Deep V3 Sequencing for HIV Type 1 Tropism in Treatment-Naive Patients: A Reanalysis of the MERIT Trial of Maraviroc

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Background. Deep sequencing is a highly sensitive technique that can detect and quantify the proportion of non-R5 human immunodeficiency virus (HIV) variants, including small minorities, that may emerge and cause virologic failure in patients who receive maraviroc-containing regimens. We retrospectively tested the ability of deep sequencing to predict response to a maraviroc-containing regimen in the Maraviroc versus Efavirenz in Treatment-Naive Patients (MERIT) trial. Results were compared with those obtained using the Enhanced Sensitivity Trofile Assay (ESTA), which is widely used in clinical practice.

Methods. Screening plasma samples from treatment-naive patients who received maraviroc and efavirenz in the MERIT trial were assessed. Samples were extracted, and the V3 region of HIV type 1 glycoprotein 120 was amplified in triplicate and combined in equal quantities before sequencing on a Roche/454 Genome Sequencer-FLX (n = 859). Tropism was inferred from third variable (V3) sequences, with samples classified as non-R5 if \( \geq 3.5 \) using geno2pheno.

Results. Deep sequencing distinguished between responders and nonresponders to maraviroc. Among patients identified as having R5-HIV by deep sequencing, 67% of maraviroc recipients and 69% of efavirenz recipients had a plasma viral load <50 copies/mL at week 48, similar to the ESTA results: 68% and 68%, respectively.

Conclusions. Reanalysis of the MERIT trial using deep V3 loop sequencing indicates that, had patients originally been screened using this method, the maraviroc arm would have likely been found to be noninferior to the efavirenz arm.

Human immunodeficiency virus type 1 (HIV-1) infects cells using the CD4 receptor and a coreceptor. The chemokine receptor CCR5 is a necessary coreceptor for strains of HIV called R5 [1], which predominate in antiretroviral-naive individuals [2–4]. The CCR5 coreceptor is also the target of the HIV entry inhibitor maraviroc, which inhibits the ability of HIV to interact with and infect cells via CCR5 [5]. Because the use of an alternative coreceptor emerges in approximately half of clade B–infected individuals [6], a tropism test is performed prior to maraviroc administration to exclude patients whose viral population (or some subpopulation of it) is non-R5 and unlikely to respond to maraviroc.

A number of genotypic HIV tropism approaches have been developed to provide alternatives to phenotypic tropism assays such as the Monogram Biosciences Trofile assay [7] and Enhanced Sensitivity Trofile Assay (ESTA) [8]. Commonly, genotypic approaches use the sequence of the third variable (V3) loop of the HIV glycoprotein (gp) 120 gene, because the V3 loop itself interacts with the HIV coreceptor [9], and mutations encoded by V3 are associated with measurable changes in HIV tropism [10, 11]. Tropism is then inferred using a bioinformatic algorithm, such as geno2pheno [12].
Although population-based genotypic tropism assays can infer the coreceptor use of a patient’s most common HIV quasispecies, these tests may miss non-R5 variants comprising low-level minorities within a predominantly R5 population [13]. The ability to detect minority non-R5 variants is important, because these subpopulations may undergo selection by maraviroc treatment and lead to virologic failure [14–16].

There have been 4 large clinical trials of maraviroc to date [16–18]. The Maraviroc versus Efavirenz in Treatment-Naive Patients (MERIT) trial assessed 2 doses of maraviroc (plus lamivudine-zidovudine) in antiretroviral-naïve patients, with a comparator arm of efavirenz (plus lamivudine-zidovudine) [18]. The trial consisted only of patients with R5 HIV infection at screening with the original Trofile assay. The maraviroc once daily (QD) arm was discontinued early after failing to meet prespecified efficacy criteria.

Although superior to placebo in the Maraviroc versus Optimi- zed Therapy in Viremic Antiretroviral Treatment-Experienced Patients trials, maraviroc failed to demonstrate noninferiority to efavirenz in the primary analysis of the MERIT trial using the original screening population. However, when patients in the MERIT trial were retrospectively rescreened using the higher sensitivity ESTA, with exclusion of those now identified as having non-R5 HIV infection, maraviroc twice daily (BID) was noninferior to efavirenz for the primary study end point [19].

