Despite advances in the antiretroviral treatment of HIV infection, the AIDS epidemic claimed 3.1 million lives in 2005. It is estimated that 40.3 million people worldwide are now living with HIV, and that approximately five million people were newly infected with the virus in 2005.

There are currently several classes of drugs available which target different stages of the HIV lifecycle including: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors (e.g. enfuvirtide). Highly active antiretroviral therapy (HAART) with regimens consisting of a combination of these drugs has effectively reduced viral load and prolonged survival of patients with HIV. However, the inconvenience of these drug regimens (e.g. high pill burden and frequent dosing) and short- and long-term drug toxicity often leads to poor adherence to therapy and facilitates viral resistance to drug classes. Therefore, treatment options are limited in patients resistant to one or more drug classes, and drug-resistant virus may be transmitted to treatment-naive patients. New drugs with novel mechanisms of action are therefore being developed, targeting alternative stages of the HIV life cycle, that are effective against both wild type HIV and strains of HIV resistant to commonly used anti-HIV agents.

The CCR5 antagonists are a novel class of antiretroviral agent that prevent entry of HIV into host cells by blocking the CCR5 co-receptor. Initially five CCR5 antagonists were being developed, however only two remain in development, maraviroc and TAK-652. Maraviroc is furthest along in development, currently being evaluated in phase IIb/III trials in adults with HIV-1 infection, and is therefore most likely to be used first in the clinic.

This educational activity is designed for physicians in various specialties, including but not limited to infectious disease specialists, as well as for other healthcare professionals interested in or involved in the management of patients with HIV.

Learning Objectives

- Comprehend the disease burden and economic burden of HIV
- Understand existing therapy options for HIV
- Understand the unmet needs in therapy of HIV
- Understand the mechanism of action, drug interactions and adverse effects of maraviroc
- Understand the evidence base regarding the efficacy of maraviroc in the identified outcomes (HIV viral load, rebound of viral load, selectivity, resistance, etc.)

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the post-test and evaluation form, which can be found at the end of this article or online.

Disclosures

The authors and editor of this activity disclose no conflict of interest with any of the commercial interests related to this activity.

Commercial Support

This activity was not supported by any commercial interests.

CME Mission Statement

Core's CME Mission statement is intended to provide a description of the purposes of the overall CME program, the content areas and target audience of its CME effort, the general types of activities and services provided as well as an account of the expected results.

Core's CME mission and purpose is to develop a model CME program based on the ACCME Essentials and Standards; demonstrate 'exemplary' compliance in all of its CME program areas; and to develop model CME activities by use of its three continuing medical education goals.

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The goals of Core's continuing medical education program are to:

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2. Deliver continuing medical education activities that will be of value to physicians addressing the identified content area and information most relevant to patients.
3. Publish evidence-based, outcomes-oriented reviews of FDA-approved uses of drugs as well as off-label uses.

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The expected outcome of the CME Program is that studies of participants will show a high degree of correlation between satisfaction and patient care applicability regarding the subjects addressed by Core Medical Publishing. A secondary outcome will be continued ACCME accreditation and recognition its CME program.

Core Medical Publishing will continually improve its CME program through application of the ACCME Essentials and Standards and assessing the results of its individual activities and the overall CME program.
Proof of concept review

Maraviroc: the evidence for its potential in the management of HIV

Louise Profit

Core Medical Publishing, Knutsford, UK

Abstract

Introduction: New antiretroviral agents that are more convenient, better tolerated with fewer short- and long-term side effects, and that have novel resistance patterns are needed at all lines of therapy in patients infected with human immunodeficiency virus (HIV). Therefore, next generation products of current classes and alternative classes of antiretroviral agents are needed. The CC-chemokine receptor 5 (CCR5) antagonists are a novel class of antiretroviral agents that prevent the entry of HIV into host cells by blocking the CCR5 coreceptor. Within this class, maraviroc is the agent furthest along in development.

Aims: The aim of this review is to evaluate the emerging evidence for the use of the CCR5 antagonist maraviroc in antiretroviral treatment-naïve and treatment-experienced patients with HIV-1 infection.

Evidence review: Preliminary evidence from phase I/IIa short-term studies suggest that maraviroc monotherapy is effective at reducing HIV viral load, and is generally well tolerated. In-vitro evidence suggests that maraviroc will be effective in drug-naïve patients with CCR5-tropic virus, as well as in those with CCR5-tropic virus who have developed HIV resistance to existing antiretroviral regimens. However, it is not known how quickly resistance may develop to maraviroc in clinical practice.

Clinical potential: Current evidence supports the continued development of maraviroc as a potentially useful, alternative treatment for the management of HIV infection. Maraviroc monotherapy has a high potency and long half-life, allowing single-pill dosing. Therefore, it is expected that maraviroc will have a beneficial effect on patient adherence and viral load in combination with other antiretroviral agents. Maraviroc is only effective against CCR5-tropic virus, which predominates throughout infection but is more common in patients at the early asymptomatic stage of infection.

Key words: CCR5 antagonist, evidence, human immunodeficiency virus, maraviroc, outcomes, UK-427,857

Core evidence proof of concept summary for maraviroc in HIV infection

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Emerging evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-oriented evidence</strong></td>
<td></td>
</tr>
<tr>
<td>HIV viral load</td>
<td>Mean maximum viral load reduction between 1.6 and 1.84 log_{10} copies/mL after 10 days of monotherapy with maraviroc at clinical doses</td>
</tr>
<tr>
<td>Rebound of viral load</td>
<td>Delay in viral rebound after discontinuation of maraviroc monotherapy</td>
</tr>
<tr>
<td>Selectivity</td>
<td>Maraviroc selectively binds to CCR5, causing an allosteric change, and preventing R5 HIV from entering CD4 cells</td>
</tr>
<tr>
<td>Resistance</td>
<td>In vitro, maraviroc is effective against HIV variants resistant to existing antiretroviral agents. Preliminary evidence of CD4 cell increases in dual-tropic patients. Further confirmation is required</td>
</tr>
<tr>
<td><strong>Patient-oriented evidence</strong></td>
<td></td>
</tr>
<tr>
<td>Tolerability</td>
<td>Maraviroc is well tolerated in short-term studies, with a similar tolerability to placebo</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
<td>No evidence of prolongation of QTc interval. Postural hypotension at unit doses ≥600 mg</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>One case of serious hepatotoxicity reported. The DSMB considered this case highly unlikely to be related to maraviroc treatment, but could not rule out a contribution by maraviroc. Phase III data are required to fully assess hepatotoxicity</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Maraviroc is metabolized by CYP3A4 and is a substrate for Pgp. Dose adjustments are required when administered concomitantly with potent CYP3A4 inhibitors or inducers</td>
</tr>
</tbody>
</table>

CCR5, CC-chemokine receptor 5; CYP3A4, cytochrome P450 3A4; DSMB, Data Safety Monitoring Board; HIV, human immunodeficiency virus; Pgp, P-glycoprotein; R5 HIV, HIV that only uses the CCR5 receptor.
Maraviroc | proof of concept review

Scope, aims, and objectives

Maraviroc (UK-427,857; Pfizer) is a CC-chemokine receptor 5 (CCR5)-receptor antagonist in development for the treatment of human immunodeficiency virus (HIV) infection. It is currently being evaluated in phase IIb/III trials in adults with HIV-1 infection. The objective of this article is to review the preclinical and early clinical development evidence for the effectiveness of maraviroc against HIV-1 infection, and to assess its therapeutic potential.

