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ORIGINAL ARTICLE

HIV Entry Inhibitors: Current Status

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ABSTRACT

Current therapeutic intervention in HIV infection relies upon 20 different drugs. Despite the impressive efficacy shown by these drugs, we are confronted with an unexpected frequency of adverse effects such as mitochondrial toxicity, lipodystrophy and resistance, not only to individual drugs, but to entire drug classes. Thus, there is now a great need for new antiretroviral drugs with reduced toxicity, increased activity against drug-resistant viruses and a greater capacity to reach tissue sanctuaries of the virus. Two different HIV molecules have been selected as targets of drug inhibition so far: reverse transcriptase and protease. Drugs that target the interactions between the HIV envelope and the cellular receptor complex are a `new entry' into the scenario of HIV therapy, and have recently raised great interest because of their activity against multi-drug resistant viruses.

There are several compounds that are at different developmental stages in the pipeline to counter HIV entry, some of which include:

i) the attachment inhibitor dextrin – 2 – sulfate;
ii) the inhibitors of the glycoprotein (gp) 120/CD4 interaction PRO 542, TNX 355 and BMS 488043;
iii) the co-receptor inhibitors subdivided in those targeting CCR5 and those targeting CXCR4 and
iv) fusion inhibitors enfuvirtide (T-20) and tifuvirtide (T-1249).

Key Words: HIV entry inhibitors, Mechanism of entry, Current status, Future

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Mechanism of Entry

HIV surface proteins bind to CD4 (a member of the immunoglobulin super family), thereby anchoring the virus to the surface of the host cell and enabling additional interactions with a co-receptor protein (usually a member of the chemokines receptor family) [1]. The main co-receptors used by HIV-1 are chemokine receptors CCR5 and CXCR4. The viral surface protein gp120 has a high degree of genetic variability in HIV-1 isolates. Assessment of the amino acid sequence of different HIV-1 strains led to the identification of five variable (V1-V5) and four constant (C1-C4) regions in gp120 [2]. The expression of CCR5 or CXCR4 on different CD4 + target cells, defines their susceptibility to infection by the corresponding CCR5 (R5) or CXCR4 (X4) HIV-1 strain. Thus, the use of a specific co-receptor determines virus cell tropism. Moreover, some HIV-1 strains can use both CCR5 and CXCR4, and they are referred to as dual tropic (D) R5X4 strains. Some patients have mixtures (M) of R5 and X4 HIV-1 isolates.

After CD4-virus binding and co-receptor engagement, conformational changes in gp120 enables gp41 to reorient parallel to viral and cellular membranes and promote the events leading to fusion between the two membranes. Thereafter, the present model to explain membrane fusion, assumes a transient intermediate state in which gp41 spans both viral and cellular membranes [3]. A six-helix bundle, the gp41 structure is believed to form before fusion and serve to bring the membranes into close apposition, enabling fusion-pore formation

and virus internalization. The most promising HIV entry inhibitors being developed are those targeting HIV co-receptors. [Table/Fig 1]

(Table/Fig 1) Receptors For HIV-1 Entry

	CD4	CCR5	CXCR4
Structure	Four Ig-like domain	Seven transmembrane domains G-protein coupled receptor	Seven transmembrane domains G protein coupled receptor
Function	Coreceptor for MHC Class II during stimulation of T-helper cells	Receptor for CCL3 (MIP1-α) CCL4 (MIP1-β) CCL5 (RANTES) Redundant system	Receptor for CXCL12 (SDF-1) Non-redundant system
Expression	CD4 + T cells Macrophages Microglia Dendritic cells	A subset of memory CD4 + cells Macrophages	Constitutive in many cells, including CD4 + T cells and macrophages

Attachment Inhibitors

Dextrin – 2 – Sulfate [4]

Sulfated polysaccharides or polyanions such as dextran sulfate and heparin have been shown to inhibit binding of V3 loop antibodies to HIV-1 gp120 in-vitro. Dextrin-2-sulfate (D2S) is a synthetic derivative of dextrin which exhibits the most favorable combination of high anti-HIV-1 activity and low anticoagulant activity, when compared to other structural analogues of sulfated polysaccharides[4]An intravaginal gel formation of D2S (0.125%) is currently being developed by ML Laboratories, and is under evaluation as a topical microbicide. There was no evidence of systemic toxicity or genital epithelial disruption, attributable to the D2S gel. Clinical trials of the D2S gel have been approved by the UK Medicines Control Agency, and the US FDA has approved trials of D2S in the UK, US and South Africa.

