MSAC Application 1174:

Final Decision Analytical Protocol (DAP) to guide the assessment of a pathology test to determine if a patient has been infected with CCR5 tropic HIV-1 for access to maraviroc

January 2012

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a decision analytical protocol that will be used to guide the assessment the safety, effectiveness and cost-effectiveness of tropism testing in HIV-1 as a marker for treatment with maraviroc and thus MSAC's decision-making regarding its public funding. It was finalised after inviting relevant stakeholders to provide input to the protocol. PASC noted that other matters were raised in the public and stakeholder feedback and the response from the applicant, but judged that addressing these would not substantially alter the final DAP.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
Intervention – specification of the proposed intervention
Comparator – specification of the therapy most likely to be replaced by the proposed intervention
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

An application requesting funding of genotypic HIV tropism testing for patients for which treatment with CCR5 antagonist maraviroc is being considered was received from ViiV Healthcare by the Department of Health and Ageing in May 2011. This application is seeking that genotypic HIV tropism testing 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 GART suite of tests.

2. Through the creation of a new MBS item number for HIV tropism testing alone.

Intervention

Description

Condition

HIV is a viral infection that causes immunosuppression. There are two subtypes of the HIV virus: HIV-1 and HIV-2. HIV-1 is by far the most common type of HIV virus with over 90% of HIV/AIDS cases being derived from HIV-1 infection. If untreated, infection with HIV leads to a number of different opportunistic infections and diseases that are called Acquired Immune Deficiency Syndrome (AIDS). AIDS diseases are often life-threatening and prior to the introduction of effective antiretroviral therapies, patients with AIDS had a prognosis of around two years. The treatment of HIV is complex, with the choice to treat and choice of treatment highly individualised. Treatment decisions depend on virological efficacy, degree of immunodeficiency, drug-drug interaction potential, resistance testing results, and co-morbid conditions. With early and aggressive treatment with antiretroviral agents patients infected with HIV can lead to effective long-term suppression of the levels of HIV and delayed onset of AIDS. Results from a meta-analysis on HIV treatment presented by the Antiretroviral Therapy Cohort Collaboration 2008 (Hogg *et al.*, 2008) show that with appropriate treatment the survival benefit of a patient infected with HIV at age 20 years is 43 years.

The place of existing GART

The efficacy of many antiretroviral drugs used to treat HIV infection is dependent on the genetic makeup of the virus that has infected the patient. Specific mutations within the HIV genome are known to confer resistance of the virus to specific antiretroviral agents. In order to guide the effective treatment of HIV infection various assays are available to test for genotypic resistance. In Australia these assays typically use direct sequencing of the HIV genome or nucleic acid hybridisation using specific wild-type or mutant oligonucleotides to determine the presence or absence of resistance conferring genetic mutations. 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 is 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. An assessment of GART has already been undertaken by MSAC and is not sought through this protocol.

Intervention being assessed: genotypic HIV tropism assay

HIV tropism determines the mechanism of action that HIV uses for cell invasion. HIV strains that use the beta-chemokine receptor CCR5 for cell entry are referred to as R5 viruses. HIV strains that use the alpha-chemokine receptor CXCR4 for cell entry are referred to as X4 viruses. Some strains use both receptors and these are referred to as X4R5 viruses. As a result of there being different HIV tropic classes a patient may have the following types of HIV infection:

- Infected with only R5 virus
- Infected with only X4 virus
- Infected with both R5 and X4 viruses
- Infected with only X4R5 virus.

HIV tropism is not fixed at primary infection and may shift towards CXCR4 over time. In some patients only a small amount of CXCR4 virus may be present at initial infection. If these patients are treated with a CCR5 antagonist, levels of CXCR4 virus may increase due to the selective suppression of CCR5 virus. In this circumstance the drug-associated shift in the population tropism may result in a change in the tropism call from CCR5 to dual/mixed or CXCR4 tropism.

There are currently two assays in widespread use that test for HIV tropism. There is currently no consensus on which assay should be performed to assess HIV tropism (Department of Health and Human Services, 2011, Vandekerckhove *et al.*, 2011).

The Trofile™ assay by Monogram Biosciences® is a phenotypic assay that splices the full length of patient-derived viral envelope genes into a vector to create a recombinant pseudovirus. The downstream ability of this recombinant virus to infect either: CCR5, CXCR4, or both CCR5 and CXCR4 cell lines is used to determine the tropic class of the patient's HIV infection. The Trofile™ assay was used to perform HIV tropism testing during the conduct of the pivotal clinical trials assessing the performance of maraviroc as a treatment agent in antiretroviral therapy (ART) experienced patients (Gulick *et al.*, 2008, Saag *et al.*, 2009).