Methods

English language medical literature databases were searched for appropriate articles related to the treatment of HIV infection with maraviroc. The searches were conducted on May 16, 2006 using the search terms “maraviroc OR UK-427,857.” The cut-off date was from the beginning of the database to the date of the search unless otherwise stated.

- Database of Abstracts of Reviews of Effects (DARE), http://www.york.ac.uk/inst/crd/crdatabases.htm
- Cochrane Database of Systematic Reviews (CDSR), http://www.cochrane.org/index0.htm
- Clinical Evidence (BMJ), http://www.clinicalevidence.com
- National Institute for Health and Clinical Excellence (NICE), http://www.nice.org.uk

After removal of duplicates, a total of 28 records were retrieved from PubMed and EMBASE; no additional citations were identified from the other databases (Table 1). Records were manually reviewed and 22 citations were excluded: nonsystematic reviews (n=3), and citations that mentioned maraviroc but did not investigate its preclinical or clinical use (n=19). No systematic reviews of maraviroc have been published. ClinicalTrials.gov identified four ongoing phase IIb/III clinical trials. Guidelines for the treatment of HIV were identified from the website of the British HIV Association (http://www.bhiva.org) and the AIDSinfo website (http://AIDSinfo.nih.gov).

Online abstracts from the following congresses were searched using the search strategy “maraviroc OR UK-427,857”, or were hand-searched:

- XVI International HIV Drug Resistance Workshop 2005, http://www.intmedpress.com/General/showSectionSub.cfm?SectionID=2&SectionSubID=1&SectionSubSubID=1
- 5th International Workshop on Clinical Pharmacology of HIV Therapy, 2004
- 7th International Workshop on Clinical Pharmacology of HIV Therapy, 2004
- 10th European AIDS Conference, 2005
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), all conferences from 2003 to 2005

A total of 21 abstracts were identified (Table 1). Among the relevant abstracts, six reported on the outcomes of preclinical studies, ten on the pharmacokinetics of maraviroc, and five on clinical data.

The searches on PubMed and IAS were updated on October 2, 2006. Two new records were identified, one of which was included in the review.

Disease overview

The AIDS epidemic

Despite advances in the antiretroviral treatment of HIV infection, the acquired immune deficiency syndrome (AIDS) epidemic claimed 3.1 million lives in 2005 (UNAIDS/WHO 2005). It is estimated that 40.3 million people worldwide are now living with HIV, and that approximately five million people were newly infected with the virus in 2005.

Table 1 | Evidence base included in the review

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of records</th>
<th>Full papers</th>
<th>Abstracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial search</td>
<td>28</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>records excluded</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>records included</td>
<td>6</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Search update, new records</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>records excluded</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>records included</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Level 2 clinical evidence (RCT)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

For definition of levels of evidence, see Editorial Information on inside back cover. RCT, randomized controlled trial.
**Pathophysiology of HIV infection**

HIV infects and destroys CD4-positive cells during the process of replication. As the virus continues to replicate, CD4-positive T cells are progressively depleted which leads to the onset of immunodeficiency, i.e. AIDS. When AIDS develops, the individual becomes vulnerable to opportunistic infections and rare malignancies such as pneumocystis carinii, cytomegalovirus, and Kaposi’s sarcoma.

**The HIV lifecycle**

The initial step in the HIV-1 lifecycle is viral attachment to the CD4-positive T-cell surface, followed by viral entry. This process involves the viral envelope protein (Env), which undergoes receptor-induced conformational changes and thereby mediates fusion between the viral and cellular membranes (Moore & Doms 2003; Fig. 1).

Env consists of a glycoprotein (gp) 120 subunit which binds to the cell surface CD4-positive receptor and induces a conformational change in gp120, exposing the coreceptor binding site in the V3 region of gp120. This site binds to one of the chemokine coreceptors, CCR5 (Deng et al. 1996; Dragic et al. 1996) or CXCR4 (Feng et al. 1996) and induces an additional conformational change in the Env transmembrane protein gp41, which leads to the insertion of its N-terminal fusion peptide into the target cell membrane. A triple-stranded coiled coil is formed by three HR1 domains from the N-terminal helical regions of each of the three gp41 ectodomains. The gp41 subunit then folds back on itself to allow the C-terminal helical region (HR2) to pack into grooves on the outside of HR1 to form a six-helical bundle formation. Consequently, the virus and cell membranes are brought into close proximity to initiate fusion and ultimately entry of the viral core into the target cell.

Once internalized, the virus is uncoated releasing genomic RNA and reverse transcriptase into the cytoplasm. Reverse transcriptase synthesizes a DNA copy of the single-stranded viral RNA. This is then integrated randomly into the host's chromosomal DNA by viral integrase (Chow et al. 1992). The provirus remains dormant until the cell is activated (Fauci 1988). Upon cell activation, the proviral DNA is transcribed into viral genomic RNA and viral mRNA by cellular enzymes. Subsequently, viral mRNA is translated into viral proteins. The enzyme HIV protease mediates the modification and assembly of these proteins into a mature, infectious virion. The virus particle is then released by budding from the cell membrane (Ho et al. 1987; Debouck 1992).

**HIV-1 variants**

HIV-1 variants differ in their use of coreceptors for entry. Variants may exclusively use the CCR5 coreceptor (CCR5-tropic or R5 viruses) or exclusively use the CXCR4 coreceptor (CXCR4-tropic or X4 viruses). Those variants that use either receptor (i.e. a mixture of R5 and X4 virus) are termed dual tropic or R5X4 viruses. The CCR5-tropic virus predominates in patients throughout infection.

**Current therapy options**

Currently, eradication of HIV infection cannot be achieved with existing regimens. Therefore, the goals of therapy are the prolonged suppression of viral levels to less than detection limits (<50 copies/mL for Amplicor assay, <75 copies/mL for VERSANT assay, and <80 copies/mL for NucliSens assay), with the aim to restore and preserve immunologic function, improve quality of life, and avoid HIV-associated morbidity and mortality (Gazzard 2005; DHSS 2006).

The host cells’ involvement in many stages of the virus lifecycle is a significant obstacle in the selective inhibition of viral replication without damage to the host. There are currently several classes of antiretroviral drugs available which may be used to target different stages of the HIV lifecycle, where replication may be prevented by selectively targeting the virus. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) act on intracellular viral targets, and entry/fusion inhibitors act on viral proteins to prevent viral fusion and thereby prevent virus entry into cells (Table 2). A combination of three or more drugs from these different classes (generally containing an NNRTI plus two NRTIs, or a boosted PI and two NRTIs) is commonly known as highly active antiretroviral therapy (HAART).
A comprehensive review of all current therapy options for the treatment of HIV is beyond the scope of this article. However, to aid the understanding of the mechanism of action and development of maraviroc, a review of the entry inhibitors, primarily the CCR5 antagonists, are summarized below. HIV entry inhibitors can be classified into three distinct classes, each targeting one of the three steps in the entry process: CD4 binding inhibitors, CCR5/CXCR4 coreceptor antagonists, and fusion inhibitors (Fig. 1).

**CD4 binding inhibitors**

There are several compounds in development that inhibit the initial interaction between gp120 and the CD4 receptor. Those most advanced in development include a soluble antibody-like fusion protein, PRO 542 (Progenics Pharmaceuticals Inc.); a CD4-specific monoclonal antibody, TNX-355 (Tanox Inc.); and a small molecule inhibitor, BMS-806 (Bristol-Myers Squibb).

