Genotypic resistance testing of antiretrovirals in HIV

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Contents

Tables

Figures

Executive summary

The procedure

Genotype-assisted antiretroviral resistance testing (GART) is a blood test comprising a sequence-based assay used to detect mutations that confer resistance to specific antiretroviral drugs by sequencing the viral nucleic acid of the protease and reverse transcriptase regions of the human immunodeficiency virus-1 (HIV-1) genome. The aim of GART is to accurately identify the presence of such mutations so that targeted treatment choices can be made for people with HIV infections. Because specific mutations are associated with resistance to particular antiretroviral drugs or drug classes, detecting the presence of these mutations enables clinicians and patients to choose antiretrovirals to which the virus is not resistant, thereby improving HIV viral suppression, increasing the likelihood and longevity of response to antiretroviral drug therapy, and contributing to improved long term health. There is evidence for improved patient outcomes when genotype-assisted technology is implemented, compared with decisions that are guided by clinical judgement based on virological or immunological markers alone.

Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing 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.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from IMS Health Australia was engaged to conduct a systematic review of literature on GART in HIV. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of genotypic resistance testing of antiretrovirals (GART) in HIV

Clinical need

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) and has become part of standard clinical care in Australia. Furthermore, undergoing GART is a pre-requisite for access to certain antiretroviral drugs under Pharmaceutical Benefits Scheme (PBS) criteria. The Therapeutic Goods Administration (TGA) requires commercial GART tests to be registered on the Australian Register of Therapeutic Goods (ARTG). The Medicare Benefits Schedule (MBS) does not currently fund GART for HIV. A previous application to have GART funded by the MBS (MSAC 1067) was unsuccessful. The

previous MSAC application was assessed in 2003–2004. At that time, knowledge about resistant HIV transmission had yet to achieve current levels; clinical pathways for management of acquired HIV resistance had not been established; assessment of the impact of novel antiretroviral medications was incomplete; criteria involving GART in TGA and PBS indications were still to be developed, and GART was not included in Australian treatment guidelines (DHHS 2008).

HIV is treated pharmacologically using highly-active antiretroviral therapy (HAART) involving at least three different antiretroviral agents from at least two drug classes. While highly effective, HAART can fail due to virological, immunological and clinical factors. Virological failure is defined as persistently elevated or rebound elevations in plasma HIV-1 RNA (known as viral load) while receiving antiretroviral drugs. Viral load is used as a surrogate marker of disease progression. Long term studies have confirmed that early and sustained suppression of viral load is one of the best predictors of long term outcomes. Although an increase in viral load does not necessarily indicate that resistance to drug therapy has developed, resistance to antiretroviral drugs is one of the more common causes of treatment failure in HIV (DHHS 2007). Antiretroviral drug resistance occurs when mutations arise in particular segments of the viral genome, rendering antiretroviral drugs less capable of continuing to inhibit viral replication. Failing to adequately suppress the virus can result in the rapid emergence of drug-resistant mutations in the viral genome (Shafer 2004, Zhuang et al 2002).

This assessment aims to assess the efficacy and cost-effectiveness of GART for people with HIV who require GART to guide antiretroviral treatment. 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.

Safety

Genotype-assisted antiretroviral resistance testing (GART) is a non-invasive test conducted on patients' blood samples. The GART procedure is not considered to present safety issues for patients.

Effectiveness

There were 12 studies identified in the literature search that investigated GART in HIV (Panidou et al 2004, Ena et al 2006, Torre and Tambini 2002, Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002, Clevenbergh et al 2000, De Luca et al 2006, Green et al 2006, ERA trial investigators 2005a). All of the identified studies investigated the use of GART in HAART treatment experienced HIV infected patients. No randomised studies comparing GART with clinical judgement in treatment naïve HIV infected patients or studies investigating the benefits of genotype assisted therapy in reducing the risk of HIV transmission to the infant in pregnant HIV infected woman could be sourced.

Panidou et al 2004 conducted a systematic review of five randomised controlled trials (RCTs) (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002) of HAART-experienced HIV infected patients which was included in the analysis. Virological efficacy for GART-guided treatment was demonstrated and the overall relative risk (RR) 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 (Panidou et al 2004).

The five RCTs reviewed by Panidou et al (2004) were also evaluated separately in this assessment (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). The benefits of guiding HAART by applying genotype testing are consistently evident when compared with standard of care without GART. Reduction in plasma viral load was significant in four studies at both three and six month time points (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Tural et al 2002). This did not occur in the NARVAL trial (Meynard et al 2002), although the study may not have been powered to detect a significant difference. All five trials showed significant benefits from determining genotype resistance patterns to guide HAART and reduce the level of HIV ribonucleic acid (RNA) to below threshold levels for detection. There were two additional RCTs (Green et al 2006, ERA trial investigators 2005a) identified that were not included in MSAC assessment 1067. These trials demonstrated no long term advantage of GART in HIV-infected children and among patients with limited virological failure. There were two further studies identified that comprised the open-label observational extension studies of RCTs; all patients were offered GART for a duration of one year (Clevenbergh et al 2000) or three years (De Luca et al 2006) regardless of whether they had originally been assigned to receive GART or standard of care. Both studies showed that, despite a delay in receiving genotype-guided therapy in patients who were originally randomised into the standard clinical care arm, continued benefit of this technology was evident.

On balance, the available evidence indicates that using GART to guide therapy results in significantly reduced viral load both initially and at follow-up, and therefore has the potential to improve long term health outcomes for patients.

Cost effectiveness

A Markov model incorporating a Monte Carlo simulation was considered the appropriate modelling approach for this economic evaluation. The primary health states of the model are defined based on treatment regimens (HAART1 being the first line treatment combination, HAART2 the second line treatment combination, and so forth) as well as HIV-related death, and death due to natural causes. The effectiveness of GART was determined as the relative risk (RR) of the proportion of patients whose viral load was below detectable levels at three months (RR=1.34 (95% CI: [1.10, 1.63]) was determined and included in the model. It was assumed that the cost of GART for the base case was $864.72, which was based on the cost of commercial GART. All other relevant clinical and economic inputs were sourced from the Australian literature, where available. A total of 50,000 hypothetical HIV patients were simulated through the model and average results (effectiveness, costs and cost-effectiveness) were determined.

Based on the results of the base case analysis and sensitivity analyses, GART-guided HAART was the dominant strategy (ie, less costly and more clinically effective) when compared with the standard of care (clinical judgement alone). Compared with the standard of care, GART-guided HAART resulted in an average cost saving of $3043 per person and an increase of 0.005 quality-adjusted life years (QALYs) per person over the patient's entire life span. The sensitivity analyses showed that GART-guided HAART remained the dominant strategy compared to the standard of care (clinical judgement alone) despite variation in various key model inputs. It was estimated that the total number of GART tests in Australia would decrease from 2324 tests in Year 1 to 2259 tests in Year 5. Based on these numbers and the base case cost of GART ($864.72), the annual budget impact associated with publically funding GART for HIV patients in Australia is expected to decrease from $2,009,297 in Year 1 to $1,953,386 in Year 5.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of genotypic resistance testing of antiretrovirals in human immunodeficiency virus (HIV), which is a diagnostic test to detect resistant strains of virus in HIV. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are presented at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for genotypic resistance testing of antiretrovirals in HIV.

Background

Summary

Genotype-assisted antiretroviral resistance testing (GART) is a blood test comprising a sequence-based assay to detect mutations that confer resistance to specific antiretroviral drugs by sequencing the viral nucleic acid of the protease and reverse transcriptase regions of the human immunodeficiency virus-1 (HIV-1) genome. The aim of GART is to accurately identify the presence of such mutations so that targeted treatment choices can be made for people with HIV infections. Because specific mutations are associated with resistance to particular antiretroviral drugs or drug classes, detecting the presence of these mutations enables clinicians and patients to choose antiretrovirals to which the virus is not resistant, thereby potentially improving long term health. There is evidence for improved patient outcomes when genotype-assisted technology is implemented, compared with decisions that are guided by clinical judgement based on virological or immunological markers alone.

GART is currently recommended in HIV clinical treatment guidelines in the USA (DHHS 2007), United Kingdom (BHIVA 2008), Europe (EACS 2009) and Australia (DHHS 2008, Therapeutic Guidelines 2008) at certain critical times during treatment to help guide the appropriate choice of therapy and has become part of standard clinical care in developed nations, including Australia. Furthermore, undergoing GART is a prerequisite for access to certain antiretroviral drugs under both Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Scheme (PBS) criteria. The Medicare Benefits Schedule (MBS) does not currently fund GART for HIV. A previous application to have GART funded by the MBS (MSAC 1067) was unsuccessful. The previous MSAC application was assessed in 2003–2004, before the current understanding of transmission of resistant HIV, the development of recent clinical pathways for the management of acquired HIV resistance, the impact of newer antiretroviral medications, the inclusion of criteria involving GART in TGA and PBS indications were established, and before GART was included in Australian treatment guidelines (DHHS 2008).

HIV is treated pharmacologically using highly active antiretroviral therapy (HAART) involving at least three different antiretroviral agents from a minimum of two drug classes. Although highly effective, HAART can be unsuccessful due to virological, immunological and clinical factors. Virological failure is defined as persistently elevated or rebound elevations in viral load while receiving antiretroviral drugs. Viral load is used as a surrogate marker of disease progression. Long term studies have confirmed that early and sustained suppression of viral load is one of the best predictors of long term outcomes. Although an increase in viral load does not necessarily indicate that resistance to drug therapy has developed, antiretroviral drug resistance is one of the more common causes of treatment failure in HIV (DHHS 2007). Antiretroviral drug resistance occurs when mutations arise in particular segments of the viral genome, rendering antiretroviral drugs less capable of continuing to inhibit viral replication. Failure to adequately suppress the virus while receiving HAART can result in the rapid emergence of drug-resistant mutations in the viral genome (Shafer 2004, Zhuang et al 2002).

This assessment appraises the efficacy and cost-effectiveness of GART for people with HIV who require genotypic resistance testing to guide antiretroviral treatment. 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.

Human immunodeficiency virus (HIV) is transmitted via bodily fluids. Untreated HIV infection results in a progressive disease with a number of stages. In the acute or primary phase, many infected people experience flu-like illness of varying severity, sometimes referred to as primary HIV infection, seroconversion illness or acute retroviral syndrome; others experience no symptoms at all. In its later stages, HIV may progress to acquired immune deficiency syndrome (AIDS).

Many people with HIV are treated with antiretroviral drugs with the aim of delaying or preventing disease progression and prolonging life. Antiretroviral drugs are administered in combinations of three or more agents to more effectively suppress the virus. This form of combination therapy is known as highly active antiretroviral therapy (HAART). Despite the use of HAART, failure of drug therapy is relatively common, although rational sequencing of treatments has resulted in survival benefits in treated populations, with life expectancy at age 20 years of 43 years (Antiretroviral Therapy Cohort Collaboration 2008). HIV treatment can fail in several ways. These include virological failure (persistently elevated or rebound elevations in viral load, specifically defined as an insufficient decrease or an increase in plasma HIV-1 RNA level after one to two months of treatment or a confirmed viral breakthrough in a patient with previously undetectable virus); immunological failure (decline in CD4 cell counts); or clinical progression of the disease (Hoy and Lewin 2004).

Treatment failure is associated with several factors including poor adherence to therapy regimens, malabsorption, insufficient dosage, adverse drug interactions and clinically significant minor variants. Development of resistance to antiretroviral drugs is one of the more common causes of treatment failure (Hoy and Lewin 2004). Drug resistance occurs when mutations arise in the viral genome. These mutations can render antiretroviral drugs incapable of continuing to inhibit viral replication, and can confer cross-resistance, whereby resistance to one drug also results in resistance to another drug or drugs within the same therapeutic class.

In the past decade, it has become possible to determine whether a patient has developed drug resistance by using various methods other than simply monitoring serological markers of disease progression. Genotype-assisted antiretroviral resistance testing (GART) is the most commonly used method to determine drug resistance. GART involves identifying mutations within the HIV RNA that confer resistance to drugs, and targeting therapy to avoid those drugs to which the virus has become resistant and to choose combinations least likely to select for further resistance.

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) and has become part of standard clinical care in Australia. Furthermore, undergoing GART is a prerequisite for access to certain antiretroviral drugs under both TGA and PBS criteria. Currently, the TGA-approved indications for five drugs (tipranavir, maraviroc, etravirine, darunavir and raltegravir)

require evidence of viral resistance before they can be prescribed by clinicians. Of these five drugs, four agents are currently listed on the PBS (Table 1), and all four PBS-listed therapies require evidence of previous treatment failure or viral resistance (performed in Australia using GART). State funding of the test is variable, which means that some patients are unable to access hospital-funded GART programs to enable access to subsidised antiretroviral therapy.

All commercial HIV assays for *in vitro* diagnostic use—including GART assays used for diagnostic or monitoring purposes—must be registered on the Australian Register of Therapeutic Goods (ARTG) before supply in Australia. GART assays used for research purposes are exempt from this requirement. In-house assays developed by laboratories are not explicitly captured under the *Therapeutic Goods Act 1989*.

Of the two commercial testing kits (TruGene® HIV-1 Genotyping Test, Bayer Diagnostics, Bayer AG, Germany; and the ViroSeq™ HIV-1 Genotyping System, Abbott Molecular, IL, USA), only the ViroSeq HIV-1 Genotyping System has been registered on the ARTG (October 2009).

The procedure

GART is a blood test comprising a sequence-based assay used to detect mutations that confer resistance to specific antiretroviral drugs by sequencing the viral nucleic acid of the protease and reverse transcriptase regions of the HIV-1 genome. The aim of GART is to accurately identify the presence of such mutations so that targeted treatment choices can be made for people with HIV infections. Because specific mutations are associated with resistance to particular antiretroviral drugs or drug classes, detecting the presence of these mutations enables clinicians and patients to choose antiretrovirals to which the virus is not resistant, thereby potentially improving long term health. There is evidence for improved patient outcomes when genotype-assisted technology is implemented, compared with decisions that are guided by clinical judgement based on virological or immunological markers alone (Wegner et al 2004).

There are two main steps in the GART process. The first involves analysing viral RNA, and the second step interprets the results to determine the presence of any mutations known to confer resistance to antiretroviral drugs. Numerous methods are available for conducting GART. Laboratories either develop in-house assays or use commercially available testing systems. In-house assays involve isolating, amplifying, sequencing and translating the viral RNA using standard testing methods. Interpretation of the results is then completed using either an external, commercially available interpretation tool, or by applying the approach developed by an individual laboratory. Interpretation of results can be complex and is most successful when conducted by specialists with relevant expertise (Hirsch et al 2008). Currently, 13 laboratories perform GART in Australia. All 13 laboratories are accredited by the National Association of Testing Authorities (NATA) and participate in a national quality assurance (QA) program overseen by the National Reference Laboratory (NRL). Of the 13 laboratories, six use in-house assays and the remaining seven use commercial testing kits for sequencing; 10 use the Stanford database and three use commercial kits for the interpretation of results (National Reference Laboratory 2009). A small number of laboratories are using the commercially available VirCo testing system to further support the interpretation of results.

Analysis of viral RNA

The first step in GART analysis involves isolating virions and amplification and sequencing of HIV RNA to detect resistance-conferring mutations in the viral genome. Isolation, amplification and sequencing may be accomplished either by DNA sequencing or determining the sequence of the whole of the protease and most of the reverse transcriptase gene through hybridisation to defined oligonucleotide probes (short sequences of nucleotides that complement and bind to sections of DNA known to be associated with specific mutations). Laboratories in Australia typically use DNA sequencing because it is more reliable (Sayer et al 2003).

A number of steps are required to perform GART by DNA sequencing. RNA sequencing is followed by transcription to DNA, generally using automated methods. The next steps involve amplification by polymerase chain reaction (PCR), DNA sequence alignment, editing, detection and interpretation of mutations. Sequence alignment, editing, detection and interpretation may be completed manually, or in the case of in-house assays, using an automated system. Automated methods are applied if commercial testing systems are used (Hanna and D'Aquila 2004; Sayer et al 2003). Testing is undertaken by laboratory scientists and results are interpreted by accredited pathologists.

Interpretation of results

To identify resistance-related mutations in the amplified segments of viral DNA, the amino acid sequence of the test virus is compared with the amino acid sequence of drug-sensitive wild-type virus to determine differences in the genome. Prediction of resistance to specific antiretroviral drugs is drawn from the type and patterns of mutagenic changes: particular deviations in the amino acid sequence of the test virus compared with the wild-type virus represent mutations that confer resistance to specific antiretroviral drugs or drug classes. Viruses are classified as 'susceptible', 'resistant' or 'possibly resistant' based on the results of the assay (Hirsch et al 2008).

Appropriate interpretation of genotypic drug resistance testing remains challenging for several reasons. Because resistance emerges in complex patterns, determining whether a patient with mutant HIV strains will respond to a drug regimen in the same way as a patient with wild-type virus can be difficult. Mutations that confer resistance to one drug can suppress resistance to another, and mutations selected for by one antiretroviral drug also confer resistance to other drugs in that class, making it difficult to determine the most effective treatment regimen for an individual patient (Shafer 2004).

Each patient's viral mix is heterogeneous—any variants with fewer than 1000 copies/mL cannot be detected by GART testing. This means that some undetected resistant variants can be present in small numbers (referred to as archived variants) and might not emerge until selective pressure is applied using antiretroviral drugs to which variants are resistant. This is particularly problematic among people with a complex treatment history, although the likely presence of archived drug-resistant variants can be inferred from records of prior incompletely suppressive drug regimens (Shafer 2004).

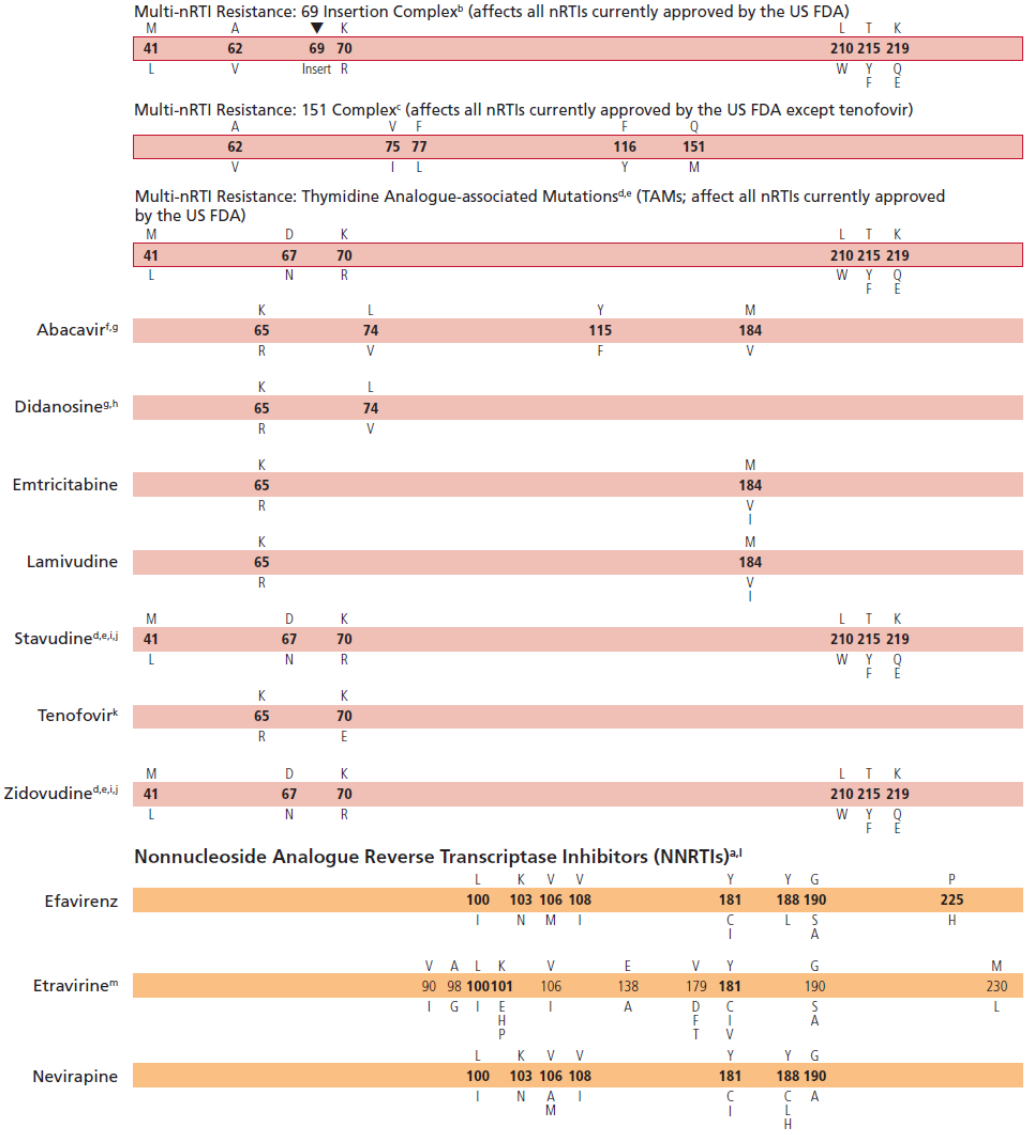
Interpretation of test results requires specialist knowledge of the mutations that match resistance to each available antiretroviral drug in the context of other mutations that are

present. To further aid interpretation of results, the International AIDS Society–USA maintains and publishes details of resistance-associated HIV-1 mutations in the protease, reverse transcriptase, envelope and integrase genes (IAS–USA 2009) (Figure 1: pp. 7–8). This data set is constantly evolving with the identification of new mutations, presenting further challenges for the accurate interpretation of GART results.

In Australia, expert interpretation of GART is undertaken by accredited pathologists. The results and interpretation are then sent to the clinician who ordered the test. The clinician uses the reported mutations and interpretation provided in the context of prior and current antiretroviral treatment and response, adherence and toxicity. Raw mutation data, together with any prior resistance mutation data, are often re-entered into international databases designed to interpret results. This helps to inform choice of the most appropriate antiviral treatment options.

MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]



Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,l]

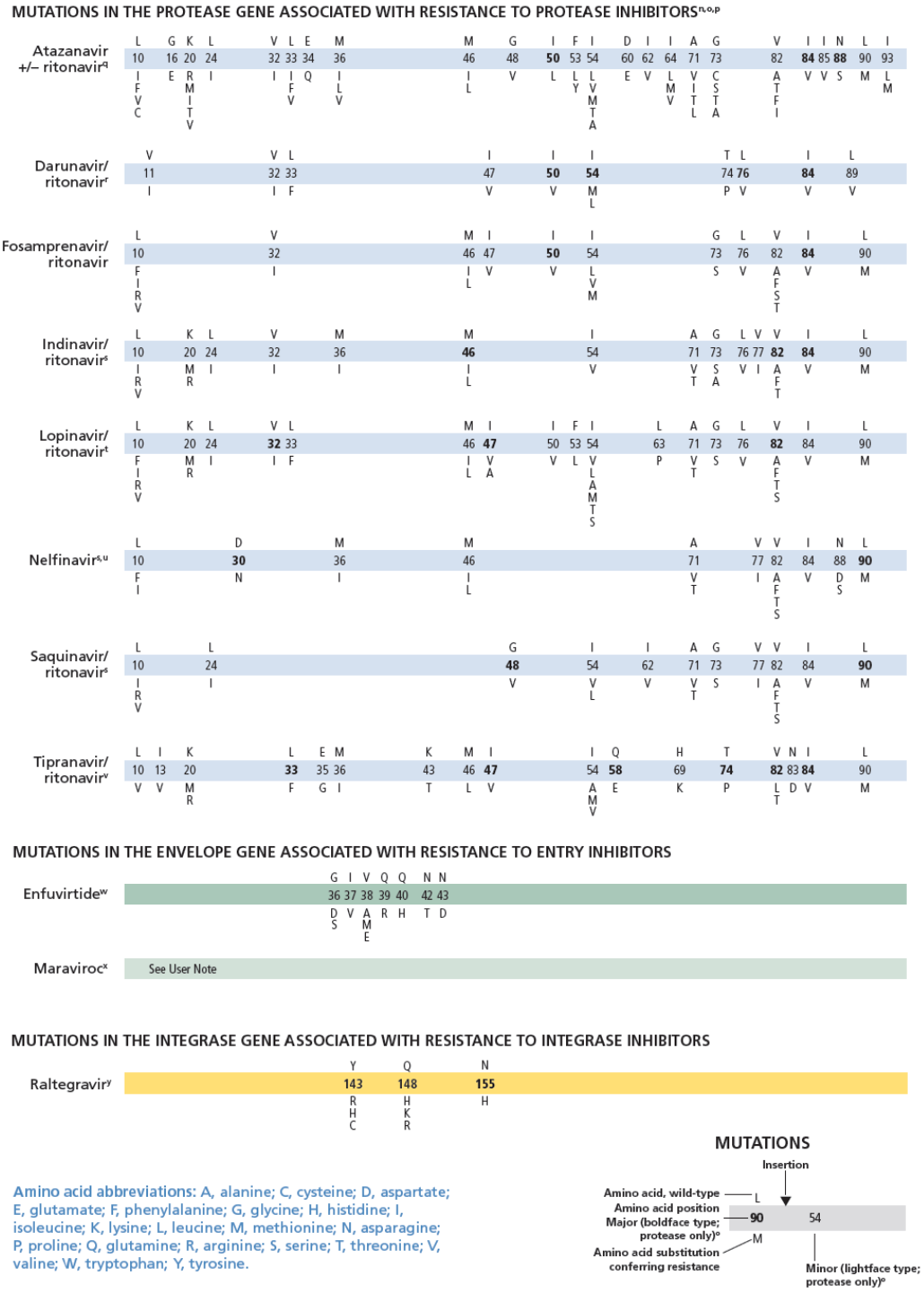


Figure 1 **Mutations in the reverse transcriptase, protease, envelope and integrase genes associated with resistance to specific antiretroviral drug classes**

Reprinted with permission from the International AIDS Society–USA. Johnson VA, Brun-Vézinet F, Clotet B et al. (2008). 'Update of the drug resistance mutations in HIV-1: December 2008', *Topics in HIV Medicine,* 16 (5), 138–145.

The complex nature of genotypic resistance in HIV has prompted development of various interpretation systems based on algorithmic modelling that aim to match mutagenic changes with drug susceptibility and anticipated patterns of response to therapy (Ravela et al 2003, Vercauteren and Vandamme 2006). Algorithms are generally rules-based. Rules are based on substantial clinical data sets that relate genotypic drug resistance mutations and their relationship to phenotypic outcomes. Rules-based algorithms are devised to enable development of recommendations derived from clinical experience and published literature linking HIV viral genotype and phenotypic outcomes to fully exploit the available information. These systems enable the patient's HIV-1 sequence to be added to a database containing the algorithmic information which is matched with other common known viral genotypes. The matching genotype is then used to report mutations known to be associated with phenotypic drug sensitivity or clinical treatment failure, and a report of the identified mutations that confer resistance to each drug class is generated. This information is used to identify the need for changes in therapy, enabling pinpointing of specific drugs that are likely to be effective, and avoiding those that are virus resistant, to ensure the best patient outcome.

Arguably, the most widely known and used publicly available database for analysing GART results is the Stanford HIV RT and Protease Sequence Database (Stanford University 2009). Several other publicly available data sets are also used (Lengauer and Sing 2006). Commercially available testing systems, such as the ViroSeq (Abbott Molecular, IL, USA) and TruGene (Siemens Healthcare Diagnostics, IL, USA) systems contain all materials and equipment needed for both analysis of viral RNA and interpretation of results. All of these data sets/testing systems use rules-based algorithms to predict viral drug resistance. Both the Stanford database and the TruGene rules system are applied to interpret results in Australia. Of the 13 laboratories that are accredited to conduct GART, 10 use the Stanford database to interpret the results of the test; the other three use the commercial system (National Reference Laboratory 2009); however, at least one laboratory reported using both the Stanford and TruGene interpretation algorithms simultaneously. A small number of laboratories also use the commercially available VirCo interpretation system. All laboratories that undertake GART in Australia must be accredited by the NATA. Laboratories can also opt to participate in a national quality assurance (QA) program which is overseen by the National Reference Laboratory. Currently, all laboratories conducting GART testing participate in the QA program.

GART is one of the more rapid, and therefore less costly, forms of resistance testing currently available. GART is the only resistance testing system for HIV currently available in Australia. GART processing takes about two weeks to complete, although turnaround times can vary among laboratories. The use of commercially available testing kits has cut testing times to as little as three days; although in some circumstances, tests can take up to 21 days (Hanna and D'Aquila 2004). Common reasons for variations include the use of automated systems versus manual assays; difficulties in recognising viral mixtures in patients who have undergone substantial levels of treatment; patients with low viral loads; and difficulty differentiating a single mutant from a mixed population of mutations (Hanna and D'Aquila 2004, Schuurman et al 2002).

