Rapid point-of-care combined Antigen/Antibody HIV test to aid in the diagnosis of HIV infection

June 2015

MSAC application no 1391

Assessment report

This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Sport 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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Rapid point-of-care combined Antigen/Antibody test for the diagnosis of human immunodeficiency virus (HIV) infection. Rapid refers to the result of the test being available within 20-30 minutes from specimen collection and "point-of-care" refers to the test being conducted near to, or at the side of, a patient by trained health professionals and/or care providers, rather than sample being sent to pathology laboratories. Combined Antigen/Antibody refers to the detection of both HIV antigen and antibodies to HIV. Currently, only a single such test has been developed - the Alere Determine HIV-1/2 Antigen/Antibody (Ag/Ab) Combo (Determine HIV Combo), referred to as the DHC test herein.

The test is a qualitative "reactive" or "non-reactive" immunoassay. This is in contrast to quantitative methods such as enzyme immune assay (EIA) where a quantitative result is obtained and a diagnostic cut off is used. Sample collection for the DHC test is a finger prick procedure.

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 Sport 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 Monash University was engaged to conduct a systematic review of the literature and an economic evaluation of rapid point-of-care combined Antigen/Antibody HIV test to aid in the diagnosis of HIV infection.

Assessment of rapid point-of-care combined Antigen/Antibody HIV test to aid in the diagnosis of HIV infection

Purpose of Application

An Application was submitted by Inverness Medical Innovations Australia Pty Ltd in May 2014 for MBS listing of a rapid point-of-care combined Antigen/Antibody test for diagnosis of HIV infection for use in GP and sexual health clinics. The DHC test for HIV infection is intended to be used in individuals where a HIV test is indicated and in those who are at a high-risk of HIV infection.

An application for the MBS listing of rapid point-of-care combined Antigen/Antibody test for HIV infection has not previously been considered by MSAC.

Current arrangements for public reimbursement

Rapid point-of-care testing is currently offered in a number of clinics Australia wide. Funding arrangements for rapid point-of-care HIV testing exist in some States and

Territories. For example, the Queensland government provides rapid point-of-care HIV tests for free under the Community HIV Education and Prevention (CHEP) program. The Victorian PRONTO! Clinics also offer the test for free, where this clinic is in partnership with the Victorian AIDS Council and the Burnet institute, who presumably fund the tests. In clinics where no external funding arrangement exists, those being tested currently pay for the test privately. One clinic reports the cost associated with the test, $25 (for cost recovery). It is presumed that the funding arrangements in place for rapid point-of-care testing apply to all individuals who undergo the test (ie, that is not only applicable to high-risk individuals).

The Applicant's proposed item descriptor and fee are presented in Table ES.1.

Table ES.1   Proposed MBS item descriptor for rapid point-of-care testing for HIV

Category 6 – Pathology	Group P9 – Simple Basic Pathology Tests
MBS [item number]	
Point of care HIV antigen/antibody test by one or more immunochemical methods in a blood sample from a high-risk patient.	
Fee:$30.00 **Benefit:** 75% = $22.50 85% = $25.50	

Source: p5 of the MSAC 1391 Final Protocol – specifies a fee of $30.00, the 75% and 85% benefits were calculated during the assessment

The MSAC 1391 Final Protocol states that "An explanatory note would need to be included or accompany the proposed MBS descriptor explaining that the test must be performed at the point-of-care and that the MBS item cannot be claimed on laboratory testing".

Consideration is required as to whether the item descriptor should be modified or whether further explanatory notes should be included addressing the following issues:

- There is no explicit statement the test should be used in GP or sexual health clinics, which is intended;
- No explicit exclusion of the use of the test for screening of blood or organ donation specimens, or use in routine pre-natal testing, which is intended; and
- How the test would be billed in the event of an invalid test result or if a clinician decides to repeat the test in the event of an initial reactive result prior to referral for serology testing (that is, could the test be billed multiple times per consultation).

An additional management fee is applicable to Group P9 simple basic pathology tests if the service is bulk-billed, $7.05 to $10.65 (85% benefit of $6.00 to $9.10) depending on location.

There are numerous MBS item numbers applicable to serology-based HIV testing, with a relevant associated direct fee of $15.65 (85% benefit of $13.35) plus additional fees of $2.40 to $9.95 (85% benefit $2.05 to $8.50) depending on the circumstances of the test.

Background

HIV (Human Immunodeficiency Virus) is a virus that weakens the immune system. It infects immune cells and uses them to reproduce itself, destroying the cells in the process. AIDS (Acquired Immune Deficiency Syndrome) is a serious weakening of the body's immune system caused by HIV. When a HIV positive person's immune cells (CD4 positive cells) drop below a certain level, they can be vulnerable to infections that their body would normally fight off.

Clinical need

In Australia, it is estimated that approximately 26,800 (plausible range of 24,500 – 30,900) people were living with HIV at the end of 2013 (Kirby Institute 2014a, 2014b). The prevalence of HIV infection varies among various groups in Australia, with the highest prevalence observed among men who have sex with men (MSM) estimated to be 8-12% (Kirby Institute 2014a, 2014b). Given the high prevalence of HIV infection among MSM, this population represents a target group for this diagnostic test, where guidelines recommend annual HIV and other sexually transmitted infection testing for all men who have had any type of sex with another man in the previous year; and up to four tests per year for HIV and other sexually transmitted infection for all high-risk men who have sex with men.

It is estimated that approximately 14% (11-21%) of all HIV cases in Australia are undiagnosed (Kirby Institute 2014b). Additionally, the proportion of people diagnosed late (defined by a CD4 positive cell count less than 350 cells/µl at diagnosis) was 29.6% in 2013. It would be anticipated that both those with undiagnosed HIV infection and those diagnosed late contribute to a significant proportion of HIV transmission and new diagnoses of HIV infection.

The Seventh National HIV Strategy 2014-2017 (2014), the Draft National HIV Testing Policy (2014) and the Melbourne Declaration 2012 all support and encourage that programs be put in place to increase access to, and uptake of, voluntary HIV testing in Australia, with the latter citing that rapid testing should be made widely available in clinical and community settings.

Data from Australian studies have identified that men are being tested less frequently than recommended (Guy 2010) and other studies indicate that there is preference for rapid tests among MSM (Yang 2014).

Comparator

The relevant comparator to assess the safety, effectiveness and cost-effectiveness of the rapid point-of-care HIV Antigen/Antibody test is serology testing for HIV. The exact testing performed by the laboratory will depend on the diagnostic algorithm in use but would typically consist of full testing protocol i.e. initial and confirmatory testing. Expert opinion sought during the assessment indicated that standard practice would be the use of a fourth generation Ag/Ab screening assay such as Abbott Architect®. The advice also indicated that in some instances, a reactive HIV sample might undergo (in total) testing in four different fourth generation HIV Ag/Ab EIAs (where only a single MBS item billing applies), as well as a HIV Western Blot (no MBS item number applies) and any other supplementary tests as indicated.

The proposed algorithm provided in the MSAC 1391 Final Protocol implies that rapid point-of-care testing will substitute for laboratory testing for HIV. Expert opinion sought during the assessment indicated that in a Melbourne clinic using the DHC test, venous samples were still being collected on the same day as the rapid test for laboratory testing (regardless of whether the DHC test was reactive or not); indicating that the DHC test may be an additional, rather than an alternative test to serology. The advice also indicated that this was an opt-out system for those who are adamant they do not want a venous sample taken (less than 10 in 100 would decline); and that individuals suspected of early HIV seroconversion were particularly encouraged to undergo

additional laboratory testing or should not be tested with a rapid test at all. Given testing for syphilis is recommended at the time of HIV testing and syphilis serology requires venepuncture, it is not unreasonable (and could perhaps be considered inappropriate not) to test for HIV at the same time.

Scientific basis of comparison

A linked evidence approach was undertaken as no direct evidence for the effectiveness of the test was identified. The linked evidence approach is undertaken in three steps, with subsequent steps relying on the findings of the previous steps, as per the framework given in Merlin (2013). Depending on the results of the diagnostic accuracy review (evidence linkage 1), evidence linkage 2 is undertaken to assess change in patient management; and depending on the results of that, evidence linkage 3, which looks at treatment effectiveness, may need to be addressed.

Two Australian studies were identified that assessed the diagnostic accuracy of the DHC test to serology testing for diagnosis of HIV infection amongst MSM in Sydney (Conway 2013a, 2013b, 2014) and Melbourne (Eu 2014). The studies are considered to be directly applicable to those for whom listing is sought.

A single randomised controlled trial reported by Read (2013) was identified which compared HIV testing frequency over an 18 month period among MSM randomised to rapid point-of-care test or conventional testing in an Australian clinic. The trial is considered to be largely applicable to those for whom listing is sought, however eligibility for enrolment was restricted to MSM who had HIV testing within the last two years thus, "never" testers were not represented.

Safety

No studies assessing the comparative safety of rapid point-of-care testing and serology testing for HIV were identified.

With respect to the procedures undertaken to collect specimens for testing, a finger-prick of venepuncture for rapid point-of-care and serology, respectively, no real safety issues are associated with either, provided the person drawing the samples is trained and sterile equipment is used. In addition, as the DHC test requires the same or fewer blood withdrawals than the comparators, it is reasonable to conclude that the test is safe.

The impact of false positive or false negative results from the rapid point-of-care test however, should be considered. With respect to false positive results, where the rapid point-of-care test indicates the presence of HIV infection, but confirmatory serology testing does not; it would be anticipated that the anxiety felt over the week prior to delivery of the serology test results would be greater than for those who are undergoing routine testing with serology testing (with no rapid point-of-care test result). The positive rapid point-of-care result would also be accompanied with counselling for the results according to the proposed clinical decision pathway.

With respect to false negative results, where the rapid point-of-care test indicates no HIV infection, but confirmatory serology testing would; there is potential for those individuals to have worse health outcomes in the longer term due to having an undiagnosed HIV infection. There is also the potential for these individuals to unknowingly transmit HIV to other individuals until such time they undergo further testing and are diagnosed. As

noted above, the current practice in at least one Melbourne clinic is to collect a venous sample on the same day as rapid testing for serology testing for HIV. If this applies nationally, the risk of false negative results should be no greater than is currently the case. The risk of false-negative results in practice may additionally be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product. Expert advice has suggested that individuals suspected of early HIV seroconversion are particularly encouraged to undergo additional laboratory testing, other advice suggested those suspected of early infection should not be tested with a rapid test at all.

Clinical effectiveness

Diagnostic accuracy

A meta-analysis of the two included studies indicated that the <u>sensitivity of the DHC test was 87.8% (95% CI: 75.2%, 95.4%) and the specificity was 99.4% (95% CI: 99.1%, 99.7%) compared with serology testing for the diagnosis of HIV infection</u>. These data differ from the sensitivity and specificity reported for the DHC test provided in the product insert which states that "the sensitivity of the Determine HIV Combo (DHC) is 100.00% across 1,179 specimens positive for various types and subtypes of HIV and who were confirmed HIV antibody positive. The specificity of the test is 99.61% for the antigen test line and the 99.21% for the antibody test line across 1,783 HIV-negative specimens".

The differences in the reported sensitivity of the DHC test from these Australian studies and the product insert are likely to result from the estimates provided in the product insert having been assessed from the two extreme ends of the disease spectrum (ie, confirmed seronegative and seropositive specimens), which tends to overestimate diagnostic accuracy (Knottnerus 2002). Of the false negatives reported in the two Australian studies, four of five (80%) were men with early HIV infection in Conway (2014) and the single false negative reported in Eu (2014) was one of three (33%) seroconverters.

Impact on patient management

The results of the trial indicate that there was <u>no statistically significant difference between those randomised to rapid point-of-care or conventional HIV testing for the primary outcome of "HIV tests over 18 months"</u> or the secondary outcomes of syphilis, chlamydia and gonorrhoea testing over 18 months. Hence, <u>the possibility of having HIV tests by rapid point-of-care testing did not result in higher testing frequency over the study period of 18 months.</u>

The authors also undertook *post-hoc* analyses considering only the first HIV test after enrolment and considering only subsequent HIV tests (excluding first tests). A statistically significantly greater number of first HIV tests/year after the enrolment test was observed in those randomised to the HIV testing by the rapid point-of-care test compared with conventional testing, however no differences were observed in the number of HIV tests/year when only considering subsequent tests. Based on these

results, the authors conclude that "Post hoc analysis showed an initial increase in their rate of testing that was not sustained".

The exclusion of "never" testers in the trial limits any increase in testing that may or may not have been observed if they had also been enrolled. This is of particular relevance when considered in the context that the results of the patient satisfaction questionnaire reported in Eu (2014) indicated that one in five men would not have been tested if rapid point-of-care testing was not available.

Economic evaluation

The data reported in Conway (2014) and Eu (2014) indicates that DHC has inferior diagnostic accuracy for detecting HIV compared to serology testing; whereas data reported in Read (2013) indicates that there was no statistically significant difference between the groups randomised to rapid point-of-care testing and serology testing in terms of number of tests/year for HIV. To account for the differential diagnostic accuracy, a cost-effectiveness analysis is appropriate.

The base case of the model assumes no differences in testing frequency between the two arms of the model. Sensitivity analyses are conducted modifying some assumptions to attempt to capture other reasonable scenarios, including the qualitative patient satisfaction evidence in Eu (2014) and the *post-hoc* analysis in Read (2013).

The type of economic evaluation presented is a novel static cost-consequences analysis which estimates cost per various test outcomes associated with the DHC test and conventional testing (fourth generation EIA) over one year. The population in the model is assumed to be all Australian MSMs without diagnosed HIV, and includes individuals who are seropositive, seroconverting and seronegative.

A decision analytic Markov model is used to estimate the cost per various test outcomes over a one year time horizon with three-monthly cycles, of a scenario where the DHC test is available for screening HIV in high-risk individuals. MSMs without a diagnosis of HIV are assumed to commence each cycle in one of four health states (i) "Seropositive", (ii) "Seroconverting", (iii) "Seronegative" , (iv) "HIV diagnosed". The population enters the model in one of the three non-HIV diagnosed health states, and only transitions to the absorbing health state "HIV diagnosed" after a confirmed HIV diagnosis is made either through HIV screening or the development of AIDS complications and symptom-based testing. The population who are "seronegative" may become infected with HIV during a cycle and transition to "seroconverting" or remain "seronegative". The population only remains in the "seroconverting" health state for one cycle. They may be screened for HIV within the cycle and if diagnosed transition to "HIV diagnosed", otherwise they will transition to "seropositive". Those with undiagnosed "seropositive" disease can transition to "HIV diagnosed" either via HIV screening, or due to development of AIDS symptoms via HIV symptom-based testing.

Monte Carlo simulation is used to accommodate the heterogeneous population, conditional transition state probabilities, and incorporates a tracker variable for number of tests required by the clinical evidence available. Therefore at the start of the model, individuals are assigned to one category for each of the following variables (i) Initial non-HIV diagnosed health state ("seronegative", "seroconverting", "seropositive"); (ii) If "seropositive", number of year seropositive (1 to 20); (iii) Undertakes routine HIV screening (yes or no); or (iv) Days since HIV infection (1 to 90).

There is no precise "window period" at which time a HIV test will detect an infection that it would not have detected prior to this time. Therefore, in the seroconverting health state, the probability of a positive diagnosis is assumed to increase over time (Owen 2008). The median window periods for fourth generation EIA and the DHC test are assumed to be approximately 20 and 25 days, respectively (Cohen 2010).

The base case of the modelled economic evaluation predicts <u>10 fewer cases of HIV will be detected via screening with the DHC test compared to standard laboratory testing</u>, largely due to the window periods assumed for the tests. Of those not diagnosed, all commenced in the seronegative health state and were infected within the year. The <u>incremental cost of the DHC test is $941,454, therefore the strategy is dominated</u>. This result is consistent with the assumption of no differences in testing frequency, and with the increased cost/test for the DHC test compared with serology testing.

The results of the sensitivity analyses demonstrate that the ICER is most sensitive to the assumption that the availability of the DHC test would encourage a greater proportion of MSM to be tested (ICER=$46,689/additional HIV detection; assuming an increase from 55% to 58% of MSM are tested) and assumed increases in testing frequency with the DHC test compared with serology testing (ICER=$32,217/additional HIV detection).

Financial/budgetary impacts

The number of tests that are likely to be undertaken amongst high risk individuals is unknown.

Assuming direct substitution and 45,000 rapid tests per year (MSAC 1391 Final Protocol p5), the total cost to the Australian healthcare system is approximately $249,300, where this additional cost is associated with fewer HIV diagnoses. Assuming sequential use and 45,000 tests per year, the total cost is approximately $1,175,850, where this additional cost is associated with no differences in the number of HIV diagnoses.

Based on the number of tests estimated in the base case of the modelled economic evaluation of 119,889 tests per year, assuming direct substitution, the total cost to the Australian healthcare system is approximately $664,185 (additional cost with fewer HIV diagnoses); assuming sequential use, the total cost is approximately $3,132,700 (additional cost is associated with no differences in the number of HIV diagnoses).

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of rapid point-of-care combined Antigen/Antibody human immunodeficiency virus (HIV) test, which is a diagnostic test for the diagnosis of HIV infection. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme 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 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 rapid point-of-care combined Antigen/Antibody HIV test to aid in the diagnosis of HIV infection.

Background

Intervention name

Rapid point-of-care combined Antigen/Antibody test for HIV infection. Rapid refers to the result of the test being available within 20-30 minutes from specimen collection and "point-of-care" refers to the test being conducted near to, or at the side of, a patient by trained health professionals and/or care providers, rather than sample being sent to pathology laboratories. Combined Antigen/Antibody refers to the detection of both HIV antigen and antibodies to HIV.

Currently, only a single such test has been developed - the Alere Determine HIV-1/2 Antigen/Antibody (Ag/Ab) Combo (Determine HIV Combo), referred to as the DHC test herein.

The test

DHC is the only rapid test which detects both HIV antigen and antibodies to HIV currently approved by the TGA for point-of-care use by medical professionals trained in its use and interpretation of results in Australia. The TGA has placed strict restrictions on the use of this test (see Appendix B).

DHC is a "fourth generation" test, which refers to it detecting both free, non-immunocomplexed HIV-1 p24 HIV antigen (Ag) and antibodies (Ab) to HIV-1 and HIV-2 in human blood. Antigen detection is important in reducing the window period for the detection of HIV infection as the virus secretes p24 antigen before antibodies to HIV are produced by the infected individual. As the DHC test detects HIV antigen, HIV infection can be detected approximately 10 days earlier than a range of antibody-only rapid tests (Masciotra 2013a).

The test is a qualitative "reactive" or "non-reactive" immunoassay. This is in contrast to quantitative methods such as enzyme immune assay (EIA) where a quantitative result is obtained and a diagnostic cut-off is used.

The test procedure for the DHC test begins with a small amount of blood, collected by a finger prick procedure. The blood sample is then added to the test strip, followed by a drop of buffer. After 20 minutes, test results are interpreted by the presence or absence of Control, Antigen and Antibody test lines. If red bars appear in the antibody or antigen or the antibody and antigen bars, the test should be interpreted as positive; if no bars appear in the antigen or antibody bars, the test should be interpreted as negative; as long as there is also a red bar in the control bar. If the result from the point-of-care test is reactive, a confirmatory laboratory test is required. Should no red bar appear in the control bar, the test should be interpreted as invalid, regardless of the appearance of red bars in antibody or antigen bars and the test should be repeated. Figure 1 presents a diagrammatic representation of the interpretation of results of the DHC test.
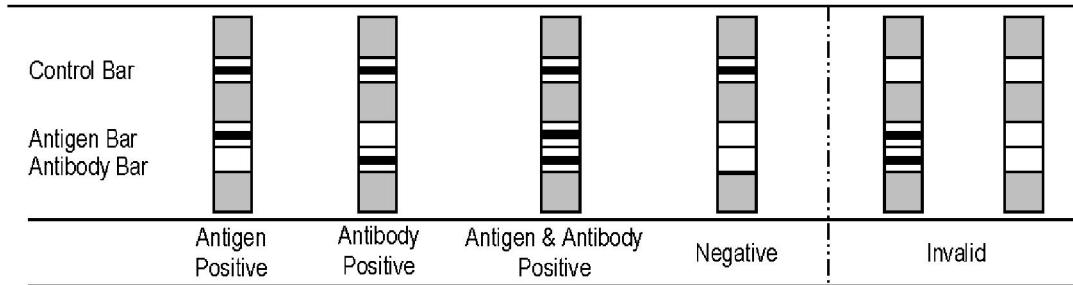
Figure 1   Interpretation of results for the DHC test
Source: adapted from the DHC product insert

The DHC test provides qualitative, reactive or non-reactive results which are used to determine sensitivity and specificity. According to the product insert, the sensitivity of DHC is 100.00% across 1,179 specimens positive for various types and subtypes of HIV and who were confirmed HIV antibody positive. The specificity of the test is 99.61% for the antigen test line and the 99.21% for the antibody test line across 1,783 HIV-negative specimens. It is noted that these estimates are derived from the two extreme ends of the disease spectrum (ie, confirmed seronegative and seropositive specimens), which tends to overestimate diagnostic accuracy (Knottnerus 2002). From the product insert, the derived sensitivity of the DHC test among early seroconversion samples is 97.6% (41 of 42 cases were identified by the DHC test).

