Although potent anti-HIV therapy has dramatically reduced the morbidity and mortality of HIV-1 infection in resource-rich settings [1], it continues to be associated with considerable toxicity, drug-drug interactions, difficulties in adherence, and elevated cost. Early immune deterioration, tissue compartmentalization, cellular reservoirs, masking by host components, subversion of the cytokine milieu for its own replicative advantage, and steady emergence of drug resistance and immune escape variants are major obstacles that HIV-1 poses to its eradication under the current treatment paradigm. As a result, better antiretroviral drugs and treatment strategies continue to be pursued.

Small-molecule chemokine receptor antagonists are a new class of antiretrovirals (ARVs) that exert noncompetitive allosteric inhibition of the chemokine receptors CCR5 and CXCR4, which are essential for HIV entry. Whereas CCR5 is the coreceptor used by macrophage-tropic viruses, CXCR4 is predominantly used by T lymphocyte–tropic variants [2, 3]. By inhibiting these coreceptors, chemokine receptor antagonists impede the release of gp41 from its metastable conformation within HIV-1 envelope, thereby blocking the fusion between the viral and the cellular membranes.

Data from different cohort studies in regions affected by clade B HIV-1 demonstrate that 81%–88% of HIV-1 variants in treatment-naive patients are CCR5 tropic and that virtually all the remaining variants are dual/mixed (D/M) tropic (i.e., are able to utilize both CCR5 and CXCR4 coreceptors). In treatment-experienced patients, 49%–78% of variants are purely CCR5 tropic, 22%–48% are D/M tropic, and 2%–5% exclusively utilize CXCR4 [4–6].

A 32-bp deletion in the CCR5 gene (CCR5Δ32), which results in a frameshift and truncation of the normal CCR5 protein, was identified in a few persons who had remained uninfected after exposure to CCR5-tropic HIV-1 viruses [7]. This allele is common in white of European origin, with prevalence near to 10%, but is absent among East Asian, American Indian, Tamil Indian, or African ethnic groups [8, 9]. HIV infection in persons homozygous for CCR5Δ32 (~1% of white Northern Europeans) is extremely rare, and, when it occurs, it is caused by viral strains that utilize CXCR4 for viral entry [10]. Moreover, HIV-infected individuals who are heterozygous for CCR5Δ32 have slower rates of disease progression [11]. Early reports suggested that this deletion had no apparent effect on the functioning of the immune system, in spite of the deletion of a CCR5 motif that is localized intracellularly [3]. These findings prompted pharmaceutical companies to develop a CCR5 antagonist for clinical use.

The small-molecule CCR5 antagonists aplaviroc (GlaxoSmithKline [GSK]), vicriviroc (Pfizer), and maraviroc (Schering-Plough) have reached phases 2b and 3 of clinical development. The antiviral potency of these compounds notwithstanding, concerns about possible detrimental consequences of CCR5 inhibition were raised from the very beginning of these clinical trials.

Numerous host defense cells express CCR5, which is important for the initiation of immune responses. Whereas the congenital absence of CCR5 may be reasonably well tolerated by natural compensatory mechanisms, it is unclear whether the acute effects of pharmacological blockade of CCR5 would be as well tolerated. CCR5 blockade precludes trafficking of effector cells to sites of tissue inflammation. This effect has been related to enhanced allograft tolerance but also to a heightened risk of serious West Nile virus infection in persons homozygous for CCR5Δ32. On the other hand, lower rates of the immune reconstitution syndrome have been suggested for HIV-infected patients treated with a regimen including a CCR5 antagonist [12]. Could the administration of a CCR5 antagonist, in addi-
tion, increase the risk of opportunistic infections and malignancies in HIV-infected persons?

Independently of concerns about possible unknown side effects of CCR5 inhibitors in clinical practice, the recently presented positive results of the MOTIVATE 1 and 2 trials at 24 weeks follow-up is a cause for cautious optimism. These studies conducted with maraviroc plus optimized background therapy (OBT) in a treatment-experienced population, harboring only CCR5 tropic virus, have shown significantly superior virologic control and increases in CD4 cell count compared with placebo plus OBT. Indeed, adverse events, severe adverse events, AIDS-defining events, and laboratory abnormalities (including those in liver enzymes) occurred with similar frequency across the placebo and maraviroc groups [13, 14].

In this issue of the Journal, Gulick et al. [15] also report a potent virologic suppression through 24 weeks, further supporting the anti–HIV-1 activity of the CCR5 inhibitor family. However, a slightly larger number of malignancies in ARV-experienced subjects receiving an optimized ARV regimen (OR) plus vicriviroc than in those treated with an OR plus placebo (6 vs. 2) were observed. Of note, neoplasms found in the vicriviroc arm were of diverse cell types (2 Hodgkin disease, 2 non-Hodgkin lymphoma, 1 gastric adenocarcinoma, and 1 human papilloma virus–related squamous cell carcinoma). Indeed, the case of Hodgkin disease and that of non-Hodgkin lymphoma occurred in subjects previously treated for Hodgkin disease. In comparison, the 2 malignancies in the placebo group were squamous carcinomas.