Intended purpose

Clinical indications for GART

GART is part of the current standard of care and is used widely to guide treatment for Australians living with HIV. Australian clinical treatment guidelines (DHHS 2008) recommend the use of GART for certain groups of HIV-positive people, all of whom are included in this assessment.

This assessment focuses on people with HIV who require GART to guide antiretroviral treatment. These patient groups include:

1. people with acute HIV infection prior to initiation of therapy

2. people with chronic HIV infection prior to initiation of therapy or prior to change of therapy in cases of virological failure, and

3. pregnant women with HIV infection prior to initiation of therapy or entering pregnancy with detectable HIV RNA levels while on therapy.

It is recommended that treatment-naïve patients undergo GART at the time of diagnosis regardless of whether therapy is initiated. If GART is not available at this time, a sample of blood is to be collected and stored for future testing. If commencement of drug therapy is delayed, GART should be repeated immediately before initiating HAART to determine the most appropriate drug regimen for the individual patient.

Virological and immunological markers should be monitored following initiation of HAART. If the viral load remains elevated, or rebounds after initial response to therapy, GART should be considered to determine if the virus has developed resistance to one or more of the drugs being administered. If this is the case, the GART results can be used to guide therapy choices.

It is also recommended that women with HIV who are pregnant undergo GART to determine patterns of resistance. If a pregnant woman is not receiving drug therapy, GART should be performed before treatment is initiated. Similarly, if viral load is detectable while undergoing drug therapy, GART should be conducted to determine if resistance is present and to guide therapy choices. Women with HIV who are pregnant constitute an important target group for GART; however, these patients should also be considered as part of the populations of groups 1 and 2.

There are some circumstances where GART results may not be reliable. Genotyping people with viral loads of less than 1000 copies/mL may be ineffective because amplification of the virus at low levels is often unsuccessful. Genotypic testing is not recommended for patients whose drug therapy has been stopped for more than four weeks because removal of the selective pressure caused by antiretroviral drugs may permit drug-resistant mutations to become minor species which are challenging to detect by GART (DHHS 2008, Hoy and Lewin 2004).

Prior tests

Before undergoing GART, patients will have had viral load testing. GART may be considered if results show that a patient has a detectable viral load. For GART to effectively identify resistance mutations the viral load must be >1000 copies/ mL.

Viral load testing determines the concentration of HIV RNA in a sample of plasma. Load is measured in terms of viral copies per millilitre of blood. Among people with HIV who are treatment-naïve, an increase in viral load is predictive of disease progression; and in those who are taking antiretroviral therapy, an increase in viral load or failure to reduce viral load can indicate treatment failure. A principal aim of therapy is to achieve and maintain undetectable levels of HIV RNA (<50 copies/mL) (Hoy and Lewin 2004).

$CD4^+$ cells are T-helper lymphocytes that express the surface protein CD4. The number and percentage of $CD4^+$ cells in the bloodstream, and the rate of decline of $CD4^+$ cell count, are predictive of progression to AIDS and the risk of development of AIDS-related opportunistic infections. Maintenance of immune function, as measured by $CD4^+$ count, is a long term goal of HIV management (Hoy and Lewin 2004).

GART is indicated for people with HIV at initiation of HAART, in cases of virological failure of therapy, and for pregnant women. Because high viral load is one of the main clinical signs used by clinicians to determine need for initiation of treatment and treatment failure, it is a particularly good indicator of when patients need to undergo GART. A drop in $CD4^+$ count tends to occur after an increase in viral load; therefore, low $CD4^+$ counts are not typically used as the main indicator of need for GART, although they may provide secondary confirmation of the need for resistance testing.

Patients who fall into the categories in focus should be referred for GART, as recommended by the Australian clinical treatment guidelines (DHHS 2008).
Clinical stage, viral load and, to a lesser extent, $CD4^+$ cell count, act as clinical indicators of the need for GART among these patient populations. For the purposes of this assessment, viral load is used as the best surrogate of long term treatment response as the main outcome measure to assess the clinical effectiveness of GART.

A broader discussion of viral load and $CD4^+$ count is provided in the 'Surrogate markers of disease progression' section of this report.

Intended role of the test in clinical practice

Genotypic resistance testing of antiretrovirals (GART) is indicated for people with HIV who are treatment-naïve, or treatment-experienced and being considered for a change in therapy. The Australian clinical treatment guidelines (DHHS 2008) recommend that GART be conducted in at specific times during therapy for:

- people with acute HIV infection prior to initiation of therapy
- people with chronic HIV infection prior to initiation of therapy or prior to change of therapy in cases of virological failure

- pregnant women with HIV infection prior to initiation of therapy or entering pregnancy with detectable HIV RNA levels while on therapy.

For the purposes of this assessment, pregnant women were considered to be a subset of one of the other two groups; that is, either treatment-naïve or treatment-experienced.

GART is intended to guide antiretroviral therapy choice by identifying the presence of antiretroviral-resistant mutations in the HIV RNA. Figure 2 illustrates the use of GART to guide treatment for the identified patient groups.

Although represented as a proposed alternative to standard clinical care (that is, guidance of treatment using clinical indicators of treatment failure and resistance such as viral load), without the use of resistance testing, GART is currently being widely used in Australian clinical practice and is recommended by Australian clinical practice guidelines (DHHS 2008) for these patient populations. Further, GART is a prerequisite for TGA- and PBS-approved indications for certain antiretroviral drugs. The 'Current reimbursement arrangement' section of this report provides details.

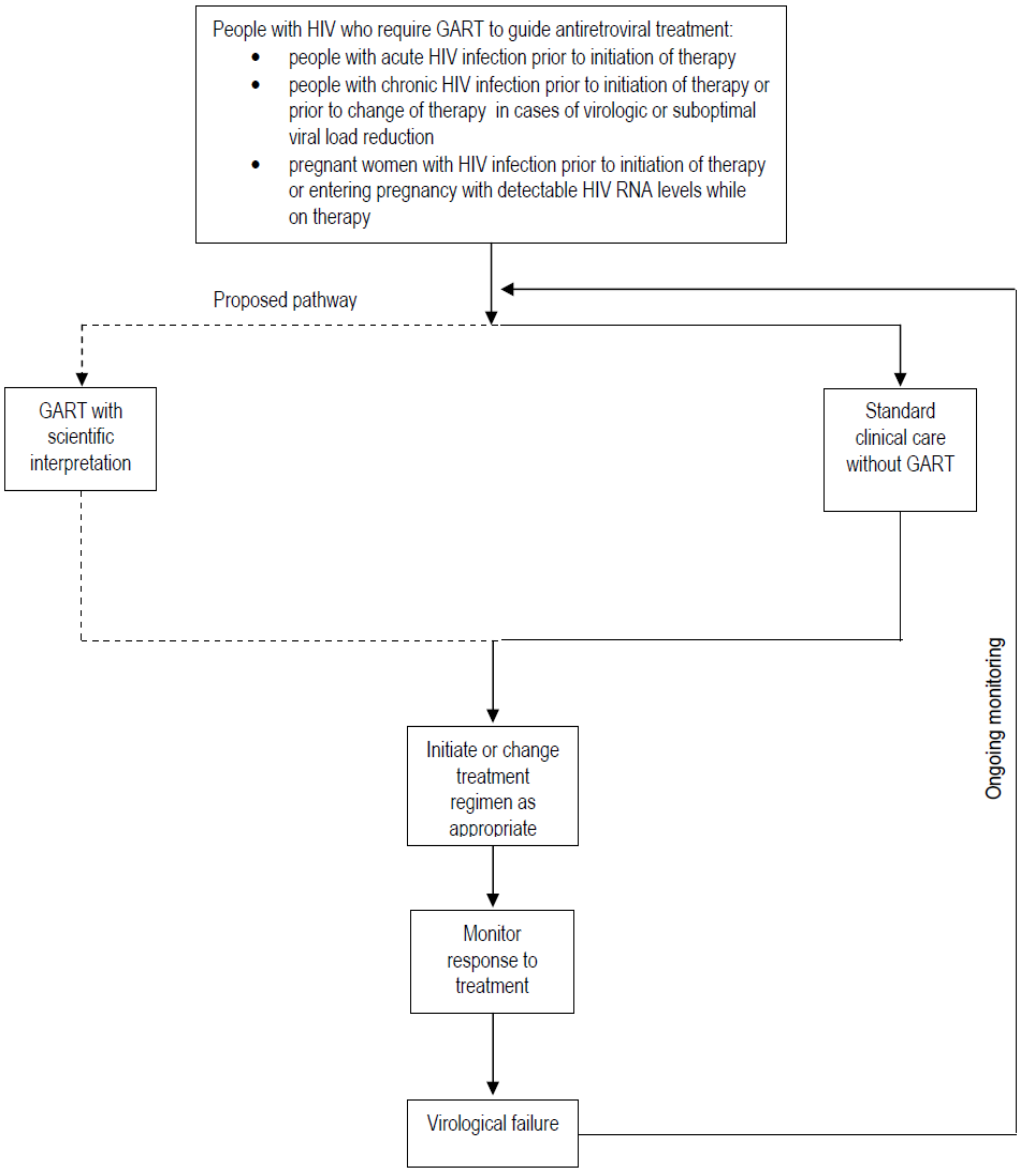


Figure 2 **Clinical pathway: Use of GART for people with acute HIV infection prior to initiation or change of therapy (i.e. with acute or chronic HIV infection prior to initiation of therapy or before change of therapy among those with virological failure or suboptimal viral load reduction, or for pregnant women with HIV infection prior to initiation of therapy or who become pregnant with detectable HIV RNA levels while undergoing therapy)**

Clinical need/burden of disease

Human immunodeficiency virus (HIV) is transmitted via bodily fluids. Its main modes of transmission are through unprotected sex, injecting drug use, and blood transfusions. The virus can also be passed from mother to child *in utero*, during childbirth or through breast milk (Kriebs 2002, Foster and Lyall 2006). There are two types of HIV: HIV-1 and HIV-2. HIV-1 is the predominant type internationally; HIV-2 most commonly occurs in western and central Africa and southern and western India, although outbreaks have occurred in other regions including the USA, Europe and Australia. HIV-2 may result in weaker infection with typically lower viral loads, and those with HIV-2 are believed to survive for longer periods than those with HIV-1 infection (Hoy and Lewin 2004, Kriebs 2002, Jaffar et al 2004). There is some evidence to indicate that the virulence of HIV has increased during the past two decades (Crum-Cianflone et al 2009).

Untreated or suboptimally treated HIV infection results in a progressive disease with a number of stages. In the acute or primary phase, many people experience flu-like illness of varying severity, sometimes referred to as a seroconversion illness or acute retroviral syndrome (ARVS); others experience no symptoms at all. In its later stages, HIV can progress to AIDS. It is common for people with HIV to be co-infected with hepatitis B or C and other sexually transmitted diseases (Hoy and Lewin 2004).

Prevalence and incidence

Internationally, it has been estimated that 33.2 million people were living with HIV at the end of 2007. In 2007, 2.5 million new cases of HIV were diagnosed, and a total of 2.1 million people died of AIDS-related illnesses globally (UNAIDS/WHO 2007). Both the incidence of HIV and the HIV-related death rate have stabilised during the twenty-first century.

Although representing a significant public health problem, the incidence of HIV in Australia remains comparatively low compared with other nations (National Centre in HIV Epidemiology and Clinical Research [NCHECR] 2007), and both incidence rates and death rates have stabilised in recent years. Up to the end of December 2007, there had been a total of 27,331 diagnoses of HIV; 10,303 diagnoses of AIDS; and 6767 AIDS-related deaths in Australia. In 2007, an estimated 16,692 people were living with HIV, and a total of 1051 new cases of HIV were reported (NCHECR 2008). The prevalence and incidence of HIV varies from state to state, and is disproportionately high among some populations, such as men who have sex with men (MSM) including MSM who inject drugs. The overall prevalence in Indigenous populations is on par with non-Indigenous populations, but transmission occurs more commonly through heterosexual contact than in non-Indigenous groups (NCHECR 2008).

Mortality and morbidity associated with HIV

Untreated HIV is a progressive condition. The natural history of the disease follows several stages. The early stages of infection are largely asymptomatic, but as the condition advances, secondary diseases emerge. These HIV-related illnesses range from mild to severe and can affect any body system, impacting on physical and mental health and substantially reducing quality of life and capacity to engage in activities of daily living.

AIDS, the final stage of the condition, may eventually prove fatal. However, the advent of HAART has resulted in a dramatic decrease in mortality rates and people with HIV may now have life expectancies similar to the overall population. The suppression of viral load achieved with HAART prolongs life and also helps to prevent morbidity, thereby also improving quality of life. Individuals with HAART-treated HIV do not progress to AIDS, generally recover immune function, regain healthy weight and function and have life expectancies at age 20 years of 43 years (Antiretroviral Therapy Cohort Collaboration 2008.)

Natural history of HIV

Transmission and acute infection

HIV is transmitted when infected bodily fluid enters the body. After the epithelial layers have been penetrated, the virus invades target cells at the site of entry and begins to replicate. Entry of the virus into the body is dependent on interaction of HIV envelope proteins gp120 and gp41 with cell surface CD4 receptors and the co-receptors CXC chemokine receptor 4 or CC chemokine receptor 5 (CCR5). The virus then targets the $CCR5^+$ $CD4^+$ effector memory T cells in the gut-associated lymphatic tissue.

Within three days of exposure, the infection takes hold at the site of entry and in the surrounding lymph nodes, and the infection becomes systemic after about a week as the virus spreads to other lymphoid tissue. By day eight, a viral load can be detected in the blood; this level doubles around every eight hours during the first two to three weeks. By day 10 post-infection, most extra-lymphoid tissue $CCR5^+$ $CD4^+$ effector-memory T cells are infected or have been in contact with HIV, and by day 21 a corresponding depletion of these T cells can be detected, resulting in irreversible damage to the $CD4^+$ T cell-mediated immune response. However, because some naïve and central T cells are spared, the overall immune response is not compromised at this stage.

Because of the availability of target cells during this early phase of the disease, viral replication occurs on a massive scale and the infection spreads rapidly, resulting in peak levels of viraemia within the first month. The immune system is constantly stimulated by the virus at this time. The degree to which this occurs is believed to predict long term clinical outcomes—low viral activation appears to be associated with a prolonged period of asymptomatic infection (Pilcher et al 2007, Fidler et al 2008, Hoy and Lewin 2004, Choudhury et al 2007).

Disease progression

Following seroconversion, people with HIV often experience a prolonged period, which may last many years, when they are asymptomatic or experience few symptoms. However, during this time the virus continues to multiply and cause damage to the immune system. Persistent lymphadenopathy, dermatitis and other skin conditions, as well as disorders brought on by immune activation including rare neurological conditions, such as such as Guillain-Barré syndrome and Bell's palsy, may present during this time (Hoy and Lewin 2004).

The disease progresses to an early symptomatic stage as the immune system continues to deteriorate. Signs and symptoms include night sweats, mouth ulcers, weight loss, opportunistic fungal and bacterial infections may also start to appear. Symptoms experienced during the earlier stages of the disease persist and may worsen. Immune cell counts continue to fall; those with CD4 counts of less than 200 cells/μL are classified as having late-stage disease (Hoy and Lewin 2004).

The final stage of the disease—AIDS—occurs when AIDS-defining illnesses begin to emerge. These include Kaposi's sarcoma and other cancers, *Pneumocystis* pneumonia (PCP) or recurrent bacterial pneumonia, recurrent *Salmonella* septicaemia, toxoplasmosis, candidiasis of the respiratory tract or oesophagus, HIV-related encephalopathy, and a range of other conditions (Centers for Disease Control and Prevention [CDC] 1993, Australian National Council on AIDS [ANCA] 1994). AIDS-defining illnesses are typically opportunistic infections, cancers and neurological disease, and eventually prove fatal if untreated among people who progress to AIDS. In the era of HAART treatment AIDS-defining illness has become exceedingly rare in Australians diagnosed with HIV. Preventing onset of the symptomatic stages of HIV and AIDS is a major goal of treatment. By suppressing viral load, symptoms can be managed, quality life prolonged and HIV transmission substantially reduced (Grierson et al 2004, Hoy and Lewin 2004).

Impact on activities of daily living and quality of life

Untreated, HIV can have a major impact on quality of life and a person's capacity to undertake normal activities. AIDS-defining illnesses and other related health issues affected people's capacity to work, socialise and undertake normal activities before effective HAART became available. Some of these health issues have physical manifestations that can make HIV status obvious, and that can affect their own and others' attitudes towards them. However, it is important to note that HAART has substantially improved both the physical health and the mental wellbeing of people living with HIV. In Australia, the rate of morbidity and mortality from HIV is low. People who are affected are primarily those who do not adhere to treatment regimens and therefore progress to the later, symptomatic stages of the disease. A return to normal activities is common among people who are treated effectively in Australia in the twenty-first century.

Physical and mental consequences of HIV

The physical effects of HIV are typically experienced in the later stages of the disease, with progression to AIDS. Progression to a symptomatic stage can result in changes that affect quality of life. At this stage of the disease, quality of life can be affected by opportunistic infections; pain and disordered sleep; weight loss; lipodystrophy or lipoatrophy (disorders of fat metabolism that result in distinctive changes to physical appearance); neuropsychological illnesses; and cognitive impairments (Davis 2004, Hoy and Lewin 2004, Gorman et al 2009). Most Australians living with HIV manage their condition well and few experience physical manifestations of the condition that impact significantly on their capacity to undertake normal activities of daily living or impair quality of life.

A diagnosis of HIV can also have an impact on a person's mental health. Depression and anxiety are common comorbidities among people living with HIV. In an Australian survey, almost 35 per cent of respondents reported having been diagnosed with a mental illness, most commonly depression. A third (33%) of respondents reported taking medication for depression (compared with around 5% of the overall Australian population), and 31 per cent reported taking anti-anxiety medication (compared with 2% of the overall population). Almost 20 per cent reported taking medication for both depression and anxiety, and 7 per cent had taken antipsychotic medication (Grierson et al 2004).

Antiretroviral medication

In recent years, HAART treatment has become simpler. Current drug therapies are less associated with toxicities and increasingly likely to be tolerable and effective in preventing progression than those used in the past. This has resulted in improved health and life expectancy, and reduced HIV transmission in those receiving modern therapies. Furthermore, the antiretroviral pill count for people with HIV used to be high, which impacted on people's overall quality of life and social life, and was associated with poor adherence. The more recent development of co-formulated pills containing two or three drugs has helped to reduce the pill count. Regimens now consist of two to three tablets per day.

Most people with HIV tolerate antiretroviral medication regimens well and do not experience significant side effects. Grierson et al (2004) found that 45 per cent of people with HIV in Australia reported that their health improved after commencing antiretroviral therapy. Similarly, Rao et al (2007) found that 64 per cent of respondents were not adversely affected by antiretroviral medication. However, the quality of life of those who do experience adverse events associated with antiretrovirals can be affected. Some common side effects include nausea and vomiting, diarrhoea, fatigue, headaches, hyperlipidaemia and disordered sleep, all of which can interfere with normal daily activities and overall wellbeing. Although some patients experience long term adverse events related to their antiretroviral drug regimens, many side effects are transient.

It is important to note that most people living with HIV continue to work as normal, are active socially, maintain relationships, have supportive networks of friends and family, and lead happy and fulfilled lives. However, aspects of the condition and associated physical, psychological, social and economic factors, particularly in the later stages of the condition, can impact upon quality of life and the capacity to undertake normal activities of daily living. In recent years, effective management of HIV has dramatically improved both quantity and quality of life for people living with the condition, and few people in Australia experience significantly diminished quality of life associated with their HIV status.

Diagnosis

Serological testing is widely considered to be the best way to diagnose HIV. Serological testing can be undertaken in various ways, with different tests returning positive results at different times post-infection during the acute phase of the illness. For this reason, a combination of tests or repeat testing may be required to accurately diagnose HIV (Hoy and Lewin 2004). A definitive diagnosis is usually reached only when circulating HIV antibodies can be detected (Hoy and Lewin 2004).

HIV antibody testing may take two forms. The first of these, the HIV enzyme-linked immunosorbent assay (ELISA), involves exposing serum to a stationary phase containing HIV antigens which then bind any HIV antibodies present in the sample. A second anti-human antibody then detects the presence of the HIV antibodies. The HIV ELISA is highly sensitive, relatively inexpensive and is often used as a screening tool.

The second, Western blot assays, are used in Australia to confirm a diagnosis of HIV. This assay involves using protein gel electrophoresis to separate viral proteins into bands based on molecular weight. The proteins are then blotted onto a solid phase, from which proteins that react with specific HIV antibodies in test samples can be identified.

The antibodies detected using this method correspond to specific HIV proteins and can be identified based on the order in which they appear during the assay. The test is positive if antibodies to the three main types of HIV proteins are detected and negative if no reaction of the test serum to the protein bands at the molecular weights corresponding to these HIV proteins is seen. If the test is inconclusive (that is, all three types of antibodies are not detected), follow-up testing three to six months later is recommended (Hoy and Lewin 2004). Typically, repeated ELISA assays followed by Western blot testing are used to definitively diagnose HIV infection (Australia and New Zealand Horizon Scanning Network [ANZHSN] 2007).

Rapid testing for HIV is also available internationally. As with more traditional testing methods, rapid tests detect the presence of HIV antibodies. Rapid testing provides results within 20–30 minutes, and can be conducted using either blood (whole blood, serum or plasma) or oral fluid. A variety of rapid testing kits is available, and most offer the advantages of being easy to use and inexpensive. In addition, most can be used without expert interpretation or additional equipment, making them well suited for use in areas where resources are scarce. They have been shown in community HIV testing programs to increase the proportion of patients who receive test results and return for confirmatory tests in comparison with traditional testing methods (Guenter et al 2008). Owing to the speed of results, rapid tests also have potential applications in emergency departments accessed by populations who do not frequently access the healthcare system; for screening of health professionals after percutaneous exposure to the virus; to determine the HIV status of mothers in labour to help reduce the risk of mother-to-child transmission; and in the penal system to identify HIV positive prisoners (Madhivanan et al 2005, Greenwald et al 2006, Walensky et al 2008). However, it has been argued that, as with other methodologies, rapid testing without appropriate counselling could have negative psychological consequences. There is also a risk that positive results may not be reported to health authorities, particularly if testing kits are used outside the healthcare system, which would impact on the veracity of recorded rates of HIV (ANZHSN 2007).

To date, four rapid testing kits have been approved for use in the USA by the Federal Drug Administration (FDA). These four kits have shown good sensitivity (range of means, 99.3–100%) and specificity (range of means, 98.6–100%) using either blood or oral fluid as appropriate when compared with ELISA assays and/or Western blot testing (Greenwald et al 2006), although some studies have found lower sensitivity and specificity results than these when using oral fluid samples (Walensky et al 2008, Zelin et al 2008). Rapid testing kits are not yet registered for general use in Australia (although some are registered for laboratory use in specific situations requiring rapid screening); therefore, traditional testing methods remain the only means of diagnosing HIV in this country (ANZHSN 2007).

Surrogate markers of disease progression

Several markers are used to monitor the progression of HIV infection, including HIV RNA concentration, $CD4^+$ count and CD38 expression on CD8 lymphocytes. A fall in $CD4^+$ count or an increase in viral load or CD38 expression are all indicators that HIV may have progressed.

Arguably the most widely used indicator of HIV progression and response to medication is HIV RNA concentration, also known as viral load. Measuring viral load involves quantifying the viral DNA present in the serum. Two types of tests are used to measure

viral load in Australia, and each is capable of measuring values as low as 40–50 copies of HIV RNA/mL of plasma. Typically, viral load is interpreted in combination with other markers to determine whether progression of HIV infection has occurred (Hoy and Lewin 2004).

Reducing viral load has been shown to reduce the risk of transmission of HIV: studies have found a direct relationship between viral load and risk of passing on the virus, either through sexual contact or from mother to child (Hoy and Lewin 2004, Volmink et al 2007). Long term studies have confirmed that early and sustained suppression of viral load is one of the best predictors of long term outcomes, as outlined below.

- Kitchen et al (2001) found that patients with a high response to HAART (reduction in viral load of >1.0 $\log_{10}$ copies/mL) in the first three months of treatment were significantly more likely to avoid long term treatment failure than patients with only a moderate (reduction in viral load 0.5–1.0 $\log_{10}$ copies/mL) or low (reduction in viral load <0.5 $\log_{10}$ copies/mL) response to HAART within the first three months (p=0.001).

- Mellors et al (1997) demonstrated that plasma viral load was the single best predictor of progression to AIDS-defining illnesses and death among people with HIV over a 10 year period, and was a particularly strong predictor when used in combination with $CD4^+$ counts. Significant differences were seen in the rate of AIDS-related morbidity and mortality rates among patients with low (<500 copies/mL) HIV RNA concentrations versus those with increasing viral loads (ranging up to >30,000 copies/mL) within six years (p<0.001).

- Similarly, O'Brien et al (1996) found that baseline viral load and $CD4^+$ counts were strongly predictive of AIDS-related morbidity and mortality; further, patients initiated on immediate antiretroviral therapy (ART) were significantly less likely to progress to AIDS during the study period than patients whose treatment was deferred (p=0.03). Reductions in viral load of at least 75 per cent were found to account for 59 per cent of the benefit of immediate over delayed treatment (95% CI: [13%, 112%]), and a 75 per cent reduction in viral load combined with a 10 per cent improvement in $CD4^+$ count accounted for 79 per cent of the benefit of immediate versus delayed treatment (95% CI: [27%, 145%]).

- Grabar et al (2005) investigated the relationship between markers of disease progression six months after initiating HAART and the risk of progressing to a new AIDS-defining event or death after five years, among over 2000 protease inhibitor-naïve HIV-positive people. The study showed that the risk was greatest among those with the highest viral load (≥5 $\log_{10}$ copies/mL) and the lowest $CD4^+$ count (<100 cells/μL) after six months of treatment, with a probability of progressing to a new AIDS-defining event or death at five years of 63 per cent. Conversely, the lowest risk (7%) was seen among those with the lowest viral load (<3 $\log_{10}$ copies/mL) and the highest $CD4^+$ count (≥350 cells/μL) after six months of treatment.

- The HIV Surrogate Marker Collaborative Group (2000) meta-analysed changes in viral load and $CD4^+$ count as markers of disease progression. The analysis found that changes in viral load and $CD4^+$ count following initiation of HAART were both independent markers of disease progression; people with the greatest decrease

in HIV RNA levels and the greatest increase in $CD4^+$ count after 24 weeks of treatment compared with baseline measures had the lowest risk of progressing to AIDS or death.

These studies indicate that reducing viral load (particularly in association with improved $CD4^+$ counts) prevents or delays the progression of HIV infection, thereby reducing the risk of HIV-associated complications and prolonging life. Furthermore, data from the Australian HIV Observational Database (AHOD 2002) were analysed to assess $CD4^+$ counts among people on HAART in the presence or absence of sustained virological response to medication. Data for over 600 people ranging up to five years in duration were included in the study. The results demonstrated that people with a viral load below 4 log copies for prolonged periods of time demonstrated continued $CD4^+$ count recovery, indicating that minimising viral load has a positive impact on $CD4^+$ cell counts (Petoumenos 2004). Hence, viral load is widely accepted as a surrogate marker for long term outcomes among people living with HIV (Hoy and Lewin 2004, Volmink et al 2007).

Management of HIV infection

The main goals of HIV treatment are to improve the length and quality of life of people living with HIV. Because eradication of HIV is not yet possible, the goals of therapy focus on preventing or delaying disease progression in the long term. This is achieved by sustained reduction of viral load and maintenance of immune function, which is measured by monitoring $CD4^+$ and other immune cell counts. To this end, a combination of pharmacological and non-pharmacological measures is used. Because life expectancy has been substantially prolonged by the use of HAART, people with HIV now need long term management, and drug therapy forms the cornerstone of their treatment.

Pharmacological therapy

HIV is treated pharmacologically using antiretroviral therapy. The field of antiretroviral therapy has evolved rapidly over the past two decades, and continues to advance with the advent of new drugs and drug classes. Antiretroviral therapy aims to improve disease-free survival through suppression of viral replication and by conserving immune function (Hammer et al 2008).