Since its initial development the Trofile™ assay has been refined leading to the marketing and use of the enhanced specificity Trofile™-ES assay. Trofile™-ES can detect X4 or dual/mixed R5/X4 variants when present at levels of 0.3% of the viral population. The Trofile™-ES assay has been used to screen samples in a clinical trial assessing the use of maraviroc versus efavirenz as part of combination therapy in ART naive patients. Results of this trial demonstrated non-inferiority in clinical outcomes when ART patients were able to access maraviroc (Cooper *et al.*, 2010).

The other assay in widespread use is the genotypic HIV tropism assay. This assay determines whether HIV infection is of the R5, X4 or X4R5 tropic class through analysing its genetic material. The assay is based on sequence analysis of the patient-derived V3 loop region of the HIV genome. Various algorithms have been developed to analyse genetic sequence data with the goal of predicting the phenotype that confers HIV tropism. Genotypic algorithms currently in use include:

1. Geno2pheno
2. Position-specific scoring matrix ($PSSM_{X4R5}$ and $PSSM_{sinsi}$)
3. The 11/25, 11/24/25 and net charge rules.

Each algorithm has unique performance characteristics and all algorithms are currently in the process of being validated.

Consistent with other assays performed under GART, HIV genotypic tropism testing may be undertaken with plasma HIV RNA loads greater than 1000 copies/mL. The platform technology for the HIV genotypic tropism assay is the same as that used for existing GART. Logistically, laboratories performing GART can also perform the HIV genotypic tropism assay.

For the purposes of this document, the aim of the HIV tropism assay is to detect the presence of X4 tropic virus. Consequently, a positive test result would be reported as being infected with either: only X4 tropic virus, both R5 and X4 viruses (dual infection), or X4R5 dual tropic virus.

Intervention, therapy

Maraviroc is an antiretroviral medicine that works as a CCR5 inhibitor through blocking entry of R5 strains of HIV into the cell by selectively binding to the CCR5 receptor. Due to this mechanism of action the use of maraviroc has been approved as a treatment option only for patients who have undergone a HIV tropism assay to determine that they are infected only with a R5 strain of the HIV virus. As outlined in the Schedule of Pharmaceutical Benefits (PBS), maraviroc is available with the following restrictions:

> Treatment, in addition to optimised background therapy in combination with other antiretroviral agents, of an antiretroviral experienced patient infected with only CCR5-tropic HIV-1, who, after each of at least three different antiretroviral regimens that have included one drug from at least 3 different antiretroviral classes, has experienced virological failure or clinical failure or genotypic resistance.

A tropism assay to determine CCR5 only strain status is required prior to initiation. Individuals with CXCR4 tropism demonstrated at any time point are not eligible.

Virological failure is defined as a viral load greater than 400 copies per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity. (Department of Health and Ageing, 2011).

Administration, dose, frequency of administration, duration of treatment

The treatment of HIV with antiretroviral therapy (ART) is complex and treatment decisions are made in consideration of a range of factors including virological efficacy, drug-drug interaction potential, resistance testing results and any co-morbid conditions. Patients are treated with a combination of antiretroviral agents in order to ensure optimal virological suppression and reduce the risk of resistance developing. The use of combination ART (cART) is the mainstay of HIV treatment (Department of Health and Human Services, 2011).

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 is seeking to have HIV tropism testing funded through the MBS. MBS funding of HIV tropism testing is being sought both as an optional test as part of the current MBS-funded GART and as a stand-alone procedure.

HIV tropism testing is 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.

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.

Currently a patient may have existing GART performed at diagnosis but not commence treatment straight away. Instead, the initiation of treatment would be delayed until the patient's CD4 count is below the threshold 500/mm^3 when they are eligible to access PBS-subsidised antiretroviral treatment. In these cases GART may not be re-performed and the development of a treatment plan would be guided from the GART results at diagnosis. However, determining HIV tropism to confirm

or exclude any shift since diagnosis would be required ahead of being able to include maraviroc in a treatment plan. This clinical scenario is the reason for the request to have HIV tropism testing funded either as part of the existing GART suite of tests or as a stand-alone procedure.

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.

Two groups will order a GART including HIV tropism test: consultant physicians and doctors who have specific extra training in HIV medicine.

