molecule CCR5 antagonist	
Maraviroc	Approved; efficacy confirmed in a pair of phase 3 randomized, placebo-controlled trials (MOTIVATE 1 and 2) of treatment-experienced patients with R5 virus by phenotypic assay[a] [37,38]	Small molecule CCR5 antagonist	
Cenicriviroc (TBR-652)	Treatment resulted in up to a 1.8-$\log_{10}$ reduction in plasma VL in early phase trials; phase 2b study of cenicriviroc in combination with TDF/FTC or EFV plus TDF/FTC in treatment-naïve patients with R5 virus is underway [46*,47*]	Small molecule CCR5 and CCR2 antagonist	Binds to CCR5 preventing interaction with gp120; binds to and inhibits CCR2
AMD-3100	Early phase studies showed inhibition of the X4 component of the virus population; development as HIV-1 treatment terminated due to QTc prolongation but in clinical use for peripheral blood stem cell mobilization (plerixafor) [49]	Small molecule CXCR4 antagonist	Binds to CXCR4 preventing interaction with gp120
Enfuvirtide (T-20)	Approved; phase 3 clinical trials demonstrated efficacy when T20 combined with an OBR in treatment experienced individuals but clinical use limited given subcutaneous delivery and occurrence of painful injection site reactions [52,53]	Fusion Inhibitor	Inhibits fusion by preventing the association of HR-1 with HR-2 regions of gp41
Sifuvirtide	Demonstrated antiviral activity in early phase human studies; has	Fusion Inhibitor	

Inhibitor	Development Status	Drug Class	Action Against Entry Stage
	activity against some HIV-1 strains resistant to enfuvirtide and further human studies may be planned [58,59*]		

Abbreviations: VL = viral load; OBR = optimized background regimen; mAb (monoclonal antibody); TDF = tenofovir; FTC = emtricitabine; EFV = efavirenz; RAL = raltegravir; ATZ = atazanavir; PI = protease inhibitor

[a]Maraviroc failed to demonstrate non-inferiority to an EFV-based regimen in treatment naïve individuals, but met criteria for noninferiority in a post-hoc analysis including only individuals with R5 virus by an enhanced phenotypic coreceptor-usage assay [41*]