The timing of initiation of antiretroviral therapy is important (Fidler et al 2008, Hammer et al 2008). Historically, it was believed that delaying drug therapy would reduce the risk of resistance to antiretrovirals and delay the experience of drug-related side effects (Fidler et al 2008, Hammer et al 2008). However, more recent evidence suggests that early initiation of antiretroviral therapy results in better long term health outcomes than delayed therapy. A large recent study by Kitahata et al (2009) analysed patient data from over 17,500 treatment-naïve people with HIV treated between 1996 and 2005. People with $CD4^+$ counts of 351–500 cells/μL at baseline for whom therapy was initiated early experienced a 69 per cent reduction in risk of death compared to those with $CD4^+$ counts in the same range for whom therapy was delayed until counts fell below this level. Of those with $CD4^+$ counts of over 500 cells/μL at baseline, early initiation of antiretroviral therapy was associated with a 94 per cent reduction in risk of death compared with delayed therapy. Clinical treatment guidelines recommend the initiation of antiretroviral therapy before $CD4^+$ counts fall below 350 cells/μL, although the

decision to start an HIV-positive person on antiretroviral therapy should be tailored to the individual and will need to consider other factors in addition to $CD4^+$ count (DHHS 2008, EACS 2008, Hammer et al 2008). Prospective randomised trials are currently underway examining the impact of early initiation of HAART compared with current guidelines and cohort-based practice.

Antiretroviral drugs currently available in Australia can be classified into six broad classes. These classes and their mechanisms of action are summarised in Table 1. Each class of drug acts on a different site in the HIV lifecycle (Boyd and Pett 2008).

Table 1 Summary of antiretroviral drug classes available in Australia and their mechanisms of action

Drug class	Compounds within class	Mechanism of action
Nucleoside/nucleotide reverse transcriptase inhibitors	Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zidovudine	Analogues of nucleosides or nucleotides that interfere with the function of reverse transcriptase
Non-nucleoside reverse transcriptase inhibitors	Efavirenz Etravirine[a, b] Nevirapine	Drugs that interfere with the function of reverse transcriptase
Protease inhibitors	Atazanavir Darunavir[a, b] Fosamprenavir Indinavir Lopinavir Ritonavir Saquinavir Tipranavir[a, b]	Inhibit HIV proteases and prevent the cleavage of the Gag-Pol polyprotein that occurs during maturation of newly formed viral particles
Fusion inhibitors	Enfuvirtide[b]	Inhibit fusion of viral gp120 protein with CD4 receptor molecules on human cell membranes
CCR5 inhibitor	Maraviroc[a]	Inhibit the entry of chemokine receptor CCR5 tropic HIV-1 from entering cells by selectively binding to CCR5
HIV integrase strand transfer inhibitor	Raltegravir [a, b]	Targets HIV integrase, an enzyme responsible for the replication of HIV in host cells

[a] Antiretroviral resistance and/or measurement for genotype are required for the TGA-approved indication for these drugs
[b] Antiretroviral resistance and/or measurement for genotype are required for the PBS-approved indication for funding of these drugs
Adapted from AFAO/NAPWA 2009; Boyd and Pett 2008; eMIMS May 2009; Hirsch et al 2008; Pugach et al 2007
Abbreviations: CCR5, chemokine receptor 5; CD, cluster of differentiation; Gag, group antigen; gp, glycoprotein; HIV, human immunodeficiency virus; Pol, reverse transcriptase

The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) act as the cornerstone of HIV therapy in Australia. NRTIs are analogues of nucleosides or nucleotides that interfere with the function of HIV viral-RNA dependent DNA polymerase, otherwise known as reverse transcriptase. This inhibits viral replication, thereby causing premature DNA chain termination (Hoy and Lewin 2004).

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) also inhibit HIV reverse transcriptase but are not analogues of nucleosides or nucleotides. NNRTIs are small hydrophobic compounds that bind to a hydrophobic pocket in the HIV reverse transcriptase. This leads to conformational changes in the enzyme, resulting in inhibition of the incorporation of the deoxyribonucleotide triphosphate (dNTP) substrate during viral complementary deoxyribonucleic acid (cDNA) synthesis (Shehu-Xhilaga et al 2005).

Protease inhibitors (PIs) act on the enzyme HIV protease. This enzyme is involved in cleavage of the group antigen (Gag) and group antigen-reverse transcriptase (Gag-Pol) precursor polyproteins into the structural and functional proteins of the virus, which are needed for the production of mature virions (Shehu-Xhilaga et al 2005).

Entry inhibitors are among the newer classes of HIV drugs. One type of entry inhibitor, fusion inhibitors, prevent virions from fusing to human cells by stopping viral glycoprotein 120 (gp120) molecules from binding to CD4 receptors expressed on human cell membranes. Under normal circumstances, gp120 binds to CD4 cell surface receptors, bringing about structural changes to the gp120 molecule that enable gp41 molecules to form a pore in the membrane through which the viral RNA can enter. By interfering with this process, fusion inhibitors prevent the fusion of virions with human body cell membranes, thereby preventing the virus from entering the cells (Boyd and Pett 2008). C-Chemokine receptor 5 (CCR5) inhibitors, or CCR5 antagonists, are another class of entry inhibitors that prevent the entry of HIV-1 into body cells by binding with chemokine receptor CCR5. This results in conformational changes that prevent the gp120 protein in the HIV envelope complex from interacting with CCR5 on human cells. CCR5 inhibitors are typically small molecules or monoclonal antibodies (Hirsch et al 2008, Pugach et al 2007).

Integrase strand transfer inhibitors (INSTIs) target the HIV integrase enzyme, which catalyses several steps that take place within the human cell cytoplasm and nucleus that enables HIV to enter and colonise host cells. By interfering with the functioning of integrase, INSTIs prevent HIV from replicating (Hirsch et al 2008).

All classes of antiretroviral therapy drugs are generally well tolerated but are associated with some side effects, which can result in poor adherence with treatment regimens. In particular, PIs are typically well tolerated but some are associated with reduced glycaemic control, lipid abnormalities and fat maldistribution (Hoy and Lewin 2004, Calmy et al 2007). NRTIs are generally well tolerated but can cause liver enzyme abnormalities and certain of them are associated with nephrotoxicity in a small number of patients (Calmy et al 2007). NNRTIs are also generally tolerated, but can be associated with skin rashes, liver enzyme elevation and hepatotoxicity, gastrointestinal upsets and dizziness (Calmy et al 2007, Shehu-Xhilaga et al 2005). The frequency and severity of adverse events are related to dosage and are highly individualistic; it can take some time to determine the optimal dosage for individual patients.

In recent years, combination antiretroviral therapy, known as highly-active antiretroviral therapy (HAART), has become the mainstay of treatment. HAART enables more aggressive control of disease progression and has resulted in significant reductions in the risk of progression to AIDS compared with the pre-HAART era. To be effective, HAART regimens should contain at least three agents from two, and preferably three (or occasionally more) different treatment classes (DHHS 2008, Rutherford et al 2003); combination therapy is typically more effective because the chances of a virus becoming resistant to three or more drugs simultaneously is slim (Frenkel and Tobin 2004). A typical first-line regimen includes two NRTIs and one NNRTI (Srasuebkul et al 2007).

Drugs containing two or more antiretroviral compounds in the same tablet or capsule are now available, which can help to reduce the pill load for people with HIV (Piacenti 2006). In Australia, most antiretroviral drugs are listed on the Pharmaceutical Benefits Schedule (PBS); in certain cases, GART is a prerequisite for receiving subsidised HAART.

Treatment failure and treatment resistance

HIV treatment can fail for several reasons, including virological, immunological and clinical failure. Toxicity failure as a result of side effects from medication can also occur.

Virological failure is the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL). It may present in either of the following ways:

- **Incomplete virological response**: Two consecutive HIV RNA levels >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient who is initiating therapy, or

- **Virological rebound**: After virological suppression, repeated detection of HIV RNA above the assay limit of detection (eg 50 copies/mL) (DHHS 2008).

Immunologic failure is defined as the failure to achieve and maintain an adequate $CD4^+$ T-cell response despite virological suppression. No specific definition exists for immunologic failure. Some studies have defined immunologic failure as a failure to increase $CD4^+$ T-cell counts above a specific threshold (eg >350 or 500 cells/mL) over a specific time period (eg 4–7 years). Others have focused on an inability to increase $CD4^+$ T-cell counts above pre-therapy levels by a certain threshold (eg >50 or 100 cells/mL) over a given time period, or the decline of the $CD4^+$ lymphocyte count to below baseline. The first approach may be preferable to the second because recent data has linked these thresholds to the risk of non-HIV related clinical events (DHHS 2008).

A number of factors can contribute to treatment failure, including poor adherence to therapy regimens, malabsorption, insufficient dosage, adverse drug interactions and clinically significant minor variants (Hanson et al 2009, Frenkel and Tobin 2004, Hoy and Lewin 2004). A lack of adherence to medication regimens can also play a part in the development of antiretroviral drug resistance (Hanson et al 2009). Missing doses of medication can allow serum medication levels to drop low enough for the virus to replicate rapidly, potentially resulting in mutations that confer resistance to drug treatments. To maintain an undetectable viral load, patients need to achieve at least 95 per cent adherence (Hoy and Lewin 2004). It has been estimated that inadequate adherence to HIV medications can reduce quality-adjusted life expectancy by up to 12 per cent compared with ideal adherence (Munakata 2006).

Although an increase in viral load or a decrease in $CD4^+$ count does not necessarily indicate that resistance to drug therapy has developed, resistance to antiretroviral drugs is one of the more common causes of treatment failure in HIV (DHHS 2007). Antiretroviral drug resistance occurs when mutations arise in particular segments of the viral genome, rendering antiretroviral drugs less capable of continuing to inhibit viral replication. HIV has a high occurrence of recombination events per genome in a single replication cycle, resulting in a high mutation rate per replication. Because viral replication occurs quickly and mistakes in replication are common, failing to adequately suppress the virus can result in the rapid emergence of drug-resistant mutations in the viral genome (Shafer 2004, Zhuang et al 2002).

Drug-resistant mutations are named according to their position in the amino acid sequence. They typically contain a letter, followed by a number then another letter. The number represents the amino acid position within the genome. The first letter

denotes the amino acid seen in wild-type HIV (subtype B), and the second letter signifies the amino acid that has been substituted. For example, mutation K65R indicates that lysine (K) is seen at amino acid position 65 in wild-type virus, but in this case arginine (R) has been substituted in this position (Johnson 2008, Shafer 2004).

When drug therapy is initiated, drug-resistant mutations are selected for and exchanged between genomic templates during replication via gene recombination, permitting a continuum of desensitisation to the drug (Rambaut et al 2004). Mutations in the sites coding for reverse transcriptase and protease are well described as the genes most commonly associated with reduced sensitivity to antiretroviral drugs (Schinazi et al 1997). Specific mutations are associated with resistance to specific drugs or drug classes. They can also confer cross-resistance, whereby resistance to one drug also provides resistance to another drug or drugs within that class. For example, a K65R mutation in the reverse transcriptase gene arising after treatment with tenofovir renders the virus resistant not only to tenofovir, but also causes immediate resistance to abacavir, didanosine and emtricitabine, and lower-level resistance to stavudine. A K65R mutation also causes hypersusceptibility to zidovudine (AZT) (Johnson et al 2008, Figure 1).

Infection with drug-resistant HIV can occur in two ways: at-risk uninfected individuals may become infected by the transmission of drug-resistant strains; or treated individuals who were initially infected with drug-sensitive strains may select drug resistance during subsequent therapy. In Australia, transmission of drug-resistant strains is relatively low—the more common means of acquiring drug resistant HIV is via selective pressure after initiation of HAART. Antiretroviral-resistant mutations are becoming increasingly recognised, concurrent with the development of new drugs and drug classes (Erice et al 1993, Conlon et al 1994, Hoy and Lewin 2004, Johnson et al 2001).

Eligible population

Under current Australian clinical treatment guidelines, all people with HIV will receive GART testing at least once during the course of their treatment.

The estimated number of people newly diagnosed with HIV in Australia in 2007 was 1051. The number of new diagnoses of HIV in Australia has been climbing at a consistent rate of around 5 per cent each year since 2003 (NCHECR 2008, Figure 3), and it is reasonable to assume that the trend will continue. Based on these figures, the number of people newly diagnosed with HIV infection is expected to rise to around 1170 in 2010 and continue to rise to around 1338 in 2014. Assuming that all people newly diagnosed with HIV undergo GART, the population of treatment-naïve patients eligible for GART would increase at the same rate.

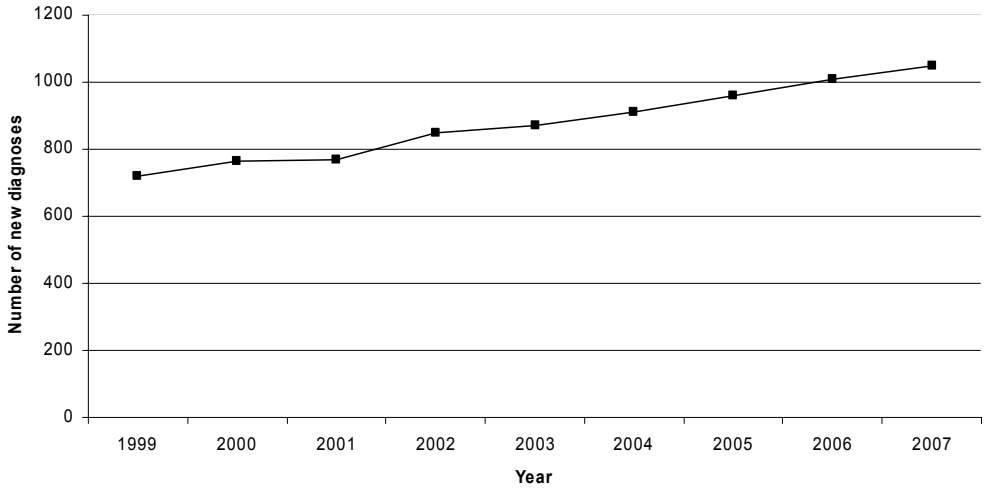


Figure 3 Number of new diagnoses of HIV in Australia by year
Source: NCHECR 2008

The number of GART tests provided for each treatment-experienced person with HIV is more difficult to estimate. Based on the proportion of the prevalent population receiving treatment who are estimated to switch treatments each year, which was generated by the economic model developed for this assessment (refer to the 'What are the economic considerations?' section), it is estimated that between 894 and 1155 treatment-experienced people would require GART tests each year over the next five years. This would result in a total of 2118 to 2324 GART tests each year over the next five years for both treatment-naïve and treatment-experienced patients. The majority of patients receiving treatment for HIV have already had GART performed at least once, therefore there is unlikely to be a sudden demand for GART if this procedure is listed on the MBS.

Data from the Australian National Reference Laboratory on the number of GART tests performed over the last five years (S. Land, personal communication) supports these estimates of eligible population. The number of tests performed has risen from 1395 tests in 2005 to 2077 tests in 2008, following the trend discussed above (Table 2). Note that these data show the number of tests actually performed, they do not represent another estimate of eligible population, because they don't capture patients who should have been tested but did not have access to GART. This is particularly relevant to patients living in some areas, for example remote areas where access to GART procedures is limited in comparison to urban areas.

Table 2 Number of GART procedures performed in Australia from 2004 to 2008

Year	Number of GART procedures
2004	1395
2005	1529
2006	1760
2007	2043
2008	2077

Abbreviations: GART, genotype-assisted antiretroviral resistance test
Source: S Land, National Reference Laboratory, personal communication

Existing procedures

Existing procedures for resistance testing in HIV include phenotypic testing and GART without scientific interpretation.

Phenotyping

Phenotyping is a form of resistance testing that involves collecting a blood sample from a person with HIV, isolating the virus and exposing it to various antiretroviral drugs. Phenotyping uses a standardised assay that measures the inhibitory concentration of a drug that reduces viral replication by 50 per cent and/or 90 per cent, also known as IC_{50} and IC_{90}. The assay entails using polymerase chain reaction (PCR) to amplify the Pol region of the viral genome, which codes for reverse transcriptase and protease, from a patient's peripheral blood mononuclear cells. The Pol region from the test sample is incorporated into a control virus that lacks this region to generate a stock of the virus. The virus stock is then titrated to elucidate the infectivity of the virus. This virus is then used to infect cultures containing various concentrations of different antiretroviral drugs. The IC_{50} is calculated based on HIV p24 antigen levels, a measure of infection. An increase in IC_{50} denotes the need for a greater dose of drug to inhibit viral replication. The ratio of IC_{50} in the test sample and the control sample is calculated and reported as the fold-increase in IC_{50} (Hanna and D'Aquila 2001, Hoy and Lewin 2004, Frenkel and Tobit 2004).

Phenotyping has disadvantages and limitations: it is both time-consuming and labour intensive, taking at least six weeks to achieve clinically meaningful results. These factors contribute to making phenotyping costly to perform. In terms of technical limitations, interpreting the likelihood of therapeutic failure *in vivo* based on the results of IC_{50} fold-increases determined by phenotypic resistance testing can be difficult, although clinical cut-offs have been determined for some drugs. The test measures the sensitivity of virus from peripheral blood mononuclear cells and not directly from plasma. Further, it is possible that *in vitro* selective pressure that may favour the growth of certain strains of virus and not others in the sample heterogeneous mix (Hanna and D'Aquila 2001, Hoy and Lewin 2004, Frenkel and Tobit 2004).

Virtual phenotyping is used to determine treatment resistance patterns. In virtual phenotyping, a patient's phenotype is estimated using the viral genotype by comparing the genotype with a database containing thousands of genotypes and matching phenotypes from patients for whom both viral genotyping and phenotyping were conducted. The phenotype can be predicted using this information. Virtual phenotyping

reports both the genotype and the predicted phenotype of the virus (Hoy and Lewin 2004, Gallant 2005).

Phenotyping is neither conducted nor available in Australia, and therefore, is not considered in this evaluation. Virtual phenotype analyses are now conducted by a small number of laboratories that have access to the VirCo testing system (a database system with both genotyping and phenotyping assays). Because virtual phenotyping is not yet widely used in Australia, it has been excluded from the analysis.

GART without expert interpretation

It is possible to conduct GART for HIV without scientific interpretation. This involves conducting HIV DNA sequencing without providing clinicians with any interpretation of the results. GART without interpretation has been used as a comparator in clinical trials that assessed efficacy of GART with scientific interpretation (Tural et al 2002, Badri et al 2003). In Australia, results of all GART tests performed are provided to clinicians with completed standardised interpretations, and therefore GART without expert interpretation was not used as a comparator in this assessment.

Comparator

For the purposes of this assessment, the comparator is standard clinical care without GART. In the absence of the availability of GART, Australian clinicians rely on outcomes from viral load tests, and to a lesser extent $CD4^+$ counts, 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. A reduction in $CD4^+$ count may also indicate that treatment resistance has occurred. However, $CD4^+$ count is slower to respond to changes in viral strain than viral load, and is a less sensitive marker of resistance. For this reason, viral load is the main marker used by clinicians to determine that drug resistance may have developed.

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 (Hoy and Lewin 2004). Assuming that drug resistance has developed in every patient who demonstrates an increased viral load may lead to unnecessary changes to treatment regimen, which is potentially more expensive and may increase costs to the patient or the government. Because there are a finite number of HAART combinations available, there is also a risk that changing treatments unnecessarily early in therapy may reduce the number of treatment choices available in the longer term. For these reasons, clinicians rule out other possible causes of increased viral load before undertaking GART.

Marketing status of the technology

There are two commercial GART testing systems available: the ViroSeq HIV Genotyping system (Abbott Diagnostics) modified by the addition of QLAquick PCR purification spin columns (Qiagen) and DyeEx spin columns (Qiagen); and the Visible Genetics TruGene HIV-1 system. Both commercial testing systems have been marketed for some time in Australia. The ViroSeq HIV Genotyping system (Abbott Diagnostics)

has recently been approved by the Therapeutic Goods Administration (TGA) (October 2009). Some laboratories develop and apply their own in-house assays. In-house assays are exempt from TGA approval.

Current reimbursement arrangement

The Medicare Benefits Schedule (MBS) does not currently fund GART for HIV. However, GART has become a component of the standard of care in Australia and is recommended in Australian HIV clinical management guidelines at certain critical times during treatment for HIV to help guide therapy choices (DHHS 2008, Therapeutic Guidelines 2008).

It should also be noted that the TGA-approved indications for certain antiretroviral drugs rely on GART test results. The TGA-approved indications for tipranavir, darunavir, etravirine, raltegavir and maraviroc specify that patients must show evidence of resistance to other antiretroviral drugs before these agents can be prescribed. Of these five drugs, four (tipranavir, darunavir, etravirine, raltegavir) are currently listed on the PBS. The fifth, maraviroc, is currently under review by the PBAC. The listed indication for tipranavir, darunavir, etravirine and raltegavir also specifies that patients must have prior treatment failure or proven resistance to other antiretroviral regimens before they can gain access to reimbursed therapy. State funding of GART is variable, meaning that some patients do not have access to hospital-funded GART programs.

A previous application to have GART funded by the MBS (MSAC 1067) was unsuccessful. The previous MSAC application was assessed before TGA and PBS criteria involving GART were established, and GART was included in Australian treatment guidelines.

Approach to assessment

Research questions and clinical pathways

Patients with acute HIV infection prior to initiation of antiretroviral therapy

The PPICO criteria (target population, prior tests, index test, comparator, outcomes) developed *a priori* for evaluation of GART in patients with acute HIV infection prior to initiation of antiretroviral therapy are presented in Table 3.

Table 3 PPICO criteria for the use of GART in patients with acute HIV infection prior to initiation of antiretroviral therapy, chronic HIV infection, and in pregnant woman with HIV infection prior to initiation of therapy or entering pregnancy with a detectable viral load

Population	Prior tests[a]	Index test	Comparator	Reference standard	Outcomes
People with acute HIV infection prior to initiation of therapy	History and physical examination Viral load CD4 count	GART[a] with scientific interpretation	Standard clinical care without GART[b]	Treatment outcome: viral load	Change in clinical outcomes[c] Change in clinical management[d] Diagnostic accuracy[e] Safety outcomes[f] Prevent mother to child transmission
People with chronic HIV infected prior to initiation of therapy or prior to change of therapy in cases of virological failure or suboptimal viral load reduction					
Pregnant women with HIV infection prior to initiation of therapy or entering pregnancy with detectable HIV RNA levels while undergoing therapy					

Abbreviations: HIV, human immunodeficiency virus; GART, genotype assisted resistance testing; HIV, human immunodeficiency virus; PPICO, target population, prior tests, index test, comparator, outcomes

[a] GART performed via in-house or commercially available assays

[b] Initiation of or change in treatment regimen based on viral load without further tests to guide treatment choice

[c] Improvement in viral load response for antiretroviral combination regimens

[d] Change in HIV therapy, ie avoiding inappropriate use of therapies to which the patient's viral strain is resistant; avoiding use of agents which result in selection of multiple or cross resistance mutations

[e] Sensitivity, specificity, likelihood ratios

[f] Adverse events known to be associated with GART, eg adverse events commonly seen with blood sampling

The research question for this indication, based on these criteria, was as follows.

To what extent is GART with scientific interpretation:

- safe
- effective (including diagnostic performance and the impact of diagnosis on changes in clinical management and changes in clinical outcomes), and
- cost-effective

in the assessment of patients with HIV with or without previous exposure to HAART relative to standard of care without GART?

The clinical pathway for all HIV patient subpopulations (eg acute infection, individuals initially commencing or changing antiretroviral drugs or optimising antiretroviral drugs when pregnant) in this assessment is presented in Figure 2.

Assessment framework

Types of evidence

A systematic review of the medical literature was undertaken to identify relevant studies that examined the value of GART with scientific interpretation to assess patients with acute HIV, chronic HIV or pregnant woman infected with HIV in relation to commencing or continuing antiviral therapy. Direct evidence regarding the impact of GART on health outcomes was sought. The literature search was not limited to systematic reviews or randomised controlled trials, and observational studies were considered for review in the absence of direct evidence for all patient populations.

Review of literature

Primary databases

The previous MSAC assessment of GART included a literature search up to 2004. Because GART has now become part of normal clinical care, few studies investigating the efficacy of GART testing have been published since 2004. Therefore, the literature search in the current assessment was limited to papers published between 2000 and 2009.

Searches were conducted in the primary databases indicated in Table 4.

Table 4 Electronic databases searched during the review of GART

Database	Date searched
Medline and EMBASE[a]	2000 to 17 February 2009
PreMedline	2000 to 17 February 2009
Cochrane Library	2000 to 17 February 2009

[a] Search performed using the EMBASE.com interface

The search terms used included:

- human immunodeficiency virus
- genotype resistance testing, genetic resistance, drug resistance, resistance mutation
- virus load, viral burden.

Complete details of the literature searches performed are presented in Appendix E.

Secondary databases

A review of databases maintained by health technology assessment (HTA) agencies was undertaken to identify existing reports on GART. The list of secondary databases searched is presented in Appendix E.

Additional searches were conducted to locate background, epidemiological and economic information.

Selection criteria

The selection criteria for studies to be included and excluded from the assessment are shown in Table 5.

Table 5 Selection criterion: Clinical benefit associated with the use of GART to guide antiretroviral treatment as measured by viral load

Research question: To what extent is GART with scientific interpretation safe, effective and cost-effective in the assessment of individuals with detectable HIV RNA prior to initiation or change of antiretroviral therapy, in comparison with standard clinical care without GART?		
Selection criteria	**Inclusion**	**Exclusion**
Study design	Systematic reviews, RCT, observational studies	Non-systematic review, letters, opinion pieces, survey, not human
Population	HIV-infected patients of all ages	Not HIV-infected patients
Index test	Genotype resistance test used to guide antiretroviral treatment. Both in-house and commercial assays	Wrong test GART not part of treatment algorithm Phenotype testing
Comparator	All types of current standard of care treatment	No comparator
Outcomes	Immunological and virological measures such as plasma viral load reduction from baseline, proportion of patients with undetectable plasma viral load	Wrong outcomes

Abbreviations: GART, genotypic antiretroviral resistance testing; HIV, human immunodeficiency virus; RCT, randomised control trial

Search results

The following flowchart (Figure 4) summarises reasons for study inclusion. A total of 3178 non-duplicate references were identified, of which 60 were reviewed for inclusion, and 12 were ultimately included in this assessment report.

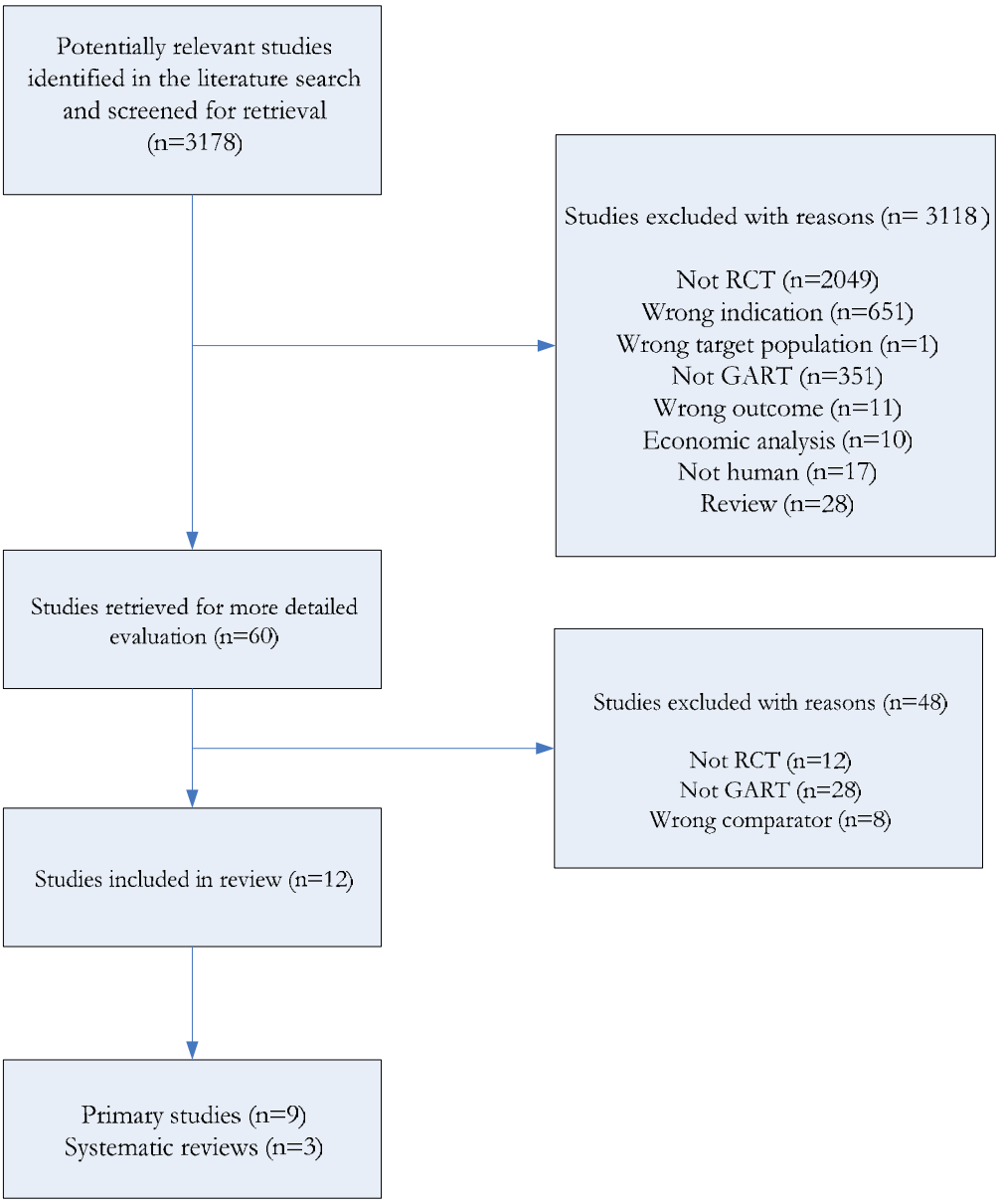


Figure 4 **Strategy for selecting articles assessing the effectiveness of genotypic resistance testing of HIV-infected patients**

Data extraction

A *pro forma* that included parameters to accommodate data collation of trial and study population characteristics, tests used, and outcomes reported was applied. This follows procedures for data collection as outlined in the *Cochrane Reviewers' Handbook* (Higgins et al 2005).