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. Although the location of specialist virology laboratories would be limited to major capital cities, there would be no access issues to the assay as the patient blood sample can be drawn locally and sent to specialist virology laboratories for testing.

The capital equipment and technical expertise required to perform HIV tropism testing is equivalent to that already used for GART.

Co-administered interventions

Existing GART is initiated after a patient has undergone the diagnostic testing required to establish a definitive diagnosis of HIV. Performing GART at the time of diagnosis is useful to assess for transmitted drug resistance, i.e. infection with a viral strain that carries mutations that confer resistance to specific treatment agents. Once a patient has commenced treatment, further GART would be performed when a patient is no longer responding to ART treatment. This testing is performed both to test for acquired mutations that confer drug resistance and to guide ongoing treatment.

Treating a patient with maraviroc is dependent on performing an HIV tropism assay. If HIV tropism testing reveals that the patient is infected with only the CCR5 strain of HIV, then the use of maraviroc as a replacement for an alternative antiretroviral agent of comparable safety and effectiveness may be considered as part of a cART regimen. Currently patients may only access PBS-subsidised maraviroc if they have experienced treatment failure with least three different antiretroviral regimens.

The PBS item codes associated with maraviroc are: 5792W, 5793X, 9572T, 9573W.

It has been indicated by the applicant that there is currently a plan to submit an application to PBAC seeking to expand the indications for the use of maraviroc to include all HIV patients requiring cART and not only those patients who have failed three treatment regimens. The clinical efficacy of maraviroc in this expanded treatment context would be considered by PBAC as part of the proposed PBAC submission. The results of this PBAC assessment are relevant to the assessment of the

genotypic HIV tropism assay being considered in this protocol, however, an assessment of the effectiveness of maraviroc does not lie within the remit of MSAC and is thus not formally sought as part of this protocol.

Not all patients accessing an HIV tropism assay will be prescribed maraviroc as access will be influenced by the results of the HIV tropism assay and the overall suitability of maraviroc in context of a cART regimen.

Background

Current arrangements for public reimbursement

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. The test is performed by specialist laboratories which are reimbursed directly by ViiV Healthcare on a fee-for-service basis.

GART testing that does not include HIV tropism testing is currently listed on the MBS. Details of this listing are given in Table 1 for reference.

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

Category 6 – Pathology Services
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: o at presentation; or o before antiretroviral therapy: or o when treatment with combination antiretroviral agents fails; maximum of 2 tests in a 12 month period Fee: $775.50 Benefit: 75% = $581.65 85% = $704.30

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.

Figures presented in the previous assessment of GART (Medical Services Advisory Committee, 2010) estimated that "approximately 1,050 new cases and between 894-1,155 individuals with resistance to HAART could be eligible for testing per annum". If HIV tropism testing is included in GART then this would put an upper estimate of use of HIV Tropism testing at 2,205 per annum. Due to the fact that patients with confirmed X4 tropism will not be eligible for further tropism testing the actual utilisation figures would be expected to be below the figure of 2,205.

Regulatory status

GART and HIV tropism testing are currently performed using either commercial kits or assays that have been developed in-house at testing laboratories. A search of the commercial GART tests listed on the Australian Register of Therapeutic Goods (ARTG) did not yield sufficient technical information to confirm or exclude the inclusion of HIV tropism in their testing kits.

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.

If an IVD assay for HIV tropism was developed in-house prior to 1 July 2010 it may legally continue to be used whilst it undergoes a technical file review ahead of registration on the ARTG. The deadline for registration on the ARTG is July 2014.

Patient population

Proposed MBS listing

The applicant has requested that new MBS item numbers be created to allow for genotypic testing for HIV tropism either as part of existing GART or individually. The proposed MBS listings are given in Table 2 and Table 3 respectively.

Table 2: Proposed MBS item descriptor for GART testing including a HIV tropism assay.

Category 6 – Pathology Services
MBS 6XXXX Genotypic testing for HIV antiretroviral resistance with genotypic HIV tropism assay 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: o before antiretroviral therapy when maraviroc is being considered: or o when treatment with combination antiretroviral agents fails; Maximum of 2 tests in a 12 month period; No further tropism assays should be conducted once the presence of X4-tropic virus has been confirmed.

Table 3: Proposed MBS item descriptor for HIV tropism testing performed separately from GART.

Category 6 – Pathology Services
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 at any of the following times: o before maraviroc therapy: or o when treatment with combination antiretroviral agents fails;

Maximum of 2 tests in a 12 month period; No further tropism assays should be conducted once the presence of X4-tropic virus has been confirmed.