The following further information was provided by the Applicant:

"The performance of the test (sensitivity and specificity) was determined by testing specimens from random blood donors, from patients with HIV infection, patients at risk of HIV infection or in other clinical categories and commercial seroconversion panels. The performance evaluations were conducted across nine clinical studies in Europe, Africa, Asia and South America.

The exact comparator or reference test(s) used varied depending on the clinical site but in each case, state of the art laboratory methods were used to characterise the samples. In most cases a combination of CE-marked fourth generation commercial enzyme immunoassay (EIA) in combination with appropriate confirmatory tests such as Western Blotting were used as the reference tests. At several sites, a combination of separate commercial CE-marked HIV Ag and HIV Ab EIA assays were used to characterise samples instead of a single fourth generation EIA assay.

The conditions under which the testing was performed also varied depending on the clinical site. At some clinical sites the testing with the DHC test was performed by trained clinicians and at other sites, the testing was performed by laboratory technicians. Reference testing was performed by laboratory technicians in all cases."

Based on information provided by the manufacturer, the analytical cut off for the p24 antigen is approximately 12.5-25 pg/mL, which is higher than laboratory-based systems. However, it is proposed that the improvement in convenience with the availability of the DHC test outweighs the decrease in sensitivity for acute infections.

Intended purpose

The DHC test for HIV infection is intended to be used in individuals where a HIV test is indicated and in those who are at a high-risk of HIV infection. The MSAC 1391 Final Protocol states that there are a number of contexts where HIV testing would be indicated, including:

- clinical suspicion of HIV infection;

- inclusion of HIV within the differential diagnosis;

- diagnosis of a condition with shared transmission route;

- reported high-risk exposure;

- unprotected sexual intercourse with a partner whose HIV status is unknown;

- reported reuse of equipment used for skin penetration; and

- in the setting of contact tracing.

The MSAC 1391 Final Protocol defines those at "high-risk of HIV infection" to be those with or more of the following risk factors:

- men who have sex with men (MSM);

- injecting drug use;

- heterosexual contact with a person from a high prevalence country;

- heterosexual contact with a partner with/at risk of HIV infection; and

- needle-stick injury.

While each of the groups listed above could be considered to be at high-risk, a population that would be a particular target group for this diagnostic test would be men who have sex with men (MSM), given the prevalence of HIV in this population (see Clinical need below).

The DHC test is NOT intended for HIV testing performed on blood donations, for other organ or tissue donations or for routine microbiological serology during pregnancy. It is also not intended to be used as a HIV screening test.

Clinical need

HIV (Human Immunodeficiency Virus) is a virus that weakens the immune system. It infects immune cells and uses them to reproduce itself, destroying the cells in the process. AIDS (Acquired Immune Deficiency Syndrome) is a serious weakening of the body's immune system caused by HIV. When a HIV positive person's immune cells (CD4 positive cells) drop below a certain level, they can be vulnerable to infections that their body would normally fight off.

In Australia, it is estimated that approximately 26,800 (plausible range of 24,500 – 30,900) people were living with HIV at the end of 2013 (Kirby Institute 2014a, 2014b). The prevalence of HIV infection varies among various groups in Australia, see Table 1.

Table 1   HIV prevalence among selected populations in Australia

Population group	Prevalence
All	0.15%
Men who have sex with men (MSM)	8-12% (among gay community-attached men)
Injecting drug users	1-2% (among people attending needle and syringe programs)
Female sex workers	<0.1%
Aboriginal and Torres Strait Islanders	0.15%[a]

Source: Kirby Institute (2014a) p12 and Kirby Institute (2014b) p1

A total of 1,236 newly diagnosed cases were notified in 2013, which is similar to the 1,253 newly diagnosed cases in 2012 (Kirby Institute 2014b). Of the newly infected cases notified in 2013, 70-75% were through sexual contact between men (Kirby Institute 2014a, 2014b). The majority of other new HIV infections are attributed to injecting drug use, heterosexual contact in a person from a high prevalence country, and heterosexual contact with a partner at risk of HIV infection. Another risk-factor is needle-stick injury (Kirby Institute 2014a).

It is estimated that approximately 14% (11-21%) of all HIV cases in Australia are undiagnosed (Kirby Institute 2014b). Additionally, the proportion of people diagnosed late (defined by a CD4 positive cell count less than 350 cells/µl at diagnosis) was 29.6% in 2013. It would be anticipated that both those with undiagnosed HIV infection and those diagnosed late contribute to a significant proportion of HIV transmission and new diagnoses of HIV infection.

Testing as a key strategy for control of HIV transmission

The Seventh National HIV Strategy 2014-2017 (2014) has identified testing for HIV as a priority area for action. The priority actions for testing indicated in the National Strategy include:

- increased access to and uptake of voluntary and appropriate HIV testing among people from priority populations, particularly gay men and other MSM;

- improve knowledge among priority populations about the personal and public health benefits of early diagnosis and the testing, treatment and support options available; and

- support high quality, safe, appropriate and accessible testing that facilitates early diagnosis through continued review of regulatory, funding, legislative and policy mechanisms associated with HIV testing.

Likewise, the Draft National HIV Testing Policy (2014) recognises the benefits of early HIV detection and contend that a person's knowledge of their status may reinforce the need to modify risk behaviour, thereby reducing onward HIV transmission. The 2014 Draft policy supports measures that will encourage greater and more frequent testing for HIV infection among those at risk of exposure to the virus.

Similarly, the Melbourne Declaration 2012 also identifies substantial increased access to, and uptake of, voluntary HIV testing in Australia as "Action Area 1", via:

- making rapid testing widely available in clinical and community settings;

- expediting TGA licensing of reliable rapid HIV tests and funding arrangements with States/Territories (including through Medicare);

- States and Territories to set up access programs for rapid HIV testing pending Commonwealth licensing and funding; and

- investigating options to make rapid test available for home use, with appropriate linkages to sexually transmitted infections (STI) screening.

As stated above, given the high prevalence of HIV infection among MSM, this population represents a target group for this diagnostic test. The Australian Sexually Transmitted Infection & HIV Testing Guidelines 2014 for men who have sex with men recommend:

- annual HIV and other sexually transmitted infection testing for all men who have had any type of sex with another man in the previous year; and

- up to four tests per year for HIV and other sexually transmitted infection for all men who have sex with men who fall into one or more of the following categories:
  - any unprotected anal sex;
  - more than 10 sexual partners in six months;
  - participate in group sex;
  - use recreational drugs during sex;
  - are HIV-positive:
    - syphilis serology – at each occasion of CD4/viral load monitoring; and
    - chlamydia/gonorrhoea – consider at each occasion of CD4/viral load monitoring.

Although these recommendations are in place, evidence in the literature suggests that these guidelines are poorly adhered to. Guy (2010) report the results of a retrospective follow-up of HIV-negative MSM at four primary care clinics which contributed to nearly half of all HIV diagnoses in Victoria among MSM annually. The study was conducted over a 9 month period (April – December 2006) to determine whether MSM were being tested as regularly as recommended. Re-testing rates for infection were calculated over 18 months. The recommendations at the time of the conduct of the study were that all MSM be tested annually for HIV, or more regularly for MSM reporting high-risk behaviours (multiple partners, attending sex-on-premises venues, use of recreational drugs or seeking partners via the internet), or following the diagnosis of other STIs (chlamydia and/or gonorrhoea). The study found that less than 40% of MSM were re-tested for HIV, chlamydia or syphilis after one year at the same clinic (although testing at other sites may have occurred), despite recommendations for annual testing. Additionally, although testing for HIV and syphilis every six months was recommended among higher risk men, re-testing rates within six months were less than 20%.

Barriers to HIV testing

Prestage (2012) reports the results of a study employing an online survey of 519 HIV-negative (by self-report) men who were asked to indicate which barriers to testing applied from a selection of potential barriers presented to them, where multiple barriers could be indicated. Among the 519 men, the group was divided into those who had never tested, men not tested in the previous 12 months and men tested in the previous six- or 12 months. Additional categorisation into those who had unprotected anal intercourse with casual partners (UAIC) and those who had not, were also analysed. The study was conducted during 2010, thus the barriers indicated are likely to be associated with conventional serology HIV testing rather than rapid testing. The results of the survey indicating the number of men identifying relevant barriers to testing according to testing history and unprotected anal intercourse with casual partners are summarised in Table 2.

Table 2   Reported barriers to conventional HIV testing indicated by men according to testing history and those who had engaged and not engaged in unprotected anal intercourse with casual partners (UAIC)

Reason to avoid or delay testing	Never tested	Tested last 12 mths	Tested last 6-12 mths	Tested last 6 mths	No UAIC last 6 mths	UAIC last 6 mths	Total
N	37; n (%)	127; n (%)	82; n (%)	273; n (%)	385; n (%)	134; n (%)	519; n (%)
I haven't done anything risky	19 (51)	57 (45)	49 (60)	89 (33)	174 (45)	40 (30)	214 (41)
Having to return another time for results	8 (22)	39 (31)	44 (54)	118 (43)	142 (37)	67 (50)	209 (40)
I haven't enough time	6 (16)	26 (21)	29 (35)	71 (26)	92 (24)	40 (30)	132 (25)
I haven't changed partners	4 (11)	32 (25)	18 (22)	49 (18)	93 (24)	10 (8)	103 (20)
I haven't had any illness or symptoms which made me worry	11 (30)	27 (21)	24 (29)	39 (14)	68 (18)	33 (25)	101 (20)
It's too much hassle	5 (14)	24 (19)	21 (26)	46 (17)	69 (18)	27 (20)	96 (19)
It's difficult to get an appointment	2 (5)	12 (9)	14 (17)	51 (19)	56 (15)	23 (17)	79 (15)
I'm afraid I might be told I have HIV	2 (5)	19 (15)	14 (17)	38 (14)	19 (13)	24 (18)	73 (15)
My doctor doesn't bulk-bill	3 (8)	14 (11)	11 (13)	43 (16)	53 (14)	18 (13)	71 (14)
I feel embarrassed talking about my sex life to the doctor or nurse	9 (24)	21 (17)	11 (13)	26 (10)	50 (13)	17 (13)	67 (13)
I don't like needles	8 (22)	15 (12)	10 (12)	33 (12)	49 (13)	17 (13)	66 (13)
I am afraid to get tested	4 (11)	14 (11)	12 (14)	30 (11)	40 (10)	20 (15)	60 (12)
I'm afraid of letting other people know if my test shows I have HIV	1 (3)	14 (11)	8 (10)	26 (10)	29 (8)	20 (15)	49 (9)
I don't have a doctor I can trust	4 (11)	13 (11)	7 (9)	17 (6)	28 (7)	13 (10)	41 (8)
I don't want to know	0 (0)	11 (9)	7 (9)	13 (5)	19 (5)	12 (9)	31 (6)
I don't want to have to tell my partners if my test shows I have HIV	0 (0)	9 (7)	6 (7)	15 (6)	19 (5)	11 (8)	30 (6)
My doctor doesn't suggest it	2 (5)	11 (9)	5 (6)	10 (4)	18 (5)	10 (8)	28 (5)
Feeling that I'm being asked to get tested too often	3 (8)	2 (2)	5 (6)	13 (5)	21 (6)	2 (2)	23 (4)
I don't know where to get tested	4 (11)	5 (4)	1 (1)	11 (3)	11 (3)	4 (3)	15 (3)
Nothing – I've never put off getting tested	1 (3)	8 (6)	11 (13)	71 (18)	71 (18)	28 (21)	99 (19)

Source: Table 2, p455 of Prestage (2012)
Items are not mutually exclusive
Shaded rows indicate the barriers that rapid point-of-care testing may address.
Abbreviations: UAIC=unprotected anal intercourse with casual partners

Prestage (2012) present the results of multivariate analyses of reasons associated with avoiding or delaying testing:

- In a comparison of those who have ever tested versus those who have never tested, a statistically significantly greater proportion of those never tested indicated that "Did not know where to get tested" and "Did not have any symptoms of illness" were cited as reasons for not testing compared with those who had ever tested. A statistically significantly greater proportion of those who had ever tested cited "Having to return to the doctor for results" compared with those who had never tested. Statistically

significant differences in education level (a greater proportion of those ever tested had university level education), time spent with gay friends (greater amount of time spent with gay friends among those ever tested) and age (those ever tested were older) were also observed between those who had ever and never tested.

- In a comparison of those who had and who had not tested in the previous 6 months, a statistically significantly greater proportion of those who had not tested indicated that "Did not do anything risky" or "Feel embarrassed to talk to doctor" were cited as reasons for not testing compared with those who had tested within the previous six months. Those who had not tested in the previous six months were statistically significantly older than those who had.

- In a comparison of those who had engaged in unprotected anal intercourse with casual partners who had or had not tested in the previous six months, a statistically significantly greater proportion of those who had not tested cited "Did not have any symptoms of illness" as a reason for not testing compared with those having testing in the previous six months. Those who had not tested in the previous six months were statistically significantly older than those who had.

It is noted that of the barriers presented in the online survey (summarised in Table 2), only the "I don't like needles" would be addressed by the DHC test given the sample can be collected from a finger-prick procedure. However, as other STI testing should be (syphilis) or should be considered to be (chlamydia/gonorrhoea) conducted alongside HIV testing; there may still be a requirement for needles as testing for syphilis requires venepuncture. While "Having to return another time for results" may have been relevant to serology testing at the time the survey was conducted, as the Draft National HIV Testing Policy (2014, p15) states that "It is preferable that a positive result is given in person. However, this Policy supports the provision of test results by phone, SMS text message, email or other mechanism when it is considered appropriate", this is no longer applicable as there is currently no requirement for a return visit for HIV test results. Expert opinion sought during the assessment confirmed that individuals are currently told that "no new is good news" with respect to test results at one large sexual health clinic in Melbourne.

Preferences for testing modalities

Yang (2014) reported the results of an online questionnaire of gay and other men who have sex with men (GMSM) residing in Sydney, Melbourne and Perth developed to ascertain self-reported preferences for testing: rapid versus non-rapid and in non-healthcare (community- or home-based) versus in healthcare settings. Participants included 827 sexually active men, with 89% having been tested for HIV (72% in the previous 12 months). Baseline characteristics included a mean age of 34.9 years, 60% were Anglo-Australian, 53% had completed university-level education and 73% were employed on a full-time basis.

The majority of participants indicated a preference for rapid testing (73%); at home (46%), in healthcare (20%) or community (7%) settings over non-rapid testing (27%); in healthcare (23%) or community (3%) settings. With respect to setting, 56% preferred non-healthcare, community or home-based settings (53% rapid, 3% non-rapid) compared with 44% citing a preference for healthcare settings (20% rapid, 23% non-rapid). The preference for the speed of the test of the location of testing was not associated with previous history of testing. A preference for rapid testing was associated with full-time

employment (OR=1.81; 95% CI: 1.16, 2.82) compared with unemployment; employment in a managerial/professional position (OR=2.03; 95% CI: 1.19, 3.46) compared with men with no occupation, unemployed or students; and men who reported unprotected anal intercourse with casual partners (OR=1.89; 95% CI: 1.29, 2.78) compared with those who had not. These characteristics were also associated with a preference for testing in non-healthcare versus health-care settings.

Yang (2014, p592) concluded that "Australian GMSM prefer alternative testing approaches, possibly due to their convenience. The availability of new testing approaches may provide more options for GMSM at risk for HIV infection, improve access to HIV testing and potentially increase HIV testing rates."

HIV rapid tests can be less specific (i.e. can have more false positives) and can be less sensitive (i.e. can miss more cases of infection) than conventional machine controlled tests used diagnostically, in contemporary laboratory based testing. However, the ease of use of HIV rapid tests and potentially their higher uptake as screening tests, particularly among people who are not accessing conventional testing, has meant that a fit-for-purpose assessment has seen them approved for use in Australia and internationally (National HIV Testing Policy, Draft 2014).

Point-of-care testing benefits people who might be otherwise reticent to accessing conventional testing. Such testing is of particular benefit for high-risk or hard-to-reach populations who may be resistant to conventional testing such men who have sex with men (MSM) who do not routinely access health services. These populations will benefit from a single point of contact and rapid results in the case of negative results and early notification of positive results.

Currently, the results from a laboratory HIV test are not available to the individual until at least several days after a blood sample is collected, whereas results from point-of-care rapid tests are generally available within 20-30 minutes of the blood sample being collected and often available within the same clinic visit. Although the results of the rapid test are available within 20-30 minutes of sample collection, positive specimens require confirmatory laboratory-based testing, thus, there is no difference in the time to a confirmed HIV diagnosis when using the DHC test.

Early diagnosis of HIV infection is important as early treatment improves chances of maintaining good health. Early treatment and knowledge of HIV status can also reduce the risk of transmitting the virus. While there are effective treatments for HIV, there is currently no cure.

Existing procedures /tests

For HIV Antibody testing, the Western Blot assay is considered the gold standard for HIV testing. The Western Blot detects HIV antibodies in the individual's serum that react with a number of different viral proteins. These viral proteins are separated into bands of distinct molecular weight using protein gel electrophoresis. After transfer (blotting) to a solid material, proteins that are reactive with specific HIV antibodies in test sera can be identified. A Western Blot result is judged to be negative if there is no reaction of the individual's serum with any protein bands at the molecular weights corresponding to these HIV gene products. A positive Western Blot result is defined by the detection of antibodies to all of the three main groups of HIV proteins – envelope (gp160, gp120 or gp41), gag (p24) and polymerase (p66 or p51) (ASHM 2009).

An alternative test, the HIV enzyme-linked immunosorbent assay (ELISA, or sometimes referred to as enzyme immunoassay, EIA) is also commonly used. Recombinant or native HIV antigens, fixed in a solid phase, are exposed to and bound by HIV antibodies in test serum. The presence of these antibodies is then detected by a second anti-human antibody, with a sensitivity of more than 99.5% (ASHM 2009).

Marketing status of device

The Determine HIV Combo is the only rapid point-of-care test for HIV infection currently approved by the TGA for use in Australia. There are specific conditions for the approval and listing on the ARTG, including requirements that the DHC may only be used by medical testing laboratories accredited by the National Association of Testing Authorities (NATA), or in sites which employ health professionals to conduct the test, have an established relationship (in relation to the referral and testing of specimens) with a NATA accredited medical testing laboratory. Further requirements include provision of training for the correct use of the device and interpretation of results by the sponsor of the device, as well as 12 monthly reports of compliance to the conditions and post marketing surveillance reports must be submitted to the TGA (see Appendix B).

Current reimbursement arrangements

Rapid point-of-care testing is currently offered in a number of clinics Australia wide. Table 3 summarises the number of clinics offering the test in each state. Some of the clinics listed are using the TGA-approved DHC test and others are using other types of rapid tests as part of research trials for other HIV rapid test devices.

Table 3   Number of clinics in Australia offering rapid point-of-care testing for HIV (March 2015)

State	Number of clinics offering rapid point-of-care HIV testing
Australian Capital Territory	2
New South Wales	24
Northern Territory	0
Queensland	31
South Australia	0
Tasmania	1
Victoria	4
Western Australia	1

Source: http://testingportal.ashm.org.au/hiv-rapid-testing/77-hiv -rapid-testing [accessed 12 March 2015]

Funding arrangements for rapid point-of-care HIV testing exist in some States and Territories. For example, the Queensland government provides rapid point-of-care HIV tests for free under the Community HIV Education and Prevention (CHEP) program. The Victorian PRONTO! Clinics also offer the test for free, where this clinic is in partnership with the Victorian AIDS Council and the Burnet institute, who presumably fund the tests. In clinics where no external funding arrangement exists, those being tested currently pay for the test privately. One clinic reports the cost associated with the test, $25 (for cost recovery). It is presumed that the funding arrangements in place for rapid point-of-care testing would apply to all individuals who undergo the test and that it would not be applicable to only high-risk individuals.

The proposed MBS item descriptor for the rapid point-of-care test is provided in Table 4. It is proposed that any TGA registered rapid fourth generation combined Antigen/Antibody HIV test could be used to deliver the service. The DHC test is the only current test available.

Table 4   Proposed MBS item descriptor for rapid point-of-care testing for HIV

Category 6 – Pathology	Group P9 – Simple Basic Pathology Tests
MBS [item number] Point of care HIV antigen/antibody test by one or more immunochemical methods in a blood sample from a high-risk patient. **Fee:**$30.00 **Benefit:** 75% = $22.50 85% = $25.50	

Source: p5 of the MSAC 1391 Final Protocol – specifies a fee of $30.00, the 75% and 85% benefits were calculated during the assessment

The MSAC 1391 Final Protocol states that "An explanatory note would need to be included or accompany the proposed MBS descriptor explaining that the test must be performed at the point-of-care and that the MBS item cannot be claimed on laboratory testing".

It is anticipated that the majority of use will be in GP clinics and sexual health clinics primarily for MSM. Some consideration is required as to whether guidelines or explanatory notes for the identification of individuals at high-risk should be provided for GPs.

Additionally, it is noted that the proposed item descriptor does not explicitly state that the test should be used in GP or sexual health clinics, which is intended; nor does it explicitly exclude use of the DHC test for screening of blood or organ donation specimens, or use in routine pre-natal testing. Modification of the item descriptor or explanatory notes may need to be considered in order to restrict use to the populations for whom the test is intended.

Moreover, clarification is required as to how the test will be billed in instances where:

- an invalid result is obtained (no red bar appears in the control bar) and the test requires repeating; or
- where a clinician decides to repeat the test in the event of an initial reactive result prior to referral for serology testing.

