Maraviroc: perspectives for use in antiretroviral-naive 
HIV-1-infected patients

Linos Vandekerckhove1,2*, Chris Verhofstede2 and Dirk Vogelaers1

1AIDS Reference Centre, Gent University Hospital, De Pintelaan 185, 9000 Gent, Belgium; 2AIDS Reference 
Laboratory, Gent University, De Pintelaan 185, 9000 Gent, Belgium

Maraviroc (Pfizer’s UK-427857, Selzentry or Celsentri outside the USA) is the first agent in the new class 
of oral HIV-1 entry inhibitors to acquire approval by the US Food and Drug Administration and the 
European Medicine Agency. Considering the mechanism of action, it is expected that this drug will 
be effective only in a subpopulation of HIV-1-infected people, namely those harbouring the R5 virus. 
The favourable toxicity profile of the drug has been demonstrated in Phase III clinical trials in treatment-
naive (MERIT) and treatment-experienced (MOTIVATE) patients. In the latter population, maraviroc 
showed a superior antiviral efficacy and immunological activity compared with optimized backbone 
therapy + placebo. However, in MERIT, a prospective double-blind, randomized trial in treatment-naive 
patients, maraviroc + zidovudine/lamivudine failed to prove non-inferiority to efavirenz + zidovudine/ 
lamivudine as standard of care regimen in the 48 week intention-to-treat analysis. Using an assay with 
higher sensitivity for minority CXCR4-using (X4) HIV variants (the enhanced Trofile™ assay— 
Monogram), non-inferiority was reached for the maraviro-c versus efavirenz-based combination. These 
data indicate the important impact of the sensitivity of tropism testing on treatment outcome of mara-
viro-c-containing regimens. This paper discusses both the prospective and retrospective analyses of 
the MERIT data and highlights the impact of these results on daily practice in HIV care.

Keywords: antiretroviral-naive patients, chemokine receptor antagonist, MERIT

Introduction

The emergence of resistance to antiretroviral agents for the treat-
ment of HIV-1 infection has fuelled the search for new drug 
classes with a novel mechanism of action.1 Chemokine (C-C 
motif) receptor 5 (CCR5) antagonists interfere with viral–cellular 
interactions in the entry process. Preceding HIV-1 entry, viral 
envelope glycoprotein (gp120) binds to the CD4 receptor, resulting 
in a conformational change that allows the subsequent interaction 
with a CCR5 or chemokine (C-X-C motif) receptor 4 (CXCR4) 
expressed on the surface of the target cell.2–4 Further molecular 
rearrangements initiate gp41-mediated membrane fusion.

Three CCR5 antagonists entered clinical evaluation, of which 
one was discontinued because of toxicity (aplaviroc, GSK), one is 
currently still in clinical investigation5 (vicriviroc, Schering-
Plough) and one is US Food and Drug Administration (FDA)/ 
European Medicine Agency-approved and marketed (maraviroc, 
Pfizer). The FDA approved the use of maraviroc in treatment-
experience HIV-1 patients on 7 August 2007. The expanded 
access programme for maraviroc was opened in June 2007 in 
several European countries. The favourable toxicity profile of 
maraviroc has been proven in Phase III trials in treatment-naive 
(MERIT: a multicenter, randomized, double-blind, comparative 
trial of a novel CCR5 antagonist, maraviroc versus efavirenz, 
both in combination with zidovudine/lamivudine, for the treatment 
of antiretroviral-naive subjects infected with R5 HIV-1)6 and 
treatment-experienced (MOTIVATE: maraviro-c plus optimized 
background therapy in viremic, ART experienced patients infected 
with CCR5-tropic HIV-1)7 patients.

This article focuses on the MERIT study. The 48 week 
results of this study were presented at the Fourth International 
AIDS Society Conference on HIV Pathogenesis, Treatment and 
Prevention (Sydney, 2007).