**CCR5 antagonists**

Individuals who lack a functional CCR5 gene are highly resistant to HIV-1 infection, and patients with only one copy of a functional CCR5 gene demonstrate delayed CD4 depletion and slower progress to AIDS and death (Liu et al. 1996; Samson et al. 1996; Moore et al. 2004). Therefore, the CCR5 coreceptor is a novel target for prevention of HIV replication and disease progression. CCR5 antagonists inhibit virus entry by binding to a host cell protein, the CCR5 receptor, and inducing an allosteric change which renders the molecule unrecognizable to wild type R5 HIV.

---

**Table 2 | Antiretroviral agents currently licensed for the treatment of HIV-1 infection**

<table>
<thead>
<tr>
<th>Class and mechanism of action</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reverse transcriptase inhibitors (RTIs)</strong></td>
<td>Nucleoside RTIs (NRTIs)</td>
</tr>
<tr>
<td>Inhibit reverse transcription of the viral RNA into double-stranded DNA by the viral enzyme reverse transcriptase</td>
<td>Retrovir® (zidovudine)</td>
</tr>
<tr>
<td></td>
<td>Hivid® (zalcitabine)</td>
</tr>
<tr>
<td></td>
<td>Epivir® (lamivudine)</td>
</tr>
<tr>
<td></td>
<td>Videx® (didanosine)</td>
</tr>
<tr>
<td></td>
<td>Zerit® (stavudine)</td>
</tr>
<tr>
<td></td>
<td>Ziafer® (abacavir)</td>
</tr>
<tr>
<td></td>
<td>Viread® (tenofovir)</td>
</tr>
<tr>
<td></td>
<td>Emtriva® (emtricitabine)</td>
</tr>
<tr>
<td></td>
<td>Combivir® (zidovudine + lamivudine)</td>
</tr>
<tr>
<td></td>
<td>Epzicom® (USA) / Kivexa® (UK) (abacavir + lamivudine)</td>
</tr>
<tr>
<td></td>
<td>Truvada® (tenofovir + emtricitabine)</td>
</tr>
<tr>
<td></td>
<td>Trizivir® (abacavir + zidovudine + lamivudine)</td>
</tr>
<tr>
<td><strong>Nonnucleoside RTIs (NNRTIs)</strong></td>
<td>Viramune® (nevirapine)</td>
</tr>
<tr>
<td></td>
<td>Rescriptor® (delavirdine)*</td>
</tr>
<tr>
<td></td>
<td>Sustiva® (efavirenz)</td>
</tr>
<tr>
<td><strong>Protease inhibitors (PIs)</strong></td>
<td>Invirase® (saquinavir hard-gel capsule)</td>
</tr>
<tr>
<td>Inhibits the HIV protease enzyme which is required to cleave the polyprotein products of the gag and gag-pol genes into functional core proteins and viral enzymes. Inhibition results in the production of immature virus</td>
<td>Fortovase® (saquinavir soft-gel capsule)</td>
</tr>
<tr>
<td></td>
<td>Norvir® (ritonavir)</td>
</tr>
<tr>
<td></td>
<td>Viracept® (nelfinavir)</td>
</tr>
<tr>
<td></td>
<td>Crixivan® (indinavir)</td>
</tr>
<tr>
<td></td>
<td>Agenerase® (amprenavir)</td>
</tr>
<tr>
<td></td>
<td>Reyataz® (atazanavir)</td>
</tr>
<tr>
<td></td>
<td>Lexiva® (USA) / Telzir® (UK) (fosamprenavir)</td>
</tr>
<tr>
<td></td>
<td>Aptivus® (tipranavir)</td>
</tr>
<tr>
<td></td>
<td>Kaletra® (lopinavir + ritonavir)</td>
</tr>
<tr>
<td><strong>Entry inhibitors</strong></td>
<td>Fuzeon™ (enfuvirtide; T-20)</td>
</tr>
</tbody>
</table>
| Enfuvirtide is a peptide based on the sequence of the HR2 region. It binds to the triple-stranded coiled coil formed by the three HR1 domains, preventing the formation of the six-helix bundle, and hence inhibiting membrane fusion with the cellular target (Chen et al. 1995) | *Currently unlicensed in the UK.*
Initially, five small, orally available CCR5 antagonists were in clinical development; SCH-C (SCH-351125; Schering-Plough); TAK-779 (Takeda Chemical Industries Ltd), aplaviroc oc (GlaxoSmithKline), vicriviroc (SCH-417690; Schering-Plough), and maraviroc (Pfizer) (Table 3). However, only two remain with maraviroc being the furthest along in clinical development. Vicriviroc is in phase II for treatment-experienced patients. AnorMED Inc. currently has multiple lead candidates in preclinical testing including AMD887, and plans to select a lead candidate for clinical studies in 2006 (Anon. 2006a).

CXCR4 antagonists are also in development. The CXCR4 antagonist (AnorMED Inc.) has been shown to strongly inhibit viral infection by CXCR4-tropic virus in vitro (Schols et al. 2003). However, a safety trial with AMD070 in HIV-infected patients has been suspended (Anon. 2006b).

**Fusion inhibitors**

Currently, there is only one licensed fusion inhibitor—enfuvirtide (Fuzeon™, T-20; Trimeris Inc., Roche Laboratories) which is administered by subcutaneous injection (90 mg twice daily). It was approved in 2003 for use in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

A second-generation fusion inhibitor, tifuvirtide (T1249; Trimeris Inc.), has been developed which is more potent against HIV than enfuvirtide. However, formulation difficulties have halted its clinical development. Two additional next-generation fusion inhibitors are also in early-stage development by Trimeris and Roche, TRI-1144 and TRI-999. Preclinical data have reported that these peptides have potent antiviral activity and durable control of HIV replication in vitro (Delmedico et al. 2006).

**Unmet needs**

The benefits of HAART in the treatment of HIV-1 infection are well documented. Over the past 8 years, HAART regimens have been successful in dramatically reducing plasma viral load, delaying disease progression to AIDS, increasing CD4 cell counts, improving quality of life, and prolonging survival (Palella et al. 1998). However, several studies have shown that HAART regimens are not durable, and patients eventually experience virologic failure.

The advantages and disadvantages of regimens for treatment-naive patients preferred by recent US [Department of Health and Human Services (DHSS)] and British HIV Association (BHIVA) guidelines are indicated in Table 4 (Gazzard 2005; DHSS 2006). In patients experiencing virologic failure, these guidelines recommend determining factors which are affecting the plasma drug levels (e.g. poor adherence, intolerability, drug interactions). If the drug exposure is optimal, it is suggested that resistance testing may be performed and that the treatment regimen is augmented/changed.

However, the HIV Outpatients Study (HOPS) demonstrated that sequential HAART regimens were progressively less durable and many patients exhausted viable antiretroviral treatment options either due to resistance/cross-resistance or tolerability issues (Palella et al. 2002). Patients derived less benefit (i.e. reduced viral suppression) from successive, increasingly complex, and expensive salvage regimens which were often more difficult to tolerate.

An observational, longitudinal study demonstrated that 6 years after starting HAART, approximately 20% of treatment-experienced patients and 10% of treatment-naive patients were estimated to have triple drug-class failure (TCF) (Mocroft et al. 2004). In addition, it has been shown that approximately 20–40% of treatment-naive patients experience virologic failure within 2–3 years of starting their first HAART regimen (Gullick et al. 2000; Kaufmann et al. 2000; Le Moing et al. 2002; Phillips et al. 2002).