That is, will the test be billed once or twice, and whether an explanatory note should be included to specify the number of times the item may be billed per consultation.

Based on Australian experience to date, uptake by General Practitioners has been limited to those whose patient mix includes a relatively high number of high-risk individuals such as MSM.

It is expected that if point-of-care HIV testing is listed on the MBS then the number of GP clinics offering the service will increase with the increases mainly additional clinics that have a high number of high-risk individuals. Although MBS funding would make it more economically viable there would still be significant hurdles for clinics to provide the service including the paperwork required to comply with TGA conditions, quality assurance program (QAP) enrolment, and the time required for training to perform the test. Unless there is significant demand from high-risk individuals it would not be worthwhile for a GP clinic to offer the service.

The MSAC 1391 Final Protocol (2015) states that "Point-of-care HIV testing provides the greatest health impact in high-risk populations and should be targeted to such groups. It is proposed that the regulatory hurdles to providing the service, even if it is MBS listed, are so significant that in practice it would only be provided by clinics serving high-risk populations. It is noted that sites currently performing point-of-care HIV testing have a relationship with a NATA accredited laboratory but are not themselves NATA accredited. Therefore, they would not normally be able to claim pathology services except for a limited number of simple basic pathology tests (P9) such as immunochemical pregnancy tests". It is not known whether the participating clinics will require independent NATA accreditation at some point.

A number of MBS items are applicable to serology HIV testing, summarised in Table 5. Although there are a number of relevant MBS items, some relate to pre-natal routine testing of pregnant women, for whom this rapid point-of-care test is not intended. Expert opinion sought during the assessment indicated that all HIV tests are bulk-billed.

The MSAC 1391 Final Protocol (2015) states that the direct cost of DHC in Australia is approximately $18.00 per test. The other equipment or resources required to perform the test are consumables to perform the finger-stick blood sample collection (alcohol wipe, lancet, waste bin). The site performing the testing is also required to enrol in a quality assurance program (QAP) which costs approximately $400 – $500 annually. Finally, practitioners performing the testing must be trained in the use of the test which takes 1 to 1½ hours.

It is acknowledged in the MSAC 1391 Final Protocol that the DHC test and other rapid HIV tests are available in other countries, particularly developing countries, at lower prices. However, high TGA registration fees (up to $84,200 + on-site audit fees every 5 years); the relatively low test volumes; and relatively higher import, staff, warehousing and distribution costs mean that comparable pricing is not feasible in Australia. The stringent conditions imposed on the TGA registration of the DHC test such as compiling training records, site declarations, site training, preparation of regulatory reports, etc. mean that supply of more product requires specialist regulatory resources and incurs additional regulatory expenses and larger testing volume does not necessarily generate economies of scale. Additional sites using the test will generate additional compliance, reporting, training and other support activities which must be covered by the direct cost of the test.

Table 5   MBS item numbers and descriptors associated with serology testing for HIV

MBS[a]	Descriptor	Fee
69384	Quantitation of 1 antibody to microbial antigens not elsewhere described in the Schedule - 1 test (This fee applies where a laboratory performs the only antibody test specified on the request form or performs 1 test and refers the rest to the laboratory of a separate APA)	$15.65 75%=$11.75 85%=$13.35
69387	2 tests described in item 69384 (This fee applies where 1 laboratory, or more than 1 laboratory belonging to the same APA, performs the only 2 estimations specified on the request form or performs 2 of the antibody estimations specified on the request form and refers the remainder to the laboratory of a separate APA)	$29.00 75%=$21.75 85%=$24.65
63690	3 tests described in item 69384 (This fee applies where 1 laboratory, or more than 1 laboratory belonging to the same APA, performs the only 3 estimations specified on the request form or performs 3 of the antibody estimations specified on the request form and refers the remainder to the laboratory of a separate APA)	$42.35 75%=$31.80 85%=$36.00
63693	4 tests described in item 69384 (This fee applies where 1 laboratory, or more than 1 laboratory belonging to the same APA, performs the only 4 estimations specified on the request form or performs 4 of the antibody estimations specified on the request form and refers the remainder to the laboratory of a separate APA)	$55.70 75%=$41.80 85%=$47.35
63696	5 or more tests described in item 69384 (This fee applies where 1 laboratory, or more than 1 laboratory belonging to the same APA, performs the only 5 estimations specified on the request form or performs 5 of the antibody tests specified on the request form and refers the remainder to the laboratory of a separate APA)	$69.10 75%=$51.85 85%=$58.75
69400	A test described in item 69384, if rendered by a receiving APP, where no tests in the item have been rendered by the referring APP - 1 test	$15.65 75%=11.75 85%=$13.35
69401	A test described in item 69384, other than that described in 69400, if rendered by a receiving APP - each test to a maximum of 4 tests	$13.35 75%=$10.05 85%=11.35
69405	Microbiological serology during a pregnancy (except in the investigation of a clinically apparent intercurrent microbial illness or close contact with a patient suffering from parvovirus infection or varicella during that pregnancy) including: a) the determination of 1 of the following - rubella immune status, specific syphilis serology, carriage of Hepatitis B, Hepatitis C antibody, HIV antibody and b) (if performed) a service described in 1 or more of items 69384, 69475, 69478 and 69481	$15.65 75%=11.75 85%=$13.35
69408	Microbiological serology during a pregnancy (except in the investigation of a clinically apparent intercurrent microbial illness or close contact with a patient suffering from parvovirus infection or varicella during that pregnancy) including: a) the determination of 2 of the following - rubella immune status, specific syphilis serology, carriage of Hepatitis B, Hepatitis C antibody, HIV antibody and b) (if performed) a service described in 1 or more of items 69384, 69475, 69478 and 69481	$29.00 75%=$21.75 85%=$24.65
69411	Microbiological serology during a pregnancy (except in the investigation of a clinically apparent intercurrent microbial illness or close contact with a patient suffering from parvovirus infection or varicella during that pregnancy) including: a) the determination of 3 of the following - rubella immune status, specific syphilis serology, carriage of Hepatitis B, Hepatitis C antibody, HIV antibody and b) (if performed) a service described in 1 or more of items 69384, 69475, 69478 and 69481	$42.35 75%=$31.80 85%=$36.00
69413	Microbiological serology during a pregnancy (except in the investigation of a clinically apparent intercurrent microbial illness or close contact with a patient suffering from parvovirus infection or varicella during that pregnancy) including: a) the determination of 4 of the following - rubella immune status, specific syphilis serology, carriage of Hepatitis B, Hepatitis C antibody, HIV antibody and b) (if performed) a service described in 1 or more of items 69384, 69475, 69478 and 69481	$55.70 75%=$41.80 85%=$47.35
69415	Microbiological serology during a pregnancy (except in the investigation of a clinically apparent intercurrent microbial illness or close contact with a patient suffering from parvovirus infection or varicella during that pregnancy) including: a) the determination of all 5 of the following - rubella immune status, specific syphilis serology, carriage of Hepatitis B, Hepatitis C antibody, HIV antibody and b) (if performed) a service described in 1 or more of items 69384, 69475, 69478 and 69481	$69.10 75%=$51.85 85%=$58.75

Source: MBS online

a   items 69384 to 69401 are subject to rule 6. Item 69400 is also subject to rule 18 and 69401 is subject to rules 18 and 18A

In 2013, a total of 817,625 specimens were tested for HIV antibody in public health laboratories (Kirby Institute, 2014a), many of which are likely to be for routine screening of blood and organ donations and routine pre-natal testing of pregnant women. In addition to these MBS item numbers, various additional pathology MBS items that may apply are summarised in Table 6. Of these additional items, only items 74990 and 74991 would be applicable to rapid point-of-care testing, and only when the test is bulk-billed.

Table 6   **Additional pathology MBS item numbers and descriptors associated with testing for HIV**

MBS Item[a]	Descriptor	Fee
73928	Initiation of a patient episode by collection of a specimen for 1 or more services (other than those services described in items 73922, 73924 or 73926) if the specimen is collected in an approved collection centre. Unless item 73920 or 73929 applies	$5.95 75%=$4.50 85%=$5.10
73929	Initiation of a patient episode by collection of a specimen for 1 or more services (other than those services described in items 73922, 73924 or 73926) if the specimen is collected by an approved pathology practitioner for a prescribed laboratory or by an employee of an approved pathology authority, who conducts a prescribed laboratory, if the specimen is collected in an approved pathology collection centre	$2.40 75%=$1.80 85%=$2.05

74990	A pathology service to which an item in this table (other than this item or item 74991) applies if:
	a) the service is an unreferred service; and
	b) the service is provided to a person who is under the age of 16 or is a Commonwealth concession card holder; and
	c) the person is not an admitted patient of a hospital; and
	d) the service is bulk-billed in respect of the fees for:
	  i) this item; and
	  ii) the other item in this table applying to the service
		$7.05
		85%=$6.00

74991	A pathology service to which an item in this table (other than this item or item 74991) applies if:
	a) the service is an unreferred service; and
	b) the service is provided to a person who is under the age of 16 or is a Commonwealth concession card holder; and
	c) the person is not an admitted patient of a hospital; and
	d) the service is bulk-billed in respect of the fees for:
	  i) this item; and
	  ii) the other item in this table applying to the service; and
	e) the service is provided at, or from, a practice location in
	  i) a regional, rural or remote area; or
	  ii) Tasmania; or
	  iii) a geographical area included in any of the following SSD spatial units (specified areas)
		$10.65
		85%=$9.10

74995	A payment when the episode is bulk-billed and includes item 73928, 73930 or 73936.	$4.00 75%=$3.00 85%=$3.40
74999	A payment when the episode is bulk-billed and includes item 73923, 73925, 73927, 73929, 73931, 73933, 73935, 73937 or 73939.	$1.60 75%=$1.20 85%=$1.40

Source: MBS online

Approach to assessment

Objective

According to the MSAC 1391 Final Protocol (2015), the objective of this assessment was to determine in individuals where an HIV test is indicated, is rapid point-of-care combined Antigen/Antibody HIV testing at least as cost-effective as laboratory-based HIV testing for the early diagnosis of HIV infection?

Clinical decision pathway

The current and proposed clinical pathways provided in the MSAC 1391 Final Protocol (2015) are summarised in Figure 2.
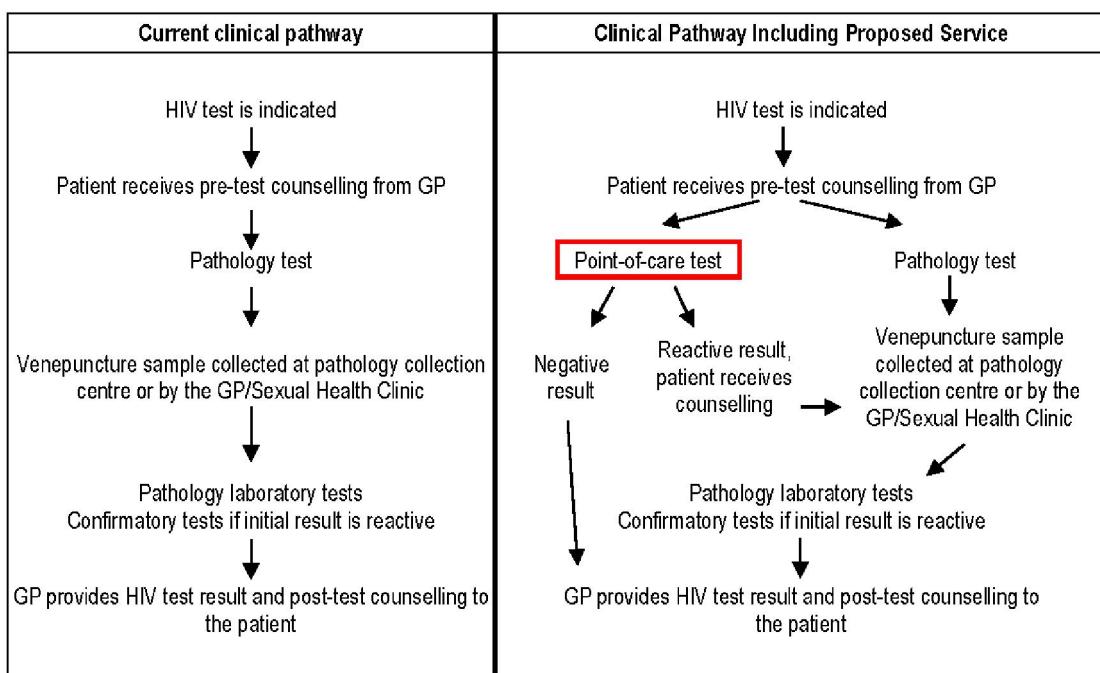
Figure 2   Current and proposed clinical decision tree

The proposed algorithm provided in the MSAC 1391 Final Protocol implies that rapid point-of-care testing will substitute for laboratory testing for HIV. Expert opinion sought during the assessment indicated that in a Melbourne clinic using the DHC test, venous samples were still being collected on the same day as the rapid test for laboratory testing (regardless of whether the DHC test was reactive or not); indicating that the DHC test may be an additional, rather than an alternative test to serology. The advice also indicated that this was an opt-out system for those who are adamant they do not want a venous sample taken (less than 10 in 100 would decline); and that individuals suspected of early HIV seroconversion were particularly encouraged to undergo additional laboratory testing; other advice suggested that those suspected of early infection should not be tested with a rapid test at all. Given testing for syphilis is recommended at the time of HIV testing and syphilis serology requires venepuncture, it is not unreasonable (and could perhaps be considered inappropriate not) to test for HIV at the same time.

As noted above, HIV rapid tests can be less specific (i.e. can have more false positives) and can be less sensitive (i.e. can miss more cases of infection) than conventional machine controlled tests used diagnostically, in contemporary laboratory based testing. The risk of false-negative results in practice may however be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product.

Comparator

The relevant comparator to assess the safety, effectiveness and cost-effectiveness of the rapid point-of-care HIV Antigen/Antibody test is serology testing for HIV. The exact testing performed by the laboratory will depend on the diagnostic algorithm in use but would typically consist of full testing protocol i.e. initial and confirmatory testing. Expert opinion sought during the assessment indicated that standard practice would be the use of a fourth generation Ag/Ab screening assay such as Abbott Architect®. The advice also indicated that in some instances, a reactive HIV sample might undergo (in total) testing in four different fourth generation HIV Ag/Ab EIAs (where only a single MBS item billing applies), as well as a HIV Western Blot (no MBS item number applies) and any other supplementary tests as indicated. Additionally, expert opinion suggested that the use of rapid HIV tests in the community, performed outside of NATA accredited laboratories, would NOT impact on the CURRENT testing algorithm at laboratories when used to confirm reactive DHC tests.

The reference standard

The gold standard for diagnosis of HIV infection is the Western Blot.

Research questions

The key research question is:

In individuals where an HIV test is indicated, is rapid point-of-care combined Antigen/Antibody HIV testing at least as cost-effective as laboratory-based HIV testing for the early diagnosis of HIV infection?

Diagnostic assessment framework

This assessment of rapid point-of-care HIV Antigen/Antibody testing is based on the framework outlined in the *MSAC guidelines for the assessment of diagnostic technologies* (MSAC 2005).

The effectiveness of a diagnostic or predictive test depends on whether it improves patient health outcomes. The clinical benefit can be assessed by studies that directly investigate the impact of the test on health outcomes or, alternatively, in some situations by linking evidence from different studies within the diagnostic or predictive pathway.

Direct evidence

Comparative **direct evidence** would present data on individuals at high-risk of HIV infection. These individuals would be tested for HIV using either the rapid point-of-care Antigen/Antibody test or serology tests. In both study arms, those who were deemed positive for HIV infection would receive relevant treatment. Should one test be better at identifying individuals with HIV infection and ensure appropriate treatment compared with the other test, this would be reflected in differences in health outcomes between the study groups.

The review of the literature indicated that no such data existed, thus a linked evidence approach was employed.

Linked evidence

The linked evidence approach is undertaken in three steps, with subsequent steps relying on the findings of the previous steps, as per the framework given in Merlin (2013) and presented in Figure 3. Depending on the results of the diagnostic accuracy review (evidence linkage 1), evidence linkage 2 is undertaken to assess change in patient management; and depending on the results of that, evidence linkage 3, which looks at treatment effectiveness, may need to be addressed.
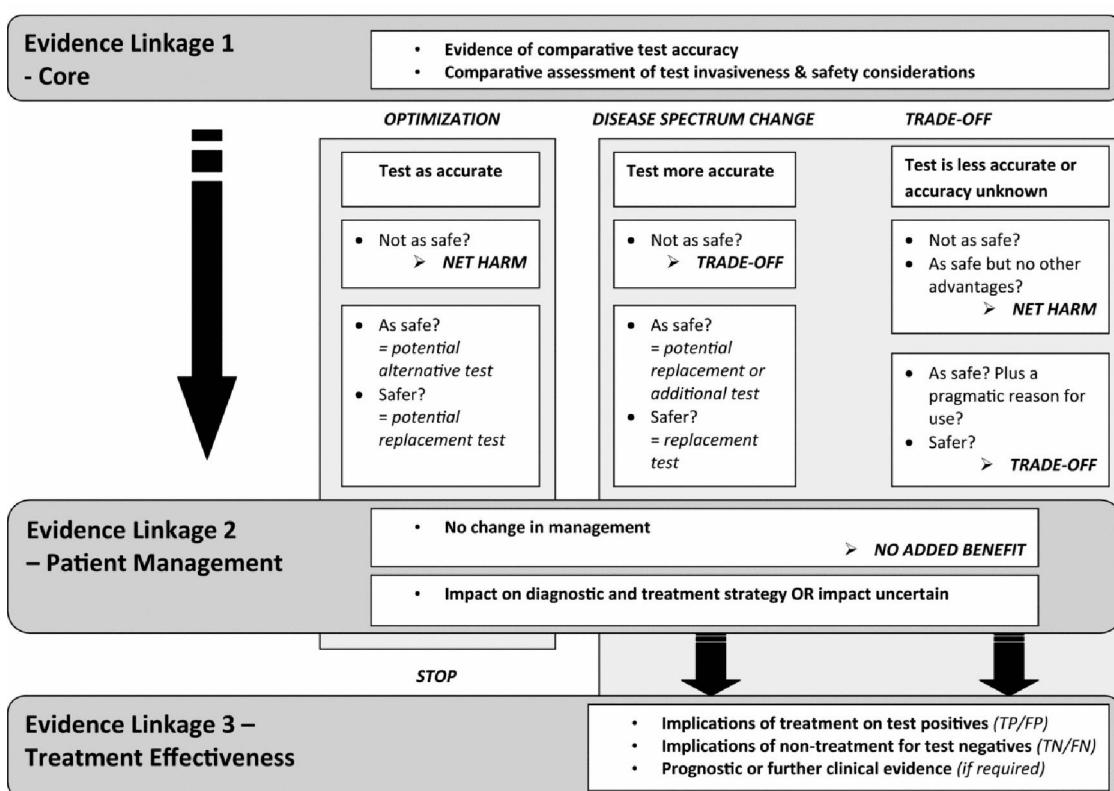
Figure 3   Decision framework to implement the linked evidence approach when evaluating medical tests

Source: Merlin (2013)

The questions addressed through the evidence linkage are:

Diagnostic accuracy:

1. Does rapid point-of-care Antigen/Antibody testing in GP or sexual health clinics have similar accuracy to the current testing strategy for diagnosis of HIV?

2. What proportion of individuals have a discordant HIV diagnosis when tested with both the proposed and current testing strategies?

Impact on clinical management:

1. Does the availability of a rapid point-of-care Antigen/Antibody test lead to improved testing rates or increased testing frequency?

2. Does the availability of a rapid point-of-care Antigen/Antibody test lead to earlier diagnosis of HIV infection? Earlier diagnosis was not defined in the MSAC 1391 Final Protocol. For the purposes of this assessment, it refers to diagnosis of HIV prior to the development of AIDS complications rather than the commonly used definition based on CD4 positive cell count. Early diagnosis in this instance would be achieved by (i) increased frequency of testing those who are currently being tested and (ii) testing among those who have never tested.

Cost-effectiveness:

1. What is the cost of rapid point-of-care Antigen/Antibody testing per case of HIV detected?

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period up to February 2015. Searches were conducted via OVID Medline, Embase and Evidence Based Medicine (EBM) Reviews on 24 February 2015.

Table 7   Electronic databases searched

Database	Period covered
OVID Medline[a]	1946 to Present
OVID Embase	1974 to 2015 February 23
OVID EBM Reviews[b]	1991 to February 2015

[a]   Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present

[b]   Cochrane Database of Systematic Reviews 2005 to January 2015, EBM Reviews - ACP Journal Club 1991 to February 2015, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2015, EBM Reviews - Cochrane Central Register of Controlled Trials January 2015, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 1st Quarter 2015, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2015

The search terms used included terms relevant to human immunodeficiency virus (HIV) and rapid point-of-care testing (see Appendix C for full search terms used and results of the number of citations identified). Hand searching of the reference lists of relevant articles was also conducted to identify any additional relevant studies/trials that may not have been identified in the electronic searches. A number of HTA websites were also searched for any relevant published HTAs (see Appendix C for the full list of HTA websites searched).

The search terms used specifically excluded any terms relating to outcomes reported, such that studies and trials relevant to the assessment of the diagnostic characteristics and effectiveness of the test, respectively, were sought from the single list of citations.

