



**Australian Government**  

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**Medical Services Advisory Committee**

**Public Summary Document**

***Application No. 1174 -Assessment of viral tropism testing of HIV to inform treatment with maraviroc***

**Applicant:** ViiV Healthcare

**Date of MSAC consideration:** 29-30 November 2012

**1. Purpose of application**

In May 2011, the Department of Health and Ageing received an application from ViiV Healthcare requesting a Medicare Benefits Schedule (MBS) listing for genotypic HIV tropism for treatment with CCR5 antagonist maraviroc.

This application was seeking genotypic HIV tropism testing to be funded through two avenues:

1. Through the creation of a new MBS item number to allow HIV tropism testing as part of the current genotype-assisted antiretroviral resistance testing (GART) suite of tests.
2. Through the creation of a new MBS item number for HIV tropism testing alone.

This application was deemed to propose a co-dependent package of two types of health technology (a pathology test and a medicine) subsidised through two different programs and therefore required advice from MSAC to be coordinated with that of the Pharmaceutical Benefits Advisory Committee (PBAC).

A tropism assay to determine that a patient is infected with only the CCR5 strain of HIV is requisite for patients to be eligible to receive PBS-subsidised access to maraviroc. As such, this application was seeking to have HIV tropism testing funded through the MBS.

HIV tropism testing was sought to be made available to patients with confirmed HIV infection if the patient's viral load is greater than 1000 copies per mL at any of the following times:

1. Before commencing antiretroviral therapy when maraviroc is being considered as a treatment option.
  2. When treatment with a combination of antiretroviral agents (including maraviroc) fails in order to ascertain if treatment failure is associated with a tropism shift from R5 to X4.
- HIV tropism testing is a current intervention privately funded by the applicant.

**2. Background**

The process of using specific assays to determine the genetic makeup of the HIV virus ahead of making treatment decisions is known as genotype-assisted antiretroviral resistance testing (GART). The overarching aim of GART is to collect patient-level information on the genetic

makeup of the infecting HIV type in order to guide treatment approaches that are more likely to reduce viral load in patients than if GART was not performed.

In Australia, GART testing is performed by sequencing areas of the HIV genome that encode the protease and reverse transcriptase genes in order to detect mutations that confer resistance to specific antiretroviral drugs. This application was seeking to complement the sequencing of these areas of the genome to allow MBS-funding of sequencing of the third variable (V3) loop gene of the HIV glycoprotein gp120.

HIV tropism testing is not currently listed on the MBS. To facilitate access to PBS-subsidised maraviroc in Australia, ViiV Healthcare has been funding the performance of HIV tropism testing.

### 3. Prerequisites to implementation of any funding advice

No genotypic tropism test has been approved by the TGA for detecting the presence of X4-using viruses.

The Therapeutic Goods Administration (TGA) is currently developing a new regulatory framework for in vitro diagnostic (IVD) devices. As part of these reforms all IVD assays (including in-house assays) will have to undergo technical file review (TFR) and inclusion on the ARTG by July 2014. Further, any new IVDs introduced to the Australian market after commencement of the new framework on 1 July 2010 must be included on the ARTG prior to legal supply.

### 4. Proposal for public funding

Genotypic tropism testing is currently funded for fourth-line patients in Australia by the sponsor.

[REDACTED]

The submission noted that if tropism testing was listed on the MBS, the sponsor's direct funding of the test would cease.

#### Proposed MBS listing

<b>Category 6 – Pathology Services</b>
MBS 6XXXX Genotypic testing for HIV tropism in a patient with confirmed HIV infection if the patient's viral load is greater than 1,000 copies per mL and a CCR5 antagonist is being considered as a treatment option.  Maximum of 2 tests in a 12 month period.  No further tropism assays should be conducted once the presence of CXCR4-tropic (X4-tropic) virus has been confirmed.
[REDACTED]

The Joint ESCs advised that a second MBS item should exist where genotypic antiretroviral resistance testing (GART) and genotypic tropism testing occurs concurrently if this would result in material cost reductions through economies of scale, given that the sample, capital equipment and skills are identical for both tests.