As the authors mention in the discussion, malignancies continue to occur commonly in patients with advanced diseases despite effective ARV therapy. This occurrence complicates the establishment of a clear correlation between vicriviroc therapy and an increased risk of cancer. Given the antiviral potency of vicriviroc, the clinical need for orally bioavailable entry inhibitors, the lack of significant differences in cancer risk between the 2 treatment arms, the absence of a clear causal relationship between vicriviroc exposure and development of cancer, and the fact that other CCR5 antagonists have not been associated with increased risk for malignancies so far warrant continuing the study of this compound and others of its class. In any case, ensuing studies of CCR5 antagonists should incorporate strict tumor surveillance and long-term follow-up to address properly the potential for immune deregulation, opportunistic infections, and malignancies.

Early clinical trials involving CCR5 antagonists also raised concerns about the potential liver toxicity of these compounds. The development of aplaviroc (GSK) had to be terminated because a number of patients developed severe hepatotoxicity [16]. The fact that one subject included in the maraviroc trials also developed severe liver toxicity suggested that hepatotoxicity could be a "class" effect. It was later shown, however, that the individual with liver toxicity while receiving maraviroc was also receiving other potentially hepatotoxic drugs and was not properly managed when liver toxicity was detected [17]. Nevertheless, this case was only among hundreds of individuals receiving that drug. In this issue, Gulick et al. [15] do not report differences in aspartate aminotransferase/alanine aminotransferase changes between the vicriviroc and placebo arms. For most of us running clinical trials, our impression is that hepatotoxicity does not seem thus far to be a major complication of CCR5 antagonists (other than for aplaviroc). Nonetheless, there is an important need for clinical trials addressing the hazard for liver toxicity of CCR5 antagonists in patients with hepatitis C virus (HCV) or HBV coinfection. These patients represent up to 50% of those followed in areas where HIV, HBV, and HCV coinfections overlap and are more likely to experience ARV-related liver toxicity.

Another important issue that remains to be defined is the outcome of individuals with advanced HIV disease harboring D/M-tropic or CXCR4-tropic viruses who are treated with a CCR5 antagonist [18]. In these subjects, incomplete virological suppression might facilitate the emergence of CXCR4 viruses, which, in turn, might accelerate disease progression. Reports suggest, however, that coreceptor switch is, at most, a rare cause of viral escape under treatment with CCR5 antagonists. Wilkin et al. [19] showed that 10% of individuals with CCR5 virus at the screening phase for the AIDS Clinical Trials Group 5211 study presented with D/M-tropic viruses at study entry. Interestingly, treatment with vicriviroc in these subjects was not associated with a reduction in CD4 cell counts [15]. Indeed, CD4 cell counts also remained stable in subjects treated with vicriviroc who experienced a confirmed switch in coreceptor usage. Although virologic and immunologic responses were lower in subjects with D/M viruses than in those with CCR5 viruses at entry, they were invariably better for subjects receiving vicriviroc than for placebo recipients, regardless of viral tropism.

The urgent need of active compounds for treating individuals with advanced HIV disease harboring multidrug-resistant viruses should foster further investigations of the role of CCR5 antagonists in salvage therapy.

CCR5 is an appealing target for inhibition. In addition to the use of small-molecule receptor antagonists discussed above, other strategies, such as use of short interfering RNAs, have also been shown to impede the expression of chemokine receptors [20]. On the completion of the ongoing pilot studies, the demonstration that this strategy is tolerable, safe, and efficacious should prompt the development of clinical trials of agents that block CCR5 gene expression.

Finally, it is also important to assess the role of CCR5 inhibitors in the prevention of HIV infection. Many carriers of the CCR5 partial deletion may be resistant to the acquisition of HIV infection [21, 22].
Given that dendritic and Langerhans’ cells in vaginal and rectal mucosa mostly express CCR5 and rarely CXCR4, several CCR5 inhibitors, as well as other entry inhibitors, are being investigated as microbicides. Issues related to safety, potency, social acceptance, and cost may determine the clinical success of microbicides. Studies are ongoing to evaluate the combined protective effect of vaccines and microbicides in nonhuman primate models.

In their study, Gulick et al. [15] help to clarify the role of CCR5 entry inhibitors in HIV therapeutics. The currently available data support the continuation of the development of CCR5 antagonists in different settings related to HIV-1 infection. If safety issues do not emerge, these compounds could be positioned for use from very early stages of HIV infection (even as first-line therapy) to salvage strategies in patients with CCR5-tropic viruses. Further assessment of drug-related side effects may be very helpful for the proper positioning of CCR5 inhibitors in the anti-HIV-1 armamentarium.

References

In the 15 July issue of the Journal, in the editorial commentary by Clotet (Clotet B. CCR5 inhibitors: promising yet challenging. J Infect Dis 2007; 196:178–80), there is an error in the fifth paragraph of the article: the first sentence should read as “The small-molecule CCR5 antagonists aplaviroc (GlaxoSmithKline [GSK]), vicriviroc (Schering-Plough), and maraviroc (Pfizer) have reached phases 2b and 3 of clinical development.” The author regrets this error.