Inhibitors Of Gp 120 / CD4 Interaction[5]

The inhibitors of Gp 120/ CD4 interaction are PRO 542, TNX 355 and BMS 488043. PRO 542 (CD4 – IgG2) is a tetravalent recombinant antibody. PRO 542 is currently being developed by Progenics pharmaceuticals, and has been tested in two phase I / II clinical trials. TNX 355 is a humanized monoclonal antibody directed against the extracellular domain 2 of human CD4. It prevents post-viral binding conformational changes required for successful entry of HIV into the cell. TNX 355 is being developed by Tanox, and currently under clinical development.

BMS 488043 is a small molecule which blocks viral entry by preventing the binding of gp120 to cellular CD4 receptors. This compound was discovered by Bristol-Myers-Squibb, and is currently in phase II / III development with the company.

Co-Receptor Antagonists [6]

A number of `first generation' molecules have been halted in their clinical development against HIV-infection. These include the CXCR4 antagonist AMD100, which is not being further developed because of cardiac abnormalities [7]. In an analogous manner, ancriviroc (SHC-C, SCH 351125), a CCR5 antagonist, has been discontinued because of heart conduction abnormalities (prolonged QT intervals) at the highest doses [6]. ALX 404C, initially developed as a Tat antagonist, but shown to be also more effective as a CXCR4 antagonist, is no longer under consideration for development, because oral formulations are unlikely to be produced, while TAK 779, a CCR5 antagonist, has been discontinued because of local toxicity around subcutaneous injection sites[6]. Nevertheless, many new compounds which are now in development hold promise for the near future.

CCR5 Antagonists

It is not surprising to enlist many candidate drugs targeting CCR5, since CCR5 is the co-receptor mainly used for HIV transmission. Furthermore, R5 viruses remain present in approximately 50-60% of individuals who progress to AIDS, whereas a switch to X4 viruses occurs in the remaining 40-50% of individuals with disease progression, and is associated with a rapid decline of CD4 + T cells.

1. Maraviroc (UK427857) [8]:

Maraviroc has been approved by US FDA in October 2007. Maraviroc inhibits the binding of chemokines (ccmolif) ligand 3 (CCL3, also known as MIP-1α), and CCL5 (RANTES) (natural ligands of CCR5) to cell-membrane preparations of CCR5-expressing cells, and block CCR5 – signaling events after binding of

chemokines [9]. Pharmacokinetic data suggest that drug absorption is rapid, with maximum concentrations achieved 1-4 hrs after dosing [9]. Maraviroc has biphasic elimination, with a measured terminal half life of 9-14 hrs, following single doses. Maraviroc is a CYP 3A4 substrate; thus concentrations are increased by potent CYP 3A4 inhibitors (such as Ketoconazole, saquinavir and ritonavir) and decreased by CYP 3A4 inducers (such as rifampicin and efavirenz)[9].

Studies have demonstrated the efficacy of short-term (10 days) Maraviroc monotherapy at a dose of 100 mg twice a day [8], and have also assessed the efficacy and safety of maraviroc in patients who received 150 or 300 mg once a day, or twice a day. Adverse events (e.g. diarrhoea, nausea, headache and fatigue) were recorded in about 90% of patients, but the rate was not different from that in the placebo plus optimized background regimen group [9]. One of the major concerns with the use of CCR5 inhibitors, is the potential switch from R5 (CCR5 – using) to X4 (CXCR4 – using) viruses.

2. Vicriviroc (SCH 41760, SCH-D) [10]

Vicriviroc specifically binds to CCR5, and blocks cell migration that depends on CCL3, CCL4 and CCL5, and CCR5-dependent intracellular signaling at nanomolar concentrations. The plasma half-life of Vicriviroc is around 3-4 hrs. This drug does not substantially inhibit CYP450 enzymes, but it is a substrate for CYP3A4. Protease inhibitors such as ritonavir might enhance the plasma concentration of maraviroc and vicriviroc[10].