Appraisal of the evidence

Appraisals of evidence were conducted at three stages.

Stage 1 Appraisal of the applicability and quality of studies included in the review

Stage 2 Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the test

Stage 3 Evidence consolidation for analysis and development of recommendations about the index test's net benefit in Australian clinical practice.

Appraisal of the quality and applicability of individual studies

The quality and applicability of included studies was assessed by applying pre-specified criteria according to the study design (Appendix C).

Ranking the evidence

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2009).

These dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect, and relevance of the evidence (Table 6). The first domain, strength of evidence, is derived directly from the literature identified for a particular intervention. The size of effect and relevance of evidence domains require expert clinical input to adequately determine their relationship with the research question.

Components of the evidence statement are shown in Table 7.

Table 6 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	Each included study is assessed according to its place in the research hierarchy. This illustrates the potential of each included study to adequately answer a particular research question and indicates the degree to which design has minimised the impact of bias on the results[a]
Quality	Included studies are critically appraised for methodological quality. Each study is assessed according to the potential that bias, confounding and/or chance has influenced the results
Statistical precision	Primary outcomes of included studies are assessed to establish if the effect is real, rather than due to chance. Using a level of significance such as a *P*-value and/or confidence interval the precision of the estimate of the effect is evaluated. This considers the degree of certainty regarding the existence of a true effect
Size of effect	The clinical importance of the findings of each study is assessed. This concept refers to the measure of effect or point estimate reported in the results of each study (e.g. mean difference, relative risk etc). For meta-analysis pooled measures of effect are assessed. Size of effect refers to the distance of the point estimate from its null value and also the values included in the corresponding 95% confidence interval. Size of effect indicates the clinical impact a particular factor or intervention will have on a patient and is considered in the context of patient relevant clinical differences
Relevance of evidence	The translation of research evidence to clinical practice is addressed by this dimension. It is regarded as potentially the most subjective of the evidence assessments. There are two questions concerning the appropriateness of outcomes and relevance of study questions: Are the outcomes measured in the study relevant to patients? How closely do the elements of the study research question match with those of the clinical question being considered?

Source NHMRC (2008). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*. Stage 2 consultation: early 2008 – end June 2009. National Health and Medical Research Council, Canberra ACT

[a] See Table 9

Table 7 Components of the evidence statement

Component	Definition
Evidence base	
Quantity	Reflects the number of studies included as the evidence base. Also takes into account the number of patients in relation to frequency of the outcomes measures (ie study statistical power). Meta-analysis can be used to combine results of studies to increase the power and statistical precision of effect estimates
Level	Reflects the best study type for the specific type of research question (intervention, prognosis). Level I evidence would be the best evidence to answer each question
Quality	Reflects how well studies were designed and conducted in order to eliminate bias
Consistency	Assesses whether findings are consistent across included studies, including a range of study populations and study designs. Meta-analysis of randomised studies should present statistical analysis of heterogeneity that demonstrates little statistical difference between studies. Presentation of an I^2 statistic illustrates the extent of heterogeneity between studies. Clinical heterogeneity between studies should also be explored
Clinical impact	Measures the potential benefit from application of the guideline to a population. Several factors need to be considered when estimating clinical impact. These include: relevance of the evidence to the clinical question; statistical precision and size of the effect; relevance of the effect to patients compared with other management options or none. Other relevant factors are the duration of therapy required to achieve the effect and the balance of risks and benefits (taking into account the size of the patient population)
Generalisability	Addresses how well the subjects and settings of included studies match those of the recommendation. Population issues that could impact recommendations include gender, age or ethnicity, baseline risk or level of care (e.g. community or hospital setting). This is an important consideration when evidence comes from randomised controlled trials, where setting and entry requirements are generally narrow and therefore may not be representative of all patients to whom the recommendation may be applied in practice. In this circumstance broader-based population studies may be useful for confirmation of evidence from randomised controlled trials
Applicability	Addresses whether the evidence base is relevant to the Australian health care setting in general or to more local settings for specific recommendations (eg rural areas or cities). Factors that will impact the applicability of study findings include organisational factors (e.g. availability of trained staff, specialised equipment and resources) and cultural factors (eg attitudes to health issues, including those that may affect compliance with guideline recommendations)

[a] Most statistical tests of heterogeneity assess whether heterogeneity exists between studies; in contrast I^2 quantifies how much heterogeneity exists between studies

The three sub-domains (level, quality, and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 8.

Table 8 NHMRC evidence hierarchy: Designations of levels of evidence for intervention studies

Level	Intervention[b]
I[a]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls:
	Non-randomised, experimental trial[c]
	Cohort study
	Case-control study
	Interrupted time series with a control group
III-3	A comparative study without concurrent controls:
	Historical control study
	Two or more single arm study[d]
	Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: National Health and Medical Research Council. 2009. *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines* Canberra: NHMRC. Available from: www.nhmrc.gov.au

[a] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[b] Definitions of these study designs are provided on pages 7–8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b)

[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie utilise A versus B and B versus C, to determine A versus C)

[d] Comparing single arm studies ie case series from two studies

Studies identified in this assessment were designated NHMRC levels for interventions rather than diagnosis. The objective of included studies was to determine if the use of GART impacts on clinical effectiveness/patient outcomes, rather than diagnostic accuracy. Therefore, included studies are considered as diagnostic effectiveness studies (intervention levels of evidence) rather than diagnostic accuracy studies (diagnostic levels of evidence). Quality appraisal of included primary studies was performed as per an RCT (Appendix D)

Studies were also graded according to pre-specified quality and applicability criteria (Table 9).

Table 9 Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium quality Q3 poor reference standard poor quality or insufficient information

Assessment of the body of evidence

The overall body of evidence was assessed. A grade from A (excellent) to D (poor) was assigned after considering all components outlined in the body of evidence matrix presented in Table 10.

Table 10 Body of evidence matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence different to target population but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: National Health and Medical Research Council. 2009. *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines,* Canberra: NHMRC. Available from: www.nhmrc.gov.au

Expert advice

An advisory panel with expertise in the area of HIV was established to evaluate the evidence and provide advice to MSAC from a clinical and laboratory perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Results of assessment

Summary

There were 12 studies identified in the literature search which investigated genotypic assisted antiretroviral therapy in HIV infected patients (Panidou et al 2004, Ena et al 2006, Torre and Tambini 2002, Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002, Clevenbergh et al 2000, De Luca et al 2006, Green et al 2006, ERA trial investigators 2005a). All 12 identified studies demonstrated the use of GART in highly active antiretroviral therapy (HAART)-treatment experienced HIV infected patients. No studies of treatment-naïve HIV infected patients or studies investigating the benefits of genotype assisted therapy in reducing the risk of HIV transmission to the child in pregnant HIV infected woman could be sourced.

There were three systematic reviews identified (Panidou et al 2004, Ena et al 2006, Torre and Tambini 2002) of HAART experienced HIV infected patients. Following critical appraisal of these systematic reviews, only Panidou et al 2004 was included for analysis. This publication directly evaluated the benefits of the GART technology by including five randomised control trials (RCTs) (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). Virological efficacy for GART-guided treatment was demonstrated and 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 (Panidou et al 2004).

The five RCTs included by Panidou et al 2004 were also evaluated in this assessment (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). The benefits of guiding HAART by applying genotype testing are consistently evident when compared with standard of care. Reduction in plasma viral load was significant in four studies at both three and six month time points (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Tural et al 2002). This did not occur in the NARVAL trial, although this study may not have been powered to detect a significant difference (Meynard et al 2002). All five trials showed significant benefits from determining genotype resistance patterns to guide HAART and reduce the level of HIV RNA to below threshold levels for detection. There were two additional RCTs identified (Green et al 2006, ERA trial investigators 2005a) that were not included in MSAC assessment 1067. These RCTs did not demonstrate any long term advantage of GART among HIV-infected children or patients with limited virological failure. There were two follow up RCT studies identified that became observational; all patients were offered GART for durations of one year (Clevenbergh et al 2000) or three years (De Luca et al 2006). Both these studies showed that despite delay in receiving genotype-guided therapy among patients who were originally randomised into the standard clinical care arm, a continued benefit of this technology with respect to suppression of viral load is evident.

Is it safe?

Specimens to be used in genotypic antiretroviral resistance testing (GART) are collected using general procedures for sampling blood. Collection of HIV-infected blood should follow the standard procedures and protocol for handling biological samples contaminated with an infectious agent; however, the safety of the GART procedure on a blood sample carries a low safety risk to the patient.

Is it effective?

There were nine primary studies identified for inclusion in this assessment report (Clevenbergh 2000, De Luca et al 2006, Green et al 2006, ERA trial investigators 2005a, Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). Of these nine studies, five (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002) were included in MSAC assessment 1067 (endorsed 2005) and are discussed briefly. Included studies represent direct evidence for the clinical impact of GART on patient outcomes.

Systematic reviews and meta-analyses of antiretroviral-experienced HIV-infected patients

There were three systematic reviews identified in the literature search (Panidou et al 2004, Ena et al 2006, Torre and Tambini 2002). Table 11 provides a summary of the systematic reviews included in the assessment. There were also two published meta-analyses (Panidou et al 2004, Ena et al 2006) identified that were not included in MSAC assessment 1067 (2005), and one study (Torre and Tambini 2002) that was included in the earlier assessment of GART (MSAC assessment 1067, 2005). There are five randomised control trials (RCTs) (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002) that are common to both MSAC assessment report 1067 (2005) and this review (MSAC assessment 1127).

The systematic review and meta-analysis by Torre and Tambini (2002) described in MSAC assessment 1067 concluded that GART provided clinical benefits.
This conclusion was based on effects measured on an odds ratio (OR) scale at three months (OR 1.7; 95% CI: [1.3, 2.2], $p<0.001$) and six months (OR 1.6, 95%CI: [1.2, 2.2]; $p=0.0005$). That is, the odds of a reduction in HIV RNA viral load in patients who received GART with scientific interpretation was 1.7 times greater, at three months, compared with standard clinical care without GART-guided therapy. Similarly, at six months, the odds of a reduction in HIV RNA viral load to below detection in patients who receive GART-guided therapy was 1.6 times greater compared to standard of care.

The review by Torre and Bambini (2002) was classified as poor quality because of its potential for publication bias: the literature search was not systematic and limited in the number of databases included. Furthermore, the study protocol did not indicate what search terms were used, nor the search strategy applied. Internal validity of the included studies is unknown because limited data are provided on the design of the systematic review, selection criteria, reviewer blinding, and details of the inclusion and exclusion criteria of the selected articles. These unaccounted variables limit the quality of this systematic review and meta-analysis.

Ena et al (2006) aimed to evaluate the net benefit of using HIV resistance testing to antiretroviral drugs, both genotype and phenotype, on patients with virological failure. Genotypic assays detect drug resistance mutation in relevant viral genes, and phenotypic assays measure the virus's ability to grow in different concentrations of antiretroviral drugs. Ena and colleagues (2006) pooled both the benefits gained by patients who received both genotype resistance testing and phenotype resistance testing in one meta-analytical calculation. Given that the outcomes of the key RCT from genotype resistance and phenotype resistance testing were pooled, this meta-analysis was excluded from further consideration because it does not exemplify the benefits of genotypic testing alone.

The systematic review by Panidou et al (2004) was designed to estimate the effectiveness of resistance assessments based on GART, phenotypic antiretroviral resistance testing, virtual phenotyping, or standard clinical practice without resistance testing in antiretroviral therapy-experienced HIV-1 patients. The studies included in the GART versus standard of care evaluation in the systematic review by Panidou and colleagues (2004) were the same five RCTs that are common to this review (MSAC assessment 1127) and the earlier MSAC assessment (1071) that directly evaluated the benefits of GART technology (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). The total sample size for the GART-treated patients was 1113 participants for the three month time point, and 959 participants for the six month time point. Baxter et al (2000) did not include the GART trial because six month data were not reported. The differences in the proportion of patients with HIV RNA levels below the detection limit, between GART-guided therapy and standard of care treatment without resistance testing, were meta-analysed. The authors also reported the weighted mean difference in viral load decrease (log_{10}) and increase in $CD4^+$ T cell count for GART compared to standard clinical practice at both three and six months. Virological efficacy for GART-guided treatment was demonstrated. The overall proportion of participants whose viral loads were below the detection limit was significantly higher (11%) at three months (95% CI: [6, 16]; relative risk [RR] 1.34, indicated by squares in Figure 5) among participants undergoing GART-guided treatment compared with standard of care. Overall benefit at six months was 10 per cent (95% CI: [5, 16], RR 1.42, indicated by diamonds in Figure 5). Similarly, the relative risk (RR) of the proportion of participants with viral loads below detection level was significantly in favour of GART-guided treatment at three months (RR 1.34, 95% CI: [1.10, 1.63]) and at six months RR 1.42, 95% CI: [1.16, 1.72]). That is, GART-guided treatment increased the proportion of patients below threshold by 1.34 times more at three months and 1.42 times more at six months (Panidou et al 2004).

Panidou et al (2004) undertook a sub-analysis of whether expert opinion made a difference in clinical outcomes. It was found that, when no expert advice was sought and GART results were interpreted by the clinician only (Cingolani et al 2002, Meynard et al 2002), no additional benefit was seen when compared with trials where expert advice was provided (Baxter et al 2000, Durant et al 1999, Tural et al 2002). However, Panidou et al (2004) did not offer a definition of expert opinion, and hence, it is unclear whether all studies of GART with expert opinion were included in this sub-analysis.

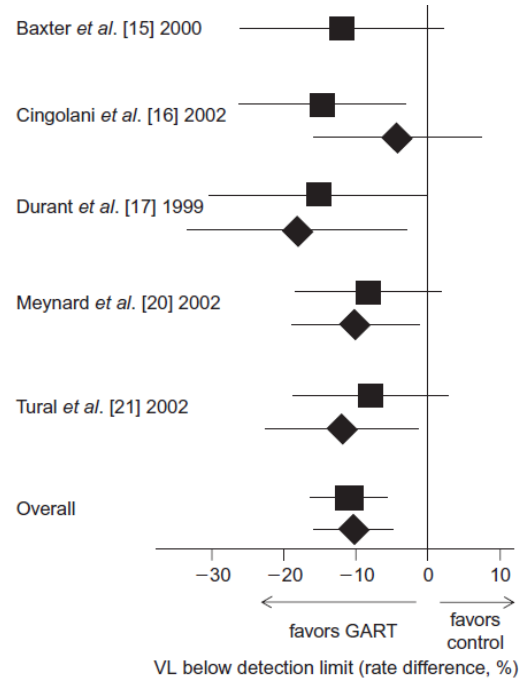


Figure 5 GART versus standard of care: Differences in the proportion of participants with HIV whose plasma HIV RNA was below detection at three and six months

Legend: Three months indicated by squares, six months indicated by diamonds
Calculated as the difference in the proportion of patients in the GART arm minus the proportion of patients in the standard of care arm. Each trial's rate difference is represented by the square and diamond symbols, and the corresponding 95% confidence intervals are indicated by horizontal lines. The line at 0 is the line of no effect
Source: Panidou et al (2004)

The systematic review by Panidou et al (2004) was assessed and evaluated as providing medium quality level evidence. Panidou and colleagues focussed on a clear research question and provided information about the patient population, index case and comparator, with clearly defined selection criteria and search methodology. Reviewers were blinded and assessment of internal validity was undertaken. Results were presented clearly, but data on the size of effect of trials included in the meta-analysis were not provided. This omission may hinder reproducibility of this meta-analysis.

Table 11 Characteristics of systematic reviews evaluating the effectiveness of GART compared with standard of care

Systematic review	Objective	Search strategy	Inclusion/exclusion criteria	Methodology	Study quality
Panidou et al (2004)	To estimate the effectiveness of resistance assessments based on GART, phenotypic antiretroviral resistance testing, or virtual phenotyping in the management of treatment-experienced HIV-1 infected patients	Medline and EMBASE (1998–2004), meeting abstracts Search terms: HIV, genotypic resistance testing, phenotypic resistance testing (PART), or virtual (v)PART. These were used in combination with RCT, controlled trial, clinical trial	Inclusion criteria: All RCTs were GART-, PART or vPART-guided therapy compared against each other or therapy without such testing Treatment experienced HIV-1 seropositive people, no language restrictions Exclusion criteria: NR (10 studies met final selection criteria 5 GART, 5 phenotype analyses) Included genotype studies GART (Baxter 2000) ARGENTA (Cingolani 2002) VIRADAPT (Durant 1999) NARVAL (Maynard 2002) HAVANA (Tural 2002)	Data abstraction by two separate reviewers using pre-specified forms Study characteristics summarised. Results for individual studies summarised An assessment of study quality was not undertaken Sources of between study heterogeneity were explored chi-squared distribution Q statistic. The extent of heterogeneity was estimated by the I-squared statistic, which ranges from 0–100%; larger values imply greater extent of heterogeneity GART vs. standard of care: The difference between GART and standard of care in the percentage of people with pVL below detection, measured at 3 and 6 months Fall in viral load (weighted mean difference log copies/mL) Increase in CD4 cell count (weighted mean x106 cells/L)	Medium quality: Heterogeneity explored by subgroup analyses Applicable search strategy with unbiased appraisal No quality assessment reported for included studies Summary of main results reported Precision estimates not reported Methods of study appraisal are reproducible

Systematic review	Objective	Search strategy	Inclusion/exclusion criteria	Methodology	Study quality
Ena et al (2006)	To evaluate the net benefit of using resistance testing in HIV-infected patients with virological failure	Medline and EMBASE (1996–2004), AIDSLINE, Cochrane Library (1996–2004) Search terms: Resistance testing, susceptibility testing, drug resistance, genotypic resistance, phenotypic resistance or phenotype or genotype. These were combined with RCT and HIV to complete the search strategy for retrieval of relevant literature	Inclusion criteria: Studies of HIV-infected patients with viral load >400 copies/mL after at least 12 weeks ART Outcomes evaluated were the proportion of patients with HIV-RNA below detection limit, changes in HIV-1 RNA and changes in CD4 cells at the end of follow-up Exclusion criteria: Different outcomes, different control group or not RCT (8 studies met final selection criteria, 5 GART, 5 phenotype analyses) Included genotype studies GART (Baxter 2000) ARGENTA (Cingolani 2002) VIRADAPT (Durant 1999) NARVAL (Maynard 2002) HAVANA (Tural 2002) Rubini (abstract only)	Data abstraction by two independent reviewers Study characteristics summarised. Results for individual studies summarised Sources of between study heterogeneity were explored chi-squared distribution Q statistic. The extent of heterogeneity was estimated by the I-squared statistic, which ranges from 0–100%; larger values imply greater extent of heterogeneity Calculated RR of achieving a non-detectable viral load and 95%CI for each study by dividing the number of patients with no detectable viral load over the total number of patients entered in the study (by ITT) GART vs. standard of care: pVL reduction (mean) Relative risk for patients with undetectable HIV-1 RNA at 3 and 6 months Increase in CD4 cell count (weighted mean $x10^6$ cells/L)	Good quality: Heterogeneity explored by subgroup analyses No quality assessment reported for included studies An assessment of study quality was not undertaken Data are pooled studies looking at 3 and 6 months and studies of both phenotype and genotype into one final meta-analysis

Systematic review	Objective	Search strategy	Inclusion/exclusion criteria	Methodology	Study quality
Torre and Tambini (2002)	To better estimate possible advantages related to routine use of resistance testing, including phenotypic and genotypic testing in different clinical settings	Medline, internet sources such as PubMed, and the most relevant HIV sites (not stated), international conference presentations (mainly Interscience conference on antimicrobial agents and chemotherapy, conference on retroviruses and opportunistic infection, AIDS international conference, and annual resistance workshop) Literature search was conducted on September 2001 Search terms: Not indicated	Inclusion criteria: Not indicated Exclusion criteria: Not indicated (6 studies met final selection criteria, 5 GART, 1 phenotype analyses) Included genotype studies GART (Baxter 2000) ARGENTA (Cingolani 2002) VIRADAPT (Durant 1999) NARVAL (Maynard 2002) HAVANA (Tural 2002)	No indication of how data was extracted Study characteristics summarised but not comprehensive for both study group and control group Results for individual studies not summarised An assessment of study quality was not undertaken Sources of between study heterogeneity were explored chi-squared distribution OR was estimated for every outcome in each trial. These were combined to provide an estimate of the overall OR according to the method described by Yusuf et al (1985) No indication on how odds ratios were calculated GART vs. standard of care Rate of patients with undetectable viraemia at 3 months and 6 months With expert advice Without expert advice	Poor quality: Search strategy poorly defined, no search terms, no inclusion/exclusion criteria indicated No data extraction methodology indicated, hence potential for bias Poorly presented study characteristics, methodology and results section

Abbreviations: AIDS, acquired immune deficiency virus; ART, antiretroviral therapy; GART, genotypic antiretroviral resistance test/ing; HIV, human immunodeficiency virus; ITT, intention-to-treat; OR, odds ratio; PART, phenotypic resistance testing; pVL, plasma viral load; RCT, randomised control trial; RNA, ribonucleic acid; RR, relative risk; vPART, virtual phenotypic resistance testing
Systematic review appraised by applying the quality criteria described in Appendix D

Primary studies of highly active antiretroviral therapy-experienced patients included in MSAC assessment 1067 (2005)

The current literature search identified five randomised control trials (RCTs) (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002) which were also included in MSAC assessment 1067 (endorsed 2005). These studies aimed to demonstrate the clinical effectiveness of GART-guided treatment for highly active antiretroviral therapy (HAART)-experienced HIV-infected patients. Of the five identified RCTs, two applied in-house genotype testing (Baxter et al 2000, Durant et al 1999). However, Durant et al (1999) reported altering the methodology to include use of a commercial assay test in the latter stage of the trial period when the assay became available. Information pertaining to in-house and commercial assays and various interpretation technologies are reported in Table 12.

Genotype testing with computer-aided interpretation packages and clinical advice about treatment options was compared with standard of care. Definitions of standard of care varied among the trials. Durant et al (1999), Cingolani et al (2002), and Tural et al (2002) based treatment on optimum care, and according to published guidelines; however, details explaining optimum care were not reported. Baxter et al (2000) and Meynard et al (2002) did not specify the definition of standard of care, nor which therapies were recommended for these participants. Expert advice was sought in four trials (Baxter et al 2000, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). Expert advice was broadly defined as input from a panel that included experts in virology and/or interpretation of genotype-resistance patterns. The VIRADAPT trial (Durant et al 1999) did not seek expert input concerning treatment options, but interpreted results of the genotype test according to a published consensus statement (Hirsch et al 1998).

The trial conducted by Baxter et al (2000) included participants over 13 years of age. Both Durant et al (1999) and Meynard et al (2002) included participants who were 18 years of age and above. Cingolani et al (2000) and Tural et al (2002) did not specify the age groups of study participants. All participants were infected with the HIV-1 virus and had previous exposure to antiretroviral treatment. The endpoints measured in the trials included change from baseline in plasma HIV RNA levels following change in antiretroviral therapy, the proportions of people with undetectable levels of viral RNA, and increase in $CD4^+$ T cell count from baseline. In the studies conducted by Baxter et al (2000) and Durant et al (1999) the primary outcome was change in plasma HIV RNA from baseline. The proportion of participants who achieved an undetectable viral load was the primary outcome of the trials conducted by Cingolani et al (2002), Meynard et al (2002) and Tural et al (2002).

Table 12 Characteristics of studies interpreted to evaluate GART among patients with HIV-1 who were HAART-experienced

Trial name, author (year) country	Study design	Population	Index test characteristics	Comparator characteristics	Study design	Level of evidence and study quality
In-house assay used for viral HIV RNA genotyping						
MSAC assessment 1067 (endorsed 2005)						
GART Baxter et al (2000) USA	MC, R, N=153, 3 months	Inclusion criteria: >13 years with virological failure (>16 weeks; >20,000 copies/ mL by Roche or >10,000 copies/mL by Chiron assay within 6 weeks) on PI or NRTI regimen, cumulative ART and CD4 cell count 50–500x10^6 cells/L Exclusion criteria ART other than in regimen or previous genotype/phenotype analyses	GART- mutation identified; interpretation of drug susceptibilities, and treatment suggestions Sequencing of viral RNA in-house, results transmitted to the Statistical Center at the University of Minnesota for expert interpretation Expert opinion: Yes Protocol virologists independently reviewed mutations, treatment history and contraindications as reported by site clinician and suggested treatment	Standard of care treatment regimen proposed before randomisation was prescribed by the site clinician	Random allocation: Yes (permuted blocks) Concealment of allocation: No—clinician to patient allocation Blinding: Yes—clinician to treatment decision (GART report was prepared without knowledge of participants, clinical site, or the group to which the participant was randomised) ITT: Yes Power: 90% to detect 0.26 log difference between treatment groups (n=80/gp)	C1 Comparison: Direct comparison P1 Applicability: Applicable Q1 Quality: High NHMRC level II evidence for an intervention study

Trial name, author (year) country	Study design	Population	Index test characteristics	Comparator characteristics	Study design	Level of evidence and study quality
VIRADAPT Durant et al (1999), France	R, OL, P, pilot study. N=108, 6 months	Inclusion criteria >18 years with pVL >10,000 copies/mL >6 months treatment with nucleoside analogues at >3 months treatment with a PI, Karnofsky score >50 Exclusion criteria Haemoglobin concentration of <6 mmol/, absolute neutrophil <0.8x10(9)/L, creatinine concentration > 200 mmol/L and liver aminotransferase value >5 times ULN	GART– if no resistance mutations were found, the choice of ART was the best clinical practice Sequencing of viral RNA in house until January 1998, then TruGene HIV–1 assay (Visible Genetics, Toronto). Classification of mutations was conducted according to consensus statement on antiretroviral drug testing (Hirsch et al 1998) GART performed every 3 months and treatment modified if HIV-1 RNA was >10,000 copies/mL or <0.5 log lower than baseline Expert opinion: No Interpretation of genotype result by a clinician	Standard of care treatment changes were based on optimum care according to published guidelines	Random allocation: Yes—consecutive Concealment of allocation: Yes—opaque sealed envelope Blinding: NR ITT: NR Power: NR	C1 Comparison: Direct comparison P1 Applicability: Applicable Q3 Quality : Poor—potential for bias due absence of blinding NHMRC level III-1 evidence for an intervention study

Trial name, author (year) country	Study design	Population	Index test characteristics	Comparator characteristics	Study design	Level of evidence and study quality
MSAC assessment 1127 (current)						
Clevenbergh et al (2000) follow-up of VIRADAPT France	Open study; follow-up from Durant et al (1999), N=108, 12 months	This study was initiated following the 6 month study conducted by Durant et al (1999). All participants had access to genotype-assisted therapy if their viral load did not exceed a 0.5 log reduction. Cross over treatment was initiated for 69% of standard of care participants during entire open label period	GART— if no resistance mutations were found, the choice of ART was considered as best clinical practice Sequencing of viral RNA was conducted in-house until January 1998, then using TruGene HIV-1 assay (Visible Genetics, Toronto). GART performed every 3 months and treatment modified if HIV-1 RNA was >10,000 copies/mL or <0.5 log lower than baseline Expert opinion: No Interpretation of genotype result by a clinician	Standard of care with or without GART	Open label study, no randomisation, no allocation concealment or blinding. Follow up of the ViIRADAPT study which was randomised and had allocation concealment.	CX Comparison: Other comparison P2 Applicability: Limited Q3 Quality : Poor—potential for bias due absence of blinding NHMRC level III-2 evidence for an intervention study
Commercial assay for genotyping of viral HIV RNA						
MSAC assessment 1067 (2005)						