The possibility of removing the phrase “if the patient’s viral load is greater than 1000 copies per mL” is not supported because that is still the accepted restriction for other genotypic testing, including the current MBS item descriptor for GART (MBS item 69380). PASC expressed concern that this might signal a future shift to peripheral blood mononuclear cell DNA-based testing which is not part of the testing options under current consideration. If this possibility is proposed in the assessment phase, it would need to be justified by specific evidence on the comparative analytical performance of the various HIV tropism assay options on samples containing viral loads less than 1000 copies per mL.

It is proposed that each patient would be allowed a maximum of 2 tests in a 12 month period. Once the presence of X4 tropic virus has been detected the use of maraviroc would no longer be effective. No further tropism assays should be conducted once the presence of X4-tropic virus has been confirmed and the use of maraviroc would cease.

A pathologist and laboratory staff would perform the assay under instruction from the treating clinician. Testing would be performed in specialist virology laboratories with National Association of Testing Authorities (NATA) accreditation.

## **5. Consumer Impact Statement**

No feedback was received.

## **6. Proposed intervention’s place in clinical management**

As indicated by the applicant, there is a proposed submission to the PBAC to have maraviroc PBS subsidised for all patients requiring ART and not only those that have failed at least three prior antiretroviral treatment regimens. If both this MSAC and the proposed PBAC applications are successful, the outcome would be that all patients will be able to access MBS-subsidised HIV tropism testing at any stage during their treatment as opposed to the current scenario where only ART experienced patients access externally funded HIV tropism testing late in their treatment pathway. HIV tropism testing would be stopped upon confirmation of CXCR4 tropic virus.

The provision of genotypic tropism testing would be used in addition to the currently available interventions.

## **7. Other options for MSAC consideration**

Not applicable.

## **8. Comparator to the proposed intervention**

The submission nominated the phenotypic tropism test Enhanced Sensitivity Trofile Assay (ESTA) as the main comparator for genotypic tropism testing, for both treatment-experienced and treatment-naïve patients.

Although neither the original Trofile phenotypic tropism test nor the ESTA phenotypic tropism test is available in Australia, the DAP identified both as relevant analytical comparators to estimate the implications of using genotypic tropism testing in predicting the variation in treatment effect of maraviroc for use in Australia.

For the proposed MBS-funded genotypic tropism testing to support the proposed PBS listing of maraviroc to include treatment-naïve patients, the most appropriate comparator is existing GART testing without early access to the genotypic HIV tropism assay and efavirenz, followed by externally funded HIV tropism testing to determine if the current PBS

requirements relating to access to maraviroc as part of a fourth-line regimen are fulfilled and the option to use maraviroc in patients infected with R5-tropic virus at that stage.

**Table 1: Current MBS item descriptor for 69380 (GART).**

Category 6 – Pathology Services
<p>MBS 69380            Genotypic testing for HIV antiretroviral resistance in a patient with confirmed HIV infection if the patient's viral load is greater than 1,000 copies per ml at any of the following times:</p> <ul style="list-style-type: none"> <li>o at presentation; or</li> <li>o before antiretroviral therapy; or</li> <li>o when treatment with combination antiretroviral agents fails;</li> </ul> <p>maximum of 2 tests in a 12 month period</p> <p><b>Fee:</b> \$770.30 <b>Benefit:</b> 75% = \$577.75 85% = \$695.80</p>

In 2009, PBAC stated that “once the test is funded under the MBS, the PBAC advised that it wished to re-examine the effect of the Government meeting this cost in a new cost-effectiveness analysis”. Consequently, the joint ESCs advised that, if the comparative assessment of tropism testing raises doubts about whether the current PBS listing remains acceptably cost-effective, then assessing the proposed listings against this current listing would not directly inform a judgement of whether the proposed listings are acceptably cost-effective. In other words, if changing the test reduces the incremental effectiveness of maraviroc in terms of virological response, then the cost-effectiveness of both the current and the proposed listings need to be considered.

Item number 69380 was listed on 1 July 2011, thus only a couple of months’ figures on the utilisation of this item are available from MBS statistics.

## 9. Comparative safety

Comparative safety of test strategy

The submission did not provide any information regarding adverse events related to the test beyond the statement: Genotypic sequencing and bioinformatic tropism prediction is an in vitro diagnostic procedure and as such, poses very few safety issues. Tropism testing only requires venepuncture of the patient to obtain the required blood sample.