Vicriviroc shows broad antiviral activity against genotypic ally diverse R5-tropic HIV-I isolates in the nanomolar range. In studies, vicriviroc given as monotherapy in HIV-infected treatment-naïve patients for 14 days lowered the HIV RNA content by up to 1.6 log10. The doses which used in these studies are 25, 50 or 75 mg, once a day for 2 weeks. However, during follow-up, upto 57% (those at the lowest dose of 25 mg) of patients who were given vicriviroc showed a rebound in viral load to more than 50 copies per ml, compared with only 4% of patients in the efavirenz group [11].

Resistance to CCR5 drugs can also appear in the absence of a co-receptor switch. HIV-I might become resistant to vicriviroc or maraviroc by using CCR5, to which the inhibitor remains bound. Studies have shown that the virus might revert to R5 after discontinuation of CCR5 treatment [12],[13]. Mutations conferring resistance to CCR5 inhibitors, in the absence of a co-receptor switch, are often present in the V3 region of gp120: in cell culture experiments and in vivo [12].

3. Aplaviroc (GSK873140) [14]

Aplaviroc is a novel spirodiketopiperazine (SDP) based CCR5 antagonist,,but because of potential toxic effects on the liver, later clinical trials of Aplaviroc were stopped[14].

4. Other CCR5 Antagonists[15]

Other CCR5 antagonists under various stages of clinical development,are PRO-140 (Progenics pharmaceuticals), TAK 220 (Takeda Chemical Industries) and AMD 887 (AnorMED).

Because HIV entry inhibitors are gaining importance as therapeutic agents, both genotypic and phenotypic assays which are used to assess drug resistance need to be in place, in particular, determination of the virus co-receptor is needed before initiation of a drug regimen containing a CCR5 inhibitor [9].

Adverse Events with CCR5 Antagonists [10]

Several studies have drawn attention to the role of CCR5 in innate immunity against several pathogens, including Toxoplasma gondii, West Nile Virus, Pox virus, tuberculosis and others. Genetic, biological or chemical CCR5 knockout could be simultaneously protective against some pathogens (i.e. HIV) and harmful for other processes implicated in pathogen containment [9].

The issue of potential adverse events with CCR5 antagonists was raised, when, in patients who received vicriviroc, five developed malignant tumours (four lymphoma and one gastric adenocarcinoma), suggesting a possible unpredicted target-related adverse effect.

However, experts who reviewed the case histories, stated that they did not establish with any certainty, whether vicriviroc has a role in cancer [10].

CXCR4 ANTAGONISTS

The CXCR4 antagonists under development are AMD 11070(Anor MED) and KRH 2731(Kureha Chemical Industry Co. Limited). AMD 11070 is a strong and selective CXCR4 antagonist. It was equally active against X4 NRTI, NNRTI and PI resistant viruses. It was additive or synergistic when combined with other entry inhibitors (Enfuvirtide, AMD 887), reverse transcriptase (zidovudine, tenofavir) or protease inhibitors. This compound is currently under clinical trials [16] [17].

KRH 2731 (KRH-2731-5Hcl) is a novel orally bioavailable CXCR4 antagonist. It inhibited HIV-1X4 and R5X4 replication in animal models. The compound is under development by Kureha Chemical Industry Co. Limited.

Fusion Inhibitors[18]

1. Enfuvirtide

The large body of literature on Enfuvirtide, witnessed the record of Enfuvirtide as the first drug of the class of entry inhibitors to be approved in March 2003 by the US FDA, and to be licensed for the treatment of HIV-1 infection in the US, Australia and Europe [19].

Mechanism of Action [18]

Enfuvirtide is a synthetic analogue of the heptad repeat region (HR) 2 domain in gp41. Until recently, it was thought that Enfuvirtide interacted with HR1 to block the formation of the 6-helix bundle. However, recent research suggests that Enfuvirtide may target multiple sites in gp41 and gp120, including the gp120 co receptor binding site.