Deep sequencing refers to the application of next-generation sequencing technology, such as the Genome Sequencer FLX (GS-FLX) [20]. The GS-FLX can simultaneously sequence and quantify thousands of individual variants within a viral population, allowing an in-depth quantification of the proportion of non-R5 variants in a given sample [14, 21], and therefore the proportion unlikely to respond to maraviroc [22]. Here, we assess whether the high-sensitivity of deep sequencing could also have been a successful screening tool for the treatment-naïve patients in the MERIT trial.

METHODS

Samples and MERIT Trial Design
A total of 859 screening samples from the MERIT trial were examined. All samples were R5 by the original Trofile assay. Most patients entered either the maraviroc BID arm (n = 347) or the efavirenz arm (n = 346). The trial’s primary end point was the proportion of patients with a plasma viral load (pVL) <50 HIV RNA copies/mL at week 48. A third arm, consisting of maraviroc QD, was also partially enrolled. Screening samples from those initially assigned to the maraviroc QD arm (n = 166) were also tested.

Third Variable Amplification Method
HIV RNA was extracted from 500 μL of each of the 859 stored screening plasma samples using automated extraction methods with a NucliSENS easyMAG (bioMérieux). One-step reverse-transcription polymerase chain reaction (RT-PCR) was performed in triplicate using 4 μL of sample extract per amplification. A second-round PCR amplification was then performed using customized primers to allow multiplexing (48 samples per sequencing run). PCR amplifications were then quantified. Each amplification was combined in equal proportions with the others to a concentration of 2 × 10^{12} DNA molecules per sample. This combined set of PCR products then underwent emulsion PCR and deep sequencing with a GS-FLX. A detailed methodology has been published [22, 23].

In addition, a second-round PCR amplification was also performed using the same triplicate reverse-transcription PCR template. These PCR products underwent individual standard, population-based sequencing on an ABI 3730 XL DNA analyzer according to previously described methods [23–25]. A full analysis of population-based sequencing in MERIT will be presented elsewhere.

Bioinformatic Analysis
The false-positive rate (FPR) cutoff for geno2pheno tropism assignments had previously been optimized and validated in the maraviroc treatment-experienced trials, as had the cutoff for the percentage of non-R5 variants needed for a sample to be classified as non-R5 [22, 26]. A sample was considered R5 if fewer than 2% of the variants detected using deep sequencing fell below a geno2pheno FPR of 3.5 [26]. Population-based V3 sequencing used a geno2pheno FPR cutoff of 5.75 [27].

Ethics Statement
Written, informed consent was obtained from all individuals, including consent to allow other tropism testing to be performed on their samples. The University of British Columbia–Providence Health Care Research Ethics Board reviewed the research project and granted ethical approval. All data were analyzed anonymously.

Data Analysis
The maraviroc BID arm was the primary dataset for assessing the utility of deep sequencing. The efavirenz arm served as a comparator. The maraviroc QD arm was also examined as a complementary analysis. Unless otherwise stated, any reference to maraviroc should be taken as a reference to maraviroc BID.

Virologic outcomes examined included the pVL change from baseline, the percentage of patients with virologic suppression, and a time to a change in a patient’s Trofile result from R5 to non-R5 (ie, a tropism “switch”). Where data were missing, the last observation was carried forward, except in the case of the percentage of patients with a pVL <50 copies/mL, where missing values were imputed to be ≥50 copies/mL (“failures”). Deep sequencing was also compared with the performance of ESTA and standard population-based sequencing in the same dataset.
Differences between tropism groups (R5 vs non-R5) were tested for statistical significance using 3 tests. The Mann-Whitney U test examined differences between median measurements, such as median pVL decreases. The Fisher’s exact test examined differences in the proportions of patients, such as differences in virologic suppression or clade. The log-rank test examined differences in the Kaplan-Meier curves for tropism changes. No statistical comparisons between the populations defined by Trofile and 454 could be performed, because these populations were not independent.

RESULTS

Patient Characteristics

Baseline characteristics of patients stratified by deep sequencing tropism result at screening are shown in Table 1 and are largely similar to those of the original MERIT population [18]. Those patients found to have non-R5 HIV by 454 genotyping were more likely to be white, men who have sex with men, infected with clade B HIV, and have lower CD4 counts than those found to have R5 HIV by 454 genotyping, although these differences were relatively minor.

