Proof of concept review

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

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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

Outcome measure	Emerging evidence
Disease-oriented evidence	
HIV viral load	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
Rebound of viral load	Delay in viral rebound after discontinuation of maraviroc monotherapy
Selectivity	Maraviroc selectively binds to CCR5, causing an allosteric change, and preventing R5 HIV from entering CD4 cells
Resistance	*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
Patient-oriented evidence	
Tolerability	Maraviroc is well tolerated in short-term studies, with a similar tolerability to placebo
Cardiovascular effects	No evidence of prolongation of QTc interval. Postural hypotension at unit doses ≥600 mg
Liver toxicity	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
Drug interactions	Maraviroc is metabolized by CYP3A4 and is a substrate for Pgp. Dose adjustments are required when administered concomitantly with potent CYP3A4 inhibitors or inducers

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.

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.

- PubMed, http://www.ncbi.nlm.nih.gov
- EMBASE, http://www.datastarweb.com
- BIOSIS, http://www.datastarweb.com
- Database of Abstracts of Reviews of Effects (DARE), http://www.york.ac.uk/inst/crd/crddatabases.htm
- Cochrane Database of Systematic Reviews (CDSR), http://www.cochrane.org/index0.htm
- Public Library of Science, http://www.plos.org/journals/index.html
- Clinical Evidence (BMJ), http://www.clinicalevidence.com
- Clinical trial registers http://www.clinicaltrials.gov, and http://www.clinicalstudyresults.org
- National Institute for Health and Clinical Excellence (NICE), http://www.nice.org.uk
- National Guideline Clearinghouse, http://www.guideline.gov

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:

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	28	21
records excluded	22	0
records included	6	21
Search update, new records	1	1
records excluded	1	0
records included	0	1
Level 2 clinical evidence (RCT)	1	1

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

- XV International AIDS Society (IAS) Conference, all conferences from 2001 to 2005, http://www.iasociety.org
- XVI International HIV Drug Resistance Workshop 2005, http://www.intmedpress.com/General/showSectionSub.cfm?SectionID=2&SectionSubID=1&SectionSubSubID=1
- 10th–13th Conferences on Retroviruses and Opportunistic Infections (CROI), 2003–2006, http://www.retroconference.org
- 5th International Workshop on Clinical Pharmacology of HIV Therapy, 2004
- 7th International Congress on Drug Therapy in HIV Infection, 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.

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.

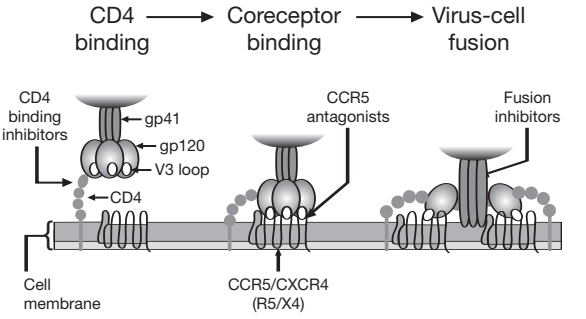

Fig. 1 | The mechanism of HIV-1 entry and fusion targets for inhibition (adapted from Moore JP, Doms RW. The entry of entry inhibitors: a fusion of science and medicine. *PNAS*. 2003;100:10598–10602. Copyright 2003 National Academy of Sciences, USA)

At the early asymptomatic stage of infection approximately 85% of patients are infected with HIV that only uses the CCR5 receptor (R5 HIV). The CXCR4-utilizing virus (X4 HIV) generally emerges with time and with CD4 depletion, with X4 virus detectable in approximately 50% of treatment-experienced patients (Philpott 2003; Brumme et al. 2005; Moyle et al. 2005; Hunt et al. 2006; Wilkin et al. 2006). The appearance of X4 HIV has been associated with rapid CD4 decline and disease progression, but it is unclear whether the emergence of X4 HIV is the cause or the effect (Koot et al. 1999; Moore et al. 2004; Troyer et al. 2005).

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 NNRTIs, or a boosted PI and two NRTIs) is commonly known as highly active antiretroviral therapy (HAART).

