Medical Services Advisory Committee

Public Summary Document

Application No.1127 – Genotypic Resistance Testing of Antiretrovirals in HIV

Applicant: **Australasian Society of HIV Medicine**
Date of MSAC consideration: **47th MSAC meeting, 4 December 2009, Canberra**

1. Purpose of application

In 2008 the Australasian Society of HIV Medicine submitted an application to MSAC for public funding of genotypic antiretroviral resistance testing (GART) for HIV infected patients with a plasma HIV-RNA level >1000 copies/ml who are planning to commence their initial regimen or about to change an existing regimen of combination antiretroviral therapy. The applicant requested GART with the use of nucleic acid sequencing of HIV and expert interpretation of resistance patterns to antiretroviral medications in patients with acute and chronic infection, as well as for pregnant women. Consideration of the pregnant cohort was merged within the other two clinical pathways due to a lack of specific evidence to separately consider this indication.

2. Background

GART is a blood test comprising a sequence-based assay used to detect mutations that confer resistance to specific antiretroviral drugs and provides information that allows treatment regimens to be specifically tailored for patients with HIV according to the pattern of mutations observed in the HIV genome. This enables clinicians to choose drugs to which the virus is not resistant, thereby improving the chances of response to antiretroviral medications. It is well accepted that suppressing HIV viral load contributes to improved long term health outcomes.

MSAC noted there was evidence for improved patient outcomes when GART is used compared with clinical judgement in highly treatment-experienced patients.

A previous MSAC application to have GART publicly funded (MSAC 1067) was unsuccessful due to insufficient evidence of effectiveness and unacceptable cost-effectiveness. The previous MSAC application was assessed in 2003–2004, before:

- the development of recent clinical guidelines for the management of acquired HIV resistance,
- the impact of newer antiretroviral medications,
- the inclusion of criteria involving GART in Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Scheme (PBS) indications for some antiretroviral medicines, and
- before GART was included in Australian treatment guidelines (DHHS 2008).

GART is currently recommended in Australian clinical treatment guidelines at certain critical times during treatment to help guide the appropriate choice of therapy (DHHS 2008, Therapeutic Guidelines 2008). Resistance testing is now part of standard clinical care of the management of HIV infection in Australia. Undergoing GART is a pre-requisite for access to certain antiretroviral drugs under both TGA and PBS criteria.

There are six broad classes of antiretroviral drugs and 20 drugs within these classes available for the treatment of HIV. PBS-listed therapies (Etravirine, Darunavir, Raltegravir and Tipranavir) require evidence of previous treatment failure or viral resistance (performed in Australia using GART). The cost of the drugs on the PBS range from $100-$2,200 per pack.

MSAC noted that funding of the test by State and Territory governments is variable, which means that some patients are unable to access hospital-funded GART programs to receive subsidised antiretroviral therapy, and the Medicare Benefits Schedule (MBS) does not currently fund GART for HIV.

When the current assessment of GART began, only in-house assays were available and one commercial kit was available for research purposes. In October 2009, GART commercial test kits were included on the Australian Register of Therapeutic Goods.

3. Clinical need

MSAC noted that in Australia there were approximately 18,000 cases of HIV nationally, with 1,050 new cases per year, increasing by five per cent per annum. Expert opinion is that GART is clinically recommended in acute HIV infection, in chronic HIV infection at the time of entry into care and in individuals with suspected virological failure whilst on HAART. It is also recommended that if treatment with HAART has been deferred then GART could be performed prior to initiation of therapy. Approximately 1,050 new cases and between 894-1,155 individuals with resistance to HAART could be eligible for testing per annum. Untreated, HIV may progress to AIDS with a high mortality rate. Using HAART, HIV has a slow progression to AIDS, with the life expectancy of a 20 year old treated with HAART being 43 years.

MSAC noted that treatment-adherent patients can stay on an antiretroviral treatment regimen for five or more years, with two-thirds of patients having had three or more regimens. Treatment failure can be associated with non-compliance, malabsorption, insufficient dosage, adverse drug reactions and most commonly drug resistance. It was also noted that approximately 1-2% of patients progress to AIDS per year.

4. Comparator

MSAC agreed that the comparator is standard clinical care without GART, which involves relying on the outcomes of viral load tests to determine whether treatment resistance has occurred. An increase in viral load may signify that treatment resistance has developed and that a change to the treatment regimen may be indicated. This method of determining whether treatment resistance has occurred is imperfect because viral load can also increase for other reasons, such as non-adherence, drug interactions, malabsorption, intercurrent illness and vaccination.

5. Safety

MSAC noted that GART is a non-invasive test conducted on patients' blood samples. The GART procedure is not considered to present safety issues for patients because it is performed in vitro. However, safety assessments did not address risks and consequences of analytical or interpretive error.