There are several factors that may limit the success of HAART including drug resistance, patient adherence, drug tolerability and toxicity, and drug interactions. Other factors which may influence success include the cost of therapy, and the presence of comorbid conditions such as substance abuse and addiction.

<table>
<thead>
<tr>
<th>CCR5 antagonist</th>
<th>Manufacturer</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc (UK-427,857)</td>
<td>Pfizer</td>
<td>Phase IIb/III (see text for details)</td>
</tr>
<tr>
<td>Vicriviroc maleate (SCH-D; SCH-417690)</td>
<td>Schering-Plough</td>
<td>Phase II</td>
</tr>
<tr>
<td>Piperazine-based antagonist</td>
<td>Schering-Plough</td>
<td>Incidence of five cases of cancer (four lymphoma, one stomach adenocarcinoma) reported in 118 patients in one phase II trial (March 2006)</td>
</tr>
<tr>
<td>SCH-C (SCH-351125)</td>
<td>Schering-Plough</td>
<td>Discontinued due to an unacceptable side-effect profile (effect on QT interval)</td>
</tr>
<tr>
<td>Aplaviroc hydrochloride (ONO-4128; GW-873140)</td>
<td>GlaxoSmithKline</td>
<td>Discontinued after cases of hepatotoxicity were reported in phase II and phase III trials (Anon. 2005d)</td>
</tr>
<tr>
<td>Spirodike-topiperazine-based antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAK-652</td>
<td>Takeda Chemical Industries Ltd</td>
<td>Under consideration for development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAK-779 lacked oral bioavailability and is no longer in clinical development</td>
</tr>
</tbody>
</table>

Table 3 | Clinical development of CCR5 antagonists: current status (May 2006)
### Table 4 | Preferred regimens for antiretroviral therapy in treatment-naïve patients (Gazzard 2005; DHSS 2006)

<table>
<thead>
<tr>
<th>Preferred regimen</th>
<th>Components</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-based regimen</td>
<td>Efavirenz</td>
<td>Efavirenz advantages: Potent antiretroviral activity, Availability of long-term efficacy data, Low pill burden and frequency (one tablet per day)</td>
<td>Efavirenz disadvantages: Neuropsychiatric side effects, Teratogenic in nonhuman primates, contraindicated in first trimester of pregnancy and avoid use in women with potential for pregnancy</td>
</tr>
<tr>
<td></td>
<td>+ lamivudine or emtricitabine + zidovudine or tenofovir</td>
<td>Zidovudine + lamivudine&lt;sup&gt;a&lt;/sup&gt; advantages: Extensive and favorable virologic experience, Ease of dosing (coformulation), No food effect Lamivudine has minimal side effects</td>
<td>Zidovudine + lamivudine&lt;sup&gt;a&lt;/sup&gt; disadvantages: Bone marrow suppression and GI intolerance with zidovudine</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir</td>
<td>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; advantages: Potent antiretroviral activity, Potential for once-daily dosing in treatment-naive patients, No food restriction with oral tablet formulation</td>
<td>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; disadvantages: Some reports of renal impairment with tenofovir Interactions with atazanavir and didanosine</td>
</tr>
<tr>
<td></td>
<td>+ lamivudine or emtricitabine + zidovudine or tenofovir</td>
<td>NRTI + emtricitabine&lt;sup&gt;b&lt;/sup&gt; advantages: Longer half-life than lamivudine, Once-daily dosing Truvada coformulation</td>
<td>NRTI + emtricitabine&lt;sup&gt;b&lt;/sup&gt; disadvantages: Less experience than lamivudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NNRTI class advantages:</strong> Established backbone of combination antiretroviral therapy</td>
<td><strong>NNRTI class disadvantages:</strong> Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; class advantages:</strong> Save NNRTI for future use, Longest prospective study data, including data on survival benefit</td>
<td><strong>Lopinavir/ritonavir&lt;sup&gt;c&lt;/sup&gt; class disadvantages:</strong> GI intolerance, Hyperlipidemia Preliminary data show lower drug exposure in pregnant women</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Zidovudine + lamivudine&lt;sup&gt;a&lt;/sup&gt; advantages:</strong> Most extensive and favorable virologic experience, Ease of dosing (coformulation), No food effect Lamivudine has minimal side effects</td>
<td><strong>Zidovudine + lamivudine&lt;sup&gt;a&lt;/sup&gt; disadvantages:</strong> Bone marrow suppression with zidovudine GI intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NRTI + emtricitabine&lt;sup&gt;b&lt;/sup&gt; advantages:</strong> Longer half-life than lamivudine, Once-daily dosing Truvada coformulation</td>
<td><strong>NRTI + emtricitabine&lt;sup&gt;b&lt;/sup&gt; disadvantages:</strong> Less experience than lamivudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NNRTI class advantages:</strong> Established backbone of combination antiretroviral therapy</td>
<td><strong>NNRTI class disadvantages:</strong> Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs</td>
</tr>
</tbody>
</table>

<sup>a</sup>Zidovudine + lamivudine coformulated as Combivir; <sup>b</sup>Tenofovir + emtricitabine coformulated as Truvada; <sup>c</sup>Lopinavir + ritonavir coformulated as Kaletra.

CYP3A4, cytochrome P450 3A4; GI, gastrointestinal; NNRTI, nonnucleotide reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.
Drug resistance

Cross-resistance between drug classes has limited the treatment options for patients who ultimately experience virologic failure to the three main classes of antiretroviral therapy. These patients typically experience viral rebound which ultimately leads to immunologic failure (decreased CD4 cell count) and clinical disease progression (Deeks et al. 2002; Ledergerber et al. 2004). A study in a random sample of HIV-infected American adults (receiving care during January and February 1996 and were alive in 1998) with a viral load of >500 copies/mL estimated that the prevalence of antiretroviral resistance to one or more drugs was 76%. The estimated prevalence of resistance ranged from 71% for NRTIs to 41% for PIs and 25% for NNRTIs, with almost 50% having multidrug resistance and 13% resistant to all three drug classes (Richman et al. 2004).

In patients with TCF the goal of treatment is to preserve immune function and to prevent clinical progression. Current salvage therapies for patients with TCF include the use of enfuvirtide which acts as an entry inhibitor, and the use of mega- and giga-HAART regimens (i.e. combining five or more drugs) (Miller et al. 2000; Fischl et al. 2003; Lazzarin et al. 2003). However, there are a number of disadvantages with these options, including potential safety and tolerability concerns with mega- and giga-HAART regimens. Enfuvirtide is generally well tolerated, apart from the high incidence of injection site reactions in 98% of patients. However, it is expensive (approximately US$20 000 per patient year) due to its complicated manufacturing process, and requires twice-daily injections.

Resistance to antiretroviral therapy is not only a problem in treatment-experienced patients, but is also an issue in treatment-naïve patients. Virus strains resistant to antiretroviral drugs may be transmitted to others (Ammaranond et al. 2003). The transmission of these drug-resistant HIV strains is associated with suboptimal virologic response to initial antiretroviral therapy, and shortens the time to first virologic failure in some patients (Little et al. 2002). A US study of 491 chronically infected treatment-naïve patients reported that approximately 9–11% of patients were infected with HIV strains conferring antiretroviral resistance, and this prevalence appeared to be increasing over time (Novak et al. 2005).

It is evident that there remains an unmet need for further treatment options for treatment-experienced patients who have exhausted all options and for treatment-naïve patients who are infected with drug-resistant virus. Alternative therapies with novel mechanisms of action, targeting alternative stages of the HIV lifecycle, and that are effective against both wild type HIV and strains of HIV resistant to commonly used antiretroviral drugs are required.