Selection criteria

The selection criteria used as the basis for the selection of articles are summarised in Box 1. If diagnostic accuracy studies conducted in Australia were identified, only studies reporting results for an Australian population would be included given Australia's unique prevalence of HIV, which is known to impact on diagnostic accuracy measures such as the positive and negative predictive values.

Box 1   Selection criteria for included studies

Characteristic	Diagnostic accuracy	Effectiveness
Study design	Cross-sectional study where all participants underwent testing with the intervention and comparator test	Randomised controlled trial
Population	High-risk individuals where an HIV test is indicated	High-risk individuals where an HIV test is indicated
Index test/Intervention	Rapid, point-of-care Ag/Ab testing for HIV	Rapid, point-of-care Ag/Ab testing for HIV
Reference standard	Western Blot	Western Blot
Comparator	Serology testing for HIV	Serology testing for HIV
Outcomes	Diagnostic accuracy: sensitivity, specificity, positive and negative predictive values	Number of HIV tests Early diagnosis of HIV infection
Language	Non-English language articles were excluded	Non-English language articles were excluded

Search results

The PRISMA flowchart detailing the search results for this assessment is shown in Figure 4.
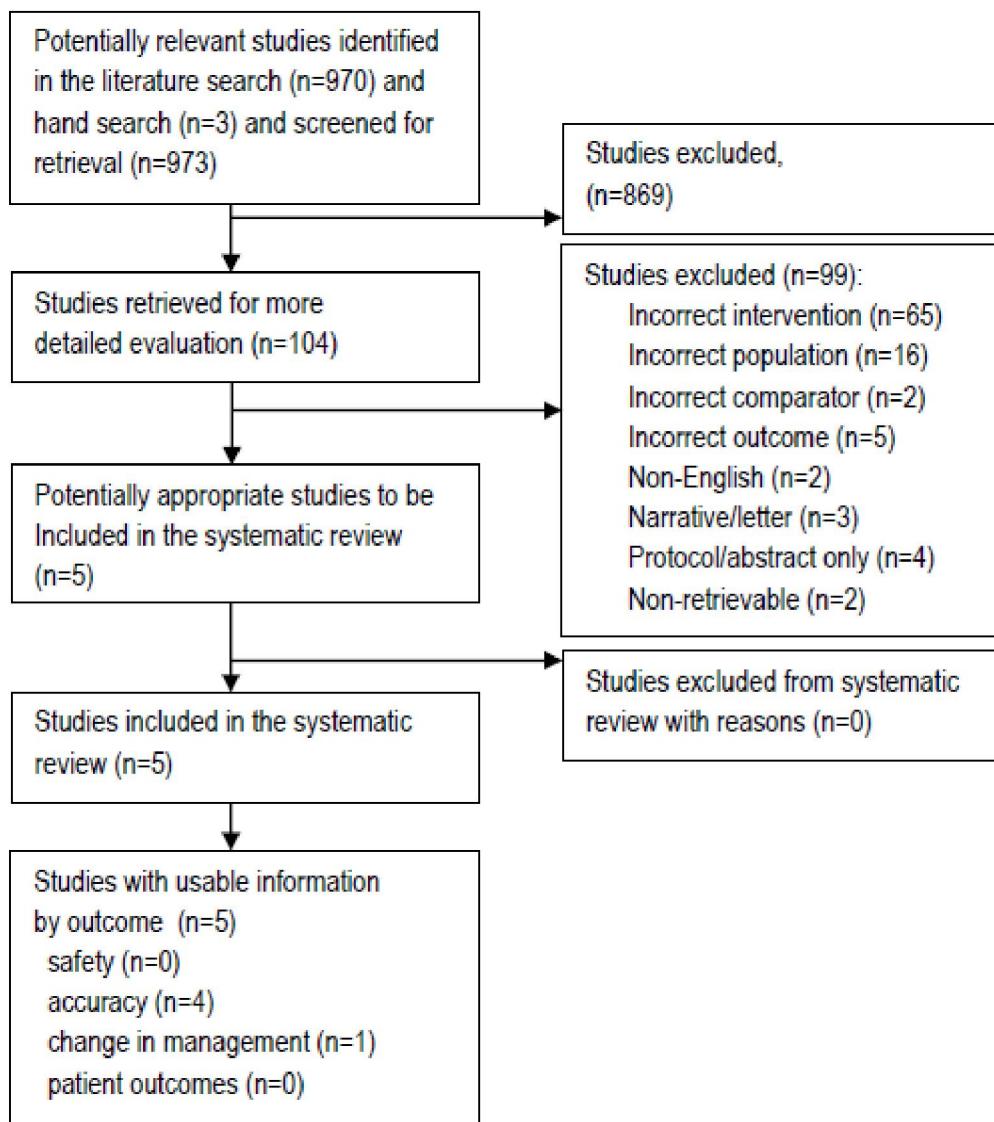
Figure 4   PRISMA flowchart - summary of the process used to identify and select studies for the review
Adapted from Liberati (2009)

The study profiles of all included studies are presented in Appendix D. Full text articles that did not meet the inclusion criteria are provided in Appendix E, where the studies are listed according to the reason for exclusion.

Data extraction and analysis

Two reviewers independently extracted data from the included studies. Meta-analyses of diagnostic accuracy data was conducted using Meta-Disc.

Appraisal of the evidence

Appraisal of the evidence was conducted at 3 stages:

Stage 1: Appraisal of the applicability and quality of individual 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 intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

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, 2000).

These dimensions (Table 8) 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. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 8   Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

* See

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The "level of evidence" reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (see Table 9).

Table 9   Designations of levels of evidence according to type of research question (including table notes) (NHMRC 2008)

Level	Intervention [1]	Diagnostic accuracy [2]
I [4]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]

Table notes

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

[2] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

[3] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

[4] 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.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting 2003).

[6] Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[10] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 10.

Table 10   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 and 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 Q3 poor reference standard poor quality or insufficient information

Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000a). This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan 2001). Studies of diagnostic accuracy were assessed using the QUADAS quality assessment tool (Whiting 2011).

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000b). Studies need to be appropriately to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

To assess the diagnostic accuracy of the rapid point-of-care Antigen/Antibody test in the included studies, data were extracted, where possible, into a classic 2x2 table in which the results of the index diagnostic test were cross-classified against the results of the reference standard, and Bayes' Theorem was applied:

	Reference test positive	Reference test negative	
Index test positive	True positive	False positive	Total test positive
Index test negative	False negative	True negative	Total test negative
	Total with HIV	Total without HIV	

The sensitivity, specificity, negative and positive predictive values (NPV, PPV) and likelihood ratios (LR) of the tests (as defined below) were calculated with corresponding 95% confidence intervals (95%CIs). Small confidence intervals give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000).

Sensitivity (true positive rate) = true positives / total with HIV

Specificity (true negative rate) = true negatives / total without HIV

PPV (proportion of positive results that are true positives) = true positives / true + false positives

NPV (proportion of negative results that are true negatives) = true negatives / true + false negatives

Positive LR (LR+) = sensitivity/1–specificity

Negative LR (LR–) = 1–sensitivity/specificity

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000b).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

- The evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients;

- The consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction ie homogenous or heterogeneous findings;

- The potential clinical impact - appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;

- The generalisability of the evidence to the target population; and

- The applicability of the evidence - integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 11) (NHMRC 2008).

Table 11   Body of evidence assessment matrix

Body of evidence Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base[a]	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/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[b]	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	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population[c]	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

Adapted from (NHMRC 2008)

[a]   Level of evidence determined from the NHMRC evidence hierarchy—Table 11

[b]   If there is only one study, rank this component as 'not applicable'.

[c]   For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

SR = systematic review; several = more than two studies

Results of assessment

Is it safe?

Summary of Safety –

No studies assessing the comparative safety of rapid point-of-care testing and serology testing for HIV were identified.

With respect to the procedures undertaken to collect specimens for testing, a finger-prick or venepuncture for rapid point-of-care and serology, respectively, no real safety issues are associated with either, provided the person drawing the samples is trained and sterile equipment is used. In addition, as the DHC test requires the same or fewer blood withdrawals than the comparators, it is reasonable to conclude that the test is safe.

The impact of false positive or false negative results from the rapid point-of-care test however, should be considered. Where false positive results occur from the DHC test, this is likely to be associated with concern and anxiety until such time that the individual's true HIV status is conveyed. With respect to false negative results, there is potential for those individuals to have worse health outcomes in the longer term due to having an undiagnosed HIV infection. There is also the potential for these individuals to unknowingly transmit HIV to other individuals until such time they undergo further testing and are diagnosed. As discussed above, the current practice in at least one Melbourne clinic is to collect a venous sample on the same day as rapid testing for serology testing for HIV. If this applies nationally, the risk of false negative results should be no greater than is currently the case. The risk of false-negative results in practice may additionally be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product.

No studies assessing the comparative safety of rapid point-of-care testing and serology testing for HIV were identified.

With respect to the procedures undertaken to collect specimens for testing, a finger-prick of venepuncture for rapid point-of-care and serology, respectively, no real safety issues are associated with either, provided the person drawing the samples is trained and sterile equipment is used. In addition, as the DHC test requires the same or fewer blood withdrawals than the comparators, it is reasonable to conclude that the test is safe.

The impact of false positive or false negative results from the rapid point-of-care test however, should be considered.

With respect to false positive results, where the rapid point-of-care test indicates the presence of HIV infection, but confirmatory serology testing does not; it would be

anticipated that the anxiety felt over the week prior to delivery of the serology test results would be greater than for those who are undergoing routine testing with serology testing (with no rapid point-of-care test result). The positive rapid point-of-care result would also be accompanied with counselling for the results according to the proposed clinical decision pathway (see Figure 2).

With respect to false negative results, where the rapid point-of-care test indicates no HIV infection, but confirmatory serology testing would; there is potential for those individuals to have worse health outcomes in the longer term due to having an undiagnosed HIV infection. There is also the potential for these individuals to unknowingly transmit HIV to other individuals until such time they undergo further testing and are diagnosed. As noted above, the current practice in at least one Melbourne clinic is to collect a venous sample on the same day as rapid testing for serology testing for HIV. If this applies nationally, the risk of false negative results should be no greater than is currently the case. The risk of false-negative results in practice may additionally be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product.

Is it effective?

Summary of effectiveness–

Diagnostic accuracy

An assessment of the diagnostic accuracy of the DHC test in an at-risk population was derived from two Australian studies offering the DHC test to MSM attending GP and sexual health clinics in Melbourne and Sydney. The attendees each also had laboratory-based testing for HIV, where a negative laboratory-based enzyme immunoassay was used to determine a true negative status and in those with positive laboratory-based immunoassay, further confirmatory analysis by Western Blot was also performed to determine true HIV status.

A meta-analysis of the two included studies indicated that the sensitivity of the DHC test was 87.8% (95% CI: 75.2%, 95.4%) and the specificity was 99.4% (95% CI: 99.1%, 99.7%).

Changes to patient management

A single randomised controlled trial was identified in which MSM who had a previous negative HIV test result within the last two years were randomised to the DHC test or conventional laboratory-based testing for HIV. The trial duration was a period of 18 months and the primary outcome of the trial was "HIV tests over 18 months".

The results of the trial indicate that there was no statistically significant difference between groups for the primary outcome of "HIV tests over 18 months" or the secondary outcomes of syphilis, chlamydia and gonorrhoea testing over 18 months. Hence, the possibility of having HIV tests by rapid point-of-care testing did not result in higher testing frequency over the study period of 18 months.

The authors also undertook *post-hoc* analyses considering only the first HIV test after enrolment and considering only subsequent HIV tests (excluding first tests). A statistically significantly greater number of first HIV tests/year after the enrolment test was observed in those randomised to the HIV testing by the rapid point-of-care test compared with conventional testing, however no differences were observed in the number of HIV tests/year when only considering subsequent tests. Based on these results, the authors conclude that "Post hoc analysis showed an initial increase in their rate of testing that was not sustained".

Direct evidence

No direct evidence comparing point-of-care HIV antibody/antigen testing with ELISA/EIA and Western Blot testing was identified.

Evidence linkage 1: Is the test accurate?

Studies comparing the diagnostic accuracy of point-of-care HIV antibody/antigen testing compared with enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay (EIA) and Western Blot (WB) amongst a high-risk population in Australia

The MSAC 1391 Final Protocol states that "According to the product insert, the sensitivity of the Determine HIV Combo (DHC) is 100.00% across 1,179 specimens positive for various types and subtypes of HIV and who were confirmed HIV antibody positive. The specificity of the test is 99.61% for the antigen test line and the 99.21% for the antibody test line across 1,783 HIV-negative specimens". Given these estimates are derived from the two extreme ends of the disease spectrum (ie, confirmed seronegative and seropositive specimens), which tends to overestimate diagnostic accuracy (Knottnerus 2002), an assessment of the diagnostic characteristics of the test amongst a high-risk Australian population, where the test was being used in GP and sexual health clinics, and was compared with current diagnostic tests used in Australia was deemed relevant to this review.

Four publications (Conway 2013a, Conway 2013b, Conway 2014, Eu 2014) reporting two Australian studies were identified. Conway 2013a, 2013b appear to be earlier conference abstracts of Conway (2014). Each study assessed the diagnostic accuracy of the Determine HIV antibody/antigen test to serology testing for HIV infection amongst men who have sex with men (MSM) in Sydney (Conway 2013a, 2013b, 2014) and Melbourne (Eu 2014).

Conway (2013a, 2013b, 2014)

Conway (2014) reports the results of a study which was conducted over four free-access publically-funded sexual health clinics with high caseloads of MSM. Two of the clinics were in central Sydney, and the remaining two in suburban Sydney. MSM, aged ≥18 years and presenting for HIV testing who attended the clinics were offered the DHC test by doctors and nurses who performed and read the tests; counsellors were available at each site to support those with a positive test result. Clinic staff (in all, 68 staff from the Kirby Institute, NSW State Reference Laboratory for HIV and National Serology Reference Laboratory) were trained in policy and theoretical and practical aspects of rapid HIV testing, which included quality assurance, conducting tests using the DHC and interpreting the results.

Venepuncture specimens for conventional, and finger-stick blood specimens for DHC testing were collected. The DHC test results were scored by clinic staff as:
- non-reactive (specimen did not react with test lines);
- reactive (specimen reacted with one (antigen or antibody) or both (antigen and antibody) test lines); or
- invalid (the control line was absent).

Participants received their DHC test result during the clinic visit, with those having a positive test result offered support and counselling. Those with negative results were asked to come back to the clinic once results of conventional testing were available and receive appropriate care.

DHC results were categorised as true or false compared with laboratory assays which are stated by the authors to be standard of care:

- fourth generation HIV screening immunoassay;
- supplementary HIV antibody;
- HIV p24 antigen immunoassay; and
- HIV Western Blot.

In those diagnosed with HIV infection, HIV RNA, CD4 positive T-cell count and genotype tests were also performed.

True negatives were defined as those who had a negative fourth generation laboratory screening immunoassay.

All specimens with a positive result on the fourth generation laboratory screening immunoassay also underwent supplementary HIV antibody, HIV p24 antigen and Western Blot testing, with true positives being defined based on the national case definition[1].

The authors state that HIV cases were categorised as acute, recent or early HIV infection, defined as:
- Acute: HIV RNA or p24 antigen positive, but antibody negative;
- Recent: HIV antibody positive, but infected in the last six months (previous testing history based on testing conducted at the clinic, or by self-report); and
- Early: cases of acute and recent infection combined.

Over the 20-month study period, 2,468 men had 3,195 HIV tests (DHC with parallel conventional serology testing) across the four clinic sites. Of the 3,195 DHC tests performed, five (0.2%) were invalid and excluded from the analysis.

Eu (2014)

Eu (2014) reports one inner city suburb of Melbourne clinic's experience with the DHC test. The clinic undertakes approximately 2,500 HIV tests per year. The DHC test was made available to all attendees to the clinic who were of consenting age and who requested the test. Of 1,527 MSM attendees to the clinic requesting a HIV test, 219 (14.3%; 95% CI: 12.5%, 16.1%) chose to have the rapid point-of-care test.

All participants having a DHC test also had a serum test (fourth generation enzyme immunoassay HIV antibody test) performed. The results presented by the authors refer to the 302 DHC tests with parallel serology testing conducted; these included tests among 219 MSM over a five and a half month period (15 March – 31 August 2013). The authors state that all fully positive HIV results and seroconverters where the Western Blot result was not fully positive were considered positive results for calculations of diagnostic accuracy.

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[1] (1) Repeatedly reactive result on a screening test for HIV antibody followed by a positive result on a Western Blot. A positive result on a Western Blot is defined by the presence of a glycoprotein band (gp41, gp120 or gp160) and at least three other HIV-specific bands OR (2) Detection of HIV by at least two virologic assays (nucleic acid testing for proviral DNA; HIV p24 antigen, with neutralisation; virus isolation) performed on at least two separate blood samples. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hivuns.htm

The results reported for the diagnostic characteristics of the DHC test compared with serology testing for HIV in Conway (2014) and Eu (2014) are reported in Table 12. Also presented are the results of a meta-analysis of the two studies.

Table 12   Diagnostic characteristics of the DHC test compared with serology testing for HIV

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Conway (2014)	87.2% (71.8%, 95.2%)	99.4% (99.1%, 99.7%)	65.4% (50.8%, 77.7%)	99.8% (99.6%, 99.9%)
Eu (2014)	90% (83.2%, 96.8%)	99.7% (99.1%, 100%)	90% (83.2%, 96.8%)	99.7% (99.1%, 100%)
Meta-analysis[a]	87.8% (75.2%, 95.4%)	99.4% (99.1%, 99.7%)	NC	NC

Abbreviations: NC=not calculable

[a]   conducted using MetaDisc. It is noted that the reported 95% confidence intervals could not be replicated when using MetaDisc, however the estimated overall confidence intervals are deemed reliable

Source: Table 3, p 5 of Conway (2014) and Figure 1, p90 of Eu (2014)

Conway (2014) reports that 34 of 39 true positives (five false negatives) were detected by DHC. There were 3,151 true negatives among the participants; the DHC test indicated that 3,133 were negative (18 false positives). Of the 18 false positives, 14 had follow-up testing and were determined to be negative; the remaining four declined or did not attend for further testing. No significant differences in the median CD4 positive T-cell count were observed amongst those who were true positive or false negative, however median HIV RNA was statistically significantly higher in those who were false negative (238,025 copies/mL) compared with true positives (37,591 copies/mL); p=0.022. Additionally, a statistically significantly greater proportion of false negatives (80%) compared with true positives (24%) were categorised as having early HIV infection (p=0.025).

Eu (2014) reports that 10 participants were diagnosed with HIV during the study period; three of whom were seroconverting and confirmed at a later time. Ten specimens were reactive to the DHC test, of which nine were true positives (one false positive). A further participant deemed non-reactive to the DHC test was subsequently determined to be seroconverting (false negative). There were no positive HIV antigen results in the sample.

Conway (2014) reports that none of the three specimens categorised as having acute infection were identified by the DHC. Eu (2014) reported that the DHC test detected two of the three seroconverters.

Additional outcomes reported in Conway (2013a, 2013b, 2014) and Eu (2014)

Diagnostic characteristics for the components (antigen and antibody) of the DHC test

Conway (2014) presents further diagnostic accuracy results based on the antigen and antibody components of the test, summarised in Table 13.

Table 13   Diagnostic characteristics of the components of the DHC test compared with serology testing for HIV reported in Conway (2014)

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Antigen	0.00% (0.00%, 37.1%)	99.8% (99.6%, 99.9%)	0.00% (0.00%, 48.3%)	99.7% (99.4%, 100%)
Antibody	94.4% (80.0%, 99.0%)	99.6% (99.2%, 99.8%)	70.8% (55.7%, 82.6%)	99.9% (99.7%, 100%)

Source: Table 3, p 5 of Conway (2014)

Conway (2014) reports that of the 36 HIV antibody cases, 34 were detected by the antibody component of the DHC test (two false negatives). Thirty-one cases were both HIV antibody and antigen positive by reference testing, of which 30 were identified as reactive by the antibody component of the DHC test.

The antigen component of the DHC failed to identify any of the nine cases who were HIV p24 antigen positive by reference testing; where these nine cases had p24 antigen titres ranging from 66 to 701 (median of 115) pg/mL. Of the 18 overall false positive results from the DHC test, four were positive to the antigen component of the test, 12 to the antibody component and two to both; such that the antigen component contributed to six of the 18 (33%) false positive results. Additionally, the antigen component of the DHC test failed to detect antigen in six of 12 specimens categorised as being early infection, where these six cases had p24 antigen titres ranging from 66 to 701 (median of 129) pg/mL. Notably, all of these specimens had viral titres above the reported analytical cut off for the p24 antigen of approximately 12.5-25pg/mL (see "The test").

Patient satisfaction

Eu (2014) reports data collected during the study period relating to patient satisfaction. A total of 146 completed questionnaires were provided by 270 participants. Responses to the questionnaires indicated that one in five (20%; 95% CI: 14-26%) would not have a HIV test if a rapid point-of-care test were not available and most (57%; 95% CI: 49-65%) said they would test more often because rapid point-of-care tests were available. Responses also indicated that satisfaction with the test was high (98.6%; 95% CI: 96.7-100%) based on whether the responder would have subsequent tests with DHC.