ARGENTA Cingolani et al (2002) Italy	R, OL, single centre, N=174, 6 months	Inclusion criteria >2 months on treatment and have either: pVL >2000 copies/mL; or <1 log_{10} reduction HIV RNA >2 months after commencement of the last regimen. All participants including injecting drug users Excluded No exclusion criteria	GART Sequencing of viral RNA by TruGene HIV-1 assay, Visible Genetics, Toronto Expert opinion: Yes Treatment decision discussed by a panel including the treating physician and 2 experts in interpretation of phenotypic resistance results	Standard of care—treatment decision based on evaluation of history, clinical picture and standard immunological and virological parameters (if pVL <1 log_{10} copies/mL then patients were offered GART-guided treatment)	Random allocation: Yes (consecutive) Concealment of allocation: NR Blinding: No (all clinicians discussed decision making) ITT: Yes Power: NR	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality : Poor—no indication of allocation concealment, potential for bias due absence of blinding NHMRC level III-1 evidence for intervention study
Trial name, author (year) country	**Study design**	**Population**	**Index test characteristics**	**Comparator characteristics**	**Study design**	**Level of evidence and study quality**
NARVAL Meynard et al (2002) France	MC, R, N=542, 12 months	Inclusion criteria >18 years with HIV-1 RNA >1000 copies/ mL, previous exposure to PI therapy >3 months, unchanged ART for 2 preceding months, Karnofsky score >70% Exclusion criteria Not indicated	GART Sequencing of viral RNA by TruGene HIV-1 kit (Visible Genetics, Toronto) Expert opinion: Yes Treatment decision made by panel consisting of 4 clinicians and 2 specialist virologists.	Standard of care–no indication of standard clinical care.	Random allocation: Yes Concealment of allocation: No—both the investigator and the participant were aware of allocation Blinding: Yes—clinician to resistance test ITT: No Power: 80% to detect difference of 15% success rate	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality: Poor— potential for selection bias from no indication of or allocation concealment. Insufficient information on patient selection NHMRC level II evidence for an intervention study

HAVANA Tural et al (2002) Spain	R, OL, MC. N=326, 6 months	Inclusion criteria Patients with plasma RNA >1000 copies/mL and to be stable ART for more than 6 months Exclusion criteria Substantial ART-related adverse events history, poor adherence or active drug abuse	GART Sequencing of viral RNA by TruGene HIV-1 Kit and interpreted (RetroGram, Virology networks, Netherlands) Expert opinion: Yes Expert advice was sought from groups of 4 clinicians and 2 virologists. Selection of ART was decided by practising physician with additional information from the expert group	Standard of care—best clinical practice and most recent guidelines	Random allocation: Yes Concealment of allocation: NR Blinding: NR ITT: Yes Power: 80% to detect difference of 50% of patients with undetectable pVL	C1 Comparison: Direct comparison P1 Applicability: Applicable Q3 Quality: Poor—potential for bias due absence of blinding. Open label trial with no allocation concealment. NHMRC level II evidence for an intervention study

Trial name, author (year) country	Study design	Population	Index test characteristics	Comparator characteristics	Study design	Level of evidence and study quality
MSAC assessment 1127 (current)						
De Luca et al (2006) Follow up of ARGENTA Italy	OL, single centre, N = 174, 36 months Follow-up study from Cingolani et al (2002)	Inclusion criteria Follow up observational trial of the ARGENTA trial (Cingolani et al 2002), following 6 months of the ARGENTA trial, participants from SOC arm with viral loads >1000 copies/mL received GART-guided treatment decisions based on access to ART.	GART Sequencing of viral RNA by TruGene HIV-1 assay, Visible Genetics, Toronto Expert opinion: Yes Treatment decision discussed by a panel including the treating physician and 2 experts in interpretation of phenotypic resistance results	Standard of care—treatment decision based on medical history, immunological and virological parameters (if there was pVL <1 log_{10} copies/mL patients were offered GART)	Open label study, no randomisation, no allocation concealment or blinding. Follow up of the ARGENTA study which was randomised, concealment of allocation was not reported and was not blinded	CX Comparison: Other comparison P1 Applicability: Applicable Q3 Quality: Poor—no indication of allocation concealment, potential for bias due absence of blinding. NHMRC level III-2 evidence for an intervention study
ERA trial investigators (2005a) UK	R, MC, N=55,12 months	Inclusion criteria >18 years pVL >2000 copies/mL Methods taken from ERA trial investigators (2005b)	GART Sequencing of viral RNA by Virco (Mechelen, Belgium) Interpretation by computer-generated interpretation system Expert advice: No Treatment decisions were made by the virologist on the steering committee; expert advice on the interpretation of the resistance test was not sought	Standard of care–no indication of standard clinical care.	Random allocation: Yes (random number generation) Concealment of allocation: NR Blinding: NR ITT: Yes Power: 90% to detect a difference of 0.3 log_{10} copies/mL	C1 Comparison: Direct comparison P1 Applicability: Applicable Q3 Quality: Poor—no indication of allocation concealment, potential for bias due absence of blinding. NHMRC level II evidence for an intervention study

Trial name, author (year) country	Study design	Population	Index test characteristics	Comparator characteristics	Study design	Level of evidence and study quality
PERA Green et al (2006) UK, France	OL, R, MC, N=180, 96 weeks	Inclusion criteria Infants from 3 months of age to participants aged 18 years old who had to change therapy due to virological failure, and patients with pVL >2000 copies/ mL Exclusion criteria Patients exposed to 2 or 3 antiretroviral drugs for <2 years and if they changed antiretroviral therapy in the month preceding the start of the trial or had received GART-guided therapy	GART Sequencing of viral RNA by Virco (Mechelen, Belgium) with computer-assisted interpretation (VirtualPhenotype, v2 to v3.2) Expert advice: No Treatment decisions were made by the virologist on the steering committee; expert advice on the interpretation of the resistance test was not sought	Standard of care–no indication of standard clinical care.	Random allocation: Yes Concealment of allocation: NR Blinding: NR ITT: Yes Power: 90% to detect difference of 0.3 $\log_{10}$ copies/mL (n=90/gp)	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality: Poor—potential for bias due absence of blinding. Open label trial with allocation concealment NHMRC level II evidence for an intervention study

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; ITT, intention-to-treat; MC, multicentre; N, number of patients; NHMRC, National Health and Medical Research Council; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitor; OL, open label; P, population; PI, protease inhibitors; pVL, plasma viral load; R, randomised; RNA, ribonucleic acid; ULN, upper limit of normal

Study outcomes

Of the five RCTs in focus for this assessment (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002), two—Baxter et al (2000) and Durant et al (1999)—applied in-house genotype resistance assays to identify mutations in specific areas of the HIV genome. Durant et al (1999) changed focus from application of an assay that was developed in-house to use of a commercial test kit during the study period. Cingolani et al (2002), Meynard et al (2002) and Tural et al (2002) applied commercial test kits (Table 12).

The mean change in viral load from baseline is reported in Table 13. Baxter et al (2000) and Durant et al (1999) reported successful plasma viral load reduction from baseline. Patients undergoing genotype-assisted treatment in the NARVAL study (Meynard et al 2002) did not show a statistically significant reduction in HIV RNA levels compared with standard of care. Statistical analyses were not provided for plasma HIV RNA by Cingolani et al (2002) or Tural et al (2002).

Baxter et al (2000) and Durant et al (1999) demonstrated the benefits of genotype-guided treatment compared with standard of care. Both studies showed that a significant reduction in plasma viral load was evident among participants whose treatment was guided by genotype-resistance patterns compared with standard care therapy. At three months, the treatment difference between GART and standard of care was demonstrated by an additional reduction in HIV RNA of 0.53 $\log_{10}$ copies/mL (p<0.0001) (Baxter et al 2000) and 0.58 $\log_{10}$/mL (p=0.01) (Durant et al 1999) in the GART arm. Durant et al (1999) showed that the benefits of GART to guide highly active antiretroviral therapy (HAART) were sustained until six months (p=0.05). Additional reduction in plasma viral load among participants who underwent GART was documented at both three months (0.24 $\log_{10}$, Cingolani et al 2002; 0.12 $\log_{10}$, Tural et al 2002) and six months (0.18 $\log_{10}$ Cingolani et al 2002; 0.21 $\log_{10}$, Tural et al 2002), although statistical analyses were not reported for these trials. The Meynard et al (2002) publication of the NARVAL study showed a non-significant mean change of plasma viral load from baseline to three months as 0.95 $\log_{10}$ copies/mL (95% CI:[1.93, –0.08] p=0.215).

Another biological proxy for examining response to antiretroviral treatment is determination of the proportion of patients with undetectable levels of HIV RNA. There are significant variations in what is considered to be the level of HIV RNA detection. In the included RCTs, the threshold for level of undetectable viral load ranged from below 200 copies/mL (Meynard et al 2002), below 400 copies/mL (Durant et al 1999, Tural et al 2002), or below 500 copies/mL (Baxter et al 2000, Cingolani et al 2002). Baxter et al (2000) reported statistically significant response to treatment leading to undetectable viral loads at four and eight weeks among patients undergoing genotype-assisted HAART. Cingolani et al (2002) and Durant et al (1999) reported benefits at three months, and Maynard et al (2002) and Tural et al (2002) indicated benefits at six months.

In the early phase of the study by Baxter et al (2000), GART-guided antiretroviral therapy significantly increased the proportion of people with plasma HIV RNA below the level of detection. After four weeks the proportion of patients with HIV RNA below detection levels for the standard clinical care group (no resistance test) was 23 per cent, vs. 45 per cent of patients in the GART group (p =0.004). This effect remained strongly significant at Week 8, where the proportion of patients with plasma viral load below

detection in the GART group was 55 per cent vs. 25 per cent in the clinical care group (p =0.0001). At three months this benefit remained evident, but was not statistically significant (standard of care 22%, GART 34% p=0.10). The odds of achieving undetectable viral load at three months following treatment guided by genotype-resistance testing was 2.19 and significantly greater than when treatment was standard care (95% CI: [1.14, 4.21] p=0.01; Cingolani et al 2002). By month six, the odds of achieving HIV RNA levels below 500 copies/mL were not significant but remained greater in the GART group in comparison to standard of care (OR: 1.26, 95% CI: [0.68, 2.33] p=0.47). Three studies reported an increased proportion of participants who had undetectable viral loads at three months following GART, compared with standard of care (15%, p=0.017, Durant et al 1999; 9%, p=NR, Maynard et al 2002; 8% p=NS, Tural et al 2002) and six months (19%, p=0.067, Durant et al 1999; 9%, p=0.052 Meynard et al 2002; 12%, p<0.05 Tural et al 2002).

VIRADAPT and ARGENTA follow-up studies which were not evaluated in MSAC Assessment 1067

Studies by Clevenbergh et al (2000) and De Luca et al (2006) were identified and found to have not been included in MSAC Assessment 1067 (2005).

Clevenbergh et al (2000) present follow-up long term data from the VIRADAPT (Durant et al 1999) study. Clevenbergh and colleagues used an in-house assay to identify genotype resistance mutations. However, the study protocol indicated that the trial investigators changed to using a commercially available kit. There is no indication by Clevenbergh et al (2000) about whether an in-house or commercially available test kit was used during the follow-up period.

Clevenbergh et al (2000) followed VIRADAPT study participants (Durant et al 1999) for six months in addition to the initial study's six month duration. The primary endpoint for the follow-up period was the proportion of participants whose plasma viral load was below the level of detection, which was set at <200 copies/mL. Trial results demonstrated that during the randomised period at six months, a greater proportion of participants had an undetectable viral load following antiretroviral treatment guided by GART. After genotype testing was made available to most participants (69%) in the original control arm of the study, the proportion of participants whose HIV RNA level at 12 months was undetectable did not differ between the groups. This was because the benefits of genotype-resistance guided therapy were evident in the participants who were originally in the standard of care arm and underwent GART (original standard of care, 30.4%; GART, 30.5%). Similarly, participants from the standard of care arm who had cross-over treatment options showed an additional decrease of 0.31 $\log_{10}(\pm 0.22)$ copies/mL in plasma HIV RNA compared with the viral load assessed in the standard of care group in the randomised VIRADAPT trial (Durant et al 1999).

De Luca et al (2006) conducted a follow-up study to the ARGENTA (Cingolani et al 2002) trial. De Luca and colleagues used a commercial kit was to identify mutations in the HIV genome required to guide antiretroviral therapy in the follow-up of the ARGENTA trial.

De Luca et al (2006) conducted a long term (30 additional months) prospective observational study with follow-up of participants with HIV infection from the ARGENTA trial (Cingolani et al 2002). In this trial, participants from the GART arm

continued to undergo treatment based on genotype-resistance patterns. However, participants in the standard of care arm whose HIV RNA levels exceeded 1000 copies/mL were also offered GART. After 30 months of the observational period, there was a mean reduction of 1.21 $\log_{10}$ HIV RNA copies/mL from baseline among all participants and 29 per cent of patients in both the GART and the standard of care arms had a plasma HIV RNA load below the level of detection (<400 copies/mL) at the end of the three year trial (by intention to treat analysis). There were no significant differences in virological outcomes between the original GART group during the randomised phase (Cingolani et al 2002) and those who did not receive GART-guided treatment until the observational phase of the trial (De Luca et al 2006). These results suggest that a continuous benefit was gained from genotype-guided therapy.

Overall, the benefits of guiding HAART by applying genotype testing are consistently apparent when compared with standard of care. Reduction in plasma viral load was evident in four studies at both three and six month time points (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Tural et al 2002). This did not occur in the NARVAL trial (Meynard et al 2002). Meynard et al (2002). The NARVAL trial was designed to measure reductions in plasma viral load from baseline as a secondary outcome. This may have compromised the statistical value of the effect. All five trials showed significant benefits from determining genotype resistance patterns to guide HAART and reduce the level of HIV RNA to below detection threshold levels. The threshold level of detection varied among trials. Early reduction of plasma viral load from baseline levels was demonstrated in the trials, and lead to a greater proportion of patients with HIV RNA below the level of detection at four and eight weeks (Baxter et al 2000), at three months (Cingolani et al 2002, Durant et al 1999), at six months post-randomisation (Meynard et al 2002, Tural et al 2002). Despite the NARVAL trial demonstrating a non-significant reduction in viral load at three months, by six months in the GART-guided care group the proportion of participants with plasma viral load below detection, set at <200 copies/mL, was significantly greater than participants who received standard care.

The RCTs that became observational studies, and that offered GART to all participants, presented follow-up data for one year (Clevenbergh et al 2000) and three years (De Luca et al 2006). These studies show that despite a delay in receiving genotype-guided therapy in patients who were originally randomised to the standard clinical care arm, continued benefit of this technology is evident.

Primary studies that included HAART-experienced patients, which were not evaluated in MSAC Assessment 1067

Assessment 1127 presents two RCTs (Green et al 2006, ERA trial investigators 2005a) that were not included in MSAC assessment 1067. Green et al (2006) reported on the *Paediatric Evaluation of Resistance Assays* (PERA) trial which was designed to evaluate longer-term utility of genotypic resistance testing of children with HIV-1 infection and virological failure. Expert advice was not sought in this trial; treatment decisions were made by the virologist on the steering committee. Green et al (2006) enrolled 171 participants who had HIV-1, and were aged from three months to 18 years, and had switched antiretroviral therapy due to virological failure, to participate in the trial which had a 96 week follow-up period. Results indicate that resistance testing led to a mean difference in plasma HIV RNA between GART and standard of care-guided treatment of 0.28 $\log_{10}$/mL at 12 months (95% CI: [–0.28, –0.84], p=0.3) and 0.03 $\log_{10}$/mL at

24 months (p=0.9). Antiretroviral treatment guided by genotype resistance patterns did not result in long term reduction in the viral load to below the threshold level of detection, which was set at <50 copies/mL or <400 copies/mL, at either 48 or 96 weeks.

The ERA trial investigators (2005) compared clinical utility of genotypic resistance testing with standard clinical care among people with HIV-1 (n=55) who had limited virological failure (one or two regimens). The standard of care treatment was not described in this trial. Study results indicated the mean difference in HIV-1 viral load reduction at 12 months between the genotype-guided treatment and standard of care was 0.21 $\log_{10}$ (p=0.9). Similarly, the proportion of participants whose viral load was below the level of detection, set at 50 copies/mL, did not differ between the GART (56%) and standard of care groups (50%). It should be noted that this threshold level for viral detection is very low. Compared with some trials included in this assessment, the viral detection level was 10 times lower (Baxter et al 2000, Cingolani et al 2002). Resistance testing was associated with a more conservative prescribing approach—there was a propensity to recycle drug combinations; however, there was no net effect of these factors on the virological endpoints measured.

Table 13 Study results: Evaluation of the impact of GART in guiding therapy in patients infected with HIV

Study	Baseline characteristics		End point	Time points at which end points were measured	Outcomes			
	Plasma viral load	CD4 T cell count			Plasma viral load	CD4 T cell count	HIV RNA below level of detection	Treatment difference
MSAC assessment 1067 (2005)								
GART Baxter et al (2000)	Standard of care: 4.37 log_{10} copies/mL (SD=0.44) (mean)	Standard of care 228.6 $x10^6$ cells/L (mean)	Primary endpoint: Change in pVL from baseline Secondary endpoint: Change in pVL at 12 weeks Change in CD4 cell count at 4, 8 and 12 weeks	4, 8, 12 weeks	At 3 months Standard of care: –0.47 log_{10} copies/mL (0.09)	4–8weeks increase Standard of care: $22x10^6$ cells/L At 3 months increase Standard of care: $18x10^6$ cells/L	<500 copies/mL At 4 weeks Standard of care: 23% At 8 weeks Standard of care: 25% At 3 months Standard of care: 22.2%	At 3 months Average treatment difference for pVL was 0.53 log_{10} copies/mL in favour of GART 95% CI: [–0.77, –0.29], p<0.00001
	GART: 4.47 log_{10} copies/ mL (SD=0.46) (mean)	GART: 230.5 $x10^6$ cells/L (mean)			At 3 months GART: –0.94 log_{10} copies/ mL (0.09)	4–8weeks increase GART: $23x10^6$ cells/L At 3 months increase GART: $25x10^6$ cells/L	<500 copies/ mL At 4 weeks GART: 45% (p=0.004) At 8 weeks GART: 55% (p=0.0001) At 3months GART:34.2% (p=0.10)	
ARGENTA Cingolani et al (2002)	Standard of care: 4.17log_{10} copies/mL (median)	Standard of care: 266 $x10^6$/L (median)	Primary endpoint: Proportion of patients with <500 copies/mL and CD4 counts from baseline	3, 6 months	At 3 months Standard of care: –0.38 log_{10} copies/mL (SD=0.96) At 6 months Standard of care: –0.39 log_{10} copies/mL (SD=1.04)	At 3 months increase Standard of care: 19 (95% CI: [–2, 39]) cells/μL At 6 months increase Standard of care: 22 (95% CI: [–4, 49]) cells/μL	<500 copies/ mL At 3 months Standard of care: 12% At 6 months Standard of care: 17%	At 3 months Average treatment difference for pVL was 0.24 log_{10} copies/mL in favour of GART At 6 months Average treatment difference for pVL was 0.12 log_{10} copies/mL in

Study	Baseline characteristics		End point	Time points at which end points were measured	Outcomes			
	Plasma viral load	CD4 T cell count			Plasma viral load	CD4 T cell count	HIV RNA below level of detection	Treatment difference
	GART: 4.36 log_{10} copies/mL (median)	GART:264 $x10^6$/L (median)			At 3 months GART: –0.62 log_{10} copies/ mL (SD=1.16) At 6 months GART: –0.57log_{10} copies/mL (SD=1.09)	At 3 months increase GART: 9 (95%CI; [–18, 27]) cells/μL At 6 months increase GART: 15 (95%CI: [–10, 39]) cells/μL	<500 copies/mL At 3 months GART: 27% (GART vs. standard of care: p=0.01) At 6 months GART: 21% (GART vs. standard of care: p=0.47)	favour of GART
VIRADAPT Durant et al (1999)	Standard of care: 4.8 log_{10} copies/mL (SD=0.5) (mean)	Standard of care201.7 $x10^6$ cells/L (SD=22)	Primary endpoint (up to 6 months): Mean change in pVL from baseline to 3 and 6 months Secondary endpoints (up to 6months): Proportion of participants with pVL <200 copies/mL at 3 and 6 months. Mean change from baseline of CD4 cells count at 3 and 6 months. Time to treatment modification	3, 6 months	At 3 months Standard of care: –0.46 log_{10} copies/mL (SD=0.17) At 6 months Standard of care: –0.67 log_{10} copies/mL (SD=0.19)	At 3 months increase Standard of care: 18 cells/μL At 6 months increase Standard of care: 33 cells/μL	<200 copies/mL At 3 months Standard of care: 14% At 6 months Standard of care: 14%	At 3 months Mean difference pVL 0.58 log_{10} copies/mL (95% CI:[0.14,–1.02] p=0.01 At 6 months Mean difference pVL 0.48 log_{10} copies/mL (95% CI: [0.01,–0.97] p=0.05
	GART: 4.7 log_{10} copies/mL (SD=0.6) (mean)	GART: 220.8 $x10^6$ cells/L (SD=18) (mean)			At 3 months GART: –1.04 log_{10} copies/mL +/–0.14 At 6 months GART:–1.15 log_{10} copies/mL (0.15)	At 3 months increase GART: 36 cells/μL At 3 months increase GART: 21 cells/μL	<200 copies/mL At 3 months GART: 29% (GART vs. standard of care: p=0.017) At 6 months GART: 32% (GART vs. standard of care: p=0.067)	

Study	Baseline characteristics		End point	Time points at which end points were measured	Outcomes			
	Plasma viral load	CD4 T cell count			Plasma viral load	CD4 T cell count	HIV RNA below level of detection	Treatment difference
NARVAL Meynard et al (2002)	Standard of care: 4.3 log_{10} copies/mL (median)	Standard of care: 260x10^6 cells/L (median)	Primary endpoint: % with pVL <200 copies/mL at week12 Secondary endpoints: % with pVL <20 copies/mL at week12; changes in pVL and CD4 counts between day 0 and week 12; (%) with <200 copies/mL at weeks12, 24, 36	12, 24, 36 weeks	At 3 months Standard of care: –0.9 log_{10} copies/mL* *Approximate from figure 4(b)	At 3 months Standard of care: 27+/–83 x10^6 cells/L	<200 copies/mL At 3 months Standard of care: 36% At 6 months Standard of care: 22%	At 3 months Mean change (GART vs. standard of care) 0.95 log_{10} copies/mL (95% CI: [1.98, –0.08]) p=0.215
	GART: 4.3 log_{10} copies/ mL (median)	GART:283 x10^6 cells/L (median)			At 3 months GART: –1.0 log_{10} copies/mL* *Approximate from figure 4(b)	At 3 months GART: 14+/–113x10^6 cells/L (p=0.45)	At 3 months GART: 44%(GART vs. standard of care: p=0.215) At 6 months GART: 31% (GART vs. standard of care: p=0.052)	
HAVANA Tural et al (2002)	Standard of care: 4.0 log_{10} copies/mL (SD=0.8) (mean)	Standard of care: 401 x10^6 cells/L (SD=225) (mean)	Primary endpoint: Proportion of patients with pVL <400 copies/ mL at 24 weeks Secondary endpoint: Change in pVL at 12 and 24 weeks from baseline	12, 24 weeks	At 3 months Standard of care: –0.8 log_{10} copies/mL (SD=0.7) At 6 months Standard of care: –0.63 log_{10} copies/mL (SD=0.8)	Not investigated	<400 copies/ mL At 3 months Standard of care: 46.6% At 6 months Standard of care: 36.2%	At 3 months Average treatment difference for pVL was 0.18 log_{10} copies/mL in favour of GART At 6 months Average treatment difference for pVL was 0.21 log_{10} copies/mL in favour of GART
	GART:4.1 log_{10} copies/ mL (SD=0.8) (mean)	GART: 372 x10^6 cells/L (SD=223) (mean)			At 3 months GART: –0.92 log_{10} copies/mL (SD=0.8) At 6 months GART: –0.84 log_{10} copies/mL (SD=0.8)		<400 copies/ mL At 3 months GART: 54.6% (GART vs. standard of care p=NS) At 6 months GART: 48.5% (GART vs.	

Study	Baseline characteristics		End point	Time points at which end points were measured	Outcomes			
	Plasma viral load	CD4 T cell count			Plasma viral load	CD4 T cell count	HIV RNA below level of detection	Treatment difference
							standard of care p<0.05)	
MSAC assessment 1127								
Clevenbergh et al (2000) follow-up of VIRADAPT	Standard of care: 4.8 log_{10} copies/mL (SD=0.5) (mean)	Standard of care: 201.7 $x10^6$ cells/L (SD=22)	Primary endpoint (6–12 months): Change of pVL from baseline to month 12 Secondary endpoint (6–12 months): Proportion of patients with pVL <200 copies/mL (level of detection)	Time series up to 12 months	At 12 months Standard of care: –0.98 log copies/mL (SD=0.22)	Not investigated	<200 copies/mL At 6 months Standard of care: 14% At 12 months Standard of care: 30.5%	
	GART: 4.7 log_{10} copies/ mL (SD=0.6) (mean)	GART: 220.8 $x10^6$ cells/L (SD=18) (mean)			At 12 months GART:– 1.15 log_{10} copies/ mL (SD=0.17)		<200 copies/mL At 6 months GART: 32.3% At 12 months GART: 30.4%	
De Luca et al (2006) follow-up of ARGENTA	Standard of care: 4.17log_{10} copies/mL (median)	Standard of care: 266 $x10^6$/L (median)	Proportion of patients with pVL below 400 copies/mL	36 months	NR	At 36 months increase Standard of care: ~72 cells/mL* *Approximated from figure 2	<400 copies/ mL At 36 months Standard of care: 28%	At 36months median difference of –1.21 log_{10} copies/mL from baseline
	GART: 4.36 log_{10} copies/ mL (median)	GART:264 $x10^6$/L (median)			NR	At 36 months increase GART:~105 cells/mL* *Approximated from figure 2	<400 copies/ mL At 36 months GART: 31.25%	

Study	Baseline characteristics		End point	Time points at which end points were measured	Outcomes			
	Plasma viral load	CD4 T cell count			Plasma viral load	CD4 T cell count	HIV RNA below level of detection	Treatment difference
PERA Green et al (2006)	Standard of care: 4.7log_{10} copies/mL (SD=0.9) (mean)	Standard of care: 437 cells/mm^3 (299–743) (median)	Primary endpoint: Change pVL at 48 weeks from baseline Secondary endpoint: Proportion of patients with undetectable pVL (<50copies/mL) at 48 weeks. Change in CD4 percentage. Progression to new AIDS defining event/death	48, 96 weeks	At 24 weeks Standard of care: –1.3 log_{10} copies/mL * At 48 weeks Standard of care: –1.23 log_{10} copies/mL (0.2) At 96 weeks Standard of care: –1.51 log_{10} copies/mL* *Approximated from figure 3	At 48 weeks Standard of care 1.7% (SD=0.9)	<400 copies/ mL At 48 weeks Standard of care: 34% At 96 weeks Standard of care: 38%	At 48 weeks Mean difference pVL 0.28 log_{10} copies/mL(95% CI: [–0.28, 0.84]) p=0.3 Mean difference $CD4^+$ T cell count 1.6% (95% CI: [–0.1, 4]) p=0.2 At 96 weeks Mean difference CD4 2.5% (95% CI: [0.1, 5.2]) p=0.06 at 96 weeks
	GART: 4.7 log_{10} copies/mL (SD=0.9)(mean)	GART: 432 cells/mm^3 (298–756) (median)	.		At 24 weeks GART:–1.5 log_{10} copies/mL * At 48 weeks GART:–1.51 log_{10} copies/mL At 96 weeks GART:–1.51 log_{10} copies/mL* *Approximated from figure 3	At 48 weeks GART: 3.2% (SD=0.9)	<400 copies/ mL At 48 weeks GART: 34% At 96 weeks GART: 37%	
ERA trial investigators (2005a)	Standard of care not provided	Standard of care not provided	Primary endpoint: Change pVL at 12 months from baseline Secondary endpoints: Change in CD4 counts at 12 months	12 months	At 12 months Standard of care: –2.19log_{10} copies/mL	Not investigated	<50 copies/mL At 12 months Standard of care: 50%	At 36 months mean difference pVL 0.21 log (95% CI: [–1.53, 1.73]) p=0.9
	GART: 4.2 log_{10} copies/mL (SD=0.9) (mean)	GART: 266 cells/ mm^3 (mean)			At 12 months GART: –2.3 log_{10} copies/mL	Not investigated	<50 copies/mL At 12 months GART: 56%	

Abbreviations: GART, genotype-assisted resistance testing; pVL, plasma viral load; SD, standard deviation; NS, not significant

Body of evidence

Individual rankings for components of the body of evidence are shown in Table 14.