Before introducing a novel class in first-line regimens, robust 
proof of potency, durability, convenience and safety comparable 
to the currently recommended first-line combinations [two 
nucleoside reverse transcriptase inhibitors (NRTIs) plus either a 
non-NRTI (NNRTI) or a boosted protease inhibitor] must be 
demonstrated. Two other challenging issues with regard to the 
introduction of maraviroc into clinical practice were: (i) to opti-
mize the accuracy and reliability of tropism determination 
assays; and (ii) to prove long-term safety (extending the conven-
tional 48 and 96 week assessment timepoints used in most 
clinical trials). In the case of maraviroc, providing convincing

*Corresponding author. Tel: +32-93323895; Fax: +32-93325690; E-mail: linos.vandekerckhove@ugent.be

© The Author 2009. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. 
For Permissions, please e-mail: journals.permissions@oxfordjournals.org
evidence for long-term safety was especially important as this drug is the first antiretroviral product that interferes with a cellular protein instead of a viral target.

The data from the MERIT study have been analysed and re-analysed and the outcome of the study differs according to the method used, complicating final conclusions. The current paper aims at providing an overview of the MERIT data and of the different methods that were used to interpret these data and discusses the potential impact of these data on treatment recommendations for naive patients.

Virus entry into target cells and tropism testing

Entry of HIV-1 into lymphocytes and monocytes requires binding of the envelope gp120 to the CD4 receptor, followed by interaction with one of two co-receptors, CCR5 or CXCR4 (Figure 1).

The use of CCR5 or CXCR4 is mainly determined by the amino acid sequence of the V3 region of the envelope gp120 protein, although regions outside V3 such as V1/V2, C4 and the bridging sheet may also be involved. Several techniques to determine HIV tropism have been developed over the years, but recombinant virus phenotypic assays are currently most frequently used. For these assays, a fragment or the whole env gene is amplified from plasma virus RNA and the amplification product is inserted into recombinant virions. These virions are then allowed to infect human cell lines expressing CD4 and either the CCR5 or the CXCR4 receptor. According to the preference for one or the other cells, viruses are then classified as R5 if they only infect the CCR5-positive cells, X4 if they only infect the CXCR4-positive cells or dual/mixed (D/M) tropic if they are able to infect both. The most well-known assay based on this recombinant virus technology is the Trofile™ assay from Monogram Biosciences (San Francisco, CA, USA).

HIV-1 co-receptor use or tropism can also be predicted based on the amino acid composition of the V3 loop. So far these genotypic assays lack sensitivity and are not clinically validated. Genotypic assays, however, have the benefit of being relatively fast and less expensive, and they can also provide viral clade and resistance information. Improvement of sensitivity can be expected using multiclone analysis or pyrosequencing. Efforts are ongoing for the clinical validation of genotypic assays.

Primary infection with the X4 virus only is very uncommon. In late-stage HIV, the prevalence of X4 or dual R5/X4 virus rises. From the MOTIVATE study, it appeared that ~44% of antiretroviral-experienced patients harboured X4 or D/M tropic viral strains. Whether the emergence of X4 viruses is the consequence or the cause of a failing immune system is still not known. Although X4 can appear at a certain stage of infection and predominate the plasma viral population, it is clear that R5 viruses persist so that these patients will have a mixed population of R5 and X4 viruses. We currently lack a surrogate marker for co-receptor use and the Trofile™ assay is the only clinically validated tropism assay available today. In general, X4 viruses emerge in ~50% of patients with a CD4 count below 50 cells/mm³, suggesting that maraviroc should be used preferably earlier in the treatment and before advanced immunodeficiency.

**Figure 1.** HIV-1 entry. Entry of HIV-1 into target cells proceeds by the fusion of viral and cellular membranes. This event involves viral and cellular protein interactions that lead to conformational changes in critical protein structures. Binding of gp120 to its primary receptor on the cell surface, CD4, is the first step in membrane fusion. Binding to CD4 typically is followed by binding to either the CCR5 or CXCR4 co-receptor, which is required for fusion to proceed. Co-receptor recognition is defined by several structural elements of gp120 that include the first and second hypervariable regions (V1–V2), the bridging sheet (an anti-parallel, four-stranded β-sheet that connects the inner and outer domains of gp120) and, most importantly, the V3 loop. The V1–V2 stem influences co-receptor usage through its amino acid composition as well as by the degree of N-linked glycosylation. The V3 loop, in contrast, is highly variable and is the principal determinant of co-receptor specificity. The CCR5 receptor functions as a monomer that traverses the cell membrane seven times. Maraviroc binds to the co-receptor allosterically, inducing conformational changes that prevent gp120 from binding. Sequential binding of gp120 to CD4 and the CCR5 or CXCR4 co-receptor lead to the release of gp41 with subsequent fusion of the viral and the host membrane.
Pharmacokinetic (PK)/pharmacodynamic properties of maraviroc