## 10. Comparative effectiveness

The primary approach taken in the submission was to present evidence to support the claim of noninferiority of maraviroc for treatment-naïve, R5-tropic HIV-1 infected patients as determined initially by the Trofile phenotypic tropism test and subsequently re-screened by the ESTA. All key evidence provided by the submission to substantiate claims of comparative test performance (presented as concordance data) and consequences for the efficacy of maraviroc (presented as predicting virological response) in treatment-naïve patients has been conducted in the MERIT trial population and published as Swenson 2011.

### Comparative studies and associated reports

This evidence was supplemented with four comparisons of genotypic tropism testing and the ESTA to support the claim of similar analytical performance. This supplementary evidence was not linked meaningfully due to the:

- confounding effect of evidence which did not stratify included patients according to treatment history
- lack of evidence presented to assess the performance of genotypic tropism testing in treatment-experienced patients.

Prognostic evidence	Retrospective cohort studies which assess viral tropism at baseline and correlates of disease progression.	☒	k=6	n=2725
Comparative analytical performance	Supportive studies of analytic performance involving various phenotypic and genotypic tropism tests in HIV-positive patients.	☒	k=4	n=765
Comparative analytical performance using deep sequencing	Retrospective re-analysis of treatment-naïve patients (recruited into the MERIT trial as having R5-tropic HIV according to the Trofile assay) using both the ESTA and genotypic tropism testing involving deep sequencing in combination with the geno2pheno algorithm ( <i>presumably using the same appropriately stored sample for all three tests</i> ).	☒	k= 1	n= 693

k=number of studies, n=number of patients.

A consistent chain of argument was not presented concerning the prognostic impact of the biomarker, comparative performance of the test and treatment effect of the drug in treatment-experienced patients.

No evidence was presented to assess the performance of the various bioinformatic algorithms relative to the various geno2pheno algorithms and to each other in the main body of the submission. Attachment 6 of the submission summarised studies comparing genotypic tropism testing to phenotypic tropism testing and different bioinformatics algorithms to each other. Insufficient detail was provided to obtain meaningful comparisons of the performance of different bioinformatics algorithms relative to each other.

A study by McGovern (2010) was not presented in the main body of the evidence in Section B; however, it formed the basis of Section D. No quality appraisal of this study was presented in the submission. Like Swenson 2011, this study compared genotypic tropism testing across various permutations of the geno2pheno algorithm to identify various subgroups of patients previously determined to have R5-tropic virus using the Trofile test to be enrolled in MOTIVATE-1, MOTIVATE-2 and A40010292 trials of 4<sup>th</sup>-line maraviroc.

### Comparative analytical performance

The Trofile test determined tropism status for enrolment in the randomised trials assessing maraviroc (first the MOTIVATE trials in the 4<sup>th</sup>-line setting and then MERIT in the treatment-naïve setting). The ESTA and various geno2pheno algorithms associated with genotypic tropism testing were subsequently used to identify different subgroups of the enrolled patients and thus to reanalyse the trial results. Patients in analyses therefore do not represent the distribution of X4 tropism in the population in regular practice who would not be prescreened in this way before having a tropism test.

Compared with ESTA in this prescreened population of treatment-naïve patients from the MERIT trial, genotypic tropism testing as defined above resulted in fewer patients being reclassified with X4/DM tropism, so more patients would be eligible for maraviroc. This may vary if the most widely used FPR of 20% in Australia is used instead. The low sensitivity and

PPV results suggest that most discordance occurs in the extra number of patients reclassified as having X4/DM tropism.

If detecting lower levels of X4/DM tropism accurately predicts a population who should not receive maraviroc, then the genotypic tropism testing as defined above appears to result in fewer false positives to X4/DM tropism than Trofile but more false positives than ESTA. The additional analyses of the MOTIVATE and MERIT trial data by excluding patients shown to have been X4/DM tropic by the ESTA despite being deemed to be R5-tropic by the Trofile assay is important to the submission’s claims that (based on the MERIT trial) maraviroc is noninferior to efavirenz in treatment-naïve patients and that (based on the MOTIVATE trials) adding maraviroc is superior to adding placebo in 4<sup>th</sup>-line patients (discussed below).

**11. Economic evaluation**

Treatment-experienced model:

The DAP sought to establish the case for MBS-funding of genotypic tropism testing in the context of the current PBS restriction. The submission presented a stepped economic evaluation (cost-utility analysis) that compared the incremental costs and benefits of maraviroc for treatment-experienced patients with genotypic compared to phenotypic tropism testing (as set out in the DAP). The submission estimated an ICER in the range of (redacted) \$15,000-\$45,000/QALY based on the proportion of patients achieving virologic success.