No fee has been proposed by the applicant. The current fee for MBS item number 69380 (GART) is $775.50. The assessment will need to present and justify a fee for genotypic HIV tropism testing, both as a stand-alone test and as part of the GART tests, with reference to the input costs of the service. A range of fees may be tested through sensitivity analysis in the cost-effectiveness and financial analyses.

Clinical place for proposed intervention

Currently patients are only eligible for access to PBS-subsidised maraviroc if they have failed previous treatment with least three different antiretroviral regimens. If these conditions are met, maraviroc may be considered as a treatment only after a patient has been confirmed as being infected with CCR5 tropic HIV.

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:

1. All patients would 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.

2. Upon confirmation of infection with CCR5 tropic virus, patients would be able to access maraviroc at any stage during their treatment pathway as opposed to the current scenario where maraviroc may only be prescribed when a patient has failed three prior antiretroviral treatment regimens.

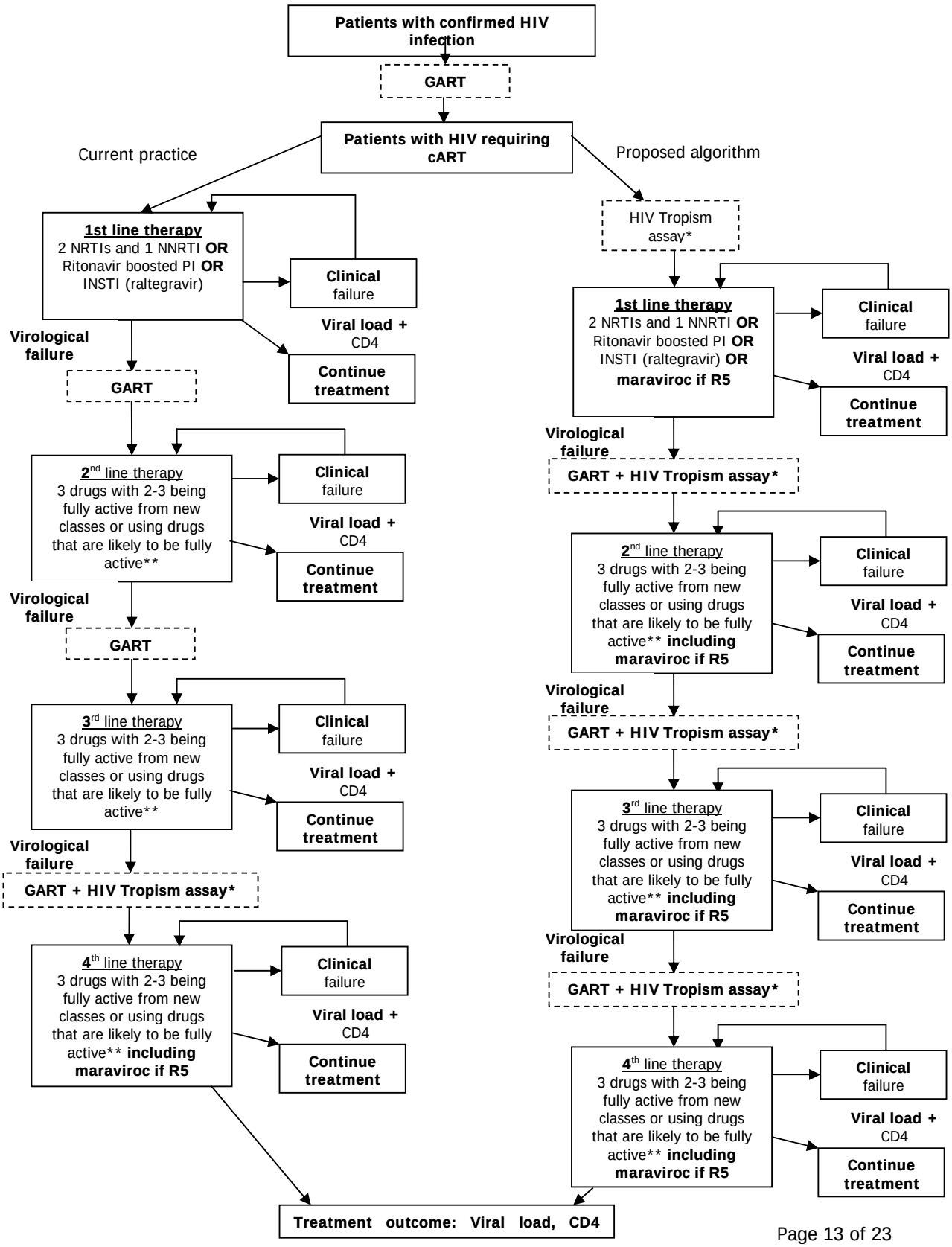
If both this MSAC application and the proposed application to the PBAC to have maraviroc PBS-subsidised for all patients requiring ART are successful, it would be expected that the use of HIV tropism testing and maraviroc would increase. Increases in the use of maraviroc may be offset by decreases in the use of other antiretroviral agents.