Identification of Non-R5 Screening Samples Using Deep Sequencing

Deep sequencing generated a mean of 5002 sequences per sample (median, 4529; interquartile range, [IQR], 3715–6024). Sequence depth did not have a discernable impact on 454 sensitivity or ability to predict virologic outcomes (data not shown). Overall, rescreening MERIT patients using deep sequencing classified an additional 10% of maraviroc BID recipients (35 of 347) as being unlikely to respond to their regimens because of the presence of ≥2% non-R5 virus prior to treatment. Similarly, 13% (22 of 166) in the maraviroc QD arm and 9% (30 of 346) in the efavirenz arm were classified as having non-R5 HIV infection by deep sequencing.

Samples screened non-R5 by deep sequencing had non-R5 variants at a median proportion of 20.9% (IQR, 5.4%–44.1%). Samples screened R5 had a median of 0% non-R5 HIV (IQR, 0%–0%). Seventy-four percent of patients (511 of 693) who were treated with maraviroc BID or efavirenz had no detectable non-R5 variants at screening by deep sequencing. In addition, 60% of all non-R5 samples had ≥10% non-R5 variants by this method, despite having been already prescreened with the Trofile assay, which has a reported cutoff of 10% non-R5 virus [28].

There were a total of 94 maraviroc recipients with detectable non-R5 virus by deep sequencing. When the non-R5 prevalence was extended to the absolute amount of non-R5 at screening, these patients had a median non-R5 viral load of 2.9 log_{10} copies/mL (IQR, 2.2–3.5 log_{10} copies/mL).

Virologic Outcomes

Overall viral load decreases from baseline through 96 weeks are shown for both arms in Figures 1 and 2, with patients grouped according to their deep sequencing result. Figure 3 shows the
maraviroc BID arm with screening by both deep sequencing and ESTA. Maraviroc recipients with R5 HIV by 454 genotyping showed a median 2.7 log₁₀ copies/mL decrease in pVL from baseline to week 8 (IQR, 2.3–3.1 log₁₀ copies/mL), whereas the non-R5 group had a smaller decrease: 2.3 log₁₀ copies/mL (IQR, 1.9–2.6 log₁₀ copies/mL) (*P* < .001). The efavirenz arm had virologic responses similar to those for the R5-infected maraviroc recipients, regardless of tropism assessment by deep sequencing: 2.8 log₁₀ copies/mL (IQR, 2.4–3.2 log₁₀ copies/mL) for R5 and 2.9 log₁₀ copies/mL (IQR, 2.5–3.2 log₁₀ copies/mL) for non-R5 (*P* = .56).

The larger pVL changes observed when patients were classified using the deep sequencing method were also reflected in the percentage of patients who achieved an undetectable viral load at 48 weeks. A total of 67% of maraviroc recipients (208 of 312) had a pVL <50 HIV RNA copies/mL at week 48 (ie, virologic suppression) among those for whom 454 genotyping had indicated R5-HIV at screening. In contrast, only 46% of non-R5–infected maraviroc recipients (16 of 35) achieved week 48 virologic suppression (*P* = .02).

In terms of non-R5 viral load, the percentages of maraviroc recipients with week 48 virologic suppression were as follows: 68% (173 of 255) of those with <1 log₁₀ non-R5 copies/mL, 77% (10 of 13) of those with 1–2 log₁₀ non-R5 copies/mL; 56% (22 of 39) of those with 2–3 log₁₀ non-R5 copies/mL; 52% (14 of 27) of those with 3–4 log₁₀ non-R5 copies/mL; and 38% (5 of 13) of those with >4 log₁₀ non-R5 copies/mL.

In the efavirenz arm, 69% (219 of 316) of those with R5 HIV infection had viral suppression, which was similar to the percentage in the maraviroc arm. The percentage with suppression was 70% (21 of 30) in efavirenz recipients with non-R5 HIV infection confirmed by 454 genotyping (*P* = .99). The percentage of patients who achieved virologic suppression is shown in Figures 4 and 5, with data to week 96. The lower bound of the 97.5% confidence interval for the difference between arms was −8.67%, which was less than the prespecified minimum value of −10% for determining noninferiority of maraviroc at week 48 (Table 2). This analysis also confirms the poor virologic response among maraviroc recipients identified as having non-R5 HIV infection at screening by deep sequencing, compared with those who received efavirenz. Together, these analyses suggest that, had patients been screened with deep sequencing rather than with the original Trofile assay, the maraviroc BID arm would have likely been found to be noninferior to the efavirenz arm (Figure 4).