**12. Financial/budgetary impacts**

**Test cost/patient**

The proposed MBS fee was (redacted)/patient.

*Drug cost/patient/year*

(redacted)/patient/year assuming 12 prescriptions per year and the proposed weighted price.

*Likely number of patients tested and treated*

[Redacted]

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5.

[Redacted]

[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

**Net financial cost to the MBS:**

Table 21 presents the financial implications to the MBS of funding genotypic tropism testing under the proposed listing for maraviroc. The estimated total net cost to the MBS over 5 years, under the proposed listing is (redacted) less than \$1 million. Uncertainty in the

estimates of the uptake of tropism testing, the exclusion of testing following virologic failure and not reportable results, and the use of inappropriate sources to estimate switching all add to the uncertainty of the overall estimate. Furthermore the submission used the schedule fee, rather than the MBS benefit (85% of the schedule fee for out-patients). The Extended Medical Safety Net is unlikely to be affected.

[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Table 22 presents the financial implications to the MBS of funding genotypic tropism testing under the **current** listing for maraviroc (currently funded by the sponsor (**redacted**))

[REDACTED]

The estimated total net cost to the MBS over 5 years, under the proposed listing is [REDACTED] less than \$1 million.

[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

### 13. Key issues for MSAC from ESC

There is no accepted reference standard for HIV tropism. The preferred basis for test assessment in terms of clinical utility would be virological response to the use of maraviroc as defined in the DAP. The “evidentiary standard” test is the Trofile phenotypic tropism test, which was the basis for identifying as R5-tropic all participants enrolled in the trials for maraviroc for this submission and the previous submission to PBAC supporting the current PBS listing. The ESTA phenotypic tropism test has since replaced the Trofile test on the basis of in vitro experiments showing that it has increased sensitivity in detecting X4-tropic virus.

The submission did not adequately address the number of times the test is likely to be ordered for a patient. The Joint ESCs agreed that a tropism test would be performed:

- before the commencement of treatment in naïve patients when maraviroc is being considered; and
- where a patient’s prior HIV treatment regimens have all excluded maraviroc and where no prior tropism test has shown X4-tropism, as part of investigating failure to an existing line of HIV treatment when considering a change in regimen to include maraviroc.

It is also possible that a tropism test might be performed:

- when adverse events occur during treatment with a maraviroc-containing regimen;
- when treatment with a maraviroc-containing regimen no longer appears effective and a shift in tropism is suspected as a cause – the Joint ESCs accepted advice reported in the

PSCR that clinicians would assume the virus is X4-tropic and cease a maraviroc-containing anti-retroviral regimen rather than waiting until the viral load reaches 1,000 copies per mL necessary for the test and then for the 2-week turnaround time; and

- the Joint ESCs also considered that a tropism test might be performed alongside GART when a patient is first diagnosed with HIV infection. As advised in the DAP, unless antiretroviral therapy were to start immediately, this would be a waste because of the shift from R5- to X4-tropism that occurs over time in a proportion of patients with HIV infection.

The submission also did not address re-testing of “not reportable” results and the delay between obtaining the bio-sample and test results, which are important as patients may switch tropism status in the intervening period. A “not reportable” result indicates that the tropism of the virus cannot be determined. “Not reportable” results are uncommon with genotypic tropism tests; causes may be low levels of viraemia or compromised samples.

The overall risk of bias across the entire evidence base is likely to be high due to:

- poorly reported selection criteria
- bias introduced by the lack of a reference standard for testing
- the process of subsequently re-analysing the MOTIVATE and MERIT randomised trials and exclusion of patients introduces the potential for reporting and interpretation bias and also means that confounding factors are unbalanced.