Factors contributing to drug resistance

The inconvenience and complexity of drug regimens with high pill burdens and frequent dosing often leads to poor adherence to therapy, and facilitates viral resistance to drug classes (Lucas 2005). Therefore, simple regimens with low pill burdens are needed to achieve a high degree of medication adherence and to help prevent the selection of drug resistance. Drug tolerability, and short-term and long-term toxicity, may also limit the duration of treatment and influence adherence. Currently available antiretroviral agents are associated with several, often severe, adverse events which compromise quality of life, and potentially impact on adherence to therapy (Table 4). These include lipid perturbations, fat redistribution (peripheral fat wasting and central adiposity), rash, diarrhea, nephrotoxicity, pancreatitis, peripheral neuropathy, and bone marrow suppression. A potent antiretroviral agent that is well tolerated, without significant short- and long-term side effects, and convenient would be an important addition to the current armamentarium, and may improve patient adherence to therapy.

Drug interactions among antiretroviral agents and with other concomitant medications are also challenging, and require specific attention when prescribing medications and monitoring patient progress. These drug interactions may lead to suboptimal levels of antiretroviral drug and emergence of resistance, or may lead to supraoptimal levels with a negative impact on tolerability and side effects. It would be desirable to have novel antiretroviral agents that are not metabolized by CYP450 to avoid pharmacokinetic interactions with existing antiretroviral agents (e.g. the PIs and efavirenz), and concomitant medications frequently administered to HIV-infected individuals (e.g. macrolide antibiotics, ketoconazole, statins, etc.).

Outcomes achieved with maraviroc in clinical development

Maraviroc is a potent and selective antagonist of CCR5, with broad-spectrum anti-HIV-1 activity (Dorr et al. 2005; Wood & Armour 2005). Maraviroc is in the late stages of clinical development, and phase llb/lll trials are ongoing (Table 5).

Reduction in viral load

A pharmacokinetic-pharmacodynamic disease model which predicted in-vivo antiviral activity of maraviroc was used to assist dosage selection for clinical phase Ila studies (Rosario et al. 2005).

The efficacy of maraviroc monotherapy was primarily assessed by studies determining the reduction in viral load, and the proportion of patients achieving a >1.0 log_{10} decrease in HIV-1 RNA. Level 2 evidence from two short-term, phase Ila studies showed that in 63 HIV-1-infected patients with CCR5-utilizing virus only (CD4 count >250 and plasma viral load >5000 copies/mL) treated with maraviroc monotherapy for 10 days, maximum viral load reductions ≥1.6 log_{10} were seen at all doses ≥100 mg twice daily (bid) (Fätkenheuer et al. 2005; Table 6). For the once-daily (qd) dosing regimen, mean viral load reductions at day 11 of 0.43, 1.13, and 1.35 log_{10} were seen for doses of 25, 100, and 300 mg, respectively. In comparison, reductions in viral load of 0.66, 1.42, 1.45, and 1.6 were seen for patients receiving 50, 100, 150, and 300 mg bid, respectively. At doses of 100 mg bid, 150 mg bid, and 300 mg qd/bid, all patients achieved a >1.0 log_{10} maximum reduction in HIV-1 RNA (Table 6).
Combination studies in vitro have shown that maraviroc is not antagonistic to existing antiretroviral agents (Dorr et al. 2005). Four ongoing phase II/III trials are currently determining the efficacy and safety of maraviroc in combination with other antiretroviral agents in both treatment-naïve and treatment-experienced patients (Table 5). An ongoing phase III study in treatment-naïve patients comparing maraviroc (300 mg qd/bid) in combination with zidovudine/lamivudine with efavirenz in combination with zidovudine/lamivudine demonstrated that after 16 weeks of treatment significantly more patients receiving maraviroc qd had detectable viral loads compared with those receiving maraviroc bid or efavirenz (Anon. 2005f). Consequently, the Data Safety Monitoring Board (DSMB) recommended the discontinuation of the once-daily dose arm in this study.

Rebound of viral load

In two short-term (10 day) monotherapy studies viral load rebound was not immediate after discontinuation of maraviroc therapy on day 11 (Fätkenheuer et al. 2005). This delay in viral rebound suggests that maraviroc may provide prolonged viral suppression which may be related to slow dissociation of the compound from the receptor.

Occupancy of the CCR5 receptor was determined by a macrophage inflammatory protein (MIP)-1-beta internalization assay. This assay demonstrated that CCR5 occupancy remained at >60% 5 days after discontinuation of maraviroc. A delay in viral rebound may be due to the prolonged occupancy of CCR5 by maraviroc, and its slow rate of dissociation (Fätkenheuer et al. 2005; Pullen et al. 2006).

Selectivity

In vitro, maraviroc was inactive against laboratory-adapted HIV-1 isolates which utilize CXCR4 as a coreceptor, indicating that the antiviral mechanism of maraviroc is exclusively CCR5-mediated. It also had no significant activity against a range of pharmacologically relevant enzymes, ion channels, and receptors, indicating the potential for a safe clinical profile (Dorr et al. 2005).

Resistance

In-vitro studies have shown that maraviroc is active against viruses resistant to existing antiretroviral agents, and that resistance to maraviroc is difficult to generate (Dorr et al. 2005). Limited evidence in abstract form suggests that there is no cross-resistance in vitro and in vitro [phytotohemoagglutinin (PHA)-stimulated peripheral blood lymphocytes] between maraviroc and other entry inhibitors (Westby et al. 2005a,b; Mosley et al. 2006). Maraviroc-resistant HIV-1 variants remained susceptible to the CCR5 antagonist aplaviroc, and to the fusion inhibitor enfuvirtide (Westby et al. 2005a; Mosley et al. 2006).

### Table 5 | Ongoing phase II/III clinical trials with maraviroc (http://www.clinicaltrials.gov, May 2006)

<table>
<thead>
<tr>
<th>ART regimen</th>
<th>Study design</th>
<th>Patient population</th>
<th>Comparator</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc 300 mg bid + Combivir&lt;sup&gt;a&lt;/sup&gt; bid</td>
<td>Multicenter (worldwide), randomized, double-blind&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HIV-1-infected (HIV-RNA &gt;2000 copies/mL) Treatment-naïve adults (1071 patients)</td>
<td>Efavirenz (600 mg qd) + Combivir&lt;sup&gt;a&lt;/sup&gt; bid</td>
<td>96 weeks, may be extended for an additional 3 years</td>
</tr>
<tr>
<td>Maraviroc 150 mg qd + OBT Maraviroc 150 mg bid + OBT Placebo + OBT</td>
<td>Multicenter (Europe and Australia, extended to US and Canada), randomized, double-blind</td>
<td>HIV-1-infected (HIV-RNA &gt;5000 copies/mL) Treatment-experienced adults failing current regimen Infected exclusively with CCR5-tropic virus (500 patients)</td>
<td>Placebo</td>
<td>48 weeks, may be extended for an additional year</td>
</tr>
<tr>
<td>Maraviroc 150 mg qd + OBT Maraviroc 150 mg bid + OBT Placebo + OBT</td>
<td>Multicenter (US and Canada), randomized, double-blind</td>
<td>HIV-1-infected (HIV-RNA &gt;5000 copies/mL) Treatment-experienced adults failing current regimen Infected exclusively with CCR5-tropic virus (500 patients)</td>
<td>Placebo</td>
<td>48 weeks, may be extended for an additional year</td>
</tr>
<tr>
<td>Maraviroc 150 mg qd + OBT Maraviroc 150 mg bid + OBT Placebo + OBT</td>
<td>Multicenter (worldwide), randomized, double-blind</td>
<td>HIV-1-infected (HIV-RNA &gt;5000 copies/mL) Treatment-experienced adults failing current regimen Not exclusively infected with CCR5-tropic virus (192 patients)</td>
<td>Placebo</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

<sup>a</sup>Zidovudine + lamivudine coformulated as Combivir.