Pharmacokinetic Properties

Being a peptide, oral administration of enfuvirtide is not feasible, and on the other hand, intravenous administration is impractical and certainly not compatible with out patient self-administration. Nevertheless, several phase II and III clinical trials have shown that subcutaneous injection of enfuvirtide is generally well tolerated, and steady state concentrations of enfuvirtide are sustained for 12 hours following subcutaneous administration. Enfuvirtide has an apparent mean half-life of 3.8 hours after a single 90 mg subcutaneous dose. Absorption of enfuvirtide following subcutaneous administration to abdomen, thigh and arm was comparable, allowing HIV-1 infected patients the freedom to choose and to rotate, if necessary, the site of enfuvirtide injection among three anatomical sites.

Enfuvirtide did not inhibit the activities of CYP1A2, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 in an open label, crossover trial in 12 HIV infected adults [20].

Potential Drug Interactions

Enfuvirtide does not significantly affect the activity of the CYP enzymes or N-acetyltransferase. The presence of enfuvirtide had no clinically important or significant effects on the metabolism of the probe drugs. Enfuvirtide pharmacokinetics were not influenced by pretreatment with rifampicin or co-administration of ritonavir or saquinavir[21].

Therapeutic Efficacy

In the US, it is indicated in patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy, and in the EU, patients must be intolerant to previous antiretroviral regimens or have experienced treatment failure with at least one agent from each of the PI, NRTI and NNRTI classes.

The recommended dosage in adults aged >16 years is 90 mg twice daily, and in children and adolescents aged 6-16 years, it is 2 mg/kg twice daily, upto a maximum dosage of 90 mg twice daily.

Subcutaneous enfuvirtide improved virological and immunological outcomes in treatment-experienced HIV-infected adults who received 90 mg twice daily, in combination with an optimized background antiretroviral regimen compared with those who received optimized background therapy alone in the TORO trials. In the TORO trials (TORO 1, n=491 and TORO 2, n=504) a greater virological response to

enfuvirtide at week 48 was observed in patients with a baseline viral load <5 log 10 copies / ml, baseline CD4 + cell count ≥ 100 cells / μL and prior treatment with ≤ 10 antiretrovirals or ≥ 2 active antiretrovirals in the background regimen. The rate of adherence to enfuvirtide treatment was high in the TORO trials, and most patients reported self-injection of enfuvirtide as `very easy' or `easy' at weeks 8, 24 and 48[22],[23].

Health Related QOL improved significantly in enfuvirtide plus optimized background therapy recipients as compared to those receiving optimized background therapy only [24].

Tolerability

According to a pooled analysis of 48 weeks TORO trial data, local injection-site reactions (pain / discomfort [96%], erythema [91%], induration [90%] and nodules or cysts [80%]) occurred in 98% of enfuvirtide recipients, on at least one occasion. Excluding injection site reactions, enfuvirtide was generally well tolerated. Pneumonia and lymphadenopathy occurred significantly more often with enfuvirtide plus optimized background therapy, than in optimized background therapy only. The incidence of systemic hypersensitivity reactions related to enfuvirtide was <1%. Tolerability data for enfuvirtide in children and adolescents are derived from clinical trials. Tolerability of the drug in this population is essentially similar to that observed in adults, with injection-site reactions as the most frequently reported adverse effect [22],[23].

Viral Resistance [25]

HIV resistance to enfuvirtide is primarily associated with mutations in the gene encoding for gp41. Resistance mutations were mapped to the usually highly conserved glycine-isoleucine-valine (GIV) sequence of the HR1 domain of gp41, following in-vitro pass aging of HIV in the presence of increasing concentrations of enfuvirtide. Development of the resistant phenotype is thought to require mutations in two of the three amino acid residues in the GIV sequence.

Resistance to other antiretroviral agents does not confer cross-resistance to enfuvirtide [25]. Genotypic enfuvirtide resistance was rare in enfuvirtide naïve patients. The primary determinants of secondary resistance to enfuvirtide in isolates, recovered from patients who received enfuvirtide as monotherapy or in combination with other antiretrovirals, were mutations at gp41 amino acids 36-45[26].Resistant mutations often disappeared on discontinuation of enfuvirtide[27].