Table 14 Assessing the body of evidence for GART among patients with HIV who are HAART-experienced

Component	Rank	Reason
Volume of evidence	A	There were three systematic reviews with meta-analyses of level II evidence, which assessed the effectiveness of GART in treatment experienced patients. These are regarded as providing level I evidence
		There were five randomised controlled trials that provided level II evidence
		Two studies that applied consecutive randomisation were regarded as pseudo-randomised controlled trials with level III-1 evidence
		Two follow-up open label trials were regarded as providing level III-2 evidence
		Five studies indicated that the number of patients in relation to the frequency of the outcomes measured was powered at 80–90% to detect a difference in viral load. The other studies did not stipulate this. All except one of the primary studies had over 100 participants and were considered sufficient to detect a significant difference between the index case and comparator
Consistency[a]	A	Findings were consistent across all included studies and are likely to be replicable
		The three included meta-analyses undertook analysis of heterogeneity among included studies and found no statistical difference
Clinical impact	A	HIV infected individuals receiving HAART, where the choice has been optimised by the addition of GART to clinical and virological assessment, had increased likelihood of virological success providing they remained adherent to the regimen over the 12 weeks of the study
Generalisibility	B	All nine primary studies focused on patients infected with HIV who were HAART-experienced
		No studies that included treatment-naïve patients or pregnant woman infected with HIV were identified. Therefore, data presented in the assessment are poorly generalised to these two patient populations
Applicability	A	Because GART is considered to be standard practice in Australia, and both the in-house and commercial assays are available for purchase in Australia, these results are highly applicable to the Australian setting

Abbreviations: GART, genotype assisted resistance testing; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus

What are the economic considerations?

Summary

A Markov model incorporating a Monte Carlo simulation was considered to be the appropriate modelling approach for this economic evaluation. The primary health states of the model were defined based on treatment regimens (HAART1 being the first line treatment combination, HAART2 the second line treatment combination, and so forth) as well as HIV-related death, and death due to natural causes. The effectiveness of genotypic antiretroviral testing (GART) was determined as the relative risk (RR) of the proportion of patients whose viral load was below detectable levels at three months (RR=1.34 (95% CI: [1.10, 1.63]) and was included in the model. It was assumed that the cost of GART for the base case was $864.72, which was based on the cost of commercial GART. All other relevant clinical and economic inputs were sourced from the Australian literature, where available. A total of 50,000 hypothetical patients with human immunodeficiency virus (HIV) were simulated through the model and average results (effectiveness, costs and cost-effectiveness) were determined.

Based on the results of the base case analysis, GART-guided highly active antiretroviral testing (HAART) was the dominant strategy (less costly and more clinically effective) when compared with the standard of care (clinical judgement alone). Compared with standard of care, GART-guided HAART resulted in an average cost saving of $3043 per person and an increase of 0.005 quality-adjusted life years per person over the patient's entire life span. The sensitivity analyses showed that GART-guided HAART remained the dominant strategy (less costly and more effective) compared to the standard of care (clinical judgement alone) despite variation in various key model inputs.

It was estimated that the total number of GART tests in Australia would decrease from 2324 tests in Year 1 to 2259 tests in Year 5. Based on these numbers and the base case cost of GART ($864.72), the annual financial implications associated with publically funding GART for patients with HIV in Australia is expected to decrease from $2,009,297 in Year 1 to $1,953,386 in Year 5.

Background

A health economic evaluation was conducted to establish the incremental cost-effectiveness of genotypic antiretroviral testing (GART)-assisted human immunodeficiency virus (HIV) treatment versus standard of care (clinical judgement alone). A Markov model was constructed and health states defined, to model progression from one health state to the next over time. Markov is a discrete health state transition model that simulates patient changes in health status over time. A patient accumulates both health outcomes and costs during time spent in a particular health state.

An incremental cost-effectiveness ratio (ICER) was calculated to determine the additional cost per quality-adjusted life year (QALY) gained associated with GART assisted HIV treatment versus standard of care alone.

$$ICER = \frac{Cost_{GART\_Assisted\_Treatment} - Cost_{Standard\_of\_Care}}{Effectiveness_{GART\_Assisted\_Treatment} - Effectiveness_{Standard\_of\_Care}}$$

Literature review

The EMBASE.com, Medline and the Cochrane Library databases were searched to identify relevant literature with no restrictions by year or language of publication. A total of 224 economic studies were identified. Of these, 212 studies were excluded upon review of the titles and abstracts, and the remaining 12 studies were included in the preliminary literature review. Of these 12 studies, a further seven were excluded from the final literature review. All non-modelled cost-effectiveness studies or studies that did not evaluate the cost-effectiveness of GART were excluded from the final literature review. A total of five studies were therefore included in the final literature review. Table 15 summarises the numbers of papers identified and excluded/included at various stages of the review process.

Table 15 Included and excluded literature

#	Strategy	Results
A	References identified in EMBASE.com (includes Medline and EMBASE)	200
B	References identified in the Cochrane Library of Economic Evaluations	24
C	Total references identified (A +B)	224
D	**Total references identified with duplicates removed**	224
E	Papers excluded on review of titles and abstracts	212
F	Papers included in preliminary literature review (D–E)	12
G	Extra papers identified during review	0
H	**Total papers included in preliminary literature review (F + G)**	12
J	Papers excluded from final literature review	7
K	**Papers included in final literature review (H–J)**	5

A total of three unique economic models were identified from the final literature review results (Weinstein et al 2001, Corzillius et al 2004, Sendi et al 2007). Another two cost-effectiveness analyses were identified that used a previously published model of GART (Weinstein et al 2001) to estimate cost-effectiveness. The first study evaluated the country specific cost-effectiveness of GART testing in France (Yazdanpanah et al 2007), and the second evaluated the cost-effectiveness of GART in patients with HIV who were treatment-naïve (Sax et al 2005).

Weinstein et al (2001) designed a state-transition model using first order Monte Carlo simulation to estimate the incremental cost-effectiveness of using genotypic testing to guide clinical judgement versus clinical judgement alone. Analysis for both primary resistance (in response to initial highly active antiretroviral therapy [HAART] for treatment-naïve patients) and secondary resistance (in response to subsequent therapy after initial HAART failure) were performed. A societal perspective was taken and outcomes were expressed as cost per QALY gained.

Health states in the model were defined by a patient's current and maximum HIV RNA level (viral load), $CD4^+$ cell count, time undergoing HAART, history of effective and

ineffective antiretroviral therapy, and previous opportunistic infections. HIV RNA levels and $CD4^+$ cell counts were divided into six separate strata, and disease progression was modelled based on monthly transitions between health states. $CD4^+$ cell counts were used as surrogate markers of disease progression and to predict the rates of opportunistic infections and HIV-related deaths. Virological failure was defined as an increase in HIV RNA level for two consecutive months while undergoing HAART. Patients receiving HAART, either as initial or subsequent treatment, were considered to be responding (defined as having a decreasing HIV RNA level or HIV RNA suppression below 500 copies per mL) or failing. Failure of HAART was modelled by defining an efficacy matrix for each HAART regimen, in which patients transitioned from 'success' to 'failure' and corresponding with changes in HIV RNA levels.

The authors concluded that the incremental cost-effectiveness ratio (ICER) associated with secondary resistance was USD$17,900/QALY gained. Similarly, the ICER associated with primary resistance was USD$22,300/QALY gained with a 20 per cent prevalence of primary resistance, decreasing in favourability to USD$69,000/QALY gained with a 4 per cent prevalence of primary resistance.

Corzillius et al (2004) constructed a decision-analytic Markov model to compare the cost-effectiveness of using GART after first and subsequent treatment failures versus using conventional wisdom alone in the selection of antiretroviral treatment among patients with HIV. The population entering the model were treatment-naïve patients and a healthcare perspective was adopted for the analysis.

In the model, the first treatment regimen is selected for all patients based on clinical judgement. At the end of a cycle, patients experience either suppression of viral load below the level of detection (less than 500 RNA copies per mL) or have detectable viral load (primary failure). Patients with primary failure are switched to another regimen; those whose treatment is initially successful continue with the regimen. In the latter group, secondary treatment failure (due to evolving resistance) may subsequently occur with increasing risk over time.

The probability of primary failure was assumed to increase with the number of treatment failures (based on linear extrapolation). The probability of secondary failure (viral rebound after initial suppression below the level of detection) was assumed to be constant. As the number of treatment failures increase, viral load and transition probabilities to AIDS also increase. Patients with AIDS either remain in this health state or die. Death due to other causes could occur at any time based on population age-specific mortality. The effectiveness of GART was expressed as a relative risk reduction in the probability of primary treatment failure, and this was assumed to be constant with increasing numbers of treatment failures. Due to limited evidence, it was assumed that secondary failure rates were not affected by GART.

The results showed that GART increased life expectancy by nine months and undiscounted lifetime costs per case by €16,406. The discounted incremental cost-effectiveness ratio was €22,510 per life year (LY) gained. Best and worst case scenarios yielded €16,512 per LY gained and €42,900 per LY gained, respectively. GART would be equally cost-effective among treatment-naïve patients if it could reduce the probability of first HAART failure by at least 36 per cent.

In their analysis, Sendi et al (2007) applied a similar modelling approach to the Weinstein et al (2001) model where health states were stratified based on $CD4^+$ cell

counts and RNA viral load levels. All patients entering the model were assumed to have failed initial HAART. The failing treatment was either maintained or replaced by another therapy based on either clinical judgement alone or clinical judgement guided by GART. A societal approach was taken and productivity costs were factored into the analysis.

HIV disease progression during the first two years was modelled by means of a transition probability matrix derived from the Swiss HIV Cohort Study (SHCS) database.
Each drug regimen in the analysis was assigned a level of resistance or resistance score (no resistance, low resistance or considerable resistance) as defined by Haupts et al (2003), a study within the SHCS that assessed the impact of GART on the selection of salvage regimens in patients presenting with treatment failure. The transition probability matrix for achieving viral suppression (and hence maintaining or switching to a new regimen) was then applied based on the resistance score of the drug regimen. At the end of the two year follow-up period, the relative risk of experiencing treatment failure using clinical judgment alone versus clinical judgment guided with GART was derived from published randomised controlled trials.

Sendi and colleagues (2007) concluded that from a healthcare perspective, the ICER associated with clinical judgement guided by GART versus clinical judgement alone was USD$35,000 per QALY gained. From a societal perspective, the gain in productivity more than offsets the additional healthcare costs due to GART. GART is therefore a dominant strategy from the societal perspective.

Sax et al (2005) adapted the state-transition economic model by Weinstein et al (2001) to project life expectancy, costs, and cost-effectiveness of GART in a hypothetical cohort of antiretroviral treatment-naïve patients with chronic HIV infection. Because of data limitations associated with treatment efficacy and primary resistance, outcomes were estimated using studies based on treatment-experienced patients, which were then varied in the sensitivity analyses. A strategy of GART at initial diagnosis of HIV infection increased per-person quality-adjusted life expectancy by one month with an ICER of USD$23,900/QALY, compared with no GART.

Yazdanpanah et al (2007) conducted a cost-effectiveness analysis in France using the model developed by Weinstein et al (2001). Health states were defined based on maximum HIV RNA levels, $CD4^+$ cell counts, and history of clinical events. The efficacy of each HAART that was included in the modelled analysis was based largely on the NARVAL trial. The authors found that median survival was estimated at 11.9 years in the resistance testing arm versus 10.4 years in the clinical judgement alone arm. Further, GART cost €69,600 (USD$88,500) per QALY gained compared with the clinical judgement alone arm.

Overview of the model in MSAC Application 1067

In a previous assessment report that considered genotypic resistance testing of antiretrovirals in HIV (MSAC Application 1067, November 2004), the evaluators adopted an approach similar to that used by Corzillius et al (2004). The model was designed using clinical rather than virological end points. A summary of the modelling approach applied by the evaluators of MSAC Application 1067, some key characteristics of the model and the cost-effectiveness results are provided in this document. The model inputs are presented in detail in the assessment report (MSAC Application 1067, November 2004).

Disease progression was not modelled based on a transition probability matrix of virological end points (HIV viral load and $CD4^+$ count), as was applied in the Weinstein et al (2001) and Yazdanpanah et al (2007) models. In this instance, disease progression was modelled by interpreting published studies that estimated the rate of observed disease progression based on a patient's response to a particular HAART[1] regimen. The evaluators of MSAC application 1067 argued against modelling HIV disease progression based on a transition probability matrix of HIV viral load and $CD4^+$ count by presenting evidence highlighting the complexities associated with this approach. The model presented 15 different health states that a cohort of patients progress through at three monthly intervals over a period of 50 years. The cost-effectiveness of GART assisted therapy versus standard therapy alone was compared and results were expressed in cost (AUD) per QALY. There were six different treatment regimens that reflect the experience of the patients followed in the Australian HIV Observational Database (AHOD) included. Both primary and secondary treatment failures associated with HAART were modelled.

Patients were defined as responders if they had an undetectable HIV RNA viral load of <400 copies/mL (or 500 copies/mL) for the first three HAART regimens and if they had an HIV-1 RNA viral load of <1000 copies/mL after HAART3 and a $CD4^+$ cell count of >250 μL. Non-responders were defined as those who did not achieve either an undetectable viral load when commencing a new HAART regimen, experience a decrease by less than a factor of 10 in HIV-1 RNA level by week eight or an increase by more than a factor of 10 above nadir measurement (and >2000 copies/mL within 24 weeks). Patients who experienced viral rebound were defined as those who had previously responded to a HAART regimen and were now experiencing an HIV-1 RNA level above 400 copies per mL after two measurements of less than 400 copies per mL over two consecutive months. The absolute risk of failing HAART1 in the first three months (primary failure) was based on the probability of first virological failure of the most effective HAART therapy (HAART1—zidovudine, lamivudine and efavirenz). The risk of primary failure associated with HAART2 onwards was assumed to increase by 50 per cent with each subsequent HAART therapy, based on both expert opinion and the assumption applied by Corzillius et al (2004) in their economic model. A constant risk of failing HAART (HAART1–HAART6) in each subsequent three month period after initial response (viral rebound or secondary failure) was assumed. The probability of experiencing toxic events of HIV-related morbidity was also modelled during each three month cycle.

The effectiveness of GART was calculated as the relative risk reduction of having an undetectable viral load (<500 copies/mL). Relative risk was calculated using a meta-analysis of three randomised controlled trials (Durant et al 1999, Cingolani et al 2002, Tural et al 2002), all of whom reported an undetectable viral load as either the primary or secondary endpoint.

The authors of the model presented in the previous application assumed that only patients, who were defined as non-responders in the three month cycle, underwent GART before switching to a new HAART regimen. Patients who respond initially, but subsequently fail therapy, are assumed not to undergo GART because the probability of failure is not modified by the test. There was no evidence provided that indicated

[1] HAART1 was defined as first line treatment, HAART2 as second line treatment and so forth.

modification of the probability of failure among initial responders who subsequently fail therapy. Therefore, inclusion of this assumption in the modelling approach could not be justified.

The evaluators of MSAC Application 1067 reported the ICER of GART-assisted HIV therapy versus standard of care (clinical judgement alone) to be $38,276/LY gained and $5623/QALY gained. These estimates increased to $73,540/LY gained and $10,804/QALY gained under the assumption of including GART during salvage therapy. Extensive sensitivity analyses were also performed. All univariate sensitivity analyses resulted in an ICER estimate below $40,527/QALY. The previous evaluators also conducted multivariate sensitivity analyses which all remained below $58,104/QALY gained. Extreme three- and four-way sensitivity analyses were also conducted. The higher range of cost-effectiveness ($78,374/QALY gained and $132,342/QALY gained for the three way and four way sensitivity analyses, respectively) was reported, but the lower range was not.

The previous evaluators also estimated the net financial impact of publicly funding GART. They estimated a budget impact of $2.5 million (including the cost of the test and net costs associated with HIV-related disease) based on a cohort size of 6000 patients who fail therapy within the first five years of initiating treatment.

Methods for the current model

The methods to conduct the economic evaluation for the current assessment of GART-assisted HIV treatment versus standard of care (clinical judgement alone) follow.

Evidence to support effectiveness of the intervention from this review

The objective of the current assessment is evaluation of the clinical effectiveness of genotype-guided HAART for patients with HIV. Of all studies that were identified based on the search strategy, only those trials that studied the use of GART among HAART-experienced patients were reviewed. The endpoints evaluated in the included randomised controlled trials (RCTs) were:

- the change from baseline in plasma HIV RNA levels, and
- the proportion of people with undetectable levels of viral RNA.

Meta-analyses of trial outcomes reported in each of the five RCTs of treatment-experienced patients were also identified in the literature.

Virological efficacy for GART-guided HAART was demonstrated. The overall proportion of patients whose viral load was below the detection limit was significantly higher (11%) at three months (95% CI: [6%, 16%]) in patients undergoing GART-guided treatment compared with standard of care. The estimate extrapolated to 10 per cent at six months (95% CI: [5%, 16%]) (Panidou et al 2004).

Similarly, the relative risk (RR) of the proportion of patients whose viral load was below detectable levels favoured GART-guided treatment at three months [RR=1.34 (95% CI: [1.10, 1.63]) and at six months (RR=1.42, 95% CI: [1.16, 1.72]). That is, the proportion

of patients whose HAART was guided by genotype-resistance patterns and had plasma viral load below the threshold level of detection was 1.34 times more than patients treated by standard of care at three months and 1.42 times at six months (Panidou et al 2004). There was limited benefit in GART-guided therapy compared with standard of care alone in long term studies.

Structure of the model

A Markov model incorporating a Monte Carlo simulation was considered to be the appropriate modelling approach for this economic evaluation. Markov modelling using Monte Carlo simulations enables hypothetical cohorts of individuals progressing through a model to be fabricated, enabling cohort analyses of groups with particular characteristics. An advantage of Markov modelling is its ability to handle complex options with multiple consequences. Markov modelling provides flexibility by enabling creation of mutually exclusive health states that represent all possible consequences of options being evaluated (Briggs et al 2006). Hypothetical individuals simulated in the model progress from one health state to the next based on pre-determined transition probabilities over a series of discrete time periods (cycles). Stage-specific costs and health outcomes are accumulated dependent on the time spent in that state. This enables overall calculation to be made of costs and outcomes over the specified model time span.

As presented in the literature review sections, two types of models were identified in the existing literature. The first modelling type defined health states based on treatment regimens and modelled the progression from one treatment regimen to the next based on the HAART specific probability of virological failure and the effectiveness of GART in reducing treatment related virological failure. The second type of modelling approach was to create health states based on combinations of $CD4^+$ cell counts and HIV RNA viral load. The transition from one health state to the next relied on modelling the effectiveness of GART at reducing the probability of virological failure based on HAART efficacy.

Treatment based health states were chosen over a virological end-point approach, which classified health states based on discrete categories associated with $CD4^+$ cell counts and HIV RNA viral load. The treatment-based approach was chosen for the same reasons specified in the previous assessment. These were based on evidence showing that:

- the increase in $CD4^+$ cell counts was not entirely predictable and GART was not always successful in lowering $CD4^+$ cell counts (Durant et al 1999)

- $CD4^+$ cell counts remained the single independent predictor of survival in a population-based cohort of treated individuals. This suggests that there might be a threshold beyond which immune reconstitution may be compromised (Hogg et al 2001).

Furthermore, the transition probabilities data necessary to populate the model was more readily available for the proposed approach rather than the more complicated virological endpoint based approach.

A cycle length of three months was applied for the current model, and simulations were conducted over the patient's entire life span. Figure 6 illustrates the structure of the decision analytic model over each three monthly cycle. All entrants into the model are

assumed to be treatment-naïve patients and all model entrants were assumed to have died before reaching 100 years of age. The two main arms of the model are: standard of care plus GART (GART-guided HAART), and standard of care (clinical judgement alone).

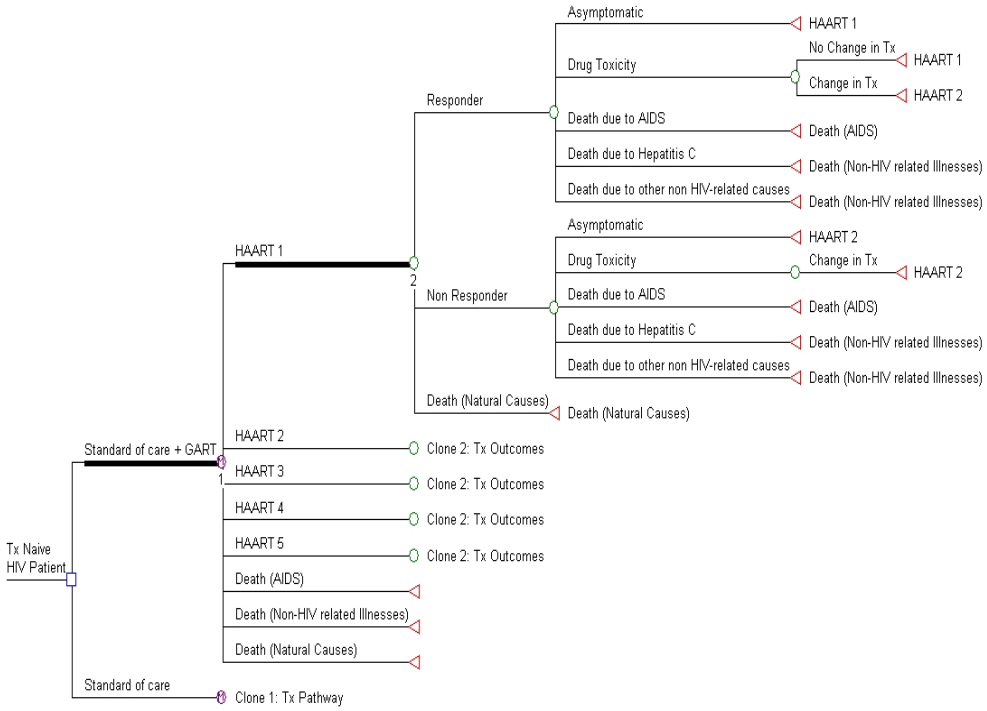


Figure 6 Model structure

The primary health states of the model are defined based on treatment regimens (HAART1 being the first treatment combination, HAART2 the second treatment combination, and so forth) as well as HIV-related death, and death due to natural causes. A number of temporary health states are also incorporated in the model to factor health outcomes (such as disutility) and costs associated with all possible consequences in each primary health state. The transition probabilities at each decision node (indicated by ovals) in the model add up to 1.

Upon commencement of a particular HAART regimen, patients are defined as responders if they have an undetectable HIV RNA viral load of <400 copies/mL (or 500 copies/mL) for the first three HAART regimens and if they have an HIV-1 RNA viral load of <1000 copies/mL and a $CD4^+$ cell count of >250 μL after HAART3. Upon responding to a HAART regimen, patients could:

- either remain asymptomatic and continue treatment in the subsequent model cycle, or
- experience drug toxicity with the possibility of switching treatment, or

- progress to AIDS and die due to AIDS, or
- die due to hepatitis C related complications, or
- die due to another non-HIV related illness.

Non-responders are defined as those patients who do not achieve an undetectable viral load when commencing a new HAART regimen, or experience a decrease by less than a factor of 10 in HIV-1 RNA level by week eight or experience an increase by more than a factor of 10 above nadir measurement (and >2000 copies/mL) within 24 weeks. Patients who experience viral rebound are defined as those who had previously responded to a HAART regimen (two previous measurements of less than 400 copies per mL for two consecutive months) and the experienced an HIV-1 RNA level above 400 copies per mL. Upon failing to respond to HAART regimen, a patient could:

- either remain asymptomatic and switch treatment in the subsequent model cycle, or
- experience drug toxicity and switch treatment, or
- progress to AIDS and die due to AIDS, or
- die to the Hepatitis C related complications, or
- die due to another non-HIV related illness.

The transition probabilities of progression to HIV and non-HIV related illnesses and death due to these illnesses were determined based on a review of the available literature and are detailed in the following sections. It was assumed that a person dying from AIDS would have remained in that health state for two years from the time of diagnosis until death. Similarly, it was assumed that a person dying from any non-HIV related illness would have remained in that health state for a period of one year. In both cases it was assumed that health care costs as well as disutility associated with the health state would be accumulated during the time spent in that health state.

Possible death due to natural causes is also included as a separate health state in the model. Treatment-naïve patients are assumed to undergo GART before initiating treatment, and treatment-experienced patients are assumed to undergo GART upon treatment switching, if the reason for switching was not drug toxicity.

A total of 50,000 hypothetical HIV patients were simulated through the model and average results (effectiveness, costs and cost-effectiveness) were determined.
This resulted in a large enough sample size to minimise variability between subsequent simulations of the model.

Clinical inputs

The transition probabilities of moving from one temporary health state to the next were determined based on Australian literature, where available.

The rate of primary failure associated with HAART1 was based on the estimates reported in two clinical trials of first line combination treatment (Gallant et al 2006, Walmsley et al 2002). Thereafter, it was assumed that the primary failure rate would increase by 50 per cent with each subsequent switch in treatment. Corzillius et al (2004) made the same assumption in their economic model which was also designed to evaluate the cost-effectiveness of using GART to guide HIV treatment. This estimate was varied from 25 per cent to 75 per cent in sensitivity analyses to determine the variation in results based on this assumption.

Secondary failure rates associated with the same HAART treatments (early versus late treatment) were based on the estimates reported by Corzillius et al (2004) in their economic model. The authors, in their model, assumed that the rate of secondary failure was 6.3 per cent for the first HAART (HAART1) and remained constant thereafter at 15 per cent until HAART4. In the current model, this was also the case. However, it was assumed that the rate of secondary failure was slightly higher at 20 per cent for HAART5.

Table 16 shows the rates of primary and secondary failure associated with each HAART regimen included in the current model.

Table 16 Annual rates of primary and secondary failure on HAART

HAART regimen	Annual Primary failure rate[1]	Annual Secondary failure rate[2]	Source/Comment
HAART1	0.16	0.063	The primary failure rate for HAART1 was based on the virological failure rates for first line treatments; tenofovir/emtricit/efavirenz from Gallant et al (2006) and abacavir/lamivudine/lopinavir from Walmsley et al (2002). It was assumed that the rate of primary failure would increase by 50% for each subsequent change in treatment. Secondary failure rates were based on Corzillius et al (2004). The rate of secondary failure was assumed to be higher for HAART2 and was assumed to remain constant thereon
HAART2	0.24	0.15	
HAART3	0.36	0.15	
HAART4	0.54	0.15	
HAART5	0.81	0.20	

[1] The primary failure rate refers to the rate of virological failure during the initial three months of commencing treatment
[2] The secondary failure rate refers to the rate of virological failure following the initial three months of commencing treatment

The probability of drug toxicity due to HAART was based on data presented in a systematic review by Carr et al (2009). The treatment toxicity rates were reported for three years only. Therefore, the toxicity rates from Year 3 onwards were extrapolated based on date from Year 1 to Year 3. It was assumed that the rate of drug toxicity associated with late treatment (HAART4 and HAART5) was 10 per cent higher than that associated with early stage treatment (HAART1, HAART2 and HAART3). It was also assumed that the rates of toxicities and rates of treatment cessation due to toxicity would remain the same from Year 5 onwards. Table 17 provides drug toxicity rates associated with early and late HAARTs and the probability of treatment cessation due to toxicity.

Table 17 Probability of HAART toxicity and rates of cessation due to toxicity

Year on HAART	Probability of toxicity associated with early treatment (HAART1, HAART2, HAART3)	Probability of toxicity associated with late treatment (HAART4 and HAART5)	Probability of HAART cessation due to toxicity	Source/Comment
Year 1	0.14	0.15	0.09	Source: Carr et al 2009 (Estimates were extrapolated beyond Year 3) It was assumed that the rate of toxicity associated with late treatments was 10% higher than early treatments
Year 2	0.13	0.14	0.08	
Year 3	0.12	0.13	0.07	
Year 4	0.11	0.12	0.06	
Year 5 onwards	0.10	0.11	0.05	

The identified RCTs reported the effectiveness of GART as the relative risk (RR) of having an undetectable viral load (<500 copies per mL). In a meta-analysis of five relevant RCTs the relative risk of the proportion of patients with viral load below detection was in favour of GART-guided treatment at three months (RR, 1.34 (95% CI: [1.10, 1.63]) and at six months (RR, 1.42 (95% CI: [1.16, 1.72]). That is, the proportion of patients whose HAART was guided by genotype resistance patterns and who had plasma viral load below the threshold level of detection was 1.34 times greater than patients treated under standard care at three months, and 1.42 times at six months (Panidou et al 2004). This estimate was applied to the response rates associated with HAART2 onwards in the GART plus standard of care arm to model the improvement in treatment response rates due to GART-guided HAART versus standard of care alone. Table 18 indicates the response rates and all other clinical inputs that were included in the model.