**1) The submission claimed that genotypic sequencing followed by bioinformatic tropism prediction represents an acceptable substitute for phenotypic tropism determination in treatment-naïve patients.**

The submission claimed that both methods were able to reliably predict response to maraviroc in treatment-naïve HIV-1 patients and showed strong concordance. These claims are not adequately supported. The following issues need to be considered:

- Patients in the MERIT (and MOTIVATE) trial were pre-screened for R5-tropic virus using the Trofile assay and therefore do not represent the distribution of the tropism biomarker in the population who would receive the test in practice.
- The submission-calculated sensitivity of genotypic tropism testing for detecting X4-using variants in the MERIT patient population was low. This has implications for the correct identification of patients who will respond to maraviroc.
- No statistical test of concordance was presented to substantiate the claim of strong concordance across test options.
- Swenson (2011) used deep-sequencing in combination with the geno2pheno algorithm which incorporated a FPR of 3.5%. This FPR was previously optimised in the re-analysis of the MOTIVATE trials using population-based sequencing. Consequently the generalisability of the results to the Australian context is limited.
- The submission indicates that within Australia the geno2pheno bioinformatics algorithm with an FPR of 20% is the most commonly used, but genotypic tropism test performance varies by the associated algorithm, prespecified false positive rate and whether deep sequencing or population-based sequencing is used.

**2) The submission made no claim regarding the superiority or noninferiority of genotype tropism testing and phenotype tropism testing in treatment-experienced HIV-1 patients.**



The evidence relating to treatment-experienced patients presented in the submission should be interpreted in consideration of the following:

- The prevalence of R5-tropic virus within the included studies is likely to be over-represented due to the use of samples from the MOTIVATE trials which were pre-screened for R5-tropic virus using the Trofile assay.
- The overall risk of bias amongst the included studies of testing is high.
- The applicability of individual study results to the population who will receive the test in practice is uncertain due to the variation in FPR used within the included studies.

**3) The submission described maraviroc as noninferior in terms of comparative effectiveness and superior in terms of comparative safety over efavirenz in HIV-1 treatment-naïve R5-tropic patients.**

This claim is reasonable in terms of safety, however the claim of noninferiority is not adequately supported by the data presented, which mainly relies on the re-analyses of the trial populations using different tropism tests. Maraviroc is inferior to efavirenz in patients with X4-tropic HIV, and the noninferiority claim relies on an acceptance that the Trofile test did not detect all patients with X4-tropic for exclusion from the MERIT trial.

Evidence for the comparative analytical performance of the genotypic tropism tests as compared to either phenotypic tropism test was confounded by the paucity of high level evidence in patient populations stratified according to treatment history. Summary measures of comparative analytical performance were presented inadequately.

Evidence of the prognostic evidence was from a diverse range of patient populations; the confounding factors of antiretroviral treatment history, means of acquiring infection and disease progression limits the generalisability of estimates to the proposed MBS population.

The studies included as prognostic evidence used either the Trofile assay and/or the SVM<sub>genomic2</sub> bioinformatic algorithm to estimate the prevalence of X4-using virus in the population. These tests have a lower sensitivity for the detection of X4-using virus as compared to the ESTA, thus the reported prevalence of X4-using virus in this evidence may be an underestimation of the true prevalence.

The number of patients receiving maraviroc and tropism testing in line 1 and lines 2 and 3 was based on the assumption that 5% of patients eligible for tropism testing will be tested for tropism. This was based on advice from the sponsor's advisory board and uptake data from the USA (1%). This estimate is highly uncertain. Attachment 3 of the submission provides a survey of 14 HIV clinicians. Clinicians were asked 'what percentage of your treatment-naïve patients are likely to be tested for the CCR5 co-receptor tropism?' (in the scenario of PBS listing for first-line maraviroc). The mean response was 71%. It is likely that 5% is a significant underestimate of uptake of tropism testing. The clinicians were also asked to nominate the proportion of patients who test positive for CCR5 tropism they would prescribe maraviroc. The mean response was 29% (compared to 100% in the submission).

Furthermore the submission did not consider re-testing of the genotypic tropism test following virologic failure or not reportable results, which compounds the underestimate of the number of genotypic tropism tests.

The number of patients estimated to receive tropism testing was underestimated resulting in an underestimate of the number estimated to receive maraviroc.

The duration of maraviroc may be underestimated due to inconsistencies across data sources and inappropriate application and questionable assumptions about switching upon virological failure.

The model structures did not allow a full assessment of the impact of varying analytical performance of phenotypic and genotypic tropism testing, including in terms of varying negative outcomes associated with inappropriately treating X4-using patients with maraviroc (i.e. the impact of false negatives for X4-tropism).

The models did not include re-testing of not reportable results of the tropism test.

The following issues were identified regarding the calculation of the weighted price:

- The calculations are not provided for private patients.
- The estimates of the proportion of treatment-experienced patients receiving maraviroc in the proposed scenario is uncertain due to uncertainty in the 5% estimate of uptake of the test in first to third-line and the use of inappropriate sources to estimate switching.