Pharmacoeconomic Considerations

The cost effectiveness of enfuvirtide has been analysed using decision-analysis models. In most analyses, the incremental cost-effectiveness ratios (ICERs) for enfuvirtide plus optimized background therapy, relative to optimized background therapy alone, were generally acceptable by current standards, remaining below the generally accepted thresholds of US$ 50,000 or 30,000 £ per life year, or quality-adjusted life-year (QALY) gained. The average cost of an enfuvirtide containing regimen is projected to range from US$ 1,617 to US$ 2,243 per 30 day supply. The 30 days cost for enfuvirtide alone is $ 1266[5].

Tifuvirtide (T-1249) [4]

Tifuvirtide is a second generation, once-daily HIV fusion inhibitor, also jointly developed by Trimeris and Roche. Similarly to enfuvirtide, tifuvirtide is administered subcutaneously, and blocks viral fusion by inhibiting the interaction of gp41 with the human cell. In case of enfuvirtide resistance, an alternative could be tifuvirtide. Inspite of promising results in phase I / II dose-escalation monotherapy studies, the announcement by Roche and Trimeris, that they have halted and put on indefinite hold further clinical development of tifuvirtide, was certainly a surprise. The decision was made not because of safety, efficacy and tolerability reasons, but because of challenges in achieving the technical profile required by the current investigational formulation of tifuvirtide. Despite halting clinical development of the drug, all participants now enrolled in clinical trial T-1249-105 will continue to receive free supplies of tifuvirtide to the 96-week endpoint, according to Roche. If necessary, Roche will amend the protocol to extend treatment with tifuvirtide beyond 96-

weeks for patients who are still receiving a benefit.

The Future of HIV Entry Inhibitors

The recent addition of entry inhibitors to the therapeutic armamentarium against HIV-1 offers new hope for HIV infected individuals, ranging from the treatment naïve to heavily treatment-experienced individuals. Enfuvirtide, an approved HIV fusion inhibitor, has a pivotal role in optimizing response in treatment-experienced patients receiving new drug combination. Maraviroc, a CCR5 antagonist, has been approved by US FDA (October, 2007), and is at present, an expanded access programme for drug-experienced patients. Other entry inhibitors are in different stages of preclinical and clinical development. With more entry inhibitors completing the complex path towards a clear clinical benefit, the number of combinations with each other, and with the other existing drugs targeting different steps of the viral life-cycle, will grow exponentially. The expectation is that the final outcome may result in extra years of life gained for individuals engaged in the battle against the HIV disease. The very rapid process of development that led to the discovery of enfuvirtide, starting from the basic investigations on viral entry, will remain in biomedical records as a successful example of 'bench to bedside' research.

(Table/Fig 2). Major Characteristics Of The HIV Entry Inhibitors.

Entry Inhibitors	Type	Target	Formulation	Stage	Company
Dextrin-2-sulfate	Compound	gp120	Vaginal gel	Phase III	ML Laboratories
PRO 542	Human Antibody like	gp 120	Intravenous infusion	Phase II (2006) Not under active development	Progenics
TNX 355	Human Antibody like	CD4	Intravenous infusion	Phase II (2006)	Tanox / Biogen
BMS 488043	Compound	gp 120 / CD4	Oral	Phase II	Bristol – Myers Squibb
VICRIVIROC (SCH 417690)	Compound	CCR5	Oral	Phase III (2007)	Schering - Plough
MARAVIROC (UK 427857)	Compound	CCR5	Oral	Approved-2007 expanded access	Pfizer
APLAVIROC (GSK 873140)	Compound	CCR5	Oral	Phase II (2006) Discontinued	Glaxo Smith Kline
PRO 140	Human Antibody	CCR5	Injection	Preclinical	Progenics
TAK 220	Compound	CCR5	Oral	Preclinical	Takeda
AMD 887	Compound	CCR5	Oral	Preclinical	Anor MED
AMD 070	Compound	CXCR4	Oral	Preclinical	Anor MED
KRH 2731	Compound	CXCR4	Oral	Preclinical	Kureha
ENFUVIRTIDE	Peptide	gp41	Subcutaneous injection	Commercially available	Trimeris / Roche
TIFUVIRTIDE	Peptide	gp41	Subcutaneous injection	Commercially available	Trimeris / Roche

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