<sup>b</sup>The maraviroc 300 mg qd + Combivir bid arm was discontinued by the Data Safety Monitoring Board for failure to meet preset criteria versus the comparator.

ART, antiretroviral therapy; bid, twice daily; HIV, human immunodeficiency syndrome; OBT, optimized background therapy (3–6 drugs based on treatment history and resistance testing); qd, once daily.
Modeling studies demonstrate that the CCR5 antagonists bind in a similar pocket of the CCR5 receptor within the transmembrane region (Westby et al. 2005b). The authors proposed that these compounds may hold the receptor in different conformations, thereby inhibiting entry of maraviroc-resistant variants.

Data from two phase II studies in 62 CCR5-tropic, HIV-infected patients treated with maraviroc for 10 days demonstrated that at day 11 CXCR4-tropic variants were detected in two patients (Westby et al. 2006). Clonal analysis suggested that this was probably due to the outgrowth of a pretreatment CXCR4-tropic reservoir, and not due to coreceptor switching under selective pressure from maraviroc.

One patient harboring virus with a dual-tropic phenotype (virus which can use CCR5 or CXCR4 to enter CD4 cells), which was an exclusion criterion for the phase Ila clinical study, was inadvertently enrolled. Despite receiving maraviroc 100 mg bid for 11 days, and CCR5 saturation and maraviroc plasma concentrations within the normal range of responding patients, the patient experienced no drop in viral load from baseline. At baseline and following cessation of maraviroc treatment, the R5 variant was dominant, suggesting a reversible predominance of CXCR4-utilizing virus in dual-tropic patients (Westby et al. 2004).

Recent data from a trial in 186 patients of whom 167 were dual-tropic showed that although viral load did not differ significantly following 24 weeks’ treatment with maraviroc 150 mg once or twice daily or placebo (mean viral load reductions of 0.91, 0.97, and 1.2 log_{10}, respectively), the mean increase in CD4 cell count was greater following maraviroc treatment compared with placebo (60 and 62 cells/L with 150 mg once or twice daily vs 35 cells/L) (Mayer et al. 2006).

### Safety and tolerability

Evidence from a combination of five phase I/lla double-blind, placebo-controlled, multiple-dose studies with maraviroc alone, and one drug–drug interaction study with oral contraceptives, in a total of 195 individuals including 66 HIV-infected patients have demonstrated that maraviroc is well tolerated at doses up to 300 mg twice daily (McHale et al. 2005). Five of these studies were of 7 to 10 days’ duration including dosing at the maximum dose of 1200 mg once daily; to date, published results from one safety study conducted for 28 days at the highest proposed clinical dose of 300 mg twice daily are available (Russell et al. 2003; McHale et al. 2005). No serious adverse events were reported and the adverse event profile was similar to placebo (Table 7).

### Cardiovascular effects

Observations of QT prolongation in healthy volunteers with SCH–C, a CCR5 antagonist developed by Schering-Plough, led to the termination of its development (Este 2002; Westby & van der Ryst 2005). QT prolongation can lead to the development of cardiac arrhythmias. Therefore, the effect of maraviroc on this clinical parameter was studied.

Preclinical studies and a clinical study in healthy subjects have demonstrated that single doses of maraviroc (100, 300, and 900 mg) have no clinically significant effect on the QTc interval (Davis et al. 2005; Mansfield et al. 2005). In addition, reported phase I/lla clinical trials have not demonstrated any evidence of clinically relevant prolongation of QTcF (McHale et al. 2005).

Postural hypotension was the dose-limiting adverse event in phase I trials, and occurred at rates in excess of placebo only at doses of ≥600 mg. Phase I/lla data from six studies reported a

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**Table 6 | Reduction in viral load with maraviroc monotherapy**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Study design</th>
<th>Treatment group</th>
<th>Mean reduction in HIV-1 RNA, log_{10} copies/mL (range)</th>
<th>Number of patients with &gt;1.0 log_{10} decrease in HIV-1 RNA/total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic HIV-infected patients with CCR5-tropic virus</td>
<td>Two 10-day studies</td>
<td>Maraviroc</td>
<td>25 mg qd</td>
<td>−0.43 (−1.08, 0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg bid</td>
<td>−0.66 (−1.37, 0.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 mg bid</td>
<td>−1.13 (−1.70, −0.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 mg bid</td>
<td>−1.42 (−1.84, −1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150 mg bid</td>
<td>−1.45 (−1.71, −0.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150 mg bid (fed)</td>
<td>−1.34 (−1.79, −0.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg qd</td>
<td>−1.35 (−1.62, −0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg bid</td>
<td>−1.60 (−2.42, −0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (study 1)</td>
<td>0.02 (−0.45, 0.56)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (study 2)</td>
<td>0.09 (−0.20, 0.27)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fed and fasted. bid, twice daily; HIV human immunodeficiency syndrome; qd, once daily.

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**Nature Medicine**

**Nat Med.**

**Fätkenheuer G et al.**

**McHale et al.**

**Russell et al.**

**Westby et al.**

**Este**

**Davis et al.**

**Mansfield et al.**

**McHale et al.**

**Westby & van der Ryst**

**Davis et al.**

**Mansfield et al.**

**Este**

**Davis et al.**

**Mansfield et al.**

**McHale et al.**
Maraviroc | proof of concept review

**Table 7 | Most frequent treatment-related adverse events reported with maraviroc (McHale et al. 2005)**

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n=111)</th>
<th>Maraviroc dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤150 mg (n=109)</td>
<td>300 mg (n=50)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (15)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (6)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (7)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Shading indicates highest proposed clinical dose.

total of two treatment-related discontinuations with maraviroc (600 mg qd) due to postural hypotension (McHale et al. 2005). A small study in healthy volunteers has suggested that maraviroc (900 mg, three times greater than the single dose suggested for clinical use) has a mild vasodilatory effect, reducing systemic vascular resistance (Russell et al. 2005).

**Liver toxicity**

Phase I and IIa safety data from six multiple-dose clinical studies (195 individuals including 66 HIV-infected patients) reported that clinically significant increases in liver function tests occurred in seven individuals at varying doses of maraviroc with no clear frequency or dose relationship (McHale et al. 2005). Four subjects had >3 x upper limit of normal (ULN) transaminases and three subjects had >1.25 to <2 x ULN bilirubin only. Mild to moderate elevations in creatinine (<2 x ULN) were observed in one study at doses of 1200 mg once daily. In addition, a pharmacokinetic crossover study in 12 healthy volunteers showed that maraviroc in combination with the PIs tipranavir (500 mg bid) plus ritonavir (200 mg bid) elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in five subjects after 8 days of dosing (Abel et al. 2005) which resolved after cessation of treatment. Four of these increases in transaminases were rated as grade 1 or 2 elevations, and one was a grade 3 change (>3 to <5 x ULN).