Changes in HIV Tropism
Maraviroc administration unmasks and can select non-R5 virus that was present prior to maraviroc administration [15]. Maraviroc recipients with non-R5 HIV infection by deep sequencing were more likely to change phenotypic tropism over the course of the study than were those with R5 HIV infection by deep sequencing (*P* < .001). Of those with non-R5 HIV infection, 43% (15 of 35) changed their Trofile result from R5 to...
Figure 2. Median log_{10}-transformed decrease in plasma viral load (pVL) from baseline in patients screened with non-R5 human immunodeficiency virus (HIV) by deep sequencing who received maraviroc twice daily (BID) or efavirenz. The black line indicates patients who received maraviroc BID (n = 35), and the dashed-dotted line indicates those who received efavirenz (n = 30). With screening by deep sequencing, those found to have non-R5 HIV infection had lower pVL decreases from baseline when treated with maraviroc BID versus efavirenz.

Figure 3. Median decrease in plasma viral load (pVL) from baseline in maraviroc twice daily (BID) recipients with screening by deep sequencing and Enhanced Sensitivity Trofile Assay (ESTA). The solid black line indicates maraviroc BID recipients identified as having R5 human immunodeficiency virus (HIV) infection by screening with deep sequencing (n = 312). The solid gray line indicates those identified as having non-R5 HIV infection by screening with deep sequencing (n = 35). The dotted and dashed lines indicate the ESTA R5 (n = 300) and ESTA non-R5 (n = 47) groups, respectively. Deep sequencing and ESTA performed similarly in terms of distinguishing between virologic responders and nonresponders receiving maraviroc.
non-R5 between screening and 96 weeks, versus only 7% (23 of 312) of the 454 genotyping R5 group (Figure 6). In the non-R5 group, patients switched tropism a mean of 5 weeks after beginning treatment, which was earlier than the 17 weeks seen in the R5 group. Maraviroc recipients who changed tropism also had a higher proportion of non-R5 variants present before treatment, according to deep sequencing, with a median of 0.8% non-R5 variants (IQR, 0.0%–7.4%) versus 0% (IQR, 0%–0%) for those who did not change tropism. Deep sequencing was able to detect at least low levels (>0%) of non-R5 HIV in a majority (61%) of maraviroc recipients who switched tropism, versus 23% of those who did not switch tropism.

**Clade**

For all patients analyzed in the current study, 60% had clade B, 29% had clade C, and 11% had other clades of HIV. Non-R5 tropism seemed to be overrepresented among clade B–infected individuals, with 74% of the deep sequencing non-R5 group consisting of clade B–infected patients, which was higher than the overall clade B composition of 60% ($P = .02$). Conversely, clade C was underrepresented among non-R5–infected patients, at 13% ($P = .001$). Global concordance in the entire study population between deep sequencing and ESTA was 79% in the clade B–infected population and 87% in the population with non–clade B infection.

Importantly, deep sequencing and ESTA had similar performance in predicting virologic outcome in non-clade B-infected patients (Supplementary Table 1).

**Comparison of Deep Sequencing With ESTA and Population-Based Sequencing**

The screening tropism assessments by both deep sequencing and the Enhanced Sensitivity Trofile Assay (ESTA) were compared. Deep sequencing and ESTA had a global concordance of 82%. Perhaps surprisingly, only 22 samples (3%) of the 693 total samples were identified as non-R5 by both methods (or only 15% of the 146 samples identified as non-R5 by either method). Consequently, both assays had low sensitivity relative to the other. Deep sequencing had 21% sensitivity and 93% specificity using ESTA as a reference; ESTA had 34% sensitivity and 87% specificity using deep sequencing as a reference. Despite this, the groups identified as having R5 and non-R5 infection by either method had similar virologic outcomes regardless of the assay.