Table 18 Clinical inputs used in the model

Variable	Estimate (95% CI]	Source/Comment
Effectiveness of GART (RR at 3 months)	1.34 [1.10, 1.63]	Panidou et al (2004) (Table 11)
Age-specific all cause mortality	Australian Life Tables (2005–2007)	Australian Bureau of Statistics (ABS) (2008)
Excess death rate in responders (without hepatitis C comorbidity)	0.34%	Jaggy et al (2003)
Excess death rate in non-responders (without hepatitis C comorbidity)	11.74%	
Excess death rate in responders (with hepatitis C comorbidity)	2%	
Excess death rate in non-responders (with hepatitis C comorbidity)	11.27%	
Increased risk of HIV-related mortality with age, compared to risk at age 40–49 years	1.41 (≥50 years)	Egger et al (2002) Based on hazard ratio of death, by age
Three year probability of progression to AIDS in responders	1%	Estimated based on graphical representation (Figure 3) in Egger et al (2002) and expert opinion
Three year probability of progression to AIDS in non-responders	2%	Estimated based on graphical representation (Figure 3) in Egger et al (2002) and expert opinion
Annual probability of progression to hepatitis C comorbidity in responders	35.91%	Jaggy et al (2003)
Annual probability of progression to hepatitis C comorbidity in non-responders	55.61%	
Increased risk of AIDS with age, compared to risk at age 40–49 years	1.51 (≥50 years)	Egger et al (2002) Based on hazard ratio of AIDS or death, by age
Annual probability of death after AIDS diagnosis	17.4%	ATCC (2008)
Discount rate	5%	
Quality of life		1 = perfect health, 0 = death
Asymptomatic responder	0.86	Sanders et al (2008) It was assumed that the quality of life of a non-responder would be 0.03 less compared to a responder
Asymptomatic non-responder	0.83	
Symptomatic responder	0.83	
Symptomatic non-responder	0.80	
HIV morbidity (AIDS)	0.73	
Toxic drug reaction (multiplier i.e. additional effect on quality of life due to drug toxicity)	0.53	

Resource use and costs

The resource use and costs associated with each temporary health state in the model were identified from Australian sources, where available.

Costs associated with the test were derived from average costs provided by two private laboratories in Australia. The cost of in-house assays (provided by only one private laboratory) was included in a sensitivity analysis and results were reported separately.

The cost of HIV related morbidity was based on Australian Refined Diagnostic Related Groups (AR-DRG, Round 11 2006–2007). All patients who were admitted based on one of the HIV categories are recorded and the average cost per episode is reported for 2006–2007. For the current model, these separations will be weighted by number of separations and an average weighted cost per hospital admission was calculated. The cost based on this approach is estimated at AUD $11,863 annually in 2006–2007. The cost was updated to 2009–2010, based on the CPI in health of 1.097 and is estimated at AUD$13,014 annually in 2009–2010.

Table 19 provides the economic inputs included in the model.

Table 19 Economic inputs used in the model

Variable	Base case estimate	Source	Comment
Cost of GART (commercial kits)	$864.72	Public laboratories	These costs were provided by two separate public laboratories in Australia
Cost of GART (in-house assays)	$444.84	Public laboratory	This cost was provided by one public laboratory in Australia
Annual cost of HIV-related morbidity and/or comorbidity	$19,702.62	AR-DRG Round 11 (2006–2007), based on DRG codes S65A, S65B, S65C	It was assumed that HIV-related morbidity would incur a hospital stay of greater than 1 day
Annual cost of drug toxicity	$1,636.72	AR-DRG Round 11 (2006–07), based on DRG codes S60Z	It was assumed that drug toxicity would incur a hospital stay of 1 day
Annual cost of HAART1, HAART2	$14,132.28	EMIMS Australia, 2009	Based on the average cost of first line HIV treatment
Annual cost of HAART3, HAART4	$14,384.28	EMIMS Australia, 2009	Based on the average cost of second line HIV treatment
Annual cost of HAART5	$52,818.48	EMIMS Australia, 2009	Based on the average cost of third line HIV treatment

Note: All costs shown are 2009 AUD

Results

The following section details the results of the current economic model comparing GART-guided HAART versus standard of care (clinical judgement) alone.

Model results

Table 20 demonstrates the derivation of the base case incremental cost-effectiveness ratio (ICER) comparing GART-guided HAART versus standard of care (clinical judgement) alone.

Table 20 Base case results of the model

Strategy	Average Cost (AUD)	Average Incremental Cost (AUD)	Average Effectiveness (QALYs)	Average Incremental Effectiveness (QALYs gained)	ICER (AUD/QALY gained)
GART-guided HAART	$109,216	–$3043	5.749	0.005	GART-guided HAART **dominates** standard of care (less costly, more effective)
Standard of care (clinical judgement alone)	$112,259		5.744		

Table 20 shows that GART-guided HAART strategy is the dominant strategy compared with standard of care (treatment guided by clinical judgement only); that is, it is less costly and more effective. GART-guided HAART results in an average cost saving of $3043 per person, and an increase of 0.005 QALYs per person over the patient's entire life span compared with standard of care.

Sensitivity analyses

Extensive sensitivity analyses were conducted to evaluate the sensitivity of the model to key input variables. The inputs that were varied in sensitivity analyses to determine the effect on cost-effectiveness were:

- effectiveness of GART (confidence intervals from meta-analyses was used as the upper and lower bounds)
- the rate at which the risk of primary failure of HAART increases with subsequent changes in treatment (assumed to be 50% for the base case, was varied from 25% to 75%)
- discount rate (5% for the base case, was varied from 0% to 10%)
- the cost of GART (cost of commercial GART test [$864.72] was assumed for the base case, the cost of in-house assays provided by private laboratories were used in the sensitivity analysis).

Table 21 shows the variation in costs, effectiveness and cost-effectiveness as a result of the sensitivity analyses.

Table 21 Results of the univariate sensitivity analyses

Variable	Average Incremental Cost (AUD)1	Average Incremental Effectiveness (QALYs gained)1	ICER (AUD/QALY gained)
Base Case	–$3043	0.005	GART-guided HAART **dominates** standard of care (less costly, more effective)
Lower estimate of the effectiveness of GART (RR=1.10)	–$654	0.002	GART-guided HAART **dominates** standard of care (less costly, more effective)
Upper estimate of the effectiveness of GART (RR=1.63)	–$4721	0.008	GART-guided HAART **dominates** standard of care (less costly, more effective)
Lower estimate of the increase in the rate of primary failure with treatment switching (25%)	–$2528	0.006	GART-guided HAART **dominates** standard of care (less costly, more effective)
Upper estimate of the increase in the rate of primary failure with treatment switching (75%)	–$4558	0.006	GART-guided HAART **dominates** standard of care (less costly, more effective)
Lower estimate of the discount rate (0%)	–$5818	0.012	GART-guided HAART **dominates** standard of care (less costly, more effective)
Upper estimate of the discount rate (10%)	–$1875	0.004	GART-guided HAART **dominates** standard of care (less costly, more effective)
Cost of GART in house assays (AUD $444.84)	–$3709	0.005	GART-guided HAART **dominates** standard of care (less costly, more effective)
Cost of GART (AUD $600)	–$3635	0.005	GART-guided HAART **dominates** standard of care (less costly, more effective)
Cost of GART (AUD $1000)	–$2996	0.005	GART-guided HAART **dominates** standard of care (less costly, more effective)

[1] Estimates are presented for a patient's entire life span

Table 21 shows that GART plus standard of care remained the dominant strategy (ie, less costly and more effective) compared with standard of care (clinical judgement alone) despite extensive sensitivity analyses with respect to various key input variables. The second column, which provides the average incremental cost, shows cost savings associated with GART-guided HAART compared with standard of care alone, despite univariate variation in various key model inputs. In terms of effectiveness, an increase in the average number of QALYs gained is evident, despite the same variation in various key model inputs.

Discussion

Based on the results of the base case analysis (Table 20) and sensitivity analyses (Table 21) GART-guided HAART was the dominant strategy when compared with the standard of care (clinical judgement alone). This meant that GART-guided HAART was less costly and more effective compared with standard of care (clinical judgement alone). Despite extensive sensitivity analyses based on a number of different key inputs GART-guided HAART remained the dominant strategy (ie, less costly and more effective).

GART-guided HAART is more effective because GART results in higher rates of treatment responders, which leads to lower mortality due to both HIV-related (AIDS) and non-HIV related illnesses (hepatitis C, renal disease, cardiovascular disease, etc) compared with standard of care. GART-guided HAART is less costly because the higher response rates compared with standard of care leads to a decrease in treatment switching to more expensive (second, third line etc) HAART treatments.

The analysis did not include indirect cost (savings) associated with increased productivity. However, inclusion of these costs would result in further cost-savings associated with GART-guided HAART compared with standard of care (clinical judgement alone). Therefore, the cost-effectiveness profile would improve even further if these indirect costs were included in the analysis.

For several reasons, results from the current model are considered to be more accurate compared with the model presented in the previous assessment report. Firstly, the baseline characteristics and clinical data inputs used to populate the model were based on the most recently published evidence. Secondly, economic data were updated to reflect current Australian healthcare costs and treatment algorithms. Thirdly, assumptions used in the previous model were replaced with either recently published evidence (where available) or expert opinion (based on current clinical experiences).

Financial implications

The overall financial implications associated with public funding of GART were estimated over a period of five years. The financial implications of public funding of GART in the Australian HIV patient population was calculated by multiplying the average number of tests over a patient's lifetime with the total number of eligible HIV patients in Australia and the average cost of the test. Sensitivity analyses were conducted to determine the variation in results with respect to each variable.

The average cost of GART was estimated at $864.72 (Table 19). The frequency of GART was estimated based on the average number of tests conducted over a patient's entire life span, as predicted by the economic model. The total numbers of HIV patients in Australia were determined based on data from the Australian HIV/AIDS Surveillance Report (NCHECR 2008). According to this report, a total of 16,692 Australians were living with HIV in 2007. The annual incidence of HIV infection from 1999 to 2007 was also reported. Due to an absence of time series HIV prevalence data from 2007 onwards, the average annual increase in incidence of HIV (from 1999 to 2007) was determined and used to project the prevalence of HIV over the following five years (2009 to 2013). Table 22 provides the annual incidence of HIV in Australia by year.

Table 22 Annual incidence of HIV in Australia, by year

Year	Incident cases	Percentage increase
Actual data		
1999	718	
2000	764	6.41%
2001	769	0.65%
2002	851	10.66%
2003	871	2.35%
2004	910	4.48%
2005	962	5.71%
2006	1007	4.68%
2007	1051	4.37%
Projected estimates		
2008	1087	
2009	1129	
2010	1170	
2011	1212	
2012	1254	
2013	1296	
2014	1338	
Average increase in incidence based on actual data		4.91%

Source: NCHECR (2008)

The average annual increase in HIV cases in Australia from 1999 to 2007 was 4.91 per cent, based on actual data (Table 22). This annual increase was applied to the HIV prevalence estimate of 16,692 persons in 2007 to project the prevalence of HIV by year from 2007 onwards (Table 23).

Table 23 Annual prevalence of HIV in Australia, by year

Year	Prevalence
2007	16,692
2008	17,512
2009	18,373
2010	19,276
2011	20,223
2012	21,217
2013	22,259

The prevalence of HIV in Australia is estimated to increase from 18,373 cases in 2009 to 22,259 cases in 2013 (Table 23). According to the Australian HIV Observational Database, an estimated 85 per cent of HIV infected patients in Australia receive treatment (AHOD 2008). Table 24 shows the derivation of the overall budget impact associated with publically funding GART for the HIV infected patient population in Australia by year.

Table 24 Annual financial implications of publically funding GART for HIV patients in Australia

	Attribute	Year 1	Year 2	Year 3	Year 4	Year 5	Source/comment
A	Prevalence of HIV in Australia	18,373	19,276	20,223	21,217	22,259	NCHECR (2008)
B	Percentage of HIV patients receiving treatment	85%					AHOD (2008)
C	Total number of HIV patients receiving treatment	15,617	16,384	17,190	18,034	18,921	C = AxB
D	Proportion of HIV patients who switch treatment	0.074	0.055	0.052	0.051	0.049	Estimates based on model output
E	Incidence of HIV infection in Australia	1170	1212	1254	1296	1338	Table 22
F	Total number of GART tests required per year	2324	2118	2145	2212	2259	F = E+(CxD) It was assumed that a GART test would be required at treatment initiation for treatment naïve patients and before each treatment switch
G	Cost of GART by commercial assay	$864.72					Table 19 (cost estimate for GART commercial assay)
H	Overall financial implications using a commercial assay	$2,009,297	$1,831,459	$1,854,634	$1,912,697	$1,953,386	H = FxG
I	Cost of GART by in-house assay	$444.84					Table 19 (cost estimate for GART in-house assay)
J	Overall financial implications using an in-house assay	$1,033,647	$942,162	$954,084	$983,953	$1,004,885	J = FxI

The annual financial implications associated with public funding of GART for HIV patients in Australia is expected to decrease over a period of five years (Table 24). Assuming the cost of commercial GART kits, the estimate is expected to vary from $2,009,297 in Year 1 to $1,953,386 in Year 5. Assuming the cost of in house assays for GART resulted in a decrease in costs from $1,033,647 in Year 1 to $1,004,885 in Year 5.

Other considerations

Summary

In addition to the evidence presented directly assessing the efficacy and cost-effectiveness of GART, a number of other studies provide indirect support for its efficacy. Several large randomised controlled trials designed to assess the effectiveness of specific antiretroviral agents showed a direct stepwise predictive relationship between GART-defined susceptible agents and viral response at 48 weeks. Further, an analysis of 12 different cohort and case-control studies by DeGruttola et al (2000) showed that GART results were important predictors of virologic failure; the risk of virologic failure was reduced twofold for each additional drug in the regimen that was sensitive by genotypic testing.

It is also important to note that GART forms an integral part of clinical treatment guidelines in the USA, Australia, UK and Europe and forms part of the standard management of people with HIV in Australia.

A limitation of GART systems is that analyses evaluate each drug separately, whereas HAART involves combinations of three or more drugs (Vercauteren and Vandamme 2006). Direct correlation of mutations to appropriate drug therapy is difficult to assess for patients who are receiving multiple therapies. However, some progress has been made in using GART to identify mutations that indicate resistance to certain drugs containing two different antiretroviral compounds (Hirsch et al 2008).

Experts in the field indicate that GART offers several advantages when performed by the highly competent linked Australian laboratories together with interpretation undertaken in consultation with an HIV specialist. GART supports optimised treatment selection for people commencing antiretroviral therapy and reduces inappropriate changes to antiretroviral therapy in individuals changing treatment. GART also offers a means for maximising options for future treatment choice by reducing viral failure and subsequent sequential increases in resistance within individuals treated. This mode of testing and interpretation offers potential to reduce mother-to-child transmission, transmission to sexual partners of people with HIV who are exposed to blood and body fluids, and to those exposed to blood and body fluids through needle stick exposure. GART also supports important clinical and public health treatment planning in the setting of the known prevalence of transmitted resistant HIV in Australia.

Additional evidence

The current assessment is intended to evaluate the efficacy and cost-effectiveness of GART for HIV. Hence, the literature search conducted as part of the assessment was designed to identify clinical research with this aim, and only studies matching these criteria were included in the clinical assessment and economic evaluation. A number of randomised controlled trials and cohort studies that included the use of GART for HIV

were identified that provide additional supporting evidence of the efficacy of GART for HIV. A number of guidelines that incorporate GART into their recommendations were also identified. This evidence is summarised below.

Randomised controlled trials

Randomised controlled trials investigating the efficacy of antiretroviral drugs

Recent studies of newer antiretroviral agents used in highly treatment-experienced individuals have shown the predictive value of resistance testing in both the optimised background and the arm where the innovator agent was included. In these highly treatment-experienced patients, the number of susceptible drugs, defined by drug resistance testing, was predictive of better viral suppression.

These randomised controlled trials utilised baseline GART for both the innovator and the comparator arms and each of the following studies showed a benefit of the innovator agent over placebo without the innovator agent (optimised background). Further, the studies showed a direct predictive relationship between GART-defined susceptible agents and viral response at 48 weeks. Similar results were seen in trials for each of the following agents.

- enfuvirtide (Lalezari et al 2003)
- tipranavir (Naeger et al 2007)
- darunavir (Clotet et al 2007, De Meyer et al 2006)
- etravirine and darunavir (Lazzarin et al 2007)
- maraviroc (Gulick et al 2008)
- raltegravir (Cooper et al 2008).

The results of these trials demonstrate that GART is able to consistently identify mutations associated with antiretroviral agents and thereby predict long term health outcomes. These results provide supporting evidence for the efficacy of GART.

Randomised controlled trial investigating GART versus other comparators

The CREST study (Hales et al 2006) was an Australian trial that investigated the use of genotyping versus genotyping plus virtual phenotyping in patients who were changing their antiretroviral therapy regimens. The study found that both methods of resistance testing were successful at guiding therapy choices that resulted in significant reductions from baseline in viral load (genotyping, 0.68 $\log_{10}$ copies/mL versus genotyping plus virtual phenotyping, 0.58 $\log_{10}$ copies/mL; p=0.23) and increases in $CD4^+$ count (37 cells/mm^3 versus 50 cell/mm^3; p=0.28) at 48 weeks. The authors concluded that resistance testing using genotyping linked to a reliable interpretation algorithm was adequate for the management of HIV. This study provides additional evidence that GART used to guide therapy can result in optimal responses and has the potential to improve long term patient outcomes.

Cohort and case-control studies

An analysis of 12 different cohort and case-control studies by DeGruttola et al (2000) selected those trials that used consistent definitions of resistance and virological outcome in order to combine clinical trial data. The primary endpoint for virological failure in this analysis was plasma HIV-1 RNA concentration >400 copies/mL, 24 weeks after initiation of a salvage regimen. GART results were shown to be important predictors of virological failure; the risk of virological failure was reduced by twofold for each additional drug in the regimen that was sensitive by genotypic testing.

A cohort study by Huang et al (2008) aimed to assess the prevalence of transmitted antiretroviral drug resistance and whether resistance testing influenced the selection of first-line antiretroviral regimens. The authors state that this information is important because it is estimated that as many as 40–80 per cent of chronically infected, treatment experienced patients with incomplete viral suppression develop resistance to antiretroviral therapy, leading to poorer survival outcomes and opportunities for transmitted drug resistance. The study was conducted at 19 HIV clinics in the USA from August 2005 to January 2007 and included 228 HIV infected treatment-naïve but treatment-ready patients. Many had signs of moderate or advanced immune system damage: one quarter had $CD4^+$ counts <200 cells; a third had $CD4^+$ counts between 200 and 350 cells; 9 per cent had been diagnosed with an AIDS defining illness; and 14 per cent had severe symptoms of HIV infection at the time of clinical visit. Study participants completed questionnaires and had genotypic testing performed. Physicians provided information on intended treatment regimens and factors influencing regimen selection prior to access to the genotypic test results. The overall prevalence of antiretroviral drug resistance was 12.1 per cent, including 9.8 per cent for NNRTIs, 4.5 per cent for NRTIs and 1.8 per cent for PIs. Pill burdens, dosing frequency and physicians experience with regimens were the major factors considered in treatment selection. The intended and actual treatment differed for 73 per cent and 44 per cent of the patients with and without antiretroviral drug resistance, respectively (OR=3.6 (95% CI [1.5, 9.0], p=0.006). NNRTI-based regimens were intended for 10 patients who were subsequently identified as being resistant to NNRTIs; these patients were prescribed PI-based regimens after genotypic testing. The results of this study demonstrate that GART can be used to more accurately determine the most appropriate course of treatment compared with treatment without GART and that clinicians rely on the results of GART to make optimal treatment choices for their patients.

Kuritzkes et al (2008) investigated the effect of baseline NNRTI resistance, as assessed by viral genotyping, on the response to regimens containing efavirenz in the AIDS Clinical Trials Group A5095 study. The sample included a random cohort of efavirenz treated subjects plus unselected subjects who experienced virological failure. Of 220 subjects in the random cohort, 57 (26%) had virological failure. The prevalence of baseline NNRTI resistance was 5 per cent. The risk of virological failure for subjects with baseline NNRTI resistance was higher than that for subjects without resistance (hazard ratio=2.27, 95% CI [1.15, 4.49], p=0.018). The study supports resistance testing before starting antiretroviral therapy by demonstrating the efficacy of GART in the context of possible treatment failure as a result of pre-existing NNRTI resistance. This study is noteworthy because few published reports document the impact of transmitted drug resistance on response to first line treatment regimens outside the setting of acute or recent HIV infection.

Guidelines

Internationally, GART is included in best practice guidelines for standards of care. These guidelines are underpinned by evidence-based medicines policy, which is current and updated on a regular basis. GART forms a part of recommendations by the following internationally recognised organisations:

- Department of Health and Human Services (DHHS) USA (2008)
- Australasian Society for HIV Medicine (ASHM) (2008)
- British HIV Association (BHIVA) UK (2008)
- European AIDS Clinical Society (EACS) (2008).

A panel of the International AIDS Society–USA (Hirsch et al 2008) updated its 2003 recommendations in 2008 for antiretroviral drug resistance testing in adult HIV-1 infection in response to a number of developments, including the availability of new drugs and classes, the standardisation of assays and the availability of viral tropism tests. The panel makes it very clear that resistance to drugs is still an important limitation to successful HIV therapy and that through the introduction of resistance testing there has been an improvement in outcomes for people with HIV (Hirsch et al 2008).

Since the 2003 recommendations were published, the panel has noted that drug resistance testing is now an important adjunct to patient management; the transmission of drug resistant virus between adults and from mother to child is increasing and there is now good reason to support testing before therapy is commenced for those who are treatment naïve (Hirsch et al 2008). Mutations to older drugs continue to evolve. The availability of new drugs and drug classes, as well as increased sensitivity of testing methodologies highlights that drug resistance will be significant in the future. Expert opinion to guide clinical practice and to manage HIV therapy will be essential.

The International AIDS Society–USA panel describes global complexities in resistance patterns; resistance invariably appears where antiretroviral drugs are used. Evolving resistance undermines successful therapy and it is important for national surveillance systems to focus on local conditions of transmission.

Future directions for GART

A limitation of GART systems is that analyses evaluate each drug separately, whereas HAART involves combinations of three or more drugs (Vercauteren and Vandamme 2006). However, some progress has been made in using GART to identify mutations that indicate resistance to certain drugs containing two different antiretroviral compounds (Hirsch et al 2008). Direct correlation of mutations to appropriate drug therapy is difficult to assess for patients receiving multiple therapies. Clinicians are encouraged to consult specialists to assist interpretation of genotype test results and inform design of optimal antiretroviral therapy regimens.

GART is the standard for clinical practice, but its interpretation is complicated by the high mutation rate of HIV and the complex population genetics of people infected with HIV. Standard genotypic testing is unable to detect drug resistant mutations where the

mutants form less than about 20 per cent of the species within a viral population. Further, GART is unable to detect and accurately identify mutants that are present in small numbers (<1000 copies) within a sample. This has the potential to impact the efficacy of treatment choices guided by GART. Schafer (2009) investigated both currently available standard genotypic testing assays and current research options used to detect low abundance drug resistant mutants. Schafer (2009) found that GART had helped clinicians to both better understand patient responses to antiretroviral therapy and make more effective choices for both initial and salvage therapy. The relationship between low abundance mutations and virological failure that can occur when mutations are not susceptible to the antiretroviral regimen were also highlighted (Schafer 2009). This situation has particular significance for mother to child transmission and use of nevirapine, as well as for development of cross resistance to drugs in the same class when switching after first virological failure. The findings reported by Schafer (2009) reflect the need to remain focused on strengthening tools used for both research and clinical purposes.

A new technology that addresses the issue of low abundance mutants is ultra deep sequencing, a form of genotypic testing that enables sequencing of HIV-1 RNA from variants of the virus present in a sample in small numbers. Simen et al (2009) present data from a random subset of patient samples (N=258) drawn from the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study. Patients were first tested using GART. If sufficient viral content existed, patients were re-tested using ultra deep sequencing technology to detect low abundance drug resistant mutants to determine the impact of minor resistant variants on virological failure. Drug resistant mutants were detected in 14 per cent of GART and 28 per cent of ultra deep sequencing samples. When combined with other study results, Simen at al (2009) demonstrated that minor drug resistant mutants are common in both acutely and chronically infected treatment-naïve and experienced patients. Low abundance drug resistant mutants may remain undetected by standard sequencing methods. The study also demonstrates that genotypic testing is an evolving technology. Since its inception, GART has significantly improved the treatment and health outcomes of patients and was able to accurately identify many mutations in the population of patients in the study. It is likely that continued improvements in genotypic testing methodologies will result in even greater improvements in patient care.

Expert opinion

The use of HIV drug resistance testing has become an integral part of HIV clinical care. Tools such as GART that enhance the clinical management of people with HIV not only improve the health and clinical outcomes of this population, but also impart a positive impact on productivity outcomes such as capacity to undertake paid or unpaid work. The impact of GART on productivity outcomes were not included in the clinical or economic analyses conducted for the assessment; this issue is nonetheless important and may help to inform decisions about whether GART should be reimbursed in Australia. The significance of enhancing tools used for clinical management of people with HIV on productivity relates directly to the success of medicines policy in implementing best practice guidelines to assist people with HIV to remain well and continue to lead productive working lives and participate fully in their communities of choice.

When performed by the highly competent, linked Australian laboratories involved in the NRL QA program, together with interpretation undertaken in consultation with a specialist experienced in the management of HIV infection, GART:

- supports optimised treatment selection for people commencing antiretroviral therapy
- reduces inappropriate changes to antiretroviral therapy in people changing treatment
- maintains maximum future treatment options by reducing viral failure and subsequent sequential increases in resistance among people being treated
- provides viral suppression support for people being treated. This confers consequent reductions in transmission from mother to child, sexual partners of people with HIV exposed to blood or body fluids, and people exposed to infection by needle stick injury
- supports important clinical and public health planning of treatment regimens in the setting of the known prevalence of transmitted resistant HIV in Australia.

For these reasons, GART is widely accepted by medical professionals working with HIV and has been extensively implemented as a fundamental component of HIV management.

Conclusions

Safety

Genotype-assisted antiretroviral resistance testing (GART) is a non-invasive test conducted on patients' blood samples. The GART procedure is not considered to present safety issues for patients.

Effectiveness

There were 12 studies identified that investigated GART in HIV in the literature search (Panidou et al 2004, Ena et al 2006, Torre and Tambini 2002, Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002, Clevenbergh et al 2000, De Luca et al 2006, Green et al 2006, ERA trial investigators 2005a). All identified studies investigated the use of GART in highly active antiretroviral therapy (HAART) treatment-experienced people infected with HIV. No studies of treatment-naïve HIV infected patients or studies investigating the benefits of genotype assisted therapy in reducing the risk of HIV transmission to babies of women infected with HIV could be sourced.

There was one systematic review (Panidou et al 2004) of five randomised controlled trials (RCTs) (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002) of people infected with HIV who were HAART-experienced included in the analysis. Virological efficacy for GART-guided treatment was demonstrated and the overall relative risk (RR) 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 (Panidou et al 2004).

The five RCTs reviewed by Panidou et al (2004) were also evaluated individually in this assessment (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Meynard et al 2002, Tural et al 2002). The benefits of guiding HAART by applying genotype testing are consistently evident when compared with standard of care without GART. Reduction in plasma viral load was significant in four studies at both three and six month time points (Baxter et al 2000, Durant et al 1999, Cingolani et al 2002, Tural et al 2002). This did not occur in the NARVAL trial (Meynard et al 2002), although this study may not have been powered to detect a significant difference. All five RCTs showed significant benefits from determining genotype resistance patterns to guide HAART and reduce the level of HIV RNA to below threshold levels for detection.

There were two additional RCTs identified that were not included in MSAC assessment 1067 (Green et al 2006, ERA trial investigators 2005a). These trials demonstrated no long term advantage of GART among HIV infected children or patients with limited virological failure. There were two studies identified that were developed as open-label observational extension studies of RCTs; all patients were offered GART for a duration of one year (Clevenbergh et al 2000) or three years (De Luca et al 2006) regardless of whether they had originally been assigned to receive GART or standard of care. Both studies showed that, despite delays in receiving genotype-guided therapy by patients who

were originally randomised to the standard clinical care arm, continued benefit of this technology is evident.

On balance, the available evidence indicated that using GART to guide therapy resulted in significantly reduced viral load, and therefore has the potential to improve long term health outcomes for patients.

Cost-effectiveness

Based on the results of the base case analysis (Table 20) and sensitivity analyses (Table 21) GART-guided HAART was the dominant strategy when compared to the standard of care (clinical judgement alone). Compared with the standard of care, GART-guided HAART resulted in an average cost saving of $3043 per person and an increase of 0.005 quality-adjusted life years (QALYs) per person over the patient's entire life span. The sensitivity analyses showed that GART-guided HAART remained the dominant strategy compared with the standard of care (clinical judgement alone) despite variation in various key model inputs (Table 21). The annual budget impact associated with publically funding GART for people with HIV in Australia is expected to decrease from $2,009,297 in Year 1 to $1,953,386 in Year 5 (Table 24).