PK studies in healthy volunteers and HIV-infected subjects have shown that maraviroc is rapidly absorbed, with peak maraviroc concentrations attained between 0.5 and 4 h following oral dosing. The absolute bioavailability of maraviroc is predicted to be 33% at the licensed dose of 300 mg (data based on findings with a 100 mg dose). The terminal half-life following oral dosing to steady state in healthy subjects is 14–18 h. Steady state is reached within 7 days. Despite a decrease of 33% in maraviroc exposure when the drug is given with a high-fat meal in healthy volunteers, the recommendation is that maraviroc may be taken with or without food. The FDA label explains the lack of need for food restrictions with the following statement: ‘There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc, therefore, maraviroc can be taken with or without food at the recommended dose’. In some patients, and certainly in some clinical situations, 33% reductions could indeed be clinically relevant, for example, when given with few other active drugs. Although it is probably not a major clinical issue in most patients, more definite data would be comforting.

Maraviroc is principally metabolized by CYP3A4 to metabolites that are inactive; it is also a substrate for the efflux transport protein P-gp. As a CYP3A (and P-gp) substrate, the disposition of maraviroc will be altered by a range of drugs that either induce or inhibit the enzymes/transporters. The CYP3A/P-gp inhibitors, atazanavir, atazanavir/ritonavir, darunavir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, elvitegravir/ritonavir and ketoconazole, all increased the area under the curve (AUC) of maraviroc (by up to 10-fold) in healthy volunteers and it is recommended to reduce the maraviroc dose by 50% if co-administered with these products. Tipranavir/ritonavir or fosamprenavir/ritonavir have no net PK interaction with maraviroc, but the CYP3A4 inducers efavirenz and rifampicin reduced the AUC and Cmax of maraviroc (by 45% and 63%, respectively); doubling the dose of maraviroc is recommended if taken together with efavirenz and rifampicin.

In the absence of CYP3A4 inhibitors, ±20% of the total clearance of maraviroc is renal. The effect of substrates and inhibitors of renal clearance such as tenofovir or co-trimoxazole has, therefore, also been assessed but neither co-trimoxazole nor tenofovir had a clinically significant effect on the PK of maraviroc. For naïve patients, when maraviroc is considered in combination with two NRTIs, no dose adaptation is required.

Effect of tropism testing sensitivity and timing of testing on MERIT outcome

In the MERIT trial, viral tropism was assessed by the ‘original Trofile™’, which is currently the only tropism assay with prospective clinical validation. Using artificial mixtures of patient-derived viral clones, it was shown that the original Trofile™ allowed the detection of minority species with a sensitivity approaching 100% when they account for at least 10% of the population, dropping to ~83% at 5% minority. Viral tropism was assessed at screening to select those patients with exclusively R5 virus for entry into the trial. Retrospectively, the baseline samples from the patients selected to participate in MERIT and taken ~4 weeks after screening (when starting treatment) were also evaluated for tropism with the Trofile™ assay. Recently, Monogram introduced a more sensitive version of their assay, called the ‘enhanced Trofile™’, allowing the detection of minority species with a sensitivity of 100% when they account for 0.3% of the population.