As access to maraviroc is co-dependent on undertaking an HIV tropism assay, the conduct of HIV tropism testing in a scenario where ART naive patients are eligible to receive maraviroc would ideally take place when they are about to commence therapy. Although GART is typically conducted at the time of diagnosing HIV infection, tropism testing at diagnosis is not warranted because it is only used to guide treatment decisions and HIV tropism can change between initial diagnosis and

commencement of treatment. Patients would not be likely to undergo further GART at this later stage and instead receive only HIV tropism testing.

A clinical algorithm of the current and proposed treatment pathways for HIV patients that includes patient eligibility for maraviroc is given in Figure 1. As per the MBS item descriptors, no HIV tropism testing may be performed once X4 tropic HIV has been found.

Figure 1. Clinical algorithm showing current and proposed access arrangements to HIV tropism testing and maraviroc. * Optional when maraviroc is being considered **Classes include NRTI, NNRTI, PI/r, INSTI



Questions for the assessment phase

The Trofile™ (and Trofile™-ES) phenotypic assays have been the most widely used HIV tropism tests to date, and these assays were used to provide tropism information in many of the pivotal clinical trials on maraviroc. Assays used in the direct generation of evidence relating to virological response can be described as an "evidentiary standard" because this evidence supports a link between use of the assay and treatment outcomes. However, the Trofile™ assays have logistical and technical limitations that make them less than convenient in clinical practice. It is also worthy of noting that corporate support for both Trofile™ phenotypic assays in Australia has ceased resulting in restricted access for Australian patients. Subsequently all HIV tropism testing in Australia is currently performed using a genotypic assay through sequencing of the V3 loop.

This DAP outlines two different subsets of HIV infected patients for which an assessment of the genotypic HIV tropism is appropriate:

1. Patients for whom 4th line treatment with maraviroc is being considered, in line with the current access arrangement to PBS-subsidised maraviroc. The aim of this assessment would be to determine the comparative analytic performance of the genotypic and phenotypic HIV tropism assays and inform a decision regarding MBS-funding of the HIV tropism testing required ahead of access to maraviroc within its current PBS restrictions.

2. Patients for whom treatment with maraviroc is being considered without a line of therapy restriction. This assessment would inform a decision regarding MBS-funding of HIV tropism testing that will be required to access maraviroc without a line of therapy restriction as per the proposed submission to the PBAC.

Current maraviroc access arrangement

The overarching aim of the proposed assessment is to establish an evidence base for introducing an MBS-funded genotypic HIV tropism assay necessary for patient access to the current PBS listing for maraviroc.

The main component of the assessment of the proposed investigative medical service is the determination of the comparative analytic performance of the genotypic HIV tropism test in comparison to <u>both</u> the original Trofile™ and Trofile™-ES phenotypic assays. In undertaking this assessment of comparative analytical performance, the following points should also be investigated:

1. The comparative performance of the genotypic assay in response to potential changes in the relative populations of X4 and R5 virus across the course of infection.

2. The comparative performance of the genotypic HIV tropism assay interpretation algorithms.

3. The rate and consequences of inappropriate treatment with maraviroc being prescribed following a false positive result (R5 tropic virus reported as X4 or dual tropic virus) or false negative result (X4 tropic virus reported as R5 tropic virus) should be presented.

4. The number of patients currently accessing maraviroc who may require re-testing should an MBS-funded genotypic HIV tropism assay be introduced.