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#### Error in the Evaluation Report correctly identified in Pre-Sub-Committee Response

In the treatment-naïve model, efficacy after the first 16 weeks in first-line was based on data from week 17 (not week 96 as stated on MSAC 6.1/PBAC 6.3.COM.23 and 32) to 240 weeks, including the open label phase of the trial.

#### **14. Other significant factors**

Not applicable.

#### **15. Summary of consideration and rationale for MSAC's advice**

##### *Whom to test?*

MSAC considered that the eligible patient population for genotypic tropism testing – to distinguish between HIV which has the co-receptor to the CD4 receptor solely in the CCR5 state (R5-tropism) or has some of this co-receptor in the CXCR4 state (X4-tropism) – would have human immunodeficiency virus (HIV-1) infection, and that there was no need or basis to enrich this population for testing.

MSAC considered that it could not adequately respond to PBAC's referral for advice on the characteristics and numbers of patients with HIV-1 infection who would be likely to receive genotypic tropism testing. In terms of the numbers of patients, MSAC noted the wide range of estimates in the submission

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MSAC noted that the prevalence of X4-tropism increases as the HIV-1 infection progresses and that maraviroc was proposed for use as first-, second- and third-line therapy. These factors would influence the number of potentially eligible patients. MSAC noted that the assistance of the relevant craft groups and experts would be helpful in preparing responses to these questions.

##### *When to test?*

MSAC considered that patients should be tested before deciding whether to treat with an anti-retroviral regimen containing maraviroc. As advised by PASC and ESC, tropism testing

should not be conducted at the initial diagnosis of HIV-1 infection because the tropism status of the virus can change between this point in time and when treatment is being considered. MSAC also accepted advice from the Joint ESC Report that repeat testing would be unlikely in the event that a maraviroc-containing anti-retroviral regimen no longer appears effective because of viral load failure. As stated in the proposed item descriptor, repeat testing would also not occur after the virus has shifted from R5-tropic to X4-tropic, which it is likely to do over time, because this tropism shift is unidirectional and maraviroc is not indicated to treat X4-tropic HIV-1 infection. At least four genotypic tropism tests could be anticipated in a patient's lifetime in the circumstance where suitability for maraviroc is assessed prior to each line of therapy.

#### *What to test?*

MSAC noted that Australian pathology practice tends to follow the European guidelines for genotypic tropism testing. MSAC considered that the tropism state of the virus should be tested when the patient's viral load is greater than 1,000 copies per mL to ensure sufficient quantities of virus to support population-based sequencing rather than deep sequencing. The V3 loop of the virus is sequenced using reverse-transcriptase polymerase chain reaction (RT-PCR) following extraction of and amplification of HIV plasma RNA, proviral DNA or whole-blood DNA. The sequencing information is then fed as inputs into a computer algorithm to aid interpretation of the results by calculating a statistical estimate of the likelihood that the virus is X4-tropic.

MSAC noted advice in the Joint ESC Report that there were several elements of this second step of genotypic tropism testing which could vary and which could have consequences for the comparative analytical performance of this type of testing:

- the choice of bioinformatic algorithm (noting Australian practice tends to use geno2pheno<sup>®</sup>)
- the inclusion of a support vector machine in the computerised algorithm to use statistical learning methods to update the algorithm continually
- the information supplied as inputs to the algorithm (for example, distinguishing between the "clinical model" and the "clonal model" for geno2pheno<sup>®</sup>)
- whether the algorithm is supported by population-based sequencing or deep sequencing (noting Australian practice tends to use population-based sequencing)
- the false positive rate (FPR) threshold set by the institution as the probability of classifying R5-tropic virus falsely as X4-tropic virus for the algorithm output. (Note that this affects the sensitivity and specificity trade-off. Australian practice tends to use an FPR of 20% rather than the lower FPRs reported overseas. This higher FPR increases the likelihood that the test result in Australia will be determined to be X4-tropic even when it is R5-tropic, and thus increases the likelihood that maraviroc will not be considered to be an appropriate therapy).