Eu (2014) states that the survey data suggests that the availability of the DHC test at their clinic was successful in increasing the uptake of HIV testing, with 77 new files for MSM. The authors state that the rate of HIV cases detected during the study period was 4.1% (95% CI: 1.9%, 7.7%), compared with 1.3% (95% CI: 1.1-1.5%) in the 32 months prior to the study period in MSM, where testing in the period prior to the study was based on serology. The authors conclude that the comparatively high detection of HIV positive cases during the study period indicated that individuals at high-risk of undiagnosed HIV preferred a rapid point-of-care test.

Experience of those conducting the tests over time

Conway (2013a) reports the results of an assessment of the acceptability rapid testing for HIV among clinical staff over time. Of the 68 staff trained to undertake testing with the DHC test, 67 completed the first (after training) and 53 completed the second (after at least 6 months) questionnaire. The questionnaires implemented a five-point Lickert

scale, with '1' indicating strong agreement and '5' indicating disagreement to a range of acceptability questions. Results of the surveys are presented in Tables 14 and 15.

Table 14   Responses to the first and second questionnaires reported in Conway (2013a)

Statement	First questionnaire, mean score	Second questionnaire, mean score	p-value[a]
Improved confidence in conducting the test	1.87	1.44	**<0.01**
Confidence in the delivery of negative results	1.52	1.25	**<0.01**
Disagreement that rapid testing was disruptive	3.27	3.83	**<0.01**
Comfort with role in rapid testing	1.71	1.41	**0.04**

Source: pA346 of Conway (2013a)
Lower mean scores indicate greater agreement with the statement
[a]   T-test, with stratification by staff profession and testing experience

Table 15   Responses by doctors and nurses for the second questionnaire reported in Conway (2013a)

Statement	Doctors, mean score	Nurses, mean score	p-value[a]
Preference for rapid tests	1.75	2.50	**0.02**
Rapid testing interferes with consultations	2.63	3.93	**0.01**

Source: pA346 of Conway (2013a)
Lower mean scores indicate greater agreement with the statement
[a]   T-test, with stratification by staff profession and testing experience

Stronger agreement with the belief that those being tested were satisfied with rapid testing was demonstrated among staff who had conducted ≥10 tests (mean score of 1.58) compared with staff having conducted <10 tests (mean score of 2.07; $p<0.01$).

The data indicates that over time and with increasing experience, clinic staff become more comfortable in conducting rapid testing.

The data presented in these two studies is directly applicable to those for whom listing is sought. While the results of these diagnostic accuracy studies yield different diagnostic characteristics of the DHC test compared with serology testing provided in the product insert, the differences are likely to result from the estimates provided in the product insert having been assessed from the two extreme ends of the disease spectrum (ie, confirmed seronegative and seropositive specimens), which tends to overestimate diagnostic accuracy (Knottnerus 2002).

The risk of false-negative results may be mitigated in Australian practice however via continued serology testing regardless of the DHC test result (as is the case in one Melbourne clinic) and through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product.

Evidence linkage 2: Does it change patient management?

A single randomised controlled trial reported by Read (2013) was identified which assessed the impact of the availability of a rapid point-of-care test compared with conventional testing for HIV. Men aged ≥18 years who reported having had a male sexual partner in the last year and a <u>negative HIV test within the last two years</u> were

randomised to receive rapid point-of-care testing with DHC or conventional, laboratory based HIV testing.

The trial was 18 months in duration and men were free to undergo HIV testing at any time – by allocated intervention at the study clinic or by conventional testing at any other clinics during the study period. Men randomised to both arms of the trial were sent text messages at three, nine and 15 months recommending regular HIV testing. They were also sent text messages referring them to a website to inform them of the tests that were available to them and a dedicated phone number for inquiries.

Men randomised to the two arms of the trial had comparable baseline characteristics with respect to age, time since last HIV test, proportion with university education, number of male sexual and anal sexual partners in previous year and proportion reporting unprotected anal sex with casual partners in the last year.

The results from the trial reported by Read (2013) are presented in Table 16.

Table 16   Outcomes reported by Read (2013)

Outcome	DHC tests/year (95% CI)[a]	Conventional tests/year (95% CI)[a]	Incidence rate ratio (95% CI) [p-value]
	N=200	N=200	
HIV tests over 18 months	1.63 (1.49, 1.79)	1.42 (1.29, 1.57)	1.15 (0.96, 1.38) [0.12]
First HIV test after enrolment test (*post-hoc*)	1.32 (1.13, 1.54)	1.01 (0.66, 1.19)	**1.32 (1.05, 1.65) [0.02]**
Subsequent HIV tests (excluding first tests; *post-hoc*)	1.86 (1.66, 2.07)	1.83 (1.62, 2.07)	1.01 (0.86, 1.20) [0.90]
Syphilis tests over 18 months	1.42 (NR)	1.32 (NR)	1.13 (0.95, 1.35) [0.18]
Chlamydia tests over 18 months	1.56 (NR)	1.42 (NR)	1.11 (0.90, 1.36) [0.33]
Gonorrhoea tests over 18 months	1.56 (NR)	1.42 (NR)	1.11 (0.90, 1.36) [0.33]

[a]   calculated from number of tests/person year
Source: Table 2, p7 and p3 of Read (2013)

The results of the trial indicate that there was no statistically significant difference between groups for the primary outcome of "HIV tests over 18 months" or the secondary outcomes of syphilis, chlamydia and gonorrhoea testing over 18 months. Hence, the possibility of having HIV tests by rapid point-of-care testing did not result in higher testing frequency over the study period of 18 months.

The authors also undertook *post-hoc* analyses considering only the first HIV test after enrolment and considering only subsequent HIV tests (excluding first tests). A statistically significantly greater number of first HIV tests/year after the enrolment test was observed in those randomised to the HIV testing by the rapid point-of-care test compared with conventional testing, however no differences were observed in the number of HIV tests/year when only considering subsequent tests. Based on these results, the authors conclude that "Post hoc analysis showed an initial increase in their rate of testing that was not sustained".

Additional outcomes reported in Read (2013)

Participants who completed all online study questionnaires were offered a $20 voucher. Participants in the trial were invited to partake in these questionnaires at months six, 12 and 18. The questionnaire asked questions relating to:

- HIV testing at clinics other than the study clinic. If information was not provided in the questionnaire, individual men were contacted via SMS to provide the details of testing which was subsequently verified by contacting the external clinics;
- Attitudes to HIV and sexual behaviour; and
- How they felt about their HIV test experience.

At baseline, most men (88%; 95% CI: 82%, 92%) in the intervention arm stated a preference for the rapid test after blood collection by finger prick. Of the 390 men who remained HIV negative over the study period, 270 completed a final study questionnaire (142/195 [73%] randomised to rapid testing and 128/195 [66%] in the conventional testing arm).

Men who were randomised to the conventional testing arm were more likely to:
- feel that the wait for results was too long (59% versus 9%, p<0.001)
- report anxiety due to the wait (63% versus 44%; p=0.002);
- report delaying their next test because of anxiety over the wait (24% versus 13%, p=0.03); and

less likely to report that obtaining the results was convenient (41% versus 74%; p<0.001) compared with men randomised to rapid point-of-care testing.

While the population enrolled in the randomised controlled trial reported by Read (2013) is directly applicable to the Australian setting, there are some limitations. The trial only enrolled MSM, where the test is intended for a wider population, such as injecting drug users. Although enrolling MSM, this was a select group of men who had tested within the last two years, i.e., those who had a history of testing. This was a requirement of the trial to increase the likelihood of men returning for subsequent testing, but this restriction limits any increase in testing that may or may not have been observed if 'never' testers had also been enrolled. This is of particular relevance when considered in the context that the results of the patient satisfaction questionnaire reported in Eu (2014) indicated that one in five men would not have been tested if rapid point-of-care testing was not available.

Evidence linkage 3: Does change in management improve patient outcomes?

Once a diagnosis of HIV infection is made there would be no difference in the time taken to commence treatment and alter high-risk behaviour.

Other relevant considerations

Consumer implications and other considerations

Two studies (Yang 2014, Eu 2014) have indicated that Australian G/MSM have a preference for rapid testing over non-rapid testing. However, in the randomised controlled trial reported by Read (2013), MSM randomised to the rapid testing arm did not demonstrate a sustained increased frequency of testing over the 18 month period of the trial. Thus, it is unclear whether the availability of a MBS-listed rapid point-of-care HIV test would actually achieve the desired effect of (i) increasing HIV testing frequency among those being tested (demonstrated to not occur in the randomised controlled trial reported by Read 2013) and (ii) testing among those who have never tested, in order to allow for earlier HIV diagnosis.

This may be attributable to the attitudes of MSM, where the reasons cited by at least 20% of those surveyed in Prestage (2012) for not being tested included:

- not feeling they have done anything "risky" (41%);
- having to return another time for results (40%);
- not having enough time (25%);
- having not changed partners (20%); or
- not having had any illness or symptoms which made them worry (20%).

These commonly cited reasons for not regularly testing, or testing at all, may contribute to the lack of an observed increased in the testing frequency in Read (2013) as rapid testing does not specifically address any of these concerns.

Of note, Knight (2014) reports the use of the DHC test in a pop-up caravan. The pop-up caravan was installed on 25 November 2013 for a period of five days, staffed by one nurse and two peer educators. Anyone requesting a HIV test was advised that the target group for the testing service were gay, bisexual and other men who have sex with men (GBM). 182 GBM requested a HIV test with DHC over the five-day period (this compares with 219 MSM over a five and half month period reported in Eu 2014 or 2468 MSM over a 22 month period in Conway 2014). Of the 182 tests conducted, none were newly reactive and most received their results by SMS, while some chose to return to the caravan for their results. The relative success of the caravan in engaging GBM for testing (36.4 individuals or 36.4 tests per day) compared with attendance to a GP or sexual health clinic (1.3 individuals or 1.8 tests per day in Eu 2014 or 3.7 individuals or 4.8 tests per day in Conway 2014) may support the use of the DHC test in more of an outreach capacity.

Alternatively, although the DHC test is not TGA-approved for "at home" use, this may represent an alternative use for the test. A rapid test (the BioSURE HIV Self Test, antibody only) has recently been approved for use "at home" in the United Kingdom. Expert opinion sought during the assessment also supported the use of home testing using the DHC test.

What are the economic considerations?

The data reported in Conway (2014) and Eu (2014) indicates that DHC has inferior diagnostic accuracy for detecting HIV compared to serology testing; whereas data reported in Read (2013) indicates that there was no statistically significant difference between the groups randomised to rapid point-of-care testing and serology testing in terms of number of tests/year for HIV. To account for the differential diagnostic accuracy, a cost-effectiveness analysis is appropriate.

The base case of the model assumes no differences in testing frequency between the two arms of the model. Sensitivity analyses are conducted modifying some assumptions to attempt to capture other reasonable scenarios, including the qualitative patient satisfaction evidence in Eu (2014) and the *post-hoc* analysis in Read (2013).

Economic evaluation

Overview

The type of economic evaluation presented is a cost-consequences analysis which estimates cost per various test outcomes associated with the DHC test and conventional testing (fourth generation EIA) over one year. Whilst it is acknowledged that HIV and HIV screening[2] programs should be modelled using dynamic transmission models to account for the dynamics of infection[3] , there is limited field data required to inform such models particularly in the Australian setting (Dibosa-Osadolor 2010, Cambiano 2014). Therefore, in consideration of the clinical evidence available relevant to Australia and more importantly the model outcomes specified in the MSAC 1391 Final Protocol ("early diagnosis of HIV infection", "false-negatives" and "false-positives"), a novel static[4] state transition model was constructed. The use of a static model is consistent with other models presented in the literature, and is considered reasonable over a short time horizon.

Population and setting for the economic evaluation

The population in the model is assumed to be all Australian MSMs without diagnosed HIV, and includes individuals who are seropositive, seroconverting and seronegative. As discussed under "Current reimbursement arrangements" in the Background section of the report, it is anticipated that the majority of use will be in GP clinics and sexual health clinics for MSM.

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[2] Reference to "screening" in this context refers to the place of the point-of-care test in the diagnostic algorithm for HIV infection and does not refer to a diagnostic test unrelated to the individual's medical condition. In the same manner the initial EIA test (or similar) used by a laboratory could be considered a "screening" test, where a reactive results is subject to additional confirmatory testing including the gold standard of Western Blotting. In other words, "screening" in this context refers to screening of diagnostic results rather than screening an at-risk population.

[3] Transmission is hinged on population prevalence per unit time, the duration of the infectious period, the diversity of sexual behaviour with its potential for assortment and number of sexual partnerships so formed within the population, as well as the presence of concomitant sexually transmitted diseases.

[4] Static models assume a constant force of infection

Structure and rationale of the economic evaluation

Economic evaluation literature review

A literature search was conducted to identify published modelled economic evaluations investigating point-of-care testing (POCT) versus conventional laboratory testing for the detection of HIV (Appendix F) and to inform the structure of, and inputs to, the economic model. The inclusion criteria were broad to identify as many studies as possible. However, studies using POCT for screening of blood donations, other organ or tissue donations or routine serology during pregnancy were excluded as being not relevant to the requested restriction (see "Intended purpose" and "Current reimbursement arrangements"). Six studies were identified, including five cost-effectiveness studies in the US and one modelled analysis in the Australian setting. A summary of these studies is presented in Table 17.

Table 17   Studies presenting modelled analyses of POCT versus laboratory HIV testing programs

Study	Comparisons	Population	POCT effectiveness	Model	Outcome(s)
Farnham 1996	- No screening - Lab test + counselling - POCT (Genie HIV-1/2 test) + counselling	US population screening, medical clinics	- Increased probability of receiving test result;	Decision tree	- Cost per HIV-infected notified; - Cost per correct notification
Ekwueme 2003	- Lab test + counselling - "two-step" POCT + counselling - "one-step" POCT + counselling	US population screening, medical clinics	- Increased probability of receiving test result; - Assumed 100% sensitivity / specificity	Decision tree	- Cost per strategy; - Cost per test by HIV status; - Cost per correct notification
Farnham 2008	- Lab test + counselling - POCT (OraQuick Advance rapid HIV-1/2 ab test) + counselling	US population screening, STD clinics and EDs	- Increased probability of accepting test (in EDs); - Increased probability of receiving test result;	Decision tree	- Cost per HIV-infected notified; - Cost per correct notification;
Sanders 2010	- Nurse referral to GP for lab test + counselling - Nurse initiated laboratory test + counselling - Nurse initiated POCT (OraQuick Advance rapid HIV-1/2 ab test) + counselling	US population screening, trial data in hospital (Anaya 2008)	- Increased probability of accepting test; - Increased probability of receiving test result;	Decision tree + Markov model	Cost per QALY
Wilson 2011	- 3rd gen. lab test - 4th gen. lab test - 3rd gen. POCT (OraQuick Advance rapid HIV-1/2 ab test) - 4th gen. POCT (Determine HIV-1/2 ag/ab test)	Australian HIV-infected. Data from Melbourne Sexual Health Clinic	- Inferior window period compared to 4th gen. laboratory test - Results provided earlier than laboratory testing	Microsimulation + transmission model	- Time to HIV-diagnosis; - Change in HIV transmissions.
Schackman 2013	- No screening (simulated) - Referral to GP for lab test + counselling - POCT (OraQuick Advance rapid HIV-1/2 ab test) + information only - POCT (OraQuick Advance	US population screening, trial data in drug abuse clinic (Metsch 2012)	- Increased probability of accepting test; - Increased probability of receiving test	Screening module + Markov model (CEPAC)	Cost per QALY

Study	Comparisons	Population	POCT effectiveness	Model	Outcome(s)
	rapid HIV-1/2 ab test) + counselling		result;		

Source: relevant publications

In the US-based studies, the modelled benefits associated with POCT, relative to conventional laboratory testing, include:

i. An increase in the probability of agreeing to test, in the context of population screening; and

ii. An increase in the probability of receiving the test result.

These studies state up to one third of individuals in the US do not receive the results of conventional HIV testing and remain unaware of their HIV status because they fail to attend the follow-up appointment. Given POCT results are provided on the same day, the probability of receiving a confirmed result is higher: a POCT negative is a final result, whereas a POCT positive may increase the likelihood of attending the follow-up appointment for the confirmatory test.

The three earliest cost-effectiveness studies present simple decision trees and estimate cost per person notified of HIV status (or similar outcome) with screening hypothetical populations in US medical clinics (Farnham 1996; Ekwueme 2003; and Farnham 2008). The two most recent studies (Sanders 2010, Schackman 2013) used microsimulation to estimate cost per QALY associated with screening in trial based populations. Sanders (2010) modelled three nurse-based screening strategies derived from an RCT (n=251) in US hospitals (Anaya 2008). A trial-based decision tree inputs individuals into a Markov model either aware or unaware of their HIV status into one of seven health states: "uninfected"; "HIV asymptomatic"; "HIV symptomatic"; "HIV on HAART"; "AIDS on HAART"; "AIDS" and "Dead". Each month, the model assessed the individuals' HIV status, whether it was identified, the clinical course of the disease, and the costs and consequences of HIV transmission and HAART for individuals identified and eligible for treatment. Schackman (2013) modelled three screening strategies derived from an RCT (n=1281) in a US substance abuse clinic (Metsch 2012), using the CEPAC (Cost-Effectiveness of Preventing AIDS Complications) Markov model. A screening module was used to compare the strategies and determine whether and when HIV-infected individuals were tested, diagnosed, informed and linked to care. The cohort of HIV-infected transitioned monthly between the four basic health states ("primary HIV infection"; "Chronic HIV infection"; "Acute clinical event"; "Death") depending on simulated immune status (CD4 positive count), viral burden (RNA level), maintenance on HAART or the presence of AIDs related complication.

By contrast, the Australian study (Wilson 2011) modelled the trade-off between earlier diagnosis with DHC since results are provided immediately and the potential for missed diagnoses due to a longer window period compared with conventional laboratory testing. A microsimulation model and a separate transmission model were used to investigate(i) the change in time to diagnosis for HIV infected individuals and (ii) the number of additional or averted HIV transmissions with DHC, assuming no change in treatment rates. Data was derived from medical records of 174 HIV positive MSM at Melbourne Sexual Health Clinic from 2002 to 2009, including frequency of sexual activity, levels of unprotected anal sex in prior 12 months, HIV viral load at diagnosis and the number of days between testing and receiving results. Distributions were generated for time

between tests, and time between final test and diagnosis based. A uniform distribution was assumed for time of infection between tests. A microsimulation with 100,000 was run such that if duration of time between infection and test is greater than the window period of the relevant test (EIA versus DHC), a diagnosis was made. If not, detection occurred at the following test. Diagnosis was assumed to occur on the same day for DHC, and sampled from the distribution for EIA. The number of days from infection and diagnosis was calculated for each simulated individual and inputted into a transmission model to estimate net HIV transmissions.

No studies were identified that modelled the cost-effectiveness of the DHC test versus conventional laboratory testing in high-risk individuals in Australian GP or sexual health clinics. It is noted that a large number of HIV transmission models were excluded during the literature review because HIV detection using POCT has become common place in the US. Therefore, the most recent modelled evaluations compared different POCT-based screening programs, and did not include laboratory only screening programs as a comparator.

Given Australia does not have a reported problem with respect to individuals receiving test results, and the proposed listing of DHC on the MBS is not for population screening, the benefits modelled in the US studies are not relevant to Australia. Expert opinion sought during the assessment confirmed a near perfect rate of reporting HIV results in Australia. Therefore the model presented was developed in consideration of (i) the reported diagnostic accuracies in given populations, (ii) the reported window periods relevant to newly infected individuals and (iii) two possible ways in which DHC <u>may</u> influence testing behaviour in Australia (for the purposes of sensitivity analyses):

- Change in the probability of undertaking any routine screening, and/or
- Change in the frequency of routine screening, given previous screening.

Structure of the economic evaluation

A decision analytic Markov model is used to estimate the cost per various test outcomes over a one year time horizon, of a scenario where the DHC test is available for screening HIV in high-risk individuals. Figure 5 presents a simple transition state diagram of the model. MSMs without a diagnosis of HIV are assumed to commence each cycle in one of four health states:

(i) "Seropositive"

(ii) "Seroconverting"

(iii) "Seronegative"
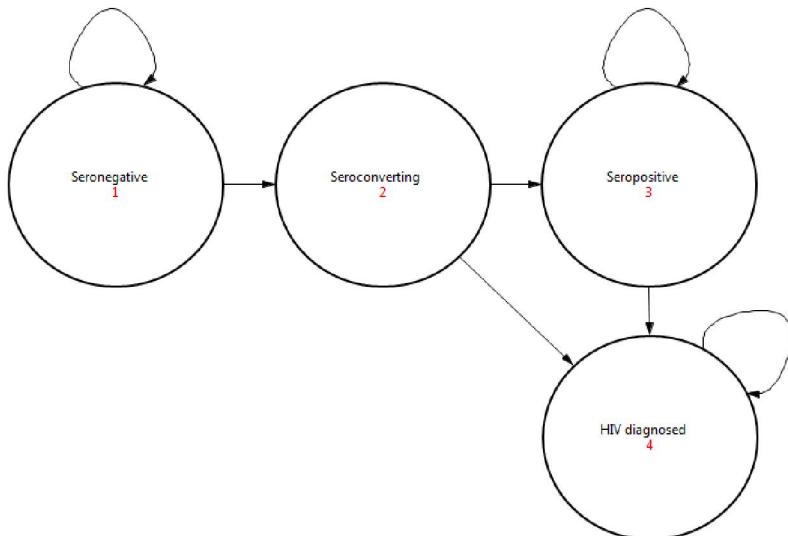
(iv) "HIV diagnosed"

Figure 5 Transition state diagram

The cohort enters the model in one of the three non-HIV diagnosed health states, and only transitions to the absorbing health state "HIV diagnosed" after a confirmed HIV diagnosis is made either through HIV screening or the development of AIDS complications and symptom-based testing. Each cycle is assumed to have a duration of three months given (i) the seroconverting window period may be up to three months after infection and (ii) high-risk MSM in Australia are recommended to test every 3 months (The Australian Sexually Transmitted Infection & HIV Testing Guidelines, 2014).