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- 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; and

- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Professor Robyn Ward, Chair	Medical oncology
Associate Professor Frederick Khafagi, Deputy Chair	Nuclear medicine
Associate Professor John Atherton	Cardiology
Professor Justin Beilby	General practice
Professor Jim Bishop, AO	Chief Medical Officer, DoHA
Professor Jim Butler	Health economics
Professor Peter Cameron	Emergency medicine
Associate Professor Kirsty Douglas	Health policy
Dr Kwun Fong	Thoracic medicine
Professor Helen Lapsley	Health economics
Mr Russell McGowan	Consumer health issues
Dr Judy Soper	Radiology
Dr Graeme Suthers	Genetic pathology
Dr Shiong Tan	General practice
Professor Ken Thomson	Radiology
Professor Andrew Wilson	Public health
Dr Caroline Wright	Surgery

Appendix B Advisory panel

Advisory panel for MSAC application 1127
GART for HIV

Professor Brendan Kearney (Chair)	Health administration and planning
Professor Andrew Carr	Clinical immunology
Professor Suzanne Crowe	Infectious diseases
Mr John Daye	Consumer health
Associate Professor Anne Mijch	Infectious diseases
Dr Judy Soper	Radiology

Evaluators for MSAC application 1127
GART for HIV

Dr John Gillespie	Engagement Manager, IMS Health
Ms Heather Phillips	Health Outcomes Consultant, IMS Health
Dr Teresa Wozniak	Health Outcomes Consultant, IMS Health
Mr Taimur Bhatti	Senior Health Economics Consultant, IMS Health
Ms Ann Jones	Senior Medical Editor, IMS Health

Appendix C Studies included in the review

Table 25 present studies included in the current review.

Table 25 Included studies

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
GART Baxter et al (2000) USA Randomised trial Random allocation: Yes Concealment of allocation: No Blinding: Yes	>13 years with virological failure (>16 weeks; >20,000 copies/ mL by Roche or >10,000 copies/mL by Chiron assay within 6 weeks) on PI or NRTI regimen, cumulative ART and CD4 cell count 50–500x106 cells/L	Index test: In-house kit for GART Mutation identified; interpretation of drug susceptibilities, and treatment suggestions Sequencing of viral RNA in-house, results transmitted to the Statistical Centre at the University of Minnesota for expert interpretation Expert opinion: Yes Comparator test: Standard of care treatment regimen proposed before randomisation was prescribed by the site clinician	Change in pVL from baseline *At 3 months* SOC:–0.47 $\log_{10}$ copies/mL (0.09) GART: –0.94 $\log_{10}$ copies/ mL (0.09) Proportion of patients with <500 copies/mL *At 4 weeks* SOC: 23% GART: 45% (GART vs SOC: *p*=0.004) *At 8 weeks* SOC 25% GART: 55% (GART vs SOC: *p*=0.0001) *At 3 months* SOC: 22.2% GART:34.2% (GART vs SOC: *p*=0.10	C1 Comparison: Direct comparison P1 Applicability: Applicable Q1 Quality: High NHMRC level II evidence for an intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
VIRADPT Durant et al (1999) France Randomised trial Random allocation: Yes Concealment of allocation: Yes Blinding: NR	>18 years with pVL >10,000 copies/mL >6 months treatment with nucleoside analogues at >3 months treatment with a PI, Karnofsky score >50	Index test: In-house kit for GART. If no resistance mutations were found, the choice of ART was the best clinical practice Sequencing of viral RNA in house until January 1998, then TruGene HIV–1 assay. Expert opinion: No Comparator test: Standard of care treatment changes were based on optimum care according to published guidelines	Change in pVL from baseline *At 3 months* SOC: –0.46 $\log_{10}$ copies/mL (SD=0.17) GART: –1.04 $\log_{10}$ copies/mL +/–0.14 *At 6 months* SOC:–0.67 $\log_{10}$ copies/mL (SD=0.19) GART:–1.15 $\log_{10}$ copies/mL (0.15) Proportion of patients with <200 copies/mL *At 3 months* SOC: 14% GART: 29% (GART vs. SOC: *p*=0.017) *At 6 months* SOC: 14% GART: 32% (GART vs. SOC: *p*=0.067)	C1 Comparison: Direct comparison P1 Applicability: Applicable Q3 Quality : Poor—potential for bias due absence of blinding NHMRC level III-1 evidence for an intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
Clevenbergh et al (2000) follow-up of VIRADAPT France Open label study Randomisation: No Allocation concealment: No Blinding: No.	This study was initiated following the 6 month study conducted by Durant et al (1999). All participants had access to genotype-assisted therapy if their viral load did not exceed a 0.5 log reduction. Cross over treatment was initiated for 69% of standard of care participants during entire open label period	Index test: In-house kit for GART. If no resistance mutations were found, the choice of ART was the best clinical practice Sequencing of viral RNA in house until January 1998, then TruGene HIV–1 assay. Expert opinion: No Comparator test: Standard of care treatment changes were based on optimum care according to published guidelines	Change in pVL from baseline *At 12 months* SOC:–0.98 log_{10} copies/ mL (SD=0.22) GART:– 1.15 log10 copies/ mL (SD=0.17) Proportion of patients with <200 copies/mL *At 6 months* SOC: 14% GART: 32.3% *At 12 months* SOC: 30.5% GART: 30.4%	CX Comparison: Other comparison P2 Applicability: Limited Q3 Quality : Poor—potential for bias due absence of blinding NHMRC level III-2 evidence for an intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
ARGENTA Cingolani et al (2002) Italy Randomised trial Random allocation: Yes Concealment of allocation: NR Blinding: No	>2 months on treatment and have either: pVL >2000 copies/mL; or <1 log_{10} reduction HIV RNA >2 months after commencement of the last regimen. All participants including injecting drug users	Index test: Commercial kits for GART Sequencing of viral RNA by TruGene HIV-1 assay, Visible Genetics, Toronto Expert opinion: Yes Comparator test: Standard clinical care treatment decision based on evaluation of history, clinical picture and standard immunological and virological parameters	Change in pVL from baseline At 3 months SOC:–0.38 log_{10} copies/mL (SD=0.96) GART: –0.62 log10 copies/ mL (SD=1.16) At 6 months SOC:–0.39 log_{10} copies/mL (SD=1.04) GART: –0.57log10 copies/mL (SD=1.09 Proportion of patients with <500 copies/mL At 3 months SOC: 12% GART: 27% (GART vs. SOC: *p*=0.01) At 6 months SOC: 17% GART: 21% (GART vs. SOC: *p*=0.47)	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality : Poor—no indication of allocation concealment, potential for bias due absence of blinding NHMRC level III-1 evidence for intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
NARVAL Meynard et al (2002) France Randomised trial Random allocation: Yes Concealment of allocation: No Blinding: Yes		Index test: Commercial kits for GART Sequencing of viral RNA by TruGene HIV-1 kit (Visible Genetics, Toronto) Expert opinion: Yes Comparator test: Standard of care–no indication of standard clinical care.	Change in pVL from baseline *At 3 months* SOC: –0.9 log_{10} copies/mL* GART: –1.0 log_{10} copies/mL* *Approximate from figure 4(b) Proportion of patients with <200 copies/mL *At 3 months* SOC: 36% GART: 44% (GART vs. SOC: *p*=0.215) *At 6 months* SOC: 22% GART: 31% (GART vs. SOC: *p*=0.052)	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality: Poor—potential for selection bias from no indication of or allocation concealment. Insufficient information on patient selection NHMRC level II evidence for an intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
HAVANA Tural et al (2002) Spain Randomised trial Random allocation: Yes Concealment of allocation: NR Blinding: NR	Patients with plasma RNA >1000 copies/mL and to be stable ART for more than 6 months	Index test: Commercial kits for GART Sequencing of viral RNA by TruGene HIV-1 Kit and interpreted (RetroGram, Virology networks, Netherlands) Expert opinion: Yes Comparator test: Standard of care as per best clinical practice and most recent guidelines	Change in pVL from baseline At 3 months SOC:–0.8 log_{10} copies/mL (SD=0.7) GART: –0.92 log_{10} copies/mL (SD=0.8) *At 6 months* SOC:–0.63 log_{10} copies/mL (SD=0.8) GART: –0.84 log10 copies/mL (SD=0.8) Proportion of patients with <400 copies/mL *At 3 months* SOC: 46.6% GART: 54.6% (GART vs. SOC: *p*=NS) *At 6 months* SOC: 36.2% GART: 48.5% (GART vs. SOC: *p*<0.05)	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality: Poor—potential for bias due absence of blinding. Open label trial with no allocation concealment. NHMRC level II evidence for an intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
De Luca et al (2006) Follow up of ARGENTA Italy Open label study Randomisation: No Allocation concealment: No Blinding: No	Follow up observational trial of the ARGENTA trial (Cingolani et al 2002), following 6 months of the ARGENTA trial, participants from SOC arm with viral loads >1000 copies/mL received GART-guided treatment decisions based on access to ART	Index test: Commercial kit for GART Sequencing of viral RNA by TruGene HIV-1 assay, Visible Genetics, Toronto Expert opinion: Yes Comparator test: Standard clinical care treatment decision based on medical history, immunological and virological parameters (if there was pVL <1 log10 copies/mL patients were offered GART)	Proportion of patients with <400 copies/mL *At 36 months* SOC: 28% GART: 31.25%	CX Comparison: Other comparison P1 Applicability: Applicable Q3 Quality: Poor—no indication of allocation concealment, potential for bias due absence of blinding. NHMRC level III-2 evidence for an intervention study
ERA trial investigators (2005a) UK Randomised trail Random allocation: Yes Concealment of allocation: NR Blinding: NR	>18 years pVL >2000 copies/mL	Index test: Commercial kit for GART. Sequencing of viral RNA by Virco (Mechelen, Belgium) Interpretation by computer-generated interpretation system Expert advice: No Comparator test: Standard of care–no indication of standard clinical care.	Change in pVL from baseline *At 12 months* SOC:–2.19log_{10} copies/mL GART:–2.3 log_{10} copies/ mL Proportion of patients with <50 copies/mL *At 12 months* SOC: 50% GART: 56%	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality: Poor—no indication of allocation concealment, potential for bias due absence of blinding. NHMRC level II evidence for an intervention study

Trial name Author (year) Country Study design	Population characteristics	Test characteristics	Study outcomes	Study quality
PERA Green et al (2006) UK, France Randomised trial Random allocation: Yes Concealment of allocation: NR Blinding: NR	Infants from 3 months of age to participants aged 18 years old who had to change therapy due to virological failure, and patients with pVL >2000 copies/ mL	Index test: Commercial kit for GART Sequencing of viral RNA by Virco (Mechelen, Belgium) with computer-assisted interpretation (VirtualPhenotype, v2 to v3.2) Expert advice: No Comparator test: Standard of care–no indication of standard clinical care	Change in pVL from baseline *At 24 weeks** SOC:–1.3 log_{10} copies/mL GART:–1.51 log_{10} copies/mL *At 48 weeks* SOC: –1.23 log_{10} copies/mL (SE=0.2) GART:–1.51 log_{10} copies/mL *At 96 weeks** SOC:–1.51 log_{10} copies/mL GART:–1.5 log10 copies/mL *Approximate from figure 3 Proportion of patients with <400 copies/mL *At 48 weeks* SOC: 34% GART: 34% *At 96 weeks* SOC: 38% GART: 37%	C1 Comparison: Direct comparison P1 Applicability : Applicable Q3 Quality: Poor—potential for bias due absence of blinding. Open label trial with allocation concealment NHMRC level II evidence for an intervention study

Abbreviations: GART, genotype assisted resistance testing; NR, not reported; NHMRC, National Health and Medical Research Council; NS, not significant; pVL, plasma viral load; SD, standard deviation; SE, standard error; SOC, standard of care

Appendix D Quality criteria

Study design	Quality checklist
Systematic review	Was the research question specified?
	Was the search strategy documented and adequate?
	Were the inclusion and exclusion criteria specified, appropriate and applied in an unbiased way?
	Was a quality assessment of included studies undertaken?
	Were the methods of the study appraisal reproducible?
	Were the characteristics and results of the individual studies summarised?
	Were the methods for pooling the data appropriate?
	Were sources of heterogeneity explored?
	Was a summary of the main results and precision estimates reported?
Studies evaluating effectiveness of an intervention on health outcomes	
Randomised controlled trial	Were the inclusion and exclusion criteria specified?
	Was the assignment to the treatment groups really random?
	Was the treatment allocation concealed from those responsible for recruiting subjects?
	Was there sufficient description about the distribution of prognostic factors for the treatment and control groups?
	Were the groups comparable at baseline for these factors?
	Were outcome assessors blinded to the treatment allocation?
	Were the care providers blinded?
	Were the subjects blinded?
	Were all randomised participants included in the analysis?
	Was a point estimates and measure of variability reported for the primary outcome?
Cohort study	Were subjects selected prospectively or retrospectively?
	Was the intervention reliably ascertained?
	Was there sufficient description about how the subjects were selected for the new intervention and comparison groups?
	Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups? Were the groups comparable for these factors?
	Did the study adequately control for potential confounding factors in the design or analysis?
	Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)?
	Was follow-up long enough for outcomes to occur?
	What proportion of the cohort was followed-up and were there exclusions from the analysis?
	Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Study design	Quality checklist
Case-control study	Was there sufficient description about how subjects were defined and selected for the case and control groups?
	Was the disease state of the cases reliably assessed and validated?
	Were the controls randomly selected from the source of population of the cases?
	Was there sufficient description about the distribution of prognostic factors for the case and control groups? Were the groups comparable for these factors?
	Did the study adequately control for potential confounding factors in the design or analysis?
	Was the new intervention and other exposures assessed in the same way for cases and controls and kept blinded to case/control status?
	How was the response rate defined?
	Were the non-response rates and reasons for non-response the same in both groups?
	Was an appropriate statistical analysis used?
	If matching was used, is it possible that cases and controls were matched on factors related to the intervention that would compromise the analysis due to over-matching?
Case series	Was the study based on a representative sample selected from a relevant population?
	Were the criteria for inclusion and exclusion explicit?
	Did all subjects enter the survey at a similar point in their disease progression?
	Was follow-up long enough for important events to occur?
	Were the techniques used adequately described?
	Were outcomes assessed using objective criteria or was blinding used?
	If comparisons of sub-series were made, was there sufficient description of the series and the distribution of prognostic factors?

Study design	Quality checklist
Study of diagnostic accuracy	Was the spectrum of patients representative of the patients who will receive the test in practice?
	Were selection criteria clearly described?
	Is the reference standard likely to correctly classify the target condition?
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
	Did patients receive the same reference standard regardless of the index test result?
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
	Was the execution of the index test described in sufficient detail to permit replication of the test?
	Was the execution of the reference standard described in sufficient detail to permit its replication?
	Were the index test results interpreted without knowledge of the results of the reference standard?
	Were the reference standard results interpreted without knowledge of the results of the index test?
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
	Were uninterpretable/ intermediate test results reported?
	Were withdrawals from the study explained?

Appendix E Literature search

Search strategies were developed and applied to identify relevant studies of urinary metabolic profiling for the detection of inborn errors of metabolism. The Medline and EMBASE databases were search using the EMBASE.com interface. The PreMedline database was searched using the PubMed interface. The CDSR, DARE, CENTRAL, CMR, HTA, NHSEED databases were searched using the Cochrane Library interface. The search results for EMBASE.com are presented in Table 26. The results from the Cochrane Library are presented in Table 27, and a breakdown of results from each database searched in the Cochrane Library is provided in Table 28. PreMedline search results are presented in Table 29. The health technology websites searched as part of the assessment are shown in Table 30.

Table 26 EMBASE.com search results for GART in guiding therapy in patients infected with HIV (conducted 17 February 2009 via EMBASE.com)

	Keywords/search history	Results
#1	'genotypic resistance testing':de	2
#2	'genotypic inhibitory quotient':de	7
#3	enotype*:ti,ab AND 'resistance testing':ti,ab	375
#4	enotype*:ti,ab AND 'resistance test':ti,ab	64
#5	enotype*:ti,ab AND 'resistance tests':ti,ab	90
#6	'genotypic testing':ti,ab	54
#7	'genotypic test':ti,ab OR 'genotyping tests':ti,ab	79
#8	'resistance *2 genotyping':ti,ab	85
#9	'genotypic inhibitory quotient':ti,ab	22
#10	'genotypic *1 score':ti,ab	24
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	692
#12	'genotype'/de	113,730
#13	enotype*:ti,ab	114,835
#14	#12 OR #13	150,531
#15	'human immunodeficiency virus infection'/exp	226,546
#16	'human immunodeficiency virus'/exp	87,302
#17	'human immunodeficiency virus infected patient'/de	5,013
#18	#15 OR #16 OR #17	264,247
#19	#14 AND #18	5,350
#20	'human immunodeficiency virus infection'/exp/dm_dr	661
#21	'antibiotic resistance'/de	81,742
#22	'multidrug resistance'/de	21,689
#23	'virus resistance'/de	4,973
#24	'antiviral resistance'/de	626
#25	'genetic resistance'/de	1,526
#26	'drug resistance':ti,ab	20,993

	Keywords/search history	Results
#27	'resistant virus':ti,ab	822
#28	'resistance mutation':ti,ab OR 'resistance mutations':ti,ab	2,230
#29	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	119,262
#30	#19 AND #29	2,030
#31	'virus load'/de	19,613
#32	'viral burden':ti,ab OR 'viral load':ti,ab	9,767
#33	#31 OR #32	22,036
#34	#19 AND #33	1,368
#35	'mutation'/de	94,375
#36	'gene mutation'/de	163,712
#37	'virus mutation'/de	7,193
#38	#35 OR #36 OR #37	264,286
#39	#19 AND #38	1,631
#40	'antiretrovirus agent'/de	22,628
#41	'highly active antiretroviral therapy'/de	15,707
#42	'antiretroviral therapy':ti,ab OR 'anti retroviral therapy':ti,ab	15,524
#43	'antiretroviral medication':ti,ab OR 'anti retroviral medication':ti,ab	278
#44	'antiretroviral medications':ti,ab OR 'anti retroviral medications':ti,ab	443
#45	'antiretroviral treatment':ti,ab OR 'anti retroviral treatment':ti,ab	2,765
#46	'antiretroviral treatments':ti,ab OR 'anti retroviral treatments':ti,ab	261
#47	'antiretroviral treated':ti,ab OR 'anti retroviral treated':ti,ab	91
#48	haart:ti,ab OR art:ti,ab	38,632
#49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	64,927
#50	#19 AND #49	2,039
#51	viroseq:ti,ab,dn OR trugene:ti,ab,dn OR retrogram:ti,ab,dn	176
#52	'genotyping kit':ti,ab,dn OR 'genotyping kits':ti,ab,dn	80
#53	'genotyping system':ti,ab,dn OR 'genotyping systems':ti,ab,dn	232
#54	'genotypic assay':ti,ab,dn OR 'genotypic assays':ti,ab,dn	114
#55	'genotyping assay':ti,ab,dn OR 'genotyping assays':ti,ab,dn	593
#56	#51 OR #52 OR #53 OR #54 OR #55	1,052
#57	#18 AND #56	254
#58	grt:ti,ab OR gart:ti,ab OR gt:ti,ab OR giq:ti,ab OR gss:ti,ab	13,703
#59	#18 AND #58	201
#60	(enotype*:ti AND guided:ti AND (treatment:ti OR therapy:ti))	14
#61	(enotype*:ab AND guided:ab AND (treatment:ab OR therapy:ab))	78
#62	#60 OR #61	84
#63	#18 AND #62	46
#64	#11 OR #30 OR #34 OR #39 OR #50 OR #57 OR #59 OR #63	3,791

	Keywords/search history	Results
#65	#64 AND [2000-2009]/py	3,313
#66	#65 AND [humans]/lim	3,056
#67	#65 AND [animals]/lim	31
#68	#65 NOT #67	3,282
#69	#66 OR #68	3,298

Table 27 Cochrane Library search results for GART in guiding therapy in patients infected with HIV (conducted 17 February 2009)

	Keywords/search history	Results
#1	enotype* AND "resistance testing"	46
#2	enotype* AND "resistance test"	10
#3	enotype* AND "resistance tests"	3
#4	"genotypic testing"	7
#5	"genotypic test" OR "genotyping tests"	5
#6	resistance NEAR genotyping	15
#7	"genotypic inhibitory quotient"	3
#8	Genotypic NEAR score	8
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	75
#10	MeSH descriptor Genotype, this term only	1421
#11	enotype*	3115
#12	(#10 OR #11)	3115
#13	MeSH descriptor HIV Infections explode all trees	5475
#14	MeSH descriptor HIV explode all trees	1703
#15	hiv	7297
#16	(#13 OR #14 OR #15)	7778
#17	(#12 AND #16)	332
#18	MeSH descriptor Drug Resistance explode all trees	4239
#19	"drug resistance"	3261
#20	"resistant virus"	39
#21	"resistance mutation" OR "resistance mutations"	131
#22	(#18 OR #19 OR #20 OR #21)	4946
#23	(#17 AND #22)	184
#24	MeSH descriptor Viral Load explode all trees	949
#25	"viral burden" OR "viral load"	1554
#26	(#24 OR #25)	1554
#27	(#17 AND #26)	146
#28	MeSH descriptor Mutation, this term only	489
#29	mutation*	1458

	Keywords/search history	Results
#30	(#28 OR #29)	1458
#31	(#17 AND #30)	150
#32	MeSH descriptor Anti-Retroviral Agents explode all trees	2639
#33	MeSH descriptor Antiretroviral Therapy, Highly Active, this term only	611
#34	“antiretroviral therapy” OR “anti retroviral therapy”	1431
#35	“antiretroviral medication” OR “anti retroviral medication”	42
#36	“antiretroviral medications” OR “anti retroviral medications”	26
#37	“antiretroviral treatment” OR “anti retroviral treatment”	255
#38	“antiretroviral treatments” OR “anti retroviral treatments”	15
#39	“antiretroviral treated” OR “anti retroviral treated”	11
#40	HAART OR ART	7921
#41	(#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40)	10609
#42	(#17 AND #41)	260
#43	viroseq OR TruGene OR Retrogram	9
#44	“genotyping kit” OR “genotyping kits”	1
#45	“Genotyping System” OR “Genotyping Systems”	6
#46	“Genotypic assay” OR “Genotypic assays”	1
#47	“genotyping assay” OR “genotyping assays”	1
#48	(#43 OR #44 OR #45 OR #46 OR #47)	13
#49	(#16 AND #48)	9
#50	grt OR gart OR gt OR GIQ OR GSS	1430
#51	(#16 AND #50)	27
#52	enotype* NEAR guided NEAR (treatment OR therapy)	18
#53	(#16 AND #52)	14
#54	(#9 OR #23 OR #27 OR #31 OR #42 OR #49 OR #51 OR #53)	307
#55	(#54), from 2000 to 2009	261

Table 28 Breakdown of database retrievals from The Cochrane Library

Database	Results
Database of Systematic Reviews	19
Database of Abstracts of Reviews of Effects (DARE)	4
Central register of Controlled Trials (CENTRAL)	215
Methodology Register	0
Health Technology Assessment Database (HTA)	6
NHS Economic Evaluation Database (NHS EED)	16
Cochrane Group	1*
TOTAL	261

Table 29 In process and other non-indexed citations from PreMedline (conducted 17 February 2009)

	Keyword/search history	Results
#1	Search genotype*[tw] AND "resistance testing"[tw]	406
#2	Search genotype*[tw] AND "resistance test"[tw]	84
#3	Search genotype*[tw] AND "resistance tests"[tw]	89
#4	Search "genotypic testing"[tw]	55
#5	Search "genotypic test"[tw] OR "genotyping tests"[tw]	74
#6	Search resistance[tw] AND genotyping[tw]	1478
#7	Search "genotypic inhibitory quotient"[tw]	19
#8	Search Genotypic[tw] AND score[tw]	196
#9	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2193
#10	Search genotype*[tw]	150891
#11	Search "Human immunodeficiency virus"[tw] OR hiv[tw]	200005
#12	Search #10 AND #11	4894
#13	Search "drug resistance"[tw]	134947
#14	Search "resistant virus"[tw]	802
#15	Search "resistance mutation"[tw] OR "resistance mutations"[tw]	2147
#16	Search #13 OR #14 OR #15	135539
#17	Search #12 AND #16	1965
#18	Search "viral burden"[tw] OR "viral load"[tw]	16894
#19	Search #12 AND #18	1114
#20	Search mutation*[tw]	438549
#21	Search #12 AND #20	1879
#22	Search "antiretroviral therapy"[tw] OR "anti retroviral therapy"[tw]	18772
#23	Search "antiretroviral medication"[tw] OR "anti retroviral medication"[tw]	260
#24	Search "antiretroviral medications"[tw] OR "anti retroviral medications"[tw]	405
#25	Search "antiretroviral treatment"[tw] OR "anti retroviral treatment"[tw]	2573
#26	Search "antiretroviral treatments"[tw] OR "anti retroviral treatments"[tw]	229
#27	Search "antiretroviral treated"[tw] OR "anti retroviral treated"[tw]	85
#28	Search HAART[tw] OR ART[tw]	39112
#29	Search #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	52158
#30	Search #12 AND #29	1274
#31	Search viroseq[tw] OR TruGene[tw] OR Retrogram[tw]	124
#32	Search "genotyping kit"[tw] OR "genotyping kits"[tw]	63
#33	Search "Genotyping System"[tw] OR "Genotyping Systems"[tw]	209
#34	Search "Genotypic assay"[tw] OR "Genotypic assays"[tw]	105
#35	Search "genotyping assay"[tw] OR "genotyping assays"[tw]	541
#36	Search #31 OR #32 OR #33 OR #34 OR #35	922
#37	Search #11 AND #36	207

	Keyword/search history	Results
#38	Search grt[tw] OR gart[tw] OR gt[tw] OR GIQ[tw] OR GSS[tw]	8062
#39	Search #11 AND #38	144
#40	Search enotype*[tw] AND guided[tw] AND (treatment[tw] OR therapy[tw])	103
#41	Search #11 and #40	48
#42	Search #9 OR #17 OR #19 OR #21 OR #30 OR #37 OR #39 OR #41	4518
#43	Search #42 NOT (medline[SB] OR oldmedline[sb])	199
#44	Search #42 AND in process[SB]	115
#45	Search #42 AND pubmednotmedline[SB]	21
#46	Search #43 OR #44 OR #45	199

Table 30 Health technology assessment websites searched

Country	Websites searched
Australia	Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S) http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
	Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/
	Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
Austria	Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm
Canada	Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home
	Institute of Health Economics (IHE) http://www.ihe.ca/index.html
	Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html
	Canadian Health Economics Research Association (CHERA/ACRES)—Cabot database http://www.mycabot.ca
	Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
	Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
	Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
	Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
Denmark	Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp
	Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html
Finland	FINOHTA http://finohta.stakes.fi/EN/index.htm
France	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/
Germany	German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/index.html
The Netherlands	Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

Country	Websites searched
New Zealand	New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
Norway	Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38
Spain	Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/index.jsp
	Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatrm.net/html/en/Du8/index.html
Sweden	Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp
	Center for Medical Health Technology Assessment (CMT) http://www.cmt.liu.se/english?l=en
Switzerland	Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/home/portal.php
United Kingdom	National Health Service Quality Improvement: Scotland (NHS QIS) http://www.nhshealthquality.org/nhsqis/43.0.140.html
	National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/
	University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
	National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/
United States	Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
	Harvard School of Public Health—Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/
	US Blue Cross/ Blue Shield Association Technology Evaluation Center http://www.bcbs.com/consumertec/index.html

Abbreviations

AIDS	acquired immune deficiency syndrome
ANCA	Australian National Council on AIDS
ANZHSN	Australian and New Zealand Horizon Scanning Network
ART	antiretroviral therapy
ARTG	Australian Register of Therapeutic Goods
CCR5	C-chemokine receptor 5
CD	cluster differentiation
CDC	Centers for Disease Control and Prevention
cDNA	complementary deoxyribonucleic acid
DNA	deoxyribonucleic acid
dNTP	deoxyribonucleotide triphosphate
EACS	European AIDS Clinical Society
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration (USA)
Gag	group antigen
GART	genotype-assisted antiretroviral resistance test
gp	glycoprotein
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
K	lysine
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
MSM	Men who have sex with men
NATA	National Association of Testing Authorities
NCHECR	National Centre in HIV Epidemiology and Clinical Research
NNRTI	non-nucleotide reverse transcriptase inhibitor
NRL	National Reference Laboratory
NRTI	nucleotide reverse transcriptase inhibitor
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PI	protease inhibitors
Pol	reverse transcriptase
QA	Quality assurance
R	arginine
RNA	ribonucleic acid

TGA	Therapeutic Goods Administration

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