Given this range of elements, the likely interplay between them and the lack of data on comparative analytical performance across the options, MSAC considered that it could not adequately respond to PBAC's referral for advice on the minimal test performance characteristics to optimise the detection of X4-tropic HIV-1. Similarly, MSAC considered that it could not adequately respond to PBAC's referral for advice on how best to implement an adequate standard of genotypic tropism testing to support decisions about the use of maraviroc, although this will inevitably involve NATA accreditation and the associated quality assurance program.

MSAC noted that the main basis for comparing across the tropism test options was their clinical utility effect on predicting a viral response to maraviroc-containing anti-retroviral regimen, with less emphasis on usual metrics of comparative analytical performance. In the absence of an agreed reference standard for proposed public funding of genotypic tropism in Australia, the original Trofile<sup>®</sup> assay used in the randomised trials of maraviroc constitutes the evidentiary standard. However, MSAC acknowledged the general preference for using the Enhanced Sensitivity Trofile Assay (ESTA<sup>®</sup>), even though it is also not available outside the United States, as closer to a reference standard because it is able to detect smaller quantities of X4-tropic virus than the Trofile<sup>®</sup> assay.

From the data presented, which mainly related to the retrospective re-analyses of the MERIT randomised trial in treatment-naïve patient comparing a maraviroc-containing anti-retroviral regimen with an efavirenz-containing anti-retroviral regimen, MSAC concluded that the strongest signal was the inferior effect of maraviroc in the small numbers of patients subsequently re-classified as X4-tropic by ESTA<sup>®</sup> or genotypic tropism testing, and this was accompanied by a smaller shift in the lower confidence limit towards strengthening the claim of noninferiority in the complementary subgroups of patients subsequently confirmed as R5-tropic. As advised in the Joint ESC Report, interpretation of the supplementary assessment of comparative analytical performance across ESTA<sup>®</sup> and genotypic tropism testing suggests high overall concordance (82%), a low kappa (17%), a high specificity for X4 tropism (93%) and a low sensitivity for X4 tropism (21%), but is hindered by being limited to a population pre-screened as R5-tropic by the Trofile<sup>®</sup> assay. Based on this analysis, 90.6% of patients tested with genotypic tropism testing would be eligible to receive maraviroc, an increase of 5.5% over the 85.1% of patients tested with ESTA<sup>®</sup>. Other comparative analytical performance involving genotypic tropism testing is not clearly examined in similar patients in terms of exposure to anti-retroviral treatment. Overall, MSAC advised that the impact of test uncertainty on overall clinical effectiveness and cost-effectiveness needed to be incorporated in any resubmitted economic evaluation.

MSAC anticipated that similar conclusions would be found with reference to the retrospective re-analyses of the MOTIVATE randomised trials comparing the addition of maraviroc or placebo to optimised background therapy in fourth-line treatment. These data were not presented in the submission, but Figure B.6i.1 of the Evaluation Report presents relevant data from McGovern et al (AIDS 2010;24(16):2517-25) comparing the original virological response results using the original Trofile<sup>®</sup> assay with retrospectively re-analysed virological response results based on subsequent re-classification of tropism status using genotypic tropism testing.

MSAC considered that it could not adequately respond to PBAC's referral for advice on the prevalence of R5-tropism as a basis for being eligible for treatment with maraviroc. Estimates vary from 83% in treatment-naïve patients to 69% in treatment-experienced in patients. Together with the difficulty above in identifying the number of patients likely to receive genotypic tropism testing, this makes it difficult to advise PBAC on the number of tests and costs of testing per patient treated with earlier maraviroc and the overall increase in the cost of testing to support earlier use of maraviroc.

#### Other considerations

MSAC noted that the genotypic tropism test for which public funding was being sought is currently funded in Australia by the applicant through an arrangement with the Department of Health and Ageing, and is used to inform eligibility to PBS subsidy for maraviroc as part of a

fourth-line anti-retroviral regimen in the treatment of HIV-1 infection. It has not previously been subject to a formal health technology assessment in Australia. MSAC noted that the application also sought public funding to use genotypic tropism testing to support a wider use of maraviroc as part of an antiretroviral regimen in the management of patients with HIV-1 infection at any line of therapy, including first-line treatment of patients who have not been treated previously for their HIV-1 infection (treatment-naïve).

MSAC also noted that genotypic tropism testing has not yet been assessed by the Therapeutic Goods Administration. MSAC was cautious in considering a test strategy where none of the available test options has regulatory approval.