Hence, the three different interpretations of the data with respect to final outcome comprise (see also Figure 2): (i) a prospective analysis of all patients who received at least one dose of study drug with respect to the number of patients who achieved undetectable viral load at week 48 [intention-to-treat (ITT) analysis]; (ii) a retrospective analysis of the number of patients who achieved undetectable viral load at week 48 after excluding the patients who were found to have X4 tropic or D/M tropic virus at baseline with the original Trofile™ assay; and (iii) a retrospective analysis of the number of patients who achieved undetectable viral load at week 48 after excluding the patients who were found to have X4 tropic or D/M tropic virus at screening with the enhanced Trofile™ tropism assay. All 48 week data discussed in this paper have been presented by Pfizer at different meetings. The 96 week results of the MERIT study are not yet available.
favouring efavirenz (proportion of subjects with <50 copies/mL on efavirenz 66.6% versus 59.6% on maraviroc). Remarkably, a still unexplained difference was seen when comparing the outcome results for the patients recruited in the Northern and Southern hemispheres, with a non-inferiority result for maraviroc in the Northern (maraviroc 68% versus efavirenz 67.8%) but not in the Southern hemisphere (maraviroc 62.1% versus efavirenz 71%). Although the number of patients in whom a shift in tropism from R5 to X4 or D/M virus between the screening and baseline sample was observed is higher in the subtype B-infected patients (4.2%) than in the subtype C-infected individuals (1.9%), the numbers are small and the difference cannot explain the outcome difference between the Northern (mainly subtype B) and Southern (more subtype C) hemispheres. Subtype differences in maraviroc sensitivity still need to be addressed. Other explanations such as a geographical difference in tolerability, distribution of viral tropism, adherence and difference in intake with or without food have to be considered. Patients might also have tolerated the efavirenz-induced side effects longer in a setting where other antiretroviral regimens are difficult to obtain, although this has still to be confirmed by analysis of the reasons for discontinuation in the two different geographical regions.

Retrospective MERIT outcome analysis using the Trofile™ tropism test at baseline

The kinetics of R5 and X4 viruses during the course of the HIV infection are not fully understood, but increasing data seem to support the statement that the majority of patients in the chronic stage of infection carry a mixture of R5 and X4 strains. The MOTIVATE studies showed that up to 10% of the patients had viral tropism fluctuations from R5 to D/M tropic between screening and the start of the regimen (baseline samples), taken ~4–6 weeks apart. Analysis of all baseline samples in the MERIT study revealed that 24 of the 721 patients (3.3%) changed from R5 at screening to D/M at baseline. Thirteen patients (3.8%) initially classified as R5 at screening and receiving maraviroc were reclassified as D/M at baseline, despite an interval shorter than 6 weeks. One patient was already identified as D/M at screening but erroneously included. The response rate in the D/M patient group was significantly lower in the maraviroc (7.1%) versus the efavirenz group (54.6%). In contrast, in patients harbouring the R5 virus at the start of maraviroc (baseline sample), similar response rates were observed in the maraviroc and efavirenz arms (69.3% and 68%, respectively).
Tropism switch and resistance development in the MERIT study

The activity of maraviroc may be diminished by two mechanisms: the presence of the X4 or D/M tropic virus before the introduction of maraviroc and the selection of viruses able to bind to the CCR5 co-receptor after binding of maraviroc. So far, all data presented on tropism switch and X4 or D/M tropic virus selection in patients on treatment were performed using the original Trofile assay. Changes in the V3 loop have been observed in patients experiencing virological failure in the maraviroc arm of the MOTIVATE trials. Mutations in the stem and tip regions of V3 were seen, but changes in other regions of the gp120 molecule were also observed. Plateaus in the maximal percentage of inhibition were identified as a marker of maraviroc resistance, clearly demonstrating the ability of the virus to use compound-bound receptors. So far, no data have been presented on the development of maraviroc resistance in the MERIT trial. Initially, for all maraviroc treatment failures, tropism and nucleoside and non-nucleoside resistance data were analysed on the last recorded on-treatment sample. The analysis results in a classification into 10 distinct groups (each group being depicted by an arrow in Figure 3a) based on tropism assignments at baseline and failure. Importantly, for approximately one-third of all failures (14/43 patients), no valid tropism result was available [below level of quantification (BLQ) + no result/non-phenotypeable] at failure. Nine patients had a viral load of <500 copies/mL at their last on-treatment timepoint and their tropism test, therefore, was cancelled (BLQ). A more detailed patient-by-patient analysis was then performed on longitudinal samples collected during the period of viral rebound. As shown in Table 2, the patient-by-patient analysis finally enabled tropism assignment for 41 of the 43 maraviroc failures. Valid resistance data were subsequently obtained for all 43 patients, showing the M184V mutation selection in 10 out of 22 patients with the R5 virus at failure and in all 19 patients with D/M or X4 viruses at failure. Overall, the M184V mutation was selected in 29 (67%) of the 43 patients for whom resistance data were available. Resistance against both NRTIs was selected for seven of these patients. In the efavirenz group, all 14 patients with valid tropism data available remained R5 at failure. Of the 14 patients in whom resistance data were obtained, efavirenz resistance was selected in 9 (64%). In four of these patients, the additional selection of M184V was observed and one of these patients showed triple drug resistance at failure. To better understand why patients with the R5 virus at baseline fail on maraviroc, maraviroc plasma levels (obtained by periodic PK sampling) were assessed (Figure 3b). Of the 32 patients with the R5 virus at baseline, 12 patients had plasma levels of maraviroc that were <1 ng/mL (shown here as PK BLQ). In all cases, this correlated with a rebound in viral load and for some patients, documented interruptions/poor adherence was registered in the patient records. Interestingly, treatment interruptions or poor adherence was recorded in the records of 5 out of 6 patients with a viral load of <500 copies/mL at discontinuation.