As neither the original Trofile™ assay nor the more recent Trofile™-ES assay can be described as a reference ('gold') standard, comparative analytical performance of the test results for the phenotypic and genotypic assays would ideally be assessed using virological response to the use of maraviroc (or other CCR5 antagonist) in patients following HIV tropism testing. For example, confirmation of a true negative test result (R5 tropic virus reported and R5 tropic virus infection) would be demonstrated by a virological response to treatment with a CCR5 antagonist, whereas confirmation of a false negative test result (R5 tropic virus reported and X4 or dual tropic virus infection) would be demonstrated by an absence of virological response to subsequent treatment with a CCR5 antagonist. Such data would enable a direct assessment of the clinical consequences of using different tropism testing options, and standard validity metrics of sensitivity, specificity etc could be used to compare test performance. The clinical consequences of false positive and false negative test results could be addressed directly and incorporated into the cost-effectiveness assessment.

In the event that there is a lack of comparative data reporting on the virological response in patients that receive maraviroc (or other CCR5 antagonist) following the different HIV tropism assay options, other appropriate standard analytic performance metrics should be used to compare their test performance. If material discordance is reported across phenotypic and genotypic assay results, the clinical consequences of this situation should be addressed within the context of the proposed introduction of a MBS-funded genotypic HIV tropism assay and of the limited availability of the Trofile™-ES assay to Australian patients. If there is no direct evidentiary link between use of the genotypic HIV tropism assay and virological response, how should evidence of material differences in assay results be interpreted when making prescribing decisions regarding the commencement and cessation of CCR5 antagonist treatment? More specifically, what are the clinical and cost-effectiveness consequences for the existing PBS-subsidised use of maraviroc of the introduction of a MBS-funded genotypic HIV tropism assay in the event that it cannot be shown to be superior (or at least non-inferior) to the phenotypic assays?

Proposed HIV tropism testing and maraviroc access arrangement

An assessment of the proposed listing to allow genotypic HIV tropism testing and patient access to maraviroc without a line of therapy restriction is also sought.

In this assessment, a comparison should be made between the current PBS-restricted access to maraviroc (with associated HIV tropism testing) and the proposed HIV management scenario that does not have a line of therapy restriction to access maraviroc (with associated HIV tropism testing).

It is expected that this assessment will use the outcome of the assessment of analytic performance described above and apply it to this wider treatment context.

The clinical consequences of false positive and false negative test results (or material differences in concordance) should be addressed and also examined in the cost-effectiveness assessment. These consequences may include the need for, and consequences of, any confirmatory re-testing.

Comparator

Current maraviroc access arrangement

For this assessment, the comparators are the original Trofile™ as well as the enhanced sensitivity Trofile™-ES phenotypic assays by Monogram Bioscience®. These comparators are to be used as this will assess the analytic performance of the genotypic HIV tropism assay in comparison to the assays used in the pivotal trials informing the current use of maraviroc in treatment experienced patients as well as the proposed use of maraviroc in treatment naive patients.

The most relevant reference standard for the assessment of the comparative performance of the Trofile™/Trofile™-ES phenotypic assays and the genotypic HIV tropism assay is how effective each assay is at predicting virological responses to the use of maraviroc (or other CCR5 antagonist drug) (Harrigan, 2011). In the absence of data reporting on this clinical endpoint, measures of analytic performance between the phenotypic tropism assays used in pivotal trials and genotypic HIV assay results may be used for this assessment.

As the clinical and cost-effectiveness outcomes of the use of maraviroc within its current PBS restrictions have already been considered by the PBAC (Department of Health and Ageing, 2009), their re-consideration is only necessary in this context if there is evidence of material discordance between thee genotypic and phenotypic HIV tropism assay options.

Proposed HIV tropism testing and maraviroc access arrangement

This application is seeking to have the genotypic HIV tropism assay, either as a standalone item or as part of the current GART item, added to the MBS. These listings could be used to fund the testing required for the proposed PBAC submission to allow maraviroc to be used as a treatment option without a line of therapy restriction. Thus, the intervention consists of two parts:

1. The option to undertake genotypic HIV tropism testing either individually or as part of the current GART procedure without a line of therapy restriction.

2. The option to use maraviroc in patients that have CCR5 tropic virus without a line of therapy restriction.

The use of existing MBS-funded GART that excludes HIV tropism testing would also exclude PBS-subsidised patient access to maraviroc. This does not reflect current practice, as ART experienced patients are able to access HIV tropism testing funded by ViiV Healthcare.

Subsequently, the most appropriate comparison for public funding in this assessment is:

- **Comparator:** Existing GART without early access to the genotypic HIV tropism assay with no early option to treat with maraviroc, followed by externally funded HIV tropism testing to determine if the current PBS requirements relating to access to maraviroc are fulfilled and the option to use maraviroc in patients infected with CCR5 tropic virus at that stage. **Versus**

- **Proposal:** Access to the genotypic HIV tropism assay followed by the option to treat with maraviroc for patients infected with CCR5 tropic virus at all lines of therapy.