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

Class and mechanism of action	Drug
Reverse transcriptase inhibitors (RTIs)	
Inhibit reverse transcription of the viral RNA into double-stranded DNA by the viral enzyme reverse transcriptase	**Nucleoside RTIs (NRTIs)** Retrovir® (zidovudine) Hivid® (zalcitabine)[a] Epivir® (lamivudine) Videx® (didanosine) Zerit® (stavudine) Ziagen® (abacavir) Viread® (tenofovir) Emtriva® (emtricitabine) Combivir® (zidovudine + lamivudine) Epzicom® (USA) / Kivexa® (UK) (abacavir + lamivudine) Truvada® (tenofovir + emtricitabine) Trizivir® (abacavir + zidovudine + lamivudine) **Nonnucleoside RTIs (NNRTIs)** Viramune® (nevirapine) Rescriptor® (delavirdine)[a] Sustiva® (efavirenz)
Protease inhibitors (PIs)	
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	Invirase® (saquinavir hard-gel capsule) Fortovase® (saquinavir soft-gel capsule) Norvir® (ritonavir) Viracept® (nelfinavir) Crixivan® (indinavir) Agenerase® (amprenavir) Reyataz® (atazanavir) Lexiva® (USA) / Telzir® (UK) (fosamprenavir) Aptivus® (tipranavir) Kaletra® (lopinavir + ritonavir)
Entry inhibitors	
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)	Fuzeon™ (enfuvirtide; T-20)

[a]Currently unlicensed in the UK.

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 3 | Clinical development of CCR5 antagonists: current status (May 2006)

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

Initially, five small, orally available CCR5 antagonists were in clinical development; SCH-C (SCH-351125; Schering-Plough); TAK-779 (Takeda Chemical Industries Ltd), aplaviroc (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-naïve 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-naïve 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-naïve 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 4 | Preferred regimens for antiretroviral therapy in treatment-naïve patients (Gazzard 2005; DHSS 2006)

Preferred regimen	Components	Advantages	Disadvantages
NNRTI-based regimen	Efavirenz	**Efavirenz advantages:**	**Efavirenz disadvantages:**
		Potent antiretroviral activity	Neuropsychiatric side effects
		Availability of long-term efficacy data	Teratogenic in nonhuman primates, contraindicated in first trimester of pregnancy and avoid use in women with potential for pregnancy
		Low pill burden and frequency (one tablet per day)	
		NNRTI class advantages:	**NNRTI class disadvantages:**
		Save PI options for later use	Low genetic barrier to resistance
		Less dyslipidemia or fat distribution than PI-based regimens	Cross-resistance among NNRTIs
			Skin rash
			Potential for CYP450 drug interactions
	+ lamivudine or emtricitabine + zidovudine or tenofovir	**Zidovudine + lamivudine[a] advantages:**	**Zidovudine + lamivudine[a] disadvantages:**
		Extensive and favorable virologic experience	Bone marrow suppression and GI intolerance with zidovudine
		Ease of dosing (coformulation)	
		No food effect	
		Lamivudine has minimal side effects	
		Lamivudine + tenofovir advantages:	**Lamivudine + tenofovir disadvantages:**
		Good virologic response when used with efavirenz	Some reports of renal impairment with tenofovir
			Interactions with atazanavir and didanosine
		Once-daily dosing	
		No food effect	
		NRTI + emtricitabine[b] advantages:	**NRTI + emtricitabine[b] disadvantages:**
		Longer half-life than lamivudine	Less experience than lamivudine
		Once-daily dosing	
		Truvada coformulation	
		NNRTI class advantages:	**NNRTI class disadvantages:**
		Established backbone of combination antiretroviral therapy	Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs
PI-based regimen	Lopinavir/ritonavir	**Lopinavir/ritonavir[c] advantages:**	**Lopinavir/ritonavir[c] disadvantages:**
		Potent antiretroviral activity	GI intolerance
		Potential for once-daily dosing in treatment-naïve patients	Hyperlipidemia
			Preliminary data show lower drug exposure in pregnant women
		No food restriction with oral tablet formulation	
		PI class advantages:	**PI class disadvantages:**
		Save NNRTI for future use	Metabolic complications—fat malnutrition, dyslipidemia, insulin resistance
		Longest prospective study data, including data on survival benefit	Potential for drug interactions with CYP3A4 inhibitors and substrates
	+ lamivudine or emtricitabine + zidovudine	**Zidovudine + lamivudine[a] advantages:**	**Zidovudine + lamivudine[a] disadvantages:**
		Most extensive and favorable virologic experience	Bone marrow suppression with zidovudine
			GI intolerance
		Ease of dosing (coformulation)	
		No food effect	
		Lamivudine has minimal side effects	
		NRTI + emtricitabine[b] advantages:	**NRTI + emtricitabine[b] disadvantages:**
		Longer half-life than lamivudine	Less experience than lamivudine
		Once-daily dosing	
		Truvada coformulation	
		NNRTI class advantages:	**NNRTI class disadvantages:**
		Established backbone of combination antiretroviral therapy	Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs

[a]Zidovudine + lamivudine coformulated as Combivir; [b]Tenofovir + emtricitabine coformulated as Truvada; [c]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 $US20 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 IIb/III 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 IIa 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 IIa 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).

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

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

[a]Zidovudine + lamivudine coformulated as Combivir.
[b]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.

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* [phytohemoagglutinin (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 6 | Reduction in viral load with maraviroc monotherapy [Reprinted by permission from Macmillan Publishers Ltd: *Nature Medicine* (Fätkenheuer G et al. *Nat Med.* 2005;11:1170–1172), copyright 2005]

Patient population	Study design	Treatment group	Mean reduction in HIV-1 RNA, log_{10} copies/mL (range)		Number of patients with >1.0 log_{10} decrease in HIV-1 RNA/total number of patients	
			Day 11	Nadir	Day 11	Nadir
Asymptomatic HIV-infected patients with CCR5-tropic virus	Two 10-day studies Phase IIa, randomized, placebo-controlled	**Maraviroc**				
		25 mg qd	–0.43 (–1.08, 0.02)	–0.59 (–1.10, 0.02)	1/8	1/8
		50 mg bid	–0.66[a] (–1.37, 0.40)	–0.86 (–1.37, –0.14)	4/8	5/8
		100 mg qd	–1.13 (–1.70, –0.43)	–1.25 (–1.70, –0.61)	5/8	6/8
		100 mg bid	–1.42[a] (–1.84, –1.04)	–1.68 (–2.10, –1.37)	7/7	7/7
		150 mg bid	–1.45 (–1.71, –0.90)	–1.77 (–2.16, –1.43)	7/8	8/8
		150 mg bid (fed)	–1.34 (–1.79, –0.51)	–1.74 (–2.09, –1.13)	7/8	8/8
		300 mg qd	–1.35 (–1.62, –0.95)	–1.60 (–2.08, –1.14)	7/8	8/8
		300 mg bid	–1.60 (–2.42, –0.78)	–1.84 (–2.42, –1.49)	7/8	8/8
		Placebo (study 1)	0.02 (–0.45, 0.56)	–0.32 (–0.63, 0.11)	0	0
		Placebo (study 2)	0.09 (–0.20, 0.27)	–0.32 (–0.63, 0.11)	0	0

[a]Fed and fasted.
bid, twice daily; HIV human immunodeficiency syndrome; 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 IIa 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/IIa 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/IIa 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/IIa data from six studies reported a

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

Adverse event, n (%)	Maraviroc dose			
	Placebo (n=111)	≤150 mg (n=109)	300 mg (n=50)	600–1200 mg (n=61)
Headache	17 (15)	19 (17)	12 (24)	18 (30)
Dizziness	7 (6)	8 (7)	5 (10)	27 (44)
Nausea	6 (5)	1 (1)	6 (12)	16 (26)
Asthenia	8 (7)	5 (5)	3 (6)	16 (26)
Flatulence	6 (5)	3 (3)	7 (14)	8 (13)
Rhinitis	1 (1)	2 (2)	2 (4)	14 (23)
Postural hypotension	1 (1)	0 (0)	0 (0)	14 (23)
Abnormal vision	2 (2)	1 (1)	1 (2)	12 (20)
Conjunctivitis	0 (0)	0 (0)	0 (0)	14 (23)
Somnolence	3 (3)	0 (0)	0 (0)	12 (20)
Abdominal pain	3 (3)	1 (1)	2 (4)	7 (11)

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 vasodilatatory 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, acetaminophen, 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 isoenzymes (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_{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 IIb/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.

Patient group/population

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-naïve 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-naïve 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-naïve 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-naïve 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-naïve 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-naïve 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-naïve 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 preexisting 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.

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