A single case of severe, possibly drug-related hepatotoxicity, with a rash, has been reported in the phase IIb/III clinical trials in a treatment-naïve patient after receiving five doses of maraviroc (300 mg qd) in combination with zidovudine and lamivudine (Anon. 2005a,b; Mayer 2005). The case is highly complex with several hepatotoxic drugs being administered prior to maraviroc, or initiated after discontinuation of blinded study drug (maraviroc) due to severe hepatotoxicity. The DSMB concluded that other potentially hepatotoxic medications administered during this episode, including isoniazid, cotrimoxazole, Combivir, acetyaminophen, and Kaletra, appeared to be more likely associated with the observed hepatotoxicity, but could not rule out that maraviroc may have contributed to the event.

**Food and drug interactions**

Food had no effect on the absorption of maraviroc in healthy volunteers (Abel et al. 2003a), or the efficacy of 10-day maraviroc monotherapy in HIV-infected patients (Fätkenheuer et al. 2005). Therefore, it is unlikely that food restrictions will be required with the administration of maraviroc in clinical practice.

Maraviroc is a substrate for CYP3A4 (cytochrome P450 3A4) but does not inhibit or induce any of the major P450 isozymes (Abel et al. 2003b, 2004a). In-vitro studies in caco-2 cells and in vivo studies in P-glycoprotein (Pgp) knockout mice suggest that it is also a substrate of Pgp (Walker et al. 2005). Several drug interaction studies in healthy volunteers have determined the effect of CYP3A4 inhibitors and inducers on maraviroc pharmacokinetics (Abel 2004b; Jenkins et al. 2004; Muirhead et al. 2004a,b; Russell et al. 2004). A study in HIV-infected patients showed that the plasma concentration [area under the plasma concentration time curve (AUC)] of a single dose of maraviroc 300 mg was reduced by 50% when administered with efavirenz 600 mg once daily. The maximum plasma concentration \(C_{\text{max}}\) was increased 1.8-fold in combination with Kaletra 400 mg twice daily (Muirhead et al. 2005).

A pharmacokinetic crossover study in 12 healthy volunteers over 8 days showed that the CYP3A4 inducer, tipranavir (500 mg bid), and the CYP3A4 inhibitor, ritonavir (200 mg bid) when dosed together with maraviroc did not have a significant impact on maraviroc (150 mg bid) drug concentrations, indicating that no dose adjustments are required when maraviroc is given with tipranavir 500 mg/ritonavir 200 mg twice daily (Abel et al. 2005).

**Resource utilization**

The treatment of HIV infection is challenging and many patients develop resistance to some or all classes of antiretroviral agents currently available. An antiretroviral agent that targets an alternative stage in the lifecycle of HIV with optimal reductions in viral load, and good tolerability with few short- and long-term toxicities, would have a significant impact on the prognosis of treatment-experienced patients.

The future use of maraviroc in the treatment of HIV infection will depend on the outcome of phase llb/III trials, and confirmation of the effect of the drug on liver function. There is no economic evidence for the use of maraviroc in the treatment of HIV. However, it is anticipated that clinical screening tests for CCR5 viral tropism may require additional resources. This increased cost will have to be offset by other clinical benefits.
Maraviroc is in the late stages of clinical development. Data from phase II/III studies determining its virologic effect compared with existing regimens are not yet available. However, it is likely that maraviroc may be used in combination with other antiretroviral drugs in both treatment-experienced and treatment-naive patients.

Initially, maraviroc may be beneficial in combination with other antiretroviral agents to treat patients infected with virus resistant to other drug classes. However, in treatment-naive patients with and without drug-resistant virus, it is likely that maraviroc will need to demonstrate an increase in the time to virologic or immunologic failure, delayed onset of new AIDS-defining events, increased life expectancy compared to current gold standard regimens, or fewer short- or long-term toxicities to generate widespread use in this patient population.

The epidemiology of R5 and X4-tropic HIV virus is important to understand what proportion of patients may benefit from a CCR5 antagonist. A cross-sectional analysis in which 979 antiretroviral-naive individuals initiating triple combination therapy were phenotyped found that 81.8% harbored R5 HIV variants, 18.1% harbored R5/X4 variants and only one individual (0.1%) harbored exclusively X4 variants (Brumme et al. 2005). Patients harboring R5/X4 variants had significantly higher plasma viral loads and lower CD4 cell counts ($P<0.0001$), and were more likely to have an AIDS-defining illness before therapy initiation compared with those patients with exclusively R5 variants (Brumme et al. 2005).

Maraviroc prevents R5 HIV from infecting otherwise healthy CD4 cells. The CCR5-tropic variant of HIV is common in the early stages of HIV infection, so maraviroc may be most useful in acute and early infection. CCR5 inhibitors are unlikely to be of benefit to patients harboring X4 viruses as the predominant or minority variant. Therefore, the effectiveness and safety of the use of maraviroc in HIV-infected patients who do not exclusively harbor CCR5-tropic virus needs to be verified. Preliminary evidence indicates that although maraviroc does not reduce viral load in dual-tropic patients, CD4 counts are increased significantly after 24 weeks (Mayer et al. 2006).

Clinical potential

Preliminary evidence indicates that maraviroc is likely to provide an alternative therapy for treatment-experienced patients, and for treatment-naive patients who are newly infected with drug-resistant virus. However, improvements in efficacy or short- and long-term side effects for maraviroc compared with currently available regimens in treatment-naive patients could positively impact on its use in this patient population provided that its use does not promote the selection of X4 HIV and more rapid disease progression.

Approximately 50–60% of treatment-experienced patients and 80–85% of treatment-naive patients are infected with the CCR5-tropic virus only. A viral tropism test (Monogram Biosciences, San Francisco, CA, USA) is available to determine the probability of successful treatment, but the cost and turnaround time (3–5 weeks) may serve as a barrier to the use of maraviroc and other CCR5 antagonists. The availability of a CXCR4 antagonist, which could be coadministered with the CCR5 antagonists, may alleviate the need for this test.

In-vitro evidence suggests that maraviroc is active against HIV resistant to current classes of antiretroviral agents. Although it has not been shown in vivo, it may be expected that HIV will develop resistance to CCR5 antagonists as with other antiretroviral agents. It has been suggested that there are three ways in which resistance may develop (Leonard & Roy 2006). Firstly, selective inhibition of CCR5-tropic virus with CCR5 antagonist therapy may lead to an increased rate of emergence of CXCR4 variants in patients who harbor both the R5 and X4 virus, and vice versa. Although this has not been observed in vitro or in vivo during short-course monotherapy studies, the potential for emergence of X4 HIV-1 variants during maraviroc therapy, and the ability of the virus to adapt to using a different coreceptor or to gain the ability to use the CCR5 coreceptor despite the presence of antagonist will require close monitoring during clinical trials. In-vitro studies have demonstrated that it is difficult to select maraviroc-resistant virus. In-vitro and short-course monotherapy studies suggest that the maraviroc-resistant virus appears to gain the ability to recognize and use the maraviroc-bound CCR5 coreceptor complex (Mosley et al. 2006).

Maraviroc has a long half-life and has potent activity against R5 HIV-1 in vitro. Short-term monotherapy studies in HIV-infected patients have provided evidence for reductions in viral load with maraviroc. The impact of maraviroc on duration of viral suppression, disease progression to AIDS, and survival has not yet been reported.