Clinical claim

Current maraviroc access arrangement.

Clinical claims relevant to the current HIV tropism testing and maraviroc access arrangements relate to the safety and effectiveness of the HIV tropism assay by V3 loop sequencing and the inclusion of maraviroc only after a patient has already received three different treatment regimens.

The potential benefits of the introduction of the genotypic HIV tropism assay to support the current PBS-subsidised use of maraviroc are:

- Superior or non-inferior safety and analytical performance compared to the Trofile™-ES phenotypic assay and original Trofile™ phenotypic assay used in the pivotal trials of maraviroc.

An assessment of the clinical claims associated with the use of maraviroc within its current PBS-restrictions has already been considered by the PBAC and is not sought in this protocol.

Proposed HIV tropism testing and maraviroc access arrangement.

The potential benefits of the introduction of the genotypic HIV tropism assay to support the proposed PBS-subsidised use of maraviroc without a line of therapy restriction are:

- Superior or non-inferior safety and analytical performance compared to the Trofile™-ES phenotypic assay and original Trofile™ phenotypic assay used in the pivotal trials of maraviroc (as above).

- Superior or non-inferior effectiveness with acceptable safety of treatment including maraviroc in all lines of therapy in patients with CCR5-tropic HIV.

Presentation of evidence to substantiate the clinical claim of superior or non-inferior effectiveness when maraviroc is a treatment option in all lines of patients with CCR5-tropic HIV is required as part of this assessment. As it has been indicated that a submission to the PBAC will be prepared, the presentation of the same clinical effectiveness data used in the PBAC submission should be used to ensure consistency across the PBAC and MSAC assessments.

The potential harm of introducing the genotypic HIV tropism assay for both the current and proposed PBS-subsidised use of maraviroc is:

- Inferior clinical outcomes resulting from maraviroc being prescribed to CCR5/CXCR4 or CXCR4 tropic patients on the basis of inaccurate tropism testing results.

Table 4: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None^
	Non-inferior	CEA/CUA		CEA/CUA*	None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
		Net harms	None^			

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

On the basis of the clinical claims above it is recommended that separate cost-effectiveness analysis be undertaken for:

1. The current arrangement for access to PBS-subsidised maraviroc with a line of therapy restriction.

2. The proposed arrangement for access to HIV tropism testing and PBS-subsidised maraviroc at all lines of therapy.

Outcomes to be assessed in these cost-effectiveness analyses are described below and given in Tables 6 and 7 respectively.

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

Where comparative virological response data are available across assay options, preferred metrics used to assess the comparative analytic performance of the genotypic HIV tropism assay in comparison to both the Trofile™ and Trofile™-ES phenotypic assays include assay:

- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Diagnostic Odds Ratio (DOR)
- Summary receiver operator curve (SROC)

Clinical endpoints suitable as effectiveness measures following the inclusion of maraviroc as part of a cART regimen after HIV tropism testing to confirm infection with CCR5-tropic HIV include:

- Suppression of viral load below 50 copies/ml at 48 weeks (virological response)
- Measured and maintained rise in CD4 T-lymphocyte cell count
- Frequency and grade of adverse events
- Overall survival
- QALYs.

Health care resources

Table 5: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
• Resource 1										
• Resource 2, etc										
Resources provided to deliver comparator 1										
• Resource 1										
• Resource 2, etc										
Resources provided in association with comparator 1 (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
• Resource 1										
• Resource 2, etc										
Resources provided to deliver comparator 2, etc										
• Resource 1										
• Resource 2, etc										
Resources provided in association with comparator 2, etc										
• Resource 1										
• Resource 2, etc										
Resources provided to deliver proposed intervention										
• Resource 1										
• Resource 2, etc										
Resources provided in association with proposed intervention										
• Resource 1										
• Resource 2, etc										

Health care resources associated with the introduction of the genotypic HIV tropism assay and all subsequent patient treatment(s) were not presented for consideration in this DAP, but are relevant to the economic evaluation for the assessment phase.

Proposed structure of the economic evaluation (decision analysis)

Current maraviroc access arrangement.

The assessment is to be focussed on the clinical and economic performance of the genotypic HIV tropism assay in comparison to:

- The original Trofile™ phenotypic assay by Monogram Biosciences® as used in the pivotal trials informing the use of maraviroc in the treatment of ART experienced patients.
- The enhanced Enhanced sensitivity Trofile™-ES phenotypic assay that has subsequently been used to re-screen samples used in pivotal trials and has replaced the original Trofile™.