6. Clinical effectiveness

MSAC discussed the 12 studies which investigated GART in HIV and noted that all studies were in HAART treatment experienced patients. No randomised controlled trials (RCTs) comparing GART with clinical judgement in treatment naïve HIV infected patients were found. There were no studies which reported on the use of GART in HIV infected pregnant women.

MSAC noted the results of a meta-analysis of five RCTs of HAART experienced HIV infected patients indicated that the overall relative risk of the proportion of participants with viral loads below detection level was significantly in favour of GART-guided treatment at three months and at six months. GART guided therapy resulted in significantly reduced viral loads both initially and at follow-up and therefore has the potential to improve long term health outcomes. It was also noted that GART was only beneficial if expert interpretative advice was included as a component of the test.

MSAC further noted that most treatment failure in treatment-adherent, HIV infected patients was due to drug resistance but that other causes of failure such as non-compliance were also frequent. GART enables more informed decisions regarding the optimal drug combinations for HIV patients. MSAC noted expert opinion that, in practice, using resistance testing at the time of patient presentation for therapy enables resistance patterns to be determined prior to starting treatment and that this should occur no more than four weeks before the initiation of therapy.

MSAC noted that the current assessment does not exclude non-HIV causes of increased viral load before undertaking GART, including non-adherence which is a key driver of resistance.

7. Cost-effectiveness

MSAC noted the Markov model based on HAART1 to 5 (HAART1 being the first line treatment combination, HAART2 the second line treatment combination, and so forth) used for this economic evaluation. This model showed that at a commercial cost of GART of $864.72, GART-guided HAART is more effective and less costly, resulting in an average cost saving of $3,043 per person.

MSAC noted that the economic modelling used in the current submission generated different outputs from the economic model used in the last submission. The precise reasons for these differences were not clear to the committee. The committee speculated that the new economic model may have factored in lower hospitalisations for a range of serious conditions, such as lymphoma, pneumonia and infectious diseases than the model presented in 2004. The assumption of lower hospitalisations may be reasonable given the changes in the natural history of HIV as a consequence of broader range of drugs available in the HAART regimens.

8. Financial/budgetary impacts and/or possibility of interim funding

MSAC estimated that the total number of GART tests in Australia would decrease from 2,324 tests in Year 1 to 2,259 tests in Year 5. Based on these numbers and the base cost of GART ($864.72), the annual budget impact associated with publicly funding GART for HIV patients in Australia would be expected to decrease from $2,009,297 in Year 1 to $1,953,386 in Year 5. MSAC noted the prediction that approximately 2,300 GART tests will be conducted per year. MSAC noted that the cost of GART was currently met by the State health systems.

9. Summary of consideration and rationale for MSAC's advice

MSAC found that GART is already established nationally, guides choices of expensive drugs, four of which are listed on the PBS. GART is done in the context of specialised HIV care settings, and the test requires expert interpretation to be of clinical benefit.

MSAC determined that there is sufficient evidence that GART for HIV is safe and will improve clinical management and health outcomes for patients with HIV.

MSAC noted that the economic analysis indicates that GART will be cost saving.

MSAC voted in favour of supporting public funding for GART through the MBS for persons with HIV provided the viral load threshold is greater than 1,000 copies per ml. GART testing was supported in the context of acute or chronic presentation, or presentation before initiation of therapy and also in individuals with virological failure during combination antiretroviral therapy. MSAC further suggested including a note for prescribers about community prescribing and in-hospital prescribing to the effect that drug resistance testing in the setting of virological failure whilst on HAART should be performed while the patient is taking his/her antiretroviral drugs, or no more than four weeks prior to a change in therapy.

10. MSAC's Advice to the Minister

MSAC agreed that GART is safe, effective and cost-effective, and that it is more effective and is less costly than the comparator of clinical care without GART.

MSAC supported public funding for genotypic testing, with expert interpretation, for anti-retroviral resistance in patients with HIV infection at presentation, prior to initiation of therapy or in the setting of virological failure during combination antiretroviral therapy where the development of resistance is suspected. It was noted that patients must have a HIV viral load threshold of > 1,000 copies/ml to qualify for subsidised testing. MSAC suggested the inclusion of a note to prescribers about community and in-hospital prescribing that drug resistance testing in the setting of virological failure whilst on HAART should be performed while the patient is taking his/her antiretroviral drugs or no more than four weeks prior to a change in therapy.

11. Context for Decision

This advice was made under the MSAC Terms of Reference:

- Advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported.
- Advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness.
- Advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures.
- Undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

12. Linkages to Other Documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at

http://www.msac.gov.au/internet/msac/publishing.nsf/Content/MSACCompletedAssessments1120-1140