Retrospective screening by ESTA identified 14% of maraviroc recipients (47 of 347) as having non-R5 HIV. This was 16% (56 of 346) in the efavirenz arm. Overall, the ESTA non-R5 group had a median of 0% non-R5 HIV (IQR, 0%–0.8%; mean, 7.4%) according to deep sequencing using the g2p algorithm; the ESTA R5 group also had a median of 0% (IQR, 0%–0%; mean, 2.2%).
Maraviroc recipients rescreened with R5 and non-R5 HIV identified with use of ESTA had week 8 pVL decreases of 2.7 log_{10} copies/mL (IQR, 2.3–3.1 log_{10} copies/mL) and 2.4 log_{10} copies/mL (IQR, 1.9–3.0 log_{10} copies/mL), respectively, similar to the deep sequencing results. The percentage of patients with week 48 virologic suppression was 68% (203 of 300) for the R5-group, compared with 45% (21 of 47) for those with non-R5 HIV identified by ESTA. Tropism changes during maraviroc treatment occurred in 36% (17 of 47) of the ESTA non-R5 group versus 7% (21 of 300) of the R5 group. Patients with discordant tropism results by deep sequencing and ESTA had intermediate pVL decreases when receiving maraviroc (Figure 7).

Deep sequencing was also compared with population-based sequencing, which was concordant with deep sequencing in 93% of cases with both results (638 of 688 cases) and gave 54% sensitivity relative to deep sequencing. Samples identified by population-based sequencing as non-R5 had a median of 9.1% non-R5 variants in their deep sequencing result (IQR, 0.7%–41.0%; mean, 26.3%). More-detailed analyses of this population-based V3 sequencing approach will be presented elsewhere.

Virologic responses of patients grouped by discordance of deep sequencing with ESTA or population-based sequencing are shown in Table 3, Figure 7, and Supplementary Figures 1–3. Overall, where screening assays differed, there was no clear

Table 2. Noninferiority Analysis Between the Maraviroc (MVC) and Efavirenz (EFV) Arms

<table>
<thead>
<tr>
<th>Assay result</th>
<th>MVC BID Arm</th>
<th>EFV Arm</th>
<th>Raw diff (MVC–EFV)</th>
<th>Diff 97.5% LCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>454 R5</td>
<td>210/312</td>
<td>67.31</td>
<td>-1.36</td>
<td>-1.48/-8.67</td>
</tr>
<tr>
<td>454 non-R5</td>
<td>17/35</td>
<td>48.57</td>
<td>-21.43</td>
<td>-42.19/-60.71</td>
</tr>
<tr>
<td>ESTA R5</td>
<td>205/300</td>
<td>68.33</td>
<td>0.75</td>
<td>0.17/-7.21</td>
</tr>
<tr>
<td>ESTA non-R5</td>
<td>22/47</td>
<td>46.81</td>
<td>-28.19</td>
<td>-31.15/-48.87</td>
</tr>
<tr>
<td>Trofile R5</td>
<td>227/347</td>
<td>65.42</td>
<td>-3.37</td>
<td>-3.73/-10.61</td>
</tr>
</tbody>
</table>

Abbreviations: Diff, difference; ESTA, Enhanced Sensitivity Trofile Assay; LCB, lower confidence bound.
indication as to which assay was the “gold standard.” Indeed, deep sequencing, ESTA, and population-based sequencing all performed quite similarly in terms of predicting virologic response to maraviroc in this population.

Maraviroc Once Daily Arm
The group of patients who were randomized into the maraviroc QD arm was also examined with deep sequencing (n = 166). This dataset served as an independent validation of the deep V3 sequencing method. The maraviroc QD arm was originally discontinued partway through the MERIT study because of a protocol-defined lack of demonstrated noninferiority to efavirenz. Maraviroc QD recipients were then allowed to switch to maraviroc BID for the remainder of the study. The performance of deep sequencing as a screening tool for tropism was assessed in this population. Analyses were performed where responses were censored or uncensored after patients switched to maraviroc BID. The week 8 pVL decreases from baseline were similar between the maraviroc QD and BID arms in the uncensored analysis. The median decrease of those identified at screening as having R5 HIV infection (n = 144) was $2.8 \log_{10}$ copies/mL (IQR, $2.4-3.1 \log_{10}$ copies/mL) versus $2.6 \log_{10}$ copies/mL (IQR, $1.3-3.0 \log_{10}$ copies/mL) for those with non-R5 HIV infection (n = 22). Note that 26 patients in the R5 group (18%) and 6 in the non-R5 group (27%) had discontinued therapy or switched to maraviroc BID by week 8. Viral load decreases from baseline for the uncensored groups are shown in Supplementary Figure 4. The R5 group, censored for those continuing to receive maraviroc QD, is also shown.