An assessment of the cost-effectiveness of introducing genotypic HIV tropism testing for the current PBS listing of maraviroc should take into account the parameters outlined in Table 6. Results should present the incremental cost-effectiveness ratio (cost/QALY) of introducing HIV tropism testing and maraviroc treatment in CCR5 tropic patients who have failed at least three cART regimens.

This assessment seeks to establish the case for MBS-funding of the genotypic HIV tropism testing associated with the current PBS-restricted access to maraviroc only. As such, this assessment only needs to re-establish the clinical outcomes associated with the use of maraviroc within its current PBS restrictions if material discordance is likely to affect those which have already been assessed and accepted by the PBAC. Presentation of the same clinical outcome data that was used in the PBAC submission will be accepted, and the applicability of this evidence to use of a genotypic HIV tropism assay rather than a phenotypic HIV tropism assay assessed as necessary.

Table 6: PICO criteria for the assessment of introducing MBS-funded genotypic HIV tropism testing relating to the current PBS listing of maraviroc.

Patients	Prior tests	Intervention	Reference standard (assay)	Comparator	Outcomes to be assessed
HIV patients that have received at least 3 different antiretroviral regimens that have included one drug from at least 3 different antiretroviral classes experiencing virological failure, clinical failure or genotypic resistance.	Tests required to confirm HIV infection including: HIV antibody testing CD4 T-cell count Plasma HIV RNA (viral load) GART	HIV Tropism assay by V3 loop sequencing to determine if the current PBS requirements relating to HIV tropism for access to maraviroc are fulfilled.	Virological response to the use of maraviroc or other CCR5 antagonist. Also, concordance of results between the phenotypic tropism assay and genotypic HIV assay results.	Original Trofile™ and Trofile™-ES phenotypic assay by Monogram Bioscience®	Safety: Safety of performing GART test including an HIV tropism assay. Effectiveness: Primary measures of performance of the HIV tropism assay by V3 loop sequencing: Sensitivity Specificity Positive predictive value Negative predictive value DOR SROC.

Proposed HIV tropism testing and maraviroc access arrangement.

This assessment should take into account the parameters outlined in Table 7. Results should present the incremental cost-effectiveness ratio in terms of cost/QALY of introducing maraviroc, and its associated HIV tropism testing, without a line of therapy restriction. As previously described, this assessment will need to present the clinical effectiveness of maraviroc without a line of therapy restriction. As it has been indicated that a submission to the PBAC will be prepared, the presentation of the same effectiveness data to be used in the PBAC submission is appropriate.

Table 7: PICO criteria for the assessment of introducing MBS-funded genotypic HIV tropism testing and the option to use maraviroc in all lines of therapy.

Patients	Prior tests	Intervention	Reference standard (assay)	Comparator	Outcomes to be assessed	Healthcare resources to be considered
HIV patients on commencement of treatment AND ART experienced HIV-1 patients no longer responding to therapy that have not previously been treated with a maraviroc.	Tests required to confirm HIV infection including: HIV antibody testing CD4 T-cell count Plasma HIV RNA (viral load) GART	Access to the genotypic HIV Tropism assay followed by the option to treat with maraviroc for patients infected with CCR5 tropic virus at all lines of therapy.	Virological response to the use of maraviroc or other CCR5 antagonist. Also concordance of results between the phenotypic tropism assay and genotypic HIV assay results.	Existing GART without early access to the genotypic HIV tropism assay with no early option to treat with maraviroc, followed by externally funded HIV tropism testing to determine if the current PBS requirements relating to access to maraviroc are fulfilled and the option to use maraviroc in patients Infected with CCR5 tropic virus at that stage.	Safety: Safety of performing the HIV tropism assay by V3 loop sequencing. Effectiveness: Primary measures of performance of the HIV tropism assay by V3 loop sequencing: Sensitivity Specificity Positive Predictive Value Negative Predictive Value DOR SROC Measures of clinical efficacy for maraviroc: Suppression of viral load below 50 copies/ml at 48 weeks Measured and maintained rise in CD4 T-lymphocyte cell count Frequency and grade of adverse events Overall survival. QALYs	Resources associated with treatment using cART that may include maraviroc Resources for ongoing patient monitoring. Resources for treating adverse reactions to cART that may include maraviroc Resources for treating the progression to AIDS

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