Table 1. Comparing tropism of the R5-determined samples at screening by the original Trofile assay with the tropism determined by the enhanced Trofile assay at screening

<table>
<thead>
<tr>
<th>N</th>
<th>BL</th>
<th>D/M on study</th>
<th>Rescreened as DM by enhanced Trofile assay (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFV + CBV n/N (%)</td>
</tr>
<tr>
<td>23</td>
<td>DM</td>
<td>—</td>
<td>4/10 (40.0)</td>
</tr>
<tr>
<td>29</td>
<td>R5</td>
<td>yes</td>
<td>6/9 (66.7)</td>
</tr>
<tr>
<td>615</td>
<td>R5</td>
<td>no</td>
<td>46/314 (14.6)</td>
</tr>
</tbody>
</table>

BL, baseline; EFV, efavirenz; CBV, combivir; MVC, maraviroc.

Subjects with a D/M HIV-1 tropism result or who had a non-reportable result at screening are not included. Subjects with an R5 HIV-1 tropism result at screening and baseline but without post-baseline records are not included. Subjects with an R5 HIV-1 tropism result at screening and baseline with at least one post-baseline D/M result are included in row 2. Remaining subjects with post-baseline results are included in row 3. This table does not include the one patient with D/M at screening who was randomized to the study in error.

(Figure 2). These data clearly indicate that the presence of X4 or dual tropic viruses at baseline predicts maraviroc failure.

Retrospective MERIT outcome analysis using the enhanced Trofile assay at screening

Analysis of all screening samples with the enhanced Trofile assay (re)classified 106 of the 721 patients (14.7%) as D/M tropic. For the 48 patients (13.3%) who were retrospectively classified as D/M tropic but initiated on maraviroc, the individual outcome data are not yet available. The enhanced Trofile assay would already have identified at screening 7 of the 13 patients with a tropism shift between screening and baseline tested with original Trofile (Table 1). The enhanced Trofile assay would also have identified at screening 10 of the 20 patients with a tropism shift from R5 to D/M during the study. On the other hand, 29 (9.6%) of 301 patients in whom no tropism shift was observed under the maraviroc-containing regimen would have been classified as D/M by the enhanced Trofile assay at baseline, although again no individual outcome data on this particular patient group are so far available. In an ITT analysis including all patients identified as R5 by the enhanced Trofile assay and who received at least one dose of the study medication, with missing values classified as failures/non-responders, 68.5% of the maraviroc group and 68.3% of the efavirenz group achieved an undetectable viral load at week 48. In this retrospective analysis, maraviroc proves to be non-inferior to efavirenz.
Safety profile of maraviroc in the MERIT study

The discontinuation rate was high in both arms (Figure 2). Efavirenz discontinuations (in total, 25.2%) were more likely due to an adverse event (13.2%) followed by lack of efficacy (4.2%) and other factors (7.5%). The high number of efavirenz discontinuations might be due to the well-known side effects of efavirenz in the start-up phase, partially unmasking the blinding of the study. Maraviroc discontinuations (26.9%) were more likely to be due to lack of efficacy (11.9%), and only secondly, to an adverse event (4.2%) or other factors (10.8%). There were fewer grade 3 and grade 4 adverse events and fewer category C AIDS-defining events in the maraviroc arm, and overall rates of adverse events and serious adverse events were similar in both
arms. An overall low incidence of increase in liver function tests to grade 3 or 4 was observed and was equally distributed in both treatment arms. Following concerns of an increased rate of toxicity, the rate of overall malignancies in the efavirenz group was 2.1% (3.3%) and 3.0% (4.7%), respectively, at week 24 and 2.2% (3.7%) and 3.3% (5.1%), respectively, at week 48.