The doses of maraviroc studied in phase IIb/III trials have demonstrated good short-term tolerability. A case of serious drug-related hepatotoxicity has been reported in phase IIb/III studies with maraviroc. Although maraviroc was unlikely to be the cause of hepatotoxicity it could not be ruled out. The DSMB concluded that other potentially hepatotoxic medications administered during this episode were the more likely cause for the hepatotoxicity. Because the clinical development of aplaviroc was discontinued due to hepatotoxicity, there remains concern that hepatotoxicity may be a CCR5 antagonist class effect (Anon. 2005d). However, in the limited published data available to date, there have been no reports of hepatotoxicity with vicriviroc (SCH-D). The DSMB recommended that all phase IIb/III clinical studies in antiretroviral-naive and antiretroviral-experienced patients with maraviroc continued as currently designed (Anon. 2005e). Despite the early encouraging results with maraviroc and vicriviroc, further data from long-term studies in larger patient populations are required to confirm the safety profile of maraviroc.

The short-term lack of toxicity and low pill burden (i.e. single-pill dosing) with maraviroc monotherapy imply that it would not be expected to add to the existing burden with current regimens, and may potentially result in fewer discontinuations, and improved adherence to therapy if used in place of potentially more toxic agents. Maraviroc is metabolized by CYP3A4, therefore dose...
adjustments will be required when it is used in combination with commonly used antiretroviral agents such as the PI ritonavir (an inhibitor of CYP3A4) and the NNRTI efavirenz (CYP3A4 inducer).

In summary, maraviroc meets an unmet need for a well-tolerated drug that reduces viral load and targets a novel early stage in the HIV lifecycle, without pre-existing class resistance. Long-term clinical studies in combination with other antiretroviral drugs are awaited to determine what clinical benefits (safety and resistance profile and long-term antiviral effect) may be associated with the use of maraviroc.

References


Anon. DSMB recommends maraviroc (Pfizer CCR5 drug) phase 2b/3 studies continue as designed. October 14, 2005e. Available at: http://www.natap.org/2005/HIV/101805_05.htm (accessed August 1, 2006).


Maraviroc | proof of concept review


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Pullen S, Sale H, Napier C, Mansfield R, Holbrook M. Maraviroc is a slowly reversible antagonist at the human CCR5 in a CRE luciferase gene assay. Thirteenth Conference on Retroviruses and Opportunistic Infections; February 5–8, 2006; Denver, CO. Abstract 504.


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### Post-test

Please enter your answers in the answer key box in the right hand column of the next page.

1. **Maraviroc is being studied for use in patients with HIV.**
   To which drug class does maraviroc belong?
   - A. NNRTIs
   - B. NRTIs
   - C. CCR5 inhibitors
   - D. Protease inhibitors
   - E. Fusion inhibitors

2. **HIV-1 variants differ in their use of coreceptors for entry.**
   Variants may exclusively use the CCR5 coreceptor or the CXCR4 receptor. Which of the following statements is not true?
   - A. CCR5-tropic viruses predominate in patients throughout infection
   - B. CXCR4 trophic viruses emerge with time and with CD4 depletion
   - C. CXCR4 trophic viruses are detectable in about 50% of treatment-experienced patients
   - D. At the early asymptomatic stage of infection about 85% of patients are infected with HIV that is CXCR4 tropic
   - E. None of the above

3. **Several small, orally available CCR5 inhibitors were in clinical development; only maraviroc and vicriviroc remain.** The other CCR5 inhibitors were discontinued due to:
   - A. QT prolongation
   - B. Hepatotoxicity
   - C. Poor efficacy
   - D. Drug resistance
   - E. A, B and D

4. **The initial step in the HIV-1 lifecycle is viral attachment to the CD4-positive T-cell surface, followed by viral entry.**
   Pharmacologic entities that target this initial step include:
   - A. Fusion inhibitors (eg, Fuzeon)
   - B. CD4 binding inhibitors (eg, PRO 542; TNX-355)
   - C. Protease inhibitors (eg, Inverase; Kaletra)
   - D. CCR5 inhibitors (eg, Maraviroc)
   - E. A, B and D

5. **Acquired immune deficiency syndrome (AIDS) has claimed 3.1 million lives in 2005; 40.3 million people worldwide are infected with HIV.** Which of the below are considered current unmet needs in the use of HAART for treatment of HIV?
   - A. A drug with activity against viruses resistant to other therapies
   - B. A drug with improved tolerability
   - C. A drug with reduced pill burden
   - D. A drug with fewer drug-drug interactions
   - E. All of the above

6. **HIV therapies, particularly protease inhibitors, may be problematic due to drug-drug and drug-food interactions.** Maraviroc has clinically relevant interactions with the following:
   - A. Efavirenz
   - B. Tipranavir/ritonavir
   - C. Food
   - D. None of the above

7. **Adverse effects associated with existing HIV therapies include neuropsychiatric side effects, rash, and bone marrow suppression.** Adverse effects associated with maraviroc in clinical trials to date (phase IIb/III) include:
   - A. QT prolongation
   - B. Renal impairment
   - C. Hyperlipidemia
   - D. Insulin resistance
   - E. None of the above

8. **Maraviroc is in the late stages of clinical development, and phase IIb/III trials are ongoing.** Preliminary outcomes evidence regarding use of maraviroc for the treatment of HIV includes:
   - A. Clinically relevant HIV viral load reduction
   - B. Decrease in mortality
   - C. Improved quality of life
   - D. Delay in viral rebound after discontinuation
   - E. A and D
Evaluation of CME Activity

1. Please use the following rating scale to answer the following:
   
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<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
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<tr>
<td>Excellent</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
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</table>

   The clinical information was: □ □ □ □
   Author's command of the subject matter was: □ □ □ □

2. How well did the presentation method match your preferred learning style?
   □ Very well matched □ Quite well □ Fairly well
   □ Somewhat well □ Not well matched

3. Please rate how important this CME topic was to you as compared to other CME.
   
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<td>High</td>
<td>Average</td>
<td>Fair</td>
<td>Low</td>
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   My need for this particular topic □ □ □ □
   My need for this topic compared to other CME needs □ □ □ □
   Potential impact of this CME activity on my patients □ □ □ □

4a. Do you feel that your knowledge acquisition from this CME activity will potentially improve clinical outcome of patients?
   □ Yes □ No □ Not sure

4b. If you said “yes” to question 4a, what mechanism is likely to affect change?
   (Check all that apply.)
   □ Allowing selection of the most appropriate agent for the particular setting
   □ Increasing my understanding of the potential of this drug class
   □ Influencing my institutions protocols/guidelines for use of these agents
   Other

5. How well do you think the educational objectives were addressed?
   □ Fully □ Mostly □ Partially □ Not addressed

6. Please rate the educational components below:
   
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<tr>
<td>Strongly agree</td>
<td>Agree</td>
<td>Unsure or neutral</td>
<td>Disagree</td>
</tr>
</tbody>
</table>

   This topic addressed my knowledge gaps □ □ □ □
   This subject matter is worthwhile and useful □ □ □ □
   The information presented was well-organized □ □ □ □
   The course was engaging and interesting □ □ □ □
   The presentation provided adequate time for the topic □ □ □ □

7. Did you detect any clinical bias or product promotion?
   □ Yes □ No □ Not sure
   If yes please describe ________________________________

8. Please describe how this CME information could be useful in your practice?
   a. ________________________________
   b. ________________________________
   c. ________________________________

   Please list other CME topics that would be of value to you.
   1. ________________________________
   2. ________________________________
   3. ________________________________

9. Please provide us with any additional comments you have.
   ________________________________
   ________________________________
   ________________________________

Answer Sheet & Evaluation Form

Maraviroc: the evidence for its potential in the management of HIV

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2. A B C D E
3. A B C D E
4. A B C D E
5. A B C D E
6. A B C D E
7. A B C D E
8. A B C D E

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