The cohort commencing in the "seronegative" health state may become infected with HIV during a cycle and transition to "seroconverting" or remain "seronegative". The cohort can only remain in the "seroconverting" health state for one cycle. If screened for HIV within the cycle and diagnosed, the cohort transitions to "HIV diagnosed", otherwise they will transition to "seropositive" in the following cycle. The cohort in the "seropositive" health state either transition to "HIV diagnosed" via HIV screening or due to development of AIDS symptoms and symptom-based testing, or remain "seropositive" in the following cycle.

Monte Carlo simulation is used to model the heterogeneous population, conditional transition state probabilities, and incorporates a tracker variable for number of tests undertaken by each modelled individual. At the start of the model, individuals are assigned to one category for each of the following variables:

- Initial non-HIV diagnosed health state ("seronegative", "seroconverting", "seropositive");

- Undertakes routine HIV screening (yes or no);

- Number of year seropositive (1 to 20) – applicable only when in the "seropositive" health state; and

- Days since HIV infection (1 to 90) – applicable only when in the "seroconverting" health state.

A tracker variable is programmed to count the number of tests undertaken by each individual, given the *post-hoc* analysis reported in Read (2013) suggests a difference in the

rate of initial re-screening with the DHC test, but no difference in the rate of subsequent re-screening.

Figure 6 presents the structure of the model used to conduct the analysis. The testing algorithms vary in each arm of the model to reflect: (i) the current scenario without the DHC test ("Serology"); and (ii) the proposed scenario with the DHC test ("DHC") where a DHC negative is a final result but a DHC positive requires confirmatory serological testing. An assumption is made that serology is the gold standard for individuals who are "seropositive" or "seronegative" and the published sensitivity/specificity of the DHC test is based on samples of those with known HIV-status (The Alere HIV-1/2 Ag/Ab Combo product insert). However, the model assumes that the probability of detecting HIV for individuals who are "seroconverting" is a function of the window period of each respective test, and a diagnosis is based on a positive serological result.

Costs associated with each arm of the model are allocated as transition costs at the relevant nodes and a binary outcome (1 or 0) is assigned to the termination nodes to count the outcomes specified in the MSAC 1391 Final Protocol, summarised in Table 18. To correctly classify the DHC test negatives in the "seroconverting" health state for the assessment of test performance versus serology, a 'hypothetical' serology test is assumed to occur after a DHC negative result. Given a positive diagnosis via serology is also assumed to be a function of days since infection, only those detected by serology but not by DHC are classified as false negatives (see below).

Table 18   Outcomes reported by the model

Outcome	Description
HIV diagnosis	Total number HIV diagnosed
Early	Number diagnosed due to screening test
Late	Number diagnosed due to AIDS complications testing
Testing procedure failure	HIV positives tested but not diagnosed at time of testing
DHC test outcome	
DHC true positive	DHC arm only, number of true positives
DHC true negative	DHC arm only, number of true negative
DHC false positive	DHC arm only , number of false positives
DHC false negative	DHC arm only, number of false negative

The time horizon was limited to one year as the force of infection is assumed constant within the model and no allowance has been made for population growth.

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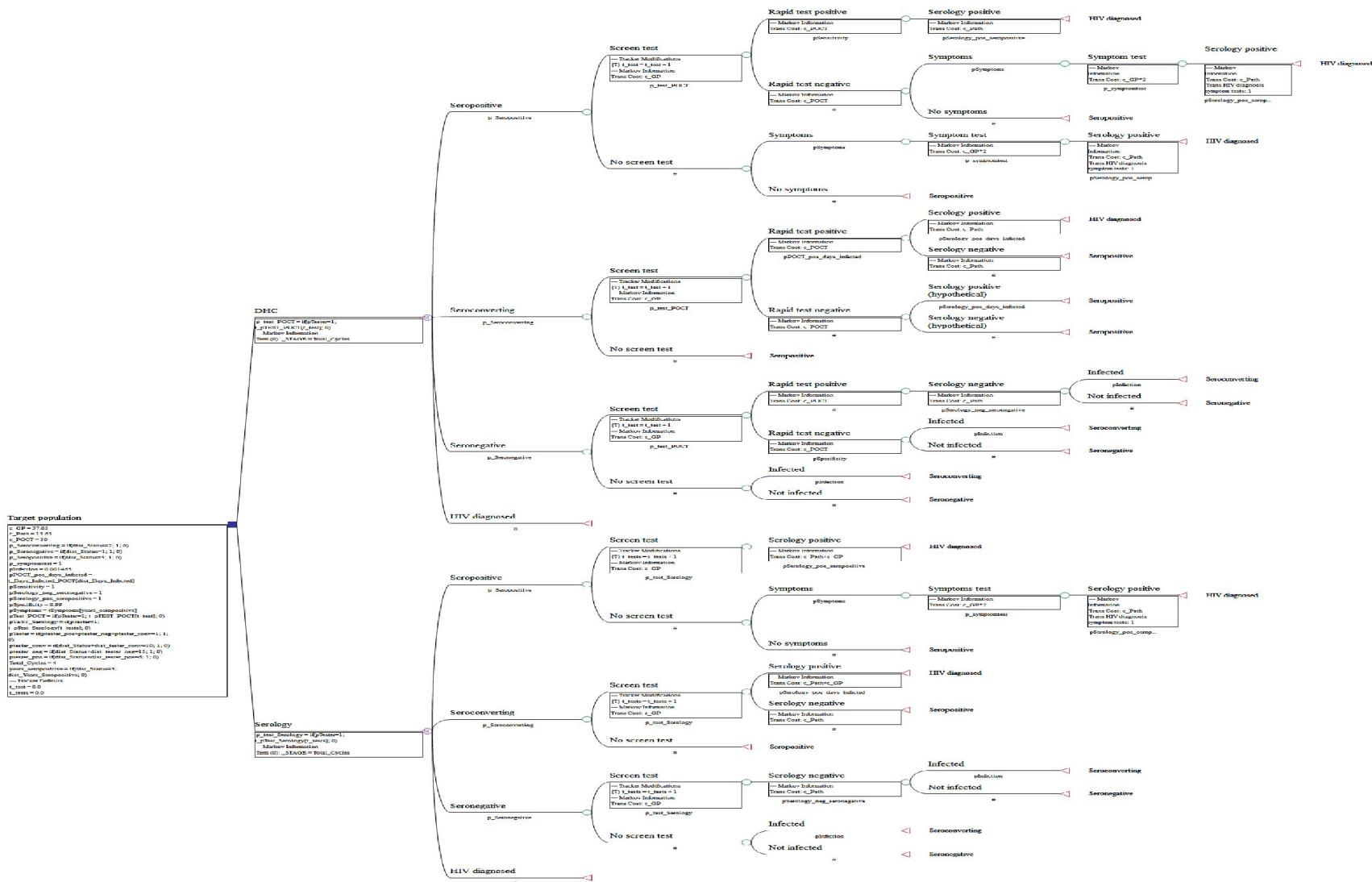
Figure 6   Structure of the modelled economic evaluation

Summary of the economic evaluation

Table 19 summarises the modelled economic evaluation.

Table 19   Summary of the economic evaluation

Time horizon	One year
Outcomes	(see Table 18 above)
Methods used to generate results	Monte Carlo simulation
Cycle length	3 months
Transition probabilities	(see Table 21 below)
Discount rate	N/A for one year time horizon
Software package	TreeAge Pro 2015

Inputs into the modelled economic evaluation

Population characteristics

DISEASE STATUS

The modelled population is the Australian population of MSM without a diagnosis of HIV, and includes individuals who are HIV seronegative, seroconverting (defined in the model as HIV infected within past three months) or seropositive. The probability of commencing the model in each of these health states were calculated in a step-wise fashion, using estimates predominately reported in two Australian HIV surveillance reports published by the Kirby Institute (2014a, 2014b).

The total MSM population in Australia is estimated by the Kirby Institute to be between 180,000 to 200,000 (Kirby 2014b); the mid-point of 190,000 is assumed for the following calculations. An estimate of 190,000 is consistent with the estimate of 182,624 in 2001 reported by Prestage (2008), based on aggregated survey data. As there were 7,562,960 Australian males aged over 15 years in 2014, the estimate implies approximately 2.4 to 2.6% of the male Australian population are MSM (ABS statistics website). This is consistent with an Australian population survey conducted in 2003 which reported 2.5% of the 9475 men aged 16 to 59 surveyed identified as either homosexual (154) or bisexual (89).

The number of Australians living with diagnosed and undiagnosed HIV is estimated by the Kirby Institute to be 26,800 (plausible range: 24,500 to 30,900) with 70-75% of infections due to male homosexual contact (Kirby Institute 2014b). The number of MSM living with HIV is therefore approximately 19,430 (range: 17,150 to 23,175). This is consistent with an estimate of 19,000 (range: 14,400 to 24,000) calculated using the total MSM population and an estimated HIV prevalence in MSM of 8-12% (Kirby Institute 2014b). Both estimates are consistent with those reported by Wand (2010) and Mallitt (2012) using back projections for 2006, 19,689 and 26,232 (95%CI: 17,923 to 34,205) respectively.

The number of Australians living with diagnosed HIV is estimated by the Kirby Institute to be 23,100 (range: 21,800 to 24,400) (Kirby 2014b), which implies 3,700 (range: 2,700 to 6,500) cases are undiagnosed. Based on the estimated number of infections due to male homosexual contact of 70-75% (mid-point 72.5%), there are approximately 2,683

MSM living with undiagnosed HIV. This is consistent with an estimate of 2,720 calculated using the estimated the total number of MSM with diagnosed and undiagnosed HIV of 19,430 and the estimated percentage of total undiagnosed cases of 14% (Kirby Institute 2014b). Both estimates are consistent with those reported by Wand (2010) and Mallitt (2012) for 2006, 2,560 or 13% (95%CI: 12, 14%) undiagnosed and 3,148 or 12% undiagnosed respectively.

Three sources were identified to estimate HIV incident population in MSM. The number of newly detected HIV cases in 2013 was 1,236, with 350 newly acquired within the past 12 months of which 85% were in MSM (Kirby Institute 2014a). Therefore the number of MSM with newly acquired and detected HIV was 308. This value could be used to estimate a lower bound for the incident population. Alternatively, the rate of infection estimated in a cohort of homosexual men in Sydney between 2001 and 2004 was estimated to be 0.87 per 100 person years, which translates into 1,481 incident infections (Jin 2008). Another analysis based on CD4 positive count at diagnosis estimated that there are approximately 1,000 incident HIV cases in MSM per year (Wilson 2011 presentation slides "Undiagnosed HIV in Australia"). Therefore, of the estimated 2,720 HIV prevalent MSM population, 1,000 are incident cases. This estimate is used for the base case analysis.

Based on these calculations the total MSM population without a diagnosis of HIV is estimated to be 173,720. Of these, 171,000 (98.43%) are estimated to be "seronegative", 250 (0.14%) are estimated to be "seroconverting" defined as incident cases in three months, and 2,470 (1.42%) are estimate to be "seropositive" and infected longer than three months.

DAYS SINCE INFECTION

The modelled population in the "seroconverting" health state is assigned to a day of infection (1 to 90) within the three-month cycle assuming a uniform distribution. It is assumed that the probability of a positive diagnosis with a given test increases over time, and is dependent on the time since infection occurs (see below). This is consistent with the approach used by Wilson (2011).

YEARS SINCE INFECTION (SEROPOSITIVE)

The modelled population who commences in the "seropositive" health state is assigned to a year of infection, between 1 and 20 years. Given the lack of data to inform the distribution "years since infection" in undiagnosed seropositive individuals, the model was used to simulate a distribution over 5 years. 10,000 individuals entered the model in the seronegative health state and were tracked for 20 cycles. Two tracker variables were used for the seropositive and HIV diagnosed health states. Individuals who remained in the seropositive health states by the end of the 20 cycles were analysed according to the number of cycles in the seropositive health state. The number of cycles seropositive was rounded up to the closest integer to correspond with the available evidence (see below). For the base-case, a log-normal distribution was used to approximate and extrapolate the simulated distribution. A second log-normal distribution was used for a sensitivity analysis which more closely matches the shape of CD4 positive count (a proxy for time infected) distribution at diagnosis presented by Wilson (undated presentation; ashm.org.au). Figure 7 presents the two log-normal distributions used in the model. The results are not sensitive to the assumed distribution. The probability of developing AIDS complications and therefore detection due to complications increases the longer

the individual has been infected and untreated. As the model is only run for one year, the tracker variable used to simulate the distribution of years seropositive is not used.
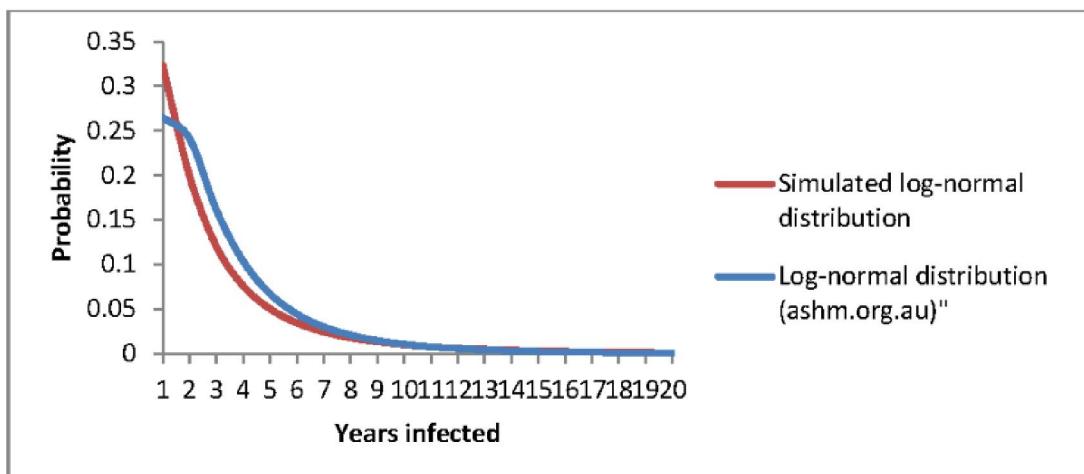
Figure 7   Estimated log-normal distribution of year infected in MSM with undiagnosed HIV

<u>Disease characteristics</u>

PROBABILITY OF TRANSMISSION

The model assumes a constant rate of infection for individuals in the "Seronegative" health state, modelled as a three-monthly probability. As discussed above, three sources were identified to estimate the HIV incident population. The lower bound estimate of newly acquired or incident infections in the MSM population is 308 (Kirby 2014a). Based on the estimated number at risk of 171,000, this translates to a three-monthly probability of infection of 0.000451. Alternatively, the cohort study in Sydney reported the rate of infection as 0.87 per 100 per years, or 0.002173 as a three-month probability (Jin 2008). The third estimate based on CD4 positive count at diagnosis approximated 1,000 incident infections in MSM (Wilson 2011 presentation slides "Undiagnosed HIV in Australia"). Similarly, assuming 171,000 at risk, the three-month probability of infection was calculated as 0.001465. This estimate was used in the base case for consistency with the modelled population estimates.

PROBABILITY OF DEVELOPING AIDS

The model assumes that individuals will be diagnosed with HIV/AIDS following the development of AIDS. The probability of progressing to AIDS within each cycle is dependent on the number of years seropositive. The estimated cumulative probability (for untreated HIV) of is reported for the first 10 years of infection by Osmond (1998), based on a modelled analysis by Bacchetti & Moss (1989). The rate of progression to AIDS is very low in the first two years after infection and increases thereafter, with a median time of approximately 9 to 10 years. The base case applies the reported probabilities, extrapolated to 20 years assuming a polynomial function. A second logistic growth function is assumed for a sensitivity analysis, used by others (Bulatao & Bos working paper 1992, projecting the demographic impact of AIDS). The model is not sensitive to the distribution used. The two distributions are presented in Figure 8.
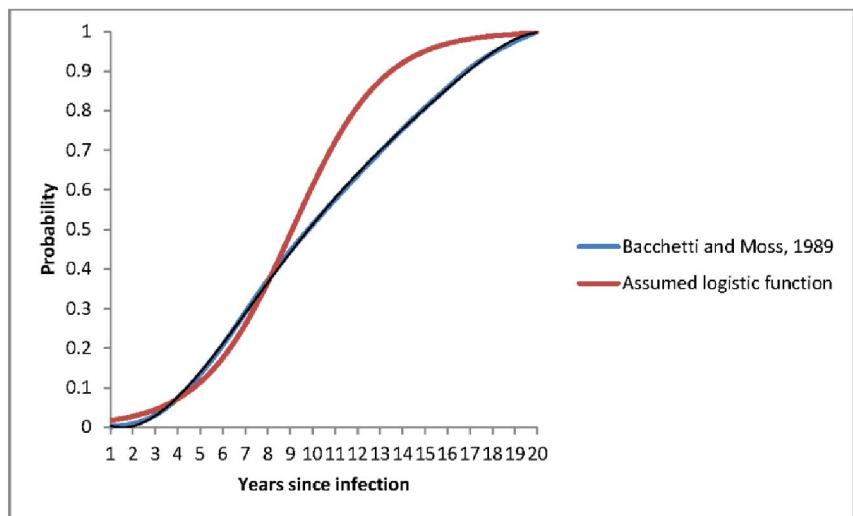
Figure 8   Cumulative probability of progressing to AIDS, years after HIV infection

Test performance

SERONEGATIVE AND SEROPOSITIVE

The model assumes laboratory testing is a perfect gold standard in known samples, and will always detect known positives and known negatives. The sensitivity and specificity of the DHC test relative to laboratory testing is based on the TGA requirement for POCT tests in Australia have a sensitivity of 100% and specificity of at least 99%.

SEROCONVERTING

There is no precise "window period" at which time a HIV test will detect an infection that it would not have detected prior to this time. Therefore, in the seroconverting health state, the probability of a positive diagnosis is assumed to increase over time (Owen 2008). Wilson (2011) modelled the window periods of the third and fourth generation EIA and point-of-care tests using a logistic growth curves. The medians are set equal to the defined window periods for each test after the detection of HIV RNA with the Nucleic Acid Test, 10 days for the DHC test and five days for fourth generation EIA. However, there is an eclipse period between the day of infection and day when HIV markers are detectable. The eclipse period is approximately 2 weeks from infection to p24 antigen, suggesting the median window periods for fourth generation EIA and the DHC test are approximately 20 and 25 days, respectively (Cohen 2010), see Figure 9.
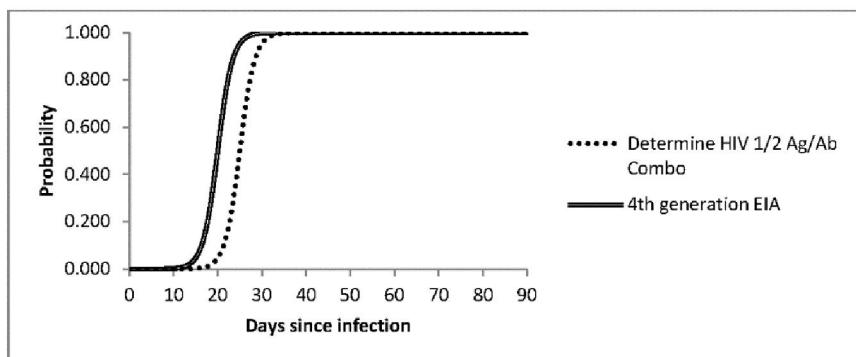
Figure 9   The median window periods for fourth generation EIA and the DHC test

COST

Table 20 summarises the cost inputs used in the modelled evaluation. For screening-based testing, the model assumes both test strategies require an initial GP consultation if a screening test is conducted. The cost of the applicable test is also allocated during this consultation. Although the Proposed Clinical Management Algorithm in the MSAC 1391 Final Protocol implies that all laboratory tests currently require a subsequent consultation to receive results, it is also acknowledged elsewhere (p11) in the Protocol that SMS messaging is utilised to convey negative results. Based on recommendations in the Draft National HIV testing Policy (2014) and expert advice sought during the assessment, it is assumed that all negative HIV screening laboratory test results will be provided via phone or text message and would not require a follow-up visit (see "Barriers to HIV testing"). Thus in the serology testing arm, only HIV positive laboratory results are assumed to require a follow-up consultation. The base-case analysis assumes there is no follow-up consultation in the DHC test arm (regardless of DHC outcome) as any required post-test counselling is assumed to occur at the initial consultation, as proposed in the clinical management algorithm provided in the MSAC 1391 Final Protocol. This assumption is tested in a sensitivity analysis.

Given a postive DHC result must be confirmed by serological testing, the cost of confirmatory testing in the DHC arm is also allocated to all DHC positive results. For symptom-based testing, the model assumes there is an initial medical consultation, a laboratory test and a follow-up consultation.