### Discussion and conclusions

In the MOTIVATE study, the first antiretroviral drug in the new class of entry inhibitors, maraviroc, has proven superiority to placebo for the treatment of triple-class experienced patients. But, as maraviroc-insensitive X4 viruses emerge in 50% of patients with a low CD4 count, it is assumed that the preferential use of maraviroc needs to be situated earlier in the treatment, before advanced immunodeficiency. Moreover, the recent finding that many of the most commonly prescribed antiretroviral drugs such as didanosine, abacavir, efavirenz and ritonavir-boosted protease inhibitors may be associated with increased cardiovascular risk, has fuelled the need for a switch to drugs that are better tolerated. The results of HIV trials on structured therapy interruption (e.g. the SMART study) showed a negative outcome due to an increase in opportunistic infections (OIs) and mortality, and revealed that uncontrolled HIV-replication can, despite higher numbers of CD4+ T cells, place patients at an increased risk of OIs/death. In the specific situation in which there is a need for switching, maraviroc can not be used so far as, even with the enhanced Trofile™ assay, a minimum viral load of 1000 copies/mL is needed before the necessary tropism test can be performed. The clinical value of determining tropism on stored plasma samples collected prior to achieving an undetectable viral load, or of determining tropism on pro-viral DNA in the latent reservoir is still under investigation, but preliminary data are promising. With regard to the initiation of maraviroc in treatment-naïve patients, three CCR5 chemokine receptor blockers, aplaviroc, vicriviroc and maraviroc, have been evaluated. Unfortunately, a number of challenges have hindered the further development as a valuable tool.

<table>
<thead>
<tr>
<th>Tropism at failure</th>
<th>MVC (300 mg twice daily)</th>
<th>EFV (600 mg once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>R5</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>D/M or X4</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>

*aLast valid tropism result while on treatment.
MVC, maraviroc; EFV, efavirenz; N, total patients in group; n, total patients with a valid resistance test; NA, not available; 2NRTIres, genotypic resistance to lamivudine and zidovudine (or substituted NRTI); EFVres, genotypic resistance to EFV; other, missing baseline tropism result (n=1) or no valid tropism data during failure (n=2).
option for first-line treatment of two of these drugs: vicriviroc and aplaviroc. The vicriviroc treatment-naïve study was terminated due to inferior performance compared with efavirenz.5 In the ACTG 5211 study, several subjects receiving vicriviroc developed malignancies; however, the observed differences in lymphoma rates between treated patients and control subjects could have been affected by the small total number of participants in the study, the 3-fold greater number of vicriviroc recipients and their significantly longer follow-up period, compared with placebo recipients.29 Vicriviroc is currently completing Phase III evaluation. The development of aplaviroc was stopped prematurely due to hepatotoxicity seen in trials.

The ITT analysis performed on all patients who were included prospectively in the MERIT study undoubtedly shows that maraviroc fails to prove non-inferiority to efavirenz. The initial re-analysis of the MERIT data performed on those patients without switch in tropism between screening and start of maraviroc (based on the original TrofileTM) demonstrates that maraviroc is as potent as efavirenz. It is important to note that in practice, a shift in tropism from R5 to X4 between screening and treatment initiation will remain unseen as clinical decision-making only relies on a single tropism testing at screening. Efforts of Monogram Biosciences to increase the sensitivity of the TrofileTM assay for minority variant strains led to the introduction of the enhanced assay, which increased the sensitivity for minority X4 variants from 10% to 0.3%. Re-analysis of all screening samples with the enhanced assay (re)classified 106 of the 721 patients (14.7%) as D/M tropic. In the retrospective ITT analysis that includes all patients who were identified by the enhanced TrofileTM as R5, maraviroc proves to be non-inferior to efavirenz. This brings us to the question that was raised prematurely due to inferior performance compared with efavirenz.5 In the MERIT study, the total number of patients who developed M184V in the maraviroc arm versus the efavirenz arm was 29 versus 4, and 7 versus 1 for the selection of a second NRTI resistance mutation, indicating that maraviroc is not protecting the NRTIs from drug resistance development. No longitudinal data were available comparing maraviroc versus efavirenz resistance development.