DISCUSSION
This study represents the first large clinical comparison of 2 highly sensitive HIV tropism assays: deep sequencing and ESTA. Retrospective screening by deep sequencing, with removal of patients classified with non-R5 HIV infection, led to similar rates of week 48 virologic suppression between the maraviroc BID and efavirenz arms. Maraviroc recipients identified as having R5 HIV infection at screening by this approach had larger pVL decreases while receiving treatment, were more likely to achieve virologic suppression, and were less likely to change tropism than were those identified as having non-R5 virus at screening.
Deep sequencing also had similar performance to that of ESTA, which is widely used in the clinic. Virologic responses were similar between groups that had discordant results by either assay, suggesting that neither assay is significantly more “correct” than the other. The decrease in viral load from baseline was $>2 \log_{10}$ copies/mL even in the maraviroc-treated non-R5 group. This is likely attributable to the activity of the background zidovudine-lamivudine and perhaps to some residual activity of maraviroc.

The additional clinical utility of deep sequencing over standard population-based sequencing was not clearly demonstrated in this study, despite a possible trend in a previous study involving treatment-experienced patients [22]. In fact, concordance was $>90\%$ between the methods in the current study.

A common critique of bioinformatic algorithms for HIV tropism is that most are trained primarily on clade B sequences. However, the deep sequencing genotypic assay presented here performed similarly to the phenotypic ESTA assay in MERIT, including in patients with non–clade B infection, lending confidence to the utility of this approach in such populations (see also [29]).

Some limitations of this study and the use of deep sequencing should be acknowledged. The MERIT trial itself only included patients who were identified as having R5 HIV infection by

### Table 3. Overall Virologic Responses of Maraviroc Recipients Grouped by Discordance of Deep Sequencing With ESTA or Population-Based Sequencing

<table>
<thead>
<tr>
<th>454 result</th>
<th>Other assay result</th>
<th>Median week 8 log pVL change from baseline (IQR) vs ESTA</th>
<th>Patients with week 48 virologic suppression, % (proportion) vs ESTA</th>
<th>Patients with week 48 virologic suppression, % (proportion) vs population-based sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5</td>
<td>R5</td>
<td>2.7 (2.3–3.1)</td>
<td>68 (188/276)</td>
<td>67 (202/301)</td>
</tr>
<tr>
<td>R5</td>
<td>Non-R5</td>
<td>2.6 (2.2–3.1)</td>
<td>56 (20/36)</td>
<td>50 (4/8)</td>
</tr>
<tr>
<td>Non-R5</td>
<td>R5</td>
<td>2.4 (2.2–2.7)</td>
<td>63 (15/24)</td>
<td>47 (8/17)</td>
</tr>
<tr>
<td>Non-R5</td>
<td>Non-R5</td>
<td>1.9 (1.3–2.1)</td>
<td>9 (1/11)</td>
<td>44 (8/18)</td>
</tr>
</tbody>
</table>

Abbreviations: ESTA, Enhanced Sensitivity Trofile Assay; IQR, interquartile range; pVL, plasma viral load.
prescreening with the original Trofile assay, so an analysis of maraviroc treatment in an antiretroviral-naive population infected with non-R5 virus by the Trofile assay was not possible, although an analysis of deep sequencing in a non-R5 treatment-experienced trial has been published [22]. The prescreening of these patients may also have diminished the ability to demonstrate improved tropism prediction of any assay over any other, given the small number of patients identified as having non-R5 HIV infection by rescreening. The analysis of the maraviroc QD arm should also be examined with caution, given the small number of patients continuing QD maraviroc treatment. Finally, the deep sequencing method itself is costly in both time and capital, which currently limits its usefulness in clinical settings.

Overall, deep sequencing is a useful tool for distinguishing between probable responders and nonresponders to maraviroc. This high-sensitivity method performed similarly to ESTA, which is currently the most commonly used clinical phenotypic tropism assay. Had deep sequencing been used to screen patients, maraviroc would have likely been found to be noninferior to efavirenz in the MERIT trial.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Financial support. This work was supported by Pfizer, the Canadian Institutes of Health Research (CIHR), and a GlaxoSmithKline/CIHR Chair in Clinical Virology (to P. R. H.).

Potential conflicts of interest. P. R. H. has received consulting fees from Viiv/Pfizer, Quest, and Vircor; holds stock options in Merck; and is a board member of Northern Lipids, D. C., S. P., M. L., I. J., J. H., and H. V. are employees of Viiv/Pfizer. All other authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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