Additional MBS fees may also be applicable for the conduct of both HIV point-of-care and laboratory testing. A "P-12 management of bulk-bill services fee" may be payable for basic pathology tests (including DHC should it be approved) conducted by general practitioners for patients with concession cards, provided the service is bulk-billed. The value of the fee, if applicable, is dependent on the location of the practice as specified in the item descriptions (see MBS 74990 and MBS 74991). For the purposes of the base-case analysis, based on professional advice sought during the evaluation, it is assumed that 100% of MSM are bulk-billed for services and 75% of tests are conducted by private laboratories (Cretikos 2014). Based on these assumptions, the average weighted fee is $0.63. For laboratory tests, a "P-10 patient episode initiation fee" is payable to the laboratory conducting the test, where a different fee is payable for public (MBS 73929) and private (MBS 73928) laboratories. An additional "P-13 builk-billed pathology incentive item" is also be payble ontop of the patient episode initiation fee if the service is bulk-billed (see MBS 74995 and MBS 74999). Based on the assumptions that 100% of MSM are bulk-billed for services, 10% have concession cards and 10% live in regional, rural or remote locations, the average weighted fee is $7.24. Four sensitivities analyses are conducted to test the range of impact these "extra" fees have on the analysis.

Table 20   Costs associated with testing in each arm of the model in the base-case analysis

	DHC test	Laboratory testing	Unit cost	Source
Screening test				
Initial consultation	√	√	$37.05	MBS 23
HIV test				
Determine test	√	x	$30.00	Section A
Laboratory test	If DHC positive	√	$15.65	MBS 69384
Extra DHC test fee	√	x	$0.74*	MBS 74990, 74991
Extra laboratory test fee	If DHC positive	√	$8.46#	MBS 74995, 74999; MBS 73928, 73929
Follow-up consultation	x	If test positive	$37.05	MBS 23
Symptom-based testing				
Initial consultation	√	√	$37.05	MBS 23
HIV test				
Laboratory test	√	√	$15.65	MBS 69384
Extra laboratory test fee	√	√	$8.46#	MBS 74995, 74999; MBS 73928, 73929
Follow-up consultation	√	√	$37.05	MBS 23

* weighted cost, assuming 100% of MSM are bulk-billed for services, and 75% of serology testing is conducted in private laboratories.
\# weighted cost, assuming 100% of MSM are bulk-billed for services, 10% are concession card holders and 10% live in regional, rural or remote locations.

Whilst the MSAC 13191 Final Protocol specifies MBS item number 69384 as the applicable item number for a laboratory HIV testing, it is noted that the STIGMA guidelines recommend that other STIs (including chlamydia, gonorrhoea, syphilis, hepatitis A/B/C) are concurrently screened along with HIV in MSM. Therefore, serology samples taken from MSM are likely to be screened for multiple infections and the DHC test for HIV will not reduce these tests. Given syphilis "should be conducted at each occasion of HIV immune monitoring" (Templeton 2014), the cost of HIV laboratory testing in this context is the incremental cost associated with reducing the number of infections tested from 4 to 3 tests, 3 to 2 tests or 2 to 1 test, equal to $13.35. A sensitivity analysis is presented using a cost of $13.35 for laboratory-based testing.

Testing behaviour

PROBABILITY OF UNDETAKING ANY ROUTINE HIV SCREENING

The model assumes that not all Australia MSM will elect to routinely test for HIV, and only those who do, are then eligible for testing in each cycle in the model. This assumption is reasonable over the one year time horizon and consistent with the enrolled population in Read (2013), from which the probability of testing is derived. Two recent studies in Australia suggested the proportion of MSM who test reguarly may be between 55% (Knight 2014) to 75% (Pedrana 2012). Knight (2014) collected data from a pop-up testing service in a major pedestrian throughfare in a gay precent in Sydney, whereas Pedrana (2012) recruited participants at gay and sex-on-premises venues in Melbourne. The estimate reported by Knight (2014) is used for the base case given the sample recruited may be more representative of a broader MSM population.

Therefore, it is assumed that only 55% of those commencing the model in the seronegative or seroconverting health states will consider screening for HIV. The same proportion however cannot be used for individuals commencing the model in the

seropositive health state given the probability of screening determines whether you are diagnosed shortly after infection and if diagnosed early, the individual would not be in the (undiagnosed) seropositive health state. That is, the proportion of those who choose to monitor HIV status are expected to be lower in a population whose HIV positive status has not been detected. Therefore, the starting proportion was simulated using the model, using the same method used to simulate the distribution of "years infected" in the seropositive population. Approximately 20% of newly infected individuals who were in seropositive health state after 20 cycles were designated as undergoing routine screening at the start of the model in the seronegative health state. Therefore, the base case analysis assumes 20% of those starting in the seropositive health state choose to be tested and hence are eligible for routine screening.

No difference in the testing rate or frequency is assumed across the arms in the base case, based on the primary outcome reported by Read (2013).

FREQUENCY OF ROUTINE MONITORING GIVEN PREVIOUS MONITORING

Based on the results reported by Read (2013), the base case assumes no statistically significant difference between testing arms; the average rate of testing reported in Read (2013) is used in both arms of the model: (1.63 + 1.42) / 2 = 1.525 tests per year; three-month probability of 0.316993.

PROBABILITY OF SYMPTOM-BASED TESTING

It is assumed that all individuals who develop AIDS symptoms will present to a medical facility and be tested using conventional laboratory testing, regardless of previous testing behaviour.

Table 21 summarises the inputs used in the model.

Table 21   Inputs used in the model

	Base case	Source
Population characteristics (at cycle 0)		
Cohort size	173,720	Estimate, (Kirby 2014a)
Prob. Seronegative	0.984343	Calculation, (Kirby 2014a, Kirby 2014b, Wand 2010, Mallitt 2012, Prestage 2008, ABS, Wilson presentation 2011))
Prob. Seroconverting	0.001439	Calculation, (Kirby 2014a 2014b, Jin 2009, Wilson presentation 2011)
Prob. Seropositive	0.014218	Calculation, (Kirby 2014a 2014b, Jin 2009, Wilson presentation 2011, Mallitt 2012, Wand 2010)
Prob. days since infection	Uniform dist. 1 to 90	Assumption (Wilson 2011 model)
Prob. years since infection	Log-norm. dist. (see Figure 7)	Simulation
Disease characteristics		
Prob. of transmission (3-month)	0.0011465	Estimate (Wilson presentation)
Prob. of AIDS (3-month)	Cum. distribution (see Figure 8)	(REF)
Prob. detection, given AIDS	100%	Assumption
Test performance		
Prob. 4th gen EIA positive, given seropositive	100%	Assumption
Prob. 4th gen. EIA negative, given seronegative	100%	Assumption
Sensitivity DHC v EIA/WB, given seronegative or -positive	100%	AMCD statement, Protocol p5
Specificity DHC v EIA/WB, given seronegative or -positive	99%	AMCD statement, Protocol p5
Prob. 4th gen. EIA positive, given seroconverting	Logistic growth function, median 20 days post infection	(Wilson 2011 model, Owen 2008, Cohen 2010)
Prob. DHC positive, given seroconverting	Logistic growth function, median 25 days post infection	(Wilson 2011 model, Owen 2008, Cohen 2010)
Cost		
Initial consultation	$37.05	MBS 23
DHC test	$30.00	Section A
Laboratory test	$15.65	MBS 69384
Extra POC fee	$0.74*	MBS 74990, 74991
Extra laboratory fee	$8.46*	MBS 74995, 74999, 73928, 73929
Follow-up consultation	$37.05	MBS 23
Testing behaviour		
Prob. symptomatic infection will be tested	100%	Assumption
Prob. an individual will monitor HIV, (by initial health state)	Seronegative & seroconverting = 55% (Seropositive = 20%)	Knight (2014), Simulation
Prob. of HIV test each cycle, given the individual monitors HIV	0.316993	Read (2013)

* weighted fees; assuming 100% bulk-billed; 10% in regional, rural or remote; 10% concession card holders; 75% serology tests in private laboratories

Results

The results of the base case of the economic evaluation are presented in Table 22.

Table 22   Base case results of the modelled economic evaluation

	DHC test	Serology
COST	$47.17/individual ($8,193,836)	$41.75 / individual ($7,252,050)
HIV diagnosis	1099	1109
Early	682	692
Commenced seropositive	(386)	(386)
Commenced seroconverting	(111)	(111)
Commenced seronegative	(185)	(195)
Late	417	417
Total Screening Tests Conducted	119889	119886
Total Unique Individuals Not Screened	99489	99505
Total Unique Individuals Screened	74211	74195
Screened once	38529	38499
Screened twice	26653	26643
Screened thrice	8094	8111
Screened four times	935	942
Total Testing Procedure Failures	96	32
DHC false negative	61	-
DHC false positive	1177	-
DHC true negative	117969	-
DHC true positive	682	-

The base case of the model predicts 10 fewer cases of HIV will be detected via screening with the DHC test compared to standard laboratory testing, largely due to the window periods assumed for the tests. Of those not diagnosed, all commenced in the seronegative health state and were infected within the year. The incremental cost of the DHC test is $941,454 therefore the strategy is dominated. This result is consistent with the assumption of no differences in testing frequency, and with the increased cost/test for the DHC test compared with serology.

As the modelled population is the estimated Australian eligible MSM population, the validity of the modelled results was assessed by comparing the modelled outcomes in the serology only arm to reported values in the literature:

- In the serology arm, the model predicts a total of 1,109 HIV cases will be detected in MSM for the year, of which 27.6% (306/1,109) are newly acquired infections within the year and 37.6% (417/1,109) are advanced or late infections. These modelled results are consistent with those reported by the Kirby Institute (2014a, 2014b) whereby ~1,050 MSM were diagnosed with HIV in 2013, ~28% with newly acquired infection and ~31% with advanced or late infections (Kirby Institute 2014b).

- The model predicts HIV positivity in 0.93% of individuals screened (or 1.48% including symptom-based testing), which is similar to a reported probability of 1.3% based on a retrospective audit of the Prahran Market Clinic in Melbourne (Eu 2014).

- In terms of diagnostic accuracy, the model predicts the sensitivity and specificity of the DHC test to laboratory testing in the clinical setting are 91.76% and 99.01% respectively. These modelled results are similarly consistent with those reported in the

meta-analysis above, 87.8% (95% CI: 75.2%, 95.4%) and 99.4% (95% CI: 99.1%, 99.7%), respectively.

Table 23 presents the results of sensitivity analyses conducted during the assessment.

Sensitivities 1 and 2 alter two of the assumed distributions used by the model to estimate the starting composition of the "Seropositive" health state by years infected and the probability of progressing to AIDS (see above). The results indicate that only the absolute number of total diagnoses is affected by these distributions, and not the incremental change between testing strategies.

Sensitivities 3 to 7 alter the costs assumed in the model. In all cases, the proposed listing of DHC is associated with an incremental cost and a fewer number of detections compared with current laboratory testing.

Sensitivities 8 to 11 alter the impact that DHC will have on current practice. Based on professional advice sought during the evaluation, the proposed listing of DHC is unlikely to change clinical practice of HIV testing and hence any use of DHC would be in addition to current laboratory testing.

- Sensitivity 8 assumes all DHC confirmed positives will return to the GP for counselling despite receiving counselling following the unconfirmed DHC positive.
- Sensitivity 9 assumes all DHC tests (positive and negative) in the "seroconverting" health state are confirmed by serology, which is further supported by recent Australian recommendations for point-of-care testing in individuals suspected of seroconverting by Chan (2015).
- Sensitivity 10 assumes all DHC tests (positive and negative) will be confirmed with serology. Given a blood sample should be concurrently taken to test for STIs such as syphilis with every HIV test (see STIGMA guidelines), it is highly likely HIV status will also be tested by serology regardless of the point-of-care test result. This is current practice at one Melbourne clinic which offers point-of-care testing[5].
- Sensitivity 11 assumes all DHC tests (positive and negative) will be confirmed with serology and all confirmed positives will return to the GP for counselling despite receiving counselling following the unconfirmed DHC positive.

The incremental cost is higher in each scenario compared to the base case.

Sensitivities 12 and 15 increase the proportion and testing frequency in the model under two scenarios where DHC will substitute for serology testing and where serology testing will be done regardless of DHC result.

- Sensitivities 12 and 14 assumes DHC is associated with 3 percentage point increase in the proportion of individuals are tested for HIV. Eu (2014) reports that of the 1,527 MSM tested for HIV, 219 requested a point-of-care test, and 1 in 5 surveyed indicated they would not have been tested should DHC not have been available. Therefore, screening participation may have increased in Eu (2014) by approximately 3% as a result of point-of-care testing.

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[5] Based on professional advice sought during the evaluation, approximately 10% of individuals who request a HIV point-of-care test at one Melbourne clinic refuse venepuncture.

- Sensitivities 13 and 15 models the rate of first-test and subsequent-tests separately in both the DHC and serology arms, based on the *post-hoc* analysis reported in Read (2013). The 3-monthly probabilities are calculated from the reported rates for the DHC and serology arms respectively: first test = 0.281017 (161 tests / 122 person years) and 0.222589 (141 tests / 140 person years); subsequent tests = 0.371865 (1.86 tests / year) and 0.367136 (1.83 tests / year).

Whilst both sensitivity analyses 12 to 15 have a positive ICER, it must be noted that a key assumption in the model is that each individual's testing behaviour is unrelated to their risk taking behaviour. Should the proposed DHC listing only influence testing behaviour in risk averse individuals who are less likely to be HIV positive or become HIV positive, despite increased testing (and increased cost) there would be no (or marginal) increase in HIV detection. More importantly however, these analyses should be viewed only as sensitivities given the lack of evidence to suggest the listing of DHC on the MBS would change testing behaviour.

Table 23   Sensitivity analyses

	DHC test	Serology	Increment
Base case			
Cost	$8,209,795	$7,398,820	$810,976
HIV detected	1,138	1,148	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 1: Years infected alternative log-normal distribution			
Cost	$8,214,125	$7,403,078	$811,047
HIV detected	1,138	1,148	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 2: logistic cumulative function for progression to AIDS			
Cost	$8,218,319	$7,407,251	$811,067
HIV detected	1,178	1,188	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 3: incremental cost of HIV laboratory test = $13.25			
Cost	$8,204,333	$7,110,093	$1,094,240
HIV detected	1,099	1,109	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 4: extra POC fee = $0.00 (min); extra lab fee = $2.40 (min)			
Cost	$8,107,321	$6,669,784	$1,437,537
HIV detected	1099	1109	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 5: extra POC fee = $0.00 (min); extra lab fee = $9.95 (max)			
Cost	$8,124,504	$7,578,071	$546,433
HIV detected	1099	1109	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 6: extra POC fee = $10.65 (max); extra lab fee = $2.40 (min)			
Cost	$9,383,627	$6,669,784	$2,713,843
HIV detected	1099	1109	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 7: extra POC fee = $10.65 (max); extra lab fee = $9.95 (max)			
Cost	$9,400,811	$7,578,071	$1,822,740
HIV detected	1099	1109	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 8: all POCT confirmed positives will have a follow-up consultation			
Cost	$8,235,064	$7,398,820	$836,244
HIV detected	1,099	1,109	-10
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 9: all POCT tests in seroconverting health state are confirmed by serology (no POCT follow-up consultation)			
Cost	$8,210,769	$7,398,820	$811,949
HIV detected	1,109	1,109	0
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 10: all POCT tests are confirmed with serology (no POCT follow-up consultation)			
Cost	$11,054,158	$7,398,820	$3,655,338
HIV detected	1,109	1,109	0
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 11: no change to current practice = all POCT are confirmed with serology + all confirmed positives have			

	DHC test	Serology	Increment
follow-up			
Cost	$11,079,833	$7,398,820	$3,681,013
HIV detected	1,109	1,109	0
		Incremental cost/ extra HIV detection	Dominated
Sensitivity analysis 12: Increase in proportion who test in POCT arm from 55% to 58%			
Cost	$8,659,409.64	$7,398,820	$1,260,590
HIV detected	1,136	1,109	27
		Incremental cost/ extra HIV detection	$46,689#
Sensitivity analysis 13: Higher rate of first test in POCT, based on Read (2013) post-hoc analysis			
Cost	$8,113,292	$6,180,282	$1,933,010
HIV detected	1105	1045	60
		Incremental cost/ extra HIV detection	$32,217#
Sensitivity analysis 14: Increase in proportion who test in POCT arm from 55% to 58% + no change to current practice (all POCT are confirmed with serology + all confirmed positives have follow-up)			
Cost	$11,687,622	$7,398,820	$4,288,802
HIV detected	1,136	1,109	27
		Incremental cost/ extra HIV detection	$158,845#
Sensitivity analysis 15: Higher rate of first test in POCT, based on Read (2013) post-hoc analysis + no change to current practice (all POCT are confirmed with serology + all confirmed positives have follow-up)			
Cost	$10,949,445	$6,180,282	$4,769,163
HIV detected	1105	1045	60
		Incremental cost/ extra HIV detection	$79,486#

\#   ICER interpretation requires consideration as the model assumes testing behaviour is unrelated to risk taking behaviour or probability of being HIV positive; therefore a change in testing behaviour is assumed to impact all individuals equally.

The results of the sensitivity analyses demonstrate that the ICER is most sensitive to the assumption that the availability of the DHC test would encourage a greater proportion of MSM to be tested and assumed increases in testing frequency with the DHC test compared with serology testing.

Costing

Costs to the Australian healthcare system overall

Table 24 presents the direct costs associated with a standard HIV pathology test and a point-of-care rapid test. As discussed above, GP consultation costs (initial and subsequent) consultations have been excluded as they are unlikely to differ across testing strategies. Should DHC be used as a substitute for serology testing, the incremental cost per test is approximately $5.54 (85% benefit). Should DHC be used in addition to serology, the incremental cost per test is approximately $26.13 (85% benefit).

Table 24   Direct costs associated with a standard HIV pathology test and a point-of-care rapid test

MBS item description	MBS item number	Weight	MBS fee (85%)	Total cost
Serology				
Pathology HIV test	69384	1	$13.35	$13.35
Patient episode initiate fee				
Public laboratories	73929	0.25*	$2.05	$0.51
Private laboratories	73928	0.75*	$5.10	$3.83
Bulk-billed pathology incentive				
Public laboratories	74999	0.25*	$1.40	$0.35
Private laboratories	74995	0.75*	$3.40	$2.55
Total				**$20.59**
DHC				
DHC test	Proposed	1	*25.50*	*25.50*
Management of bulk-billed services				
Not regional, rural or remote	74990	0.09#	$6.00	0.54
Regional, rural or remote	74991	0.01#	$9.10	0.09
Total				**$26.13**

*   Assumption of 100% bulk-billed for services and 25% of tests conducted in public laboratories
#   Assumption of 10% concession card holders; 100% bulk-billed for services and 10% in regional, rural or remote locations

The number of tests that are likely to be undertaken amongst high risk individuals is unknown.

Assuming direct substitution and 45,000 rapid tests per year (MSAC 1391 Final Protocol p5), the total cost to the Australian healthcare system is approximately $249,300, where this additional cost is associated with fewer HIV diagnoses. Assuming sequential use and 45,000 tests per year, the total cost is approximately $1,175,850, where this additional cost is associated with no differences in the number of HIV diagnoses.

Based on the number of tests estimated in the base case of the modelled economic evaluation of 119,889 tests per year, assuming direct substitution, the total cost to the Australian healthcare system is approximately $664,185 (additional cost with fewer HIV diagnoses); assuming sequential use, the total cost is approximately $3,132,700 (additional cost is associated with no differences in the number of HIV diagnoses).

Assuming that the DHC test will result in a 3% increase in the number of HIV tests (123,496 tests for DHC and 119,899 tests for serology per year) and:

- Direct substitution; total cost to the Australian healthcare system is $758,229, with additional HIV diagnoses; and
- Assuming sequential use (among those who would have tested by serology anyway); total cost to the Australian healthcare system is $5,769,732 respectively, with additional HIV diagnoses.

Differences between these estimates, and those presented in the sensitivity analyses of the model are due to the use of the 100% MBS fee and other assumptions used in the model.

Costs to the Medical Benefits Scheme (MBS)

Same as overall cost

Costs to the State and Territory health systems

None

Costs to the private health insurer and/or patient

None. Expert advice has indicated that all serology HIV tests are bulk-billed, and this is likely to be the case for rapid point-of-care testing. However, should individuals undergoing rapid point-of-care testing not be bulk-billed and be required to contribute to part of the fee, this cost would be $4.50 (15% of the $30.00 requested fee).

Discussion & Conclusions

Safety

No studies assessing the comparative safety of rapid point-of-care testing and serology testing for HIV were identified.

With respect to the procedures undertaken to collect specimens for testing, a finger-prick of venepuncture for rapid point-of-care and serology, respectively, no real safety issues are associated with either, provided the person drawing the samples is trained and sterile equipment is used. In addition, as the DHC test requires the same or fewer blood withdrawals than the comparators, it is reasonable to conclude that the test is safe.

The impact of false positive or false negative results from the rapid point-of-care test however, should be considered. Where false positive results occur from the DHC test, this is likely to be associated with concern and anxiety until such time that the individual's true HIV status is conveyed. With respect to false negative results, there is potential for those individuals to have worse health outcomes in the longer term due to having an undiagnosed HIV infection. There is also the potential for these individuals to unknowingly transmit HIV to other individuals until such time they undergo further testing and are diagnosed. As noted previously, the current practice in at least one Melbourne clinic is to collect a venous sample on the same day as rapid testing for serology testing for HIV. If this applies nationally, the risk of false negative results should be no greater than is currently the case. The risk of false-negative results in practice may additionally be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product.