In conclusion, up to now maraviroc has not met the criteria of potency, durability and convenience in a prospective analysis required for first-line regimens, and cannot be advocated for clinical use in treatment-naïve patients. It is already clear that the activity of maraviroc will depend to a large extent on the composition of the virus quasispecies with regard to co-receptor tropism. Due to the new developments in tropism testing and the resulting re-analysis of the samples, the interpretation of the final outcome of the MERIT data becomes challenging. Although the enhanced Trofile™ assay has partially addressed the shortcoming of the original Trofile™ assay, and the retrospective analysis using this enhanced Trofile™ assay re-orientates the initial conclusions, some shortcomings should not be ignored. First, the enhanced Trofile™ assay could only re-evaluate clinical outcomes in those patients who had started maraviroc and not in all patients who were initially screened with the original Trofile™ assay. Secondly, the drug was associated with increased virological failure and with increased resistance development towards NRTIs. Finally, as enhanced technology such as pyrosequencing or even more advanced tropism determination tools become available, regulatory agencies should be warned against accepting new indications for drugs based upon retrospective analysis. Therefore, it cannot be advocated that the drug should be used as a new first-line drug in naive patients unless new prospective data become available. Whether maraviroc can be used together with other drugs with a low genetic barrier, such as non-nucleoside analogues or integrase inhibitors in first-line regimens (taking into account the possibility of undetected D/M tropic virus that could undermine the effectiveness of the regimen), is unclear for the moment. In our opinion, this approach should be restricted to pilot studies and should not be part of routine clinical practice. The enhanced Trofile™ assay and the re-analysis of the MERIT data allow us to be more confident about picking up minor variants in the individual patient who, for specific reasons, might benefit from maraviroc (e.g. high cardiovascular risk + kidney impairment). The favourable lipid profile and tolerability support the use of maraviroc as a safe alternative in a consolidation or maintenance regimen after achieving full virological suppression, especially in those subjects experiencing side effects on NNRTIs, protease inhibitors or integrase inhibitors. This interesting option should be explored in future clinical trials.

Acknowledgements
All data have been presented at congresses or meetings.

We especially want to thank Jonathan Schapiro (Sheba Medical Center, Tel Aviv, Israel) and Daniel Kuritzkes (Brigham and Women’s Hospital, Harvard Medical School, 65 Landsdowne Street, Cambridge, MA, USA) for final guidance and critical reading of the manuscript.
interactions with the CCR5 coreceptor.

tinct roles in human immunodeficiency virus type 1 envelope glycoprotein

1429–41.

N Engl J Med

Abstract WESS 104.

HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007

Abstracts of the Fourth International AIDS Society (IAS) Conference on

lamivudine [3TC], for the treatment of antiretroviral naive patients

double-blind, comparative trial of a novel CCR5 antagonist, maraviroc


Landovitz RJ, Angel JB, Hoffmann C et al. Phase II study of vici-

riroc versus efavirenz (both with zidovudine/lamivudine) in treatment-


Cormier EG, Dragic T. The crown and stem of the V3 loop play dis-
tinct roles in human immunodeficiency virus type 1 envelope glycoprotein


Jensen MA, van’t Wout AB. Predicting HIV-1 coreceptor usage


Low AJ, Dong W, Chan D et al. Current V3 genotyping algo-
rithms are inadequate for predicting X4 co-receptor usage in clinical iso-


Tsigris AM, Kuritzkes DR. Chemokine antagonists as thera-


Abel S, van der Ryst E, Rosario MC et al. Assessment of the phar-


Abel S, Jenkins TM, Whitlock LA et al. Effects of CYP3A4 indu-

Whitcomb JM, Huang W, Fransen S et al. Development and


Wilkin T, Ribaudo H, Gulick R. The relationship of CCR5 inhibi-

Van Baelen K, Vandebroucke I, Rondeldez E et al. HIV-1 core-


Mori J, Mosley M, Lewis M et al. Characterisation of MVC resist-


35. Verhofstede C, Vandekerckhove L, Eygen VV et al. CXCR4-using HIV type 1 variants are more commonly found in peripheral blood mononuclear cell DNA than in plasma RNA. *J Acquir Immune Defic Syndr* 2009; 50: 126–36.