MSAC agreed that the nominated comparator of usual care without tropism testing was appropriate, and that a comparison of analytical performance of the alternative tropism test options was also appropriate.

MSAC concluded that the primary co-dependency claim had been established based on virological response in the randomised trial populations investigating maraviroc initially considered to be R5-tropic using the Trofile<sup>®</sup> phenotypic test, but whose samples were re-tested using the Enhanced Sensitivity Trofile Assay (ESTA<sup>®</sup>) – a subsequent phenotypic test with greater ability to detect X4-tropism, and also re-tested using genotypic tropism testing – which also detected X4-tropism in some patients screened as R5-tropic by Trofile<sup>®</sup>. Retrospective re-analysis of the results of the noninferiority-designed randomised trial comparing the addition of either maraviroc or efavirenz to identical first-line anti-retroviral regimens indicated that the maraviroc-containing regimen was less effective than the efavirenz-containing regimen in patients re-classified as having X4-tropic HIV-1 infection. This reanalysis was based on a small sample size, but the difference was consistent across reanalyses using ESTA<sup>®</sup> or geno2pheno<sup>®</sup> and is likely to be statistically significant with larger sample sizes. In contrast, the maraviroc-containing regimen was noninferior to the efavirenz-containing regimen in patients confirmed as having R5-tropic HIV-1 infection. MSAC also concluded that this co-dependency claim could not be clearly distinguished from the unresolved question of whether tropism status indicates a different prognosis in HIV-1 infection (prognostic data were not clearly examined in similar patients in terms of exposure to anti-retroviral treatment). MSAC advised that there were no other purposes for tropism testing in HIV-1 infection.

MSAC noted that the threshold level of X4-tropism that predicts when there is a substantial reduction in the effectiveness of maraviroc is not yet elucidated.

MSAC noted that the test is based on a blood sample, so is safe for patients.

MSAC agreed with PBAC's rejection of the results of the economic evaluation presented in the submission yielding incremental QALY gains with maraviroc for the proposed use of maraviroc in earlier lines of therapy because they do not reflect the clinical conclusion that, at best, maraviroc demonstrates clinical noninferiority with current therapeutic options. If genotypic tropism test performance can be optimised, it may support a cost-minimisation analysis for this proposed use.

MSAC noted that the considerations above and advice below addressed the matters referred to it by the November 2012 PBAC meeting.

MSAC advised that, in the absence of any reason not to do so, the proposed fee of [REDACTED] which is less than the current MBS fee of \$775.50 for the proposed benchmark MBS item of 69380 for genotypic anti-retroviral testing (GART) should apply to any MBS listing of genotypic tropism testing (and may prompt a review of the fee for GART). MSAC noted advice from the Joint ESC Report that a second MBS item should exist where GART and genotypic tropism testing occurs concurrently if this would result in material cost reductions through economies of scale.

#### **16. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of genotypic testing for HIV tropism to help determine eligibility for existing PBS-subsidised fourth-line maraviroc or for proposed PBS-subsidised earlier-line maraviroc, MSAC does not support public funding on the basis of insufficient evidence that genotypic tropism testing as proposed adequately distinguishes between HIV-infected individuals who should and should not receive maraviroc. This is important because the effectiveness of HIV treatment regimens not involving maraviroc is not predicted to vary by HIV tropism status, whereas a HIV tropism test that can be relied upon should accurately distinguish between individuals with R5-tropic virus (who will respond to HIV treatment regimens involving maraviroc to the same extent as to these alternative regimens) and individuals with X4-tropic virus (who will have a less effective response to regimens involving maraviroc). Where there are existing anti-retroviral therapy options (that is, the proposed PBS listing of maraviroc), a high level of test accuracy is required because any false positive R5-tropism results will mean that the maraviroc-containing therapy will be less effective overall. Where there are no existing anti-retroviral therapy options (that is, the existing PBS listing of maraviroc as part of a fourth-line option), a high level of test accuracy is still important because any false positive R5-tropism results will mean that the effectiveness of maraviroc-containing therapy will be reduced.

MSAC also advised that the PASC process would not need to be re-visited before lodging any resubmission addressing the matters outlined above.

#### **17. Applicant's comments on MSAC's Public Summary Document**

Viiv Healthcare Australia will respond to the requests of MSAC in a future application.

#### **18. Context for decision**

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed

clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;

- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

#### **19. Linkages to other documents**

MSAC's processes are detailed on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).