Effectiveness

Diagnostic accuracy

The product insert for the DHC test states that the sensitivity is 100.00% across 1,179 specimens positive for various types and subtypes of HIV and who were confirmed HIV antibody positive. The specificity of the test is 99.61% for the antigen test line and the 99.21% for the antibody test line across 1,783 HIV-negative specimens. Given these estimates are derived from the two extreme ends of the disease spectrum (ie, confirmed seronegative and seropositive specimens), which tends to overestimate diagnostic accuracy (Knottnerus 2002), an assessment of the diagnostic characteristics of the test amongst a high-risk Australian population, where the test was being used in GP and sexual health clinics, and was compared with current diagnostic tests used in Australia was deemed relevant to this review.

Diagnostic accuracy of the DHC test in an at-risk population was derived from two Australian studies offering the DHC test to MSM attending GP and sexual health clinics in Melbourne and Sydney. The attendees each also had laboratory-based testing for HIV, where a negative laboratory-based enzyme immunoassay was used to determine a

true negative status and in those with positive laboratory-based immunoassay were further confirmed by Western Blot analysis to determine true HIV status.

The overall findings from the body of evidence for the diagnostic accuracy component of this linked evidence assessment are summarised in Table 25.

Table 25   Body of evidence matrix for diagnostic accuracy

Component	
Evidence-base[a]	C – Satisfactory One or two level III studies with a low risk of bias All the studies were cross-sectional in nature, level III-2; and all had a low risk of bias.
Consistency	B – Good Most studies consistent and inconsistency may be explained Both studies were consistent in their respective determination of sensitivity, specificity and negative predictive value of the DHC test. The studies differed with respect to reported positive predictive values, which could be explained by one study reporting approximately double the number of false positive results compared with the other (0.6% versus 0.3%). However, the reason for this difference in observed false positive rate is not known.
Generalisability	A – Excellent Population/s studied in body of evidence are the same as the target population The populations included in the studies are directly applicable to those for whom listing is sought – Australian MSM residing in Melbourne or Sydney who attended GP or sexual health clinics for HIV testing. While including directly applicable populations, the populations were not entirely representative as they presented results only for MSM, where the test is intended for a wider population, such as injecting drug users.
Applicability	A – Excellent Directly applicable to Australian healthcare context Study settings and testing methodologies were consistent with current standard of care in Australia.

Source: adapted from(NHMRC 2008)
[a]   Level of evidence determined from the NHMRC evidence hierarchy

A meta-analysis of the two included studies indicated that the sensitivity of the DHC test was 87.8% (95% CI: 75.2%, 95.4%) and the specificity was 99.4% (95% CI: 99.1%, 99.7%) compared with serology testing.

The data presented in these two studies is directly applicable to those for whom listing is sought. While the results of these diagnostic accuracy studies yield different diagnostic characteristics of the DHC test compared with serology testing provided in the product insert, the differences are likely to result from the estimates provided in the product insert having been assessed from the two extreme ends of the disease spectrum (ie, confirmed seronegative and seropositive specimens), which tends to overestimate diagnostic accuracy (Knottnerus 2002). These data indicate that use of the DHC test in early HIV infection should be used with caution. The risk of false-negative results in practice may however be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The product's instructions for use detail the limitations of the test, including the limitation of the test at early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product. Expert advice has suggested that individuals suspected of early HIV seroconversion are

particularly encouraged to undergo additional laboratory testing, other advice suggest that those suspected of early infection should not be tested with a rapid test at all.

Impact on patient management

A single randomised controlled trial was identified in which MSM who had a previous negative HIV test result within the last two years were randomised to the DHC test or conventional laboratory-based testing for HIV. The trial duration was a period of 18 months and the primary outcome of the trial was "HIV tests over 18 months". Table 26 summarises the overall findings from the body of evidence for the patient management component of this linked evidence assessment.

Table 26   Body of evidence matrix for patient management

Component	
Evidence-base[a]	B – Good One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias The trial, level II; had a low risk of bias.
Consistency	Not applicable as there was only one trial
Generalisability	A – Excellent Population/s studied in body of evidence are the same as the target population The populations included in the studies are directly applicable to those for whom listing is sought – Australian MSM residing in Melbourne who attended a sexual health clinic for HIV testing. While including directly applicable populations, the populations were not entirely representative as they presented results only for MSM, where the test is intended for a wider population, such as injecting drug users.
Applicability	A – Excellent Directly applicable to Australian healthcare context Study settings and testing methodologies were consistent with current standard of care in Australia.

Source: adapted from(NHMRC 2008)
a   Level of evidence determined from the NHMRC evidence hierarchy

The results of the trial indicate that there was no statistically significant difference between groups for the primary outcome of "HIV tests over 18 months" or the secondary outcomes of syphilis, chlamydia and gonorrhoea testing over 18 months. Hence, the possibility of having HIV tests by rapid point-of-care testing did not result in higher testing frequency over the study period of 18 months.

The authors also undertook *post-hoc* analyses considering only the first HIV test after enrolment and considering only subsequent HIV tests (excluding first tests). A statistically significantly greater number of first HIV tests/year after the enrolment test was observed in those randomised to the HIV testing by the rapid point-of-care test compared with conventional testing, however no differences were observed in the number of HIV tests/year when only considering subsequent tests. Based on these results, the authors conclude that "Post hoc analysis showed an initial increase in their rate of testing that was not sustained".

While the population in the trial is applicable to those for whom listing is sought, the population was limited in that enrolment was restricted to men who had a history of testing, which is not entirely applicable for the Australian population for whom listing is

sought. The MBS listing would also extend to individuals who have never tested for HIV.

A potential overall limitation of the intention of the proposed MBS listing is the restriction of the use of the DHC test in GP and sexual health clinics. The use of the DHC test in such clinics requires individuals to attend the clinics for HIV testing, which is also the case for current laboratory-based testing for HIV. This requires that at-risk individuals recognise the need for HIV testing and actively seek it. While data from Eu (2014) suggests that one in five attendees to their clinic would not have tested if the DHC test were unavailable, data from Prestage (2012) indicates that a substantial proportion of men cite "I haven't done anything risky" as a reason for avoiding or delaying HIV testing, something that the availability of the DHC test would not address.

Knight (2014) report the use of the DHC test in a pop-up caravan. Of the 182 tests conducted over the period of five days that the caravan was open, no newly reactive individuals were identified and most received their results by SMS, while some chose to return to the caravan for their results. The relative success of the caravan in engaging GBM for testing (36.4 individuals or 36.4 tests per day) compared with attendance to a GP or sexual health clinic (1.3 individuals or 1.8 tests per day in Eu 2014 or 3.7 individuals or 4.8 tests per day in Conway 2014) may support the use of the DHC test in more of an outreach capacity.

Impact on health outcomes

Once a diagnosis of HIV infection is made there would be no difference in the time taken to commence treatment and alter high-risk behaviour.

Economic considerations

The data reported in Conway (2014) and Eu (2014) indicates that DHC has inferior diagnostic accuracy for detecting HIV compared to serology testing; whereas data reported in Read (2013) indicates that there was no statistically significant difference between the groups randomised to rapid point-of-care testing and serology testing in terms of number of tests/year for HIV. To account for the differential diagnostic accuracy, a cost-effectiveness analysis is appropriate.

The base case of the model assumes no differences in testing frequency between the two arms of the model. Sensitivity analyses are conducted modifying some assumptions to attempt to capture other reasonable scenarios, including the qualitative patient satisfaction evidence in Eu (2014) and the *post-hoc* analysis in Read (2013).

The type of economic evaluation presented is a novel static cost-consequences analysis which estimates cost per various test outcomes associated with the DHC test and conventional testing (fourth generation EIA) over one year. The population in the model is assumed to be all Australian MSMs without diagnosed HIV, and includes individuals who are seropositive, seroconverting and seronegative.

A decision analytic Markov model is used to estimate the cost per various test outcomes over a one year time horizon with three-monthly cycles, of a scenario where the DHC test is available for screening HIV in high-risk individuals. MSMs without a diagnosis of HIV are assumed to commence each cycle in one of four health states (i) "Seropositive", (ii) "Seroconverting", (iii) "Seronegative" , (iv) "HIV diagnosed". The population enters

the model in one of the three non-HIV diagnosed health states, and only transitions to the absorbing health state "HIV diagnosed" after a confirmed HIV diagnosis is made either through HIV screening or the development of AIDS complications and symptom-based testing. The population who are "seronegative" may become infected with HIV during a cycle and transition to "seroconverting" or remain "seronegative". The population only remains in the "seroconverting" health state for one cycle. They may be screened for HIV within the cycle and if diagnosed transition to "HIV diagnosed", otherwise they will transition to "seropositive". Those with undiagnosed "seropositive" disease can transition to "HIV diagnosed" either via HIV screening, or due to development of AIDS symptoms via HIV symptom-based testing.

Monte Carlo simulation is used to accommodate the heterogeneous population, conditional transition state probabilities, and incorporates a tracker variable for number of tests required by the clinical evidence available. Therefore at the start of the model, individuals are assigned to one category for each of the following variables (i) Initial non-HIV diagnosed health state ("seronegative", "seroconverting", "seropositive"); (ii) If "seropositive", number of year seropositive (1 to 20); (iii) Undertakes routine HIV screening (yes or no); or (iv) Days since HIV infection (1 to 90).

There is no precise "window period" at which time a HIV test will detect an infection that it would not have detected prior to this time. Therefore, in the seroconverting health state, the probability of a positive diagnosis is assumed to increase over time (Owen 2008). Wilson (2011) modelled the window periods of the third and fourth generation EIA and point-of-care tests using a logistic growth curves. The medians are set equal to the defined window periods for each test after the detection of HIV RNA with the Nucleic Acid Test, 10 days for the DHC test and five days for fourth generation EIA. However, there is an eclipse period between the day of infection and day when HIV markers are detectable. The eclipse period is approximately 2 weeks from infection to p24 antigen, suggesting the median window periods for fourth generation EIA and the DHC test are approximately 20 and 25 days respectively (Cohen 2010).

The base case of the modelled economic evaluation predicts 10 fewer cases of HIV will be detected via screening with the DHC test compared to standard laboratory testing, largely due to the window periods assumed for the tests. Of those not diagnosed, all commenced in the seronegative health state and were infected within the year. The incremental cost of the DHC test is $941,454, therefore the strategy is dominated. This result is consistent with the assumption of no differences in testing frequency, and with the increased cost/test for the DHC test compared with serology testing.

The results of the sensitivity analyses demonstrate that the ICER is most sensitive to the assumption that the availability of the DHC test would encourage a greater proportion of MSM to be tested (ICER=$46,689/additional HIV detection; assuming an increase from 55% to 58% of MSM are tested) and assumed increases in testing frequency with the DHC test compared with serology testing (ICER=$32,217/additional HIV detection).

Costing

The number of tests that are likely to be undertaken amongst high risk individuals is unknown.

Assuming direct substitution and 45,000 rapid tests per year (MSAC 1391 Final Protocol p5), the total cost to the Australian healthcare system is approximately $249,300, where this additional cost is associated with fewer HIV diagnoses. Assuming sequential use and

45,000 tests per year, the total cost is approximately $1,175,850, where this additional cost is associated with no differences in the number of HIV diagnoses.

Based on the number of tests estimated in the base case of the modelled economic evaluation of 119,889 tests per year, assuming direct substitution, the total cost to the Australian healthcare system is approximately $664,185 (additional cost with fewer HIV diagnoses); assuming sequential use, the total cost is approximately $3,132,700 (additional cost is associated with no differences in the number of HIV diagnoses).

Appendix A   Rapid point-of-care combined Antigen/antibody HIV test to aid in the diagnosis of HIV infection, MSAC Application 1391

Evaluators

Name	Organisation
Mr Peter Ghijben	Monash University
Associate Professor Silva Zavarsek	Monash University
Ms Karen Yong	Monash University
Mr Francis Ip	Monash University

Appendix B   TGA conditions on the use of DHC

1. The person (the sponsor) in relation to whom the Alere Determine HIV 1/2 Ag/Ab Combo (the device) is included on the Australian Register of Therapeutic Goods (the ARTG) must ensure that the device is only supplied for use by

   a) laboratories that are accredited by the National Association of Testing Authorities (NATA) as medical testing laboratories and that participate in an HIV point of care quality assurance program; or

   b) organisations that:
      i)   employ health professionals who will perform, or supervise the performance of, HIV testing using the device, and
      ii) have an established relationship (in relation to the referral and testing of specimens) with a NATA accredited medical testing laboratory, and
      iii) participate in an HIV point of care quality assurance program, and
      iv) provide a declaration to the sponsor every 12 months that all personnel using the device have received training in the delivery and administration of HIV point of care devices in accordance with the requirements of the National HIV Testing Policy.

2. The sponsor of the device (Alere Determine HIV 1/2 Ag/Ab Combo) must make available training in the correct use of the device and interpretation of results.

3. The sponsor must maintain records that demonstrate that the device has been supplied in compliance with condition 1 and that it has complied with condition 2.

4. The sponsor must provide to the Post-market Surveillance Branch (PSB) of the Therapeutic Goods Administration (TGA), a post market surveillance report for each period of six (6) months commencing on the date of inclusion of the device in the ARTG identifying any adverse events, problems or complaints relating to the use or application of the device. The first report must be provided at the end of eight (8) months from the date of inclusion of the device in the ARTG and each six (6) months thereafter, for a period of three years.

5. The sponsor must provide to the TGA a report and documents for each period of twelve (12) months commencing on the date of inclusion of the device on the ARTG. The first report must be provided at the end of fourteen (14) months from the date of inclusion of the device on the ARTG and each twelve (12) months thereafter. Information about the distribution of the device and evidence of compliance with the conditions of ARTG inclusion for that twelve months (the period) must be provided, including:

   a) copies of the current NATA accreditation certificate for each laboratory to which the device has been supplied during the period and documented evidence of participation of the laboratory in a HIV point of care quality assurance program.

   b) in relation to each organisation that is not an accredited medical testing laboratory:

      i)   documented evidence of a relationship of the kind referred to in condition 1b. above with a NATA accredited laboratory, and

      ii)   documented evidence of the participation by the organisation in a HIV point of care quality assurance program, and

c) documented evidence that condition 2 has been complied with by the sponsor during the period, and

d) documented evidence that each person using the device during the period has satisfactorily completed training in the correct use of the device and interpretation of results being evidence that:

      i)   identifies the name and qualifications of health professionals who use or supervise the use of the device, the date of their training and provider of the training,

      ii)   identifies the names of all other users of the device, the date of their training and provider of the training,

      iii)   lists the specific skills and knowledge evaluated in the training, and

e) declarations, including certificates or other evidence, that each person using the device has received training in the delivery and administration of HIV point of care devices in accordance with the requirements of the National HIV Testing Policy.

6. Post market reports must be sent to the PSB at the following email address, postmarketdevices@tga.gov.au

Appendix C   Search strategies

Search strategy employed to identify relevant studies to assess the diagnostic characteristics and effectiveness of rapid point-of-care Antigen/Antibody HIV tests compared with serology testing for HIV.

		Embase	Medline	EBM
1	exp Human immunodeficiency virus infection/di [Diagnosis]	27783	0	0
2	exp HIV infection/di [Diagnosis]	277863	23694	141
3	exp Human immunodeficiency virus test/	4479	0	0
4	exp HIV test/	4479	0	0
5	rapid.mp.	572901	479065	18278
6	exp "point of care testing"/	5373	0	0
7	(point of care or POC or point of care test* or POCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	15211	13403	900
8	((fourth or 4th) adj generation).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2650	1992	123
9	(determine and alere).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	94	15	6
10	1 or 2 or 3 or 4	31436	23694	141
11	5 or 6 or 7	585350	490301	19019
12	8 or 9	2735	2004	129
13	11 and 12	249	121	14
14	**10 and 13**	89	44	0
15	(rapid adj human immunodeficiency virus adj test*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	24	17	1
16	(rapid adj HIV adj test*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	707	540	53
17	((point of care or POC) adj human immunodeficiency virus adj test*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	0	0	0
18	((point of care or POC) adj HIV adj test*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	56	32	5
19	exp HIV rapid test/	162	0	0
20	**15 or 16 or 17 or 18 or 19**	878	570	55
21	**14 or 20**	**920**	**603**	**55**

The following Health Technology Assessment (HTA) websites were also searched for relevant reviews.

HTA organisation	Website
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/
Centre for Clinical Effectiveness, Monash University	http://www.southernhealth.org.au/page/Health_Professionals/CCE/
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	http://www.ryerson.ca/library/info/databases/cabot.html
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
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta
Danish Institute for Health Services Research (DSI)	http://dsi.dk/
Finnish Office for Health Technology Assessment (FINOHTA)	http://www.thl.fi/en_US/web/en/aboutus/organisation/units/technologies_and_practices_assessment
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en/index.html
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.ac.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
National Information Centre of Health Services	http://www.nlm.nih.gov/hsrph.html
Research and Health Care Technology (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Oregon Health Resources Commission (US)	http://www.nlm.nih.gov/hsrph.html
Office of Health Technology Assessment Archive (US)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association	http://www.bcbs.com/blueresources/tec/

Technology Evaluation Center (Tec)	
U.S. Blue Cross/ Blue Shield of Alabama	https://www.bcbsal.org/web/index.html

Appendix D   Studies included in the review

Study profiles of included studies on diagnostic accuracy

Table D1   Study profiles of included studies on diagnostic accuracy of rapid point-of-care testing for diagnosing HIV compared with serology testing

Study and location Grade	Diagnostic level of evidence and study design	Quality assessment	Study population Inclusion/exclusion criteria	Reference standard	Index test	Comparator(s)	Outcomes
Conway (2014) Australia C1, P1, Q1	Level III-1 Prospective, cross-sectional.	Low risk of bias as all participants had POC and serology tests. No applicability concerns in terms of setting or population.	N=2,468 men who have sex with men (MSM) aged over 18 years were offered rapid HIV testing with the Determine HIV Combo (DHC). Testing was conducted at four free access publically funded sexual health clinics in Sydney. A total of 3,195 tests were performed. Participants enrolled between October 2011 and July 2013. N=5 invalid rapid tests were excluded.	Laboratory assays which are standard of care in this setting: • 4th generation screening immunoassay • Supplementary HIV antibody • HIV p24 antigen immunoassay • HIV Western Blot	Alere Determine Combo HIV Ab/Ag test	All participant samples were tested using a laboratory 4th generation screening immunoassay. If this test was negative, the participant's true status was deemed negative. Supplementary HIV antibody, HIV p24 antigen and Western blot testing were performed on all specimens positive by the 4th generation HIV screening immunoassay with true HIV status deemed positive if consistent with the national case definition[a].	Sensitivity for the test overall (antibody and antigen) and the antibody and antigen components separately and amongst those with acute/early infection; specificity and positive predictive value of the test overall
Eu (2014) Australia C1, P1, Q1	Level III-1 Prospective, cross-sectional	Low risk of bias as all participants had POC and serology tests. No applicability concerns in terms of setting or population.	All persons of consenting age requesting rapid POC testing were included. N=219 MSM (of 1,527 who chose to have POC testing). A total of 302 tests were conducted. Participants enrolled between March and August 2013.		Alere Determine Combo HIV Ab/Ag test	All participant samples were tested using a laboratory 4th generation enzyme immunoassay antibody test. Western blot testing was performed on all specimens positive by a 4th generation HIV screening immunoassay (POC or laboratory), according to Figure 1, p90 of the publication.	Sensitivity, specificity and positive and negative predictive values. Patient satisfaction survey

[a]   A confirmed case requires laboratory definitive evidence only AND that the case does not meet any of the criteria for a newly acquired case. Laboratory definitive evidence is defined as (1) Repeatedly reactive result on a screening test for HIV antibody followed by a positive result on a Western Blot. A positive result on a Western Blot is defined by the presence of a glycoprotein band (gp41, gp120 or gp160) and at least three other HIV-specific bands OR (2) Detection of HIV by at least two virologic assays (nucleic acid testing for proviral DNA; HIV p24 antigen, with neutralisation; virus isolation) performed on at least two separate blood samples. Source: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hivuns.htm

Study profiles of included studies on changes in patient management

Table D2   Study profiles of included studies on effectiveness of rapid point-of-care testing for diagnosing HIV compared with serology testing

Study Grade	Level of evidence	Location Duration of follow-up	Study design	Study participants	Interventions	Outcomes assessed
Read (2013) C1, P1, Q1	Level II	Australia. The Melbourne Sexual Health Centre – the major public clinic for sexually transmitted infections in Victoria. 18 months	Randomised controlled trial, not blinded. Men were randomised 1:1 with a randomised block design using two computer generated random sequences per block to each study arm.	Men (n=400) aged ≥18 years attending for medical care who reported having sex with a man within the previous year and who had a negative HV test within the previous two years. <u>Those who had previously been tested were specifically sought to increase the likelihood that men would re-test within the study period.</u> Men were excluded if they were seeking post-exposure prophylaxis as were those planning to live outside of Victoria for greater than six months.	Men were randomised to: • Testing with the DHC test with whole blood obtained from finger pricks. These men were advised that could return to the clinic at any time over the study period and would be tested with the DHC test. Test results were received 20 minutes after the finger prick. Men in this arm were allowed to have conventional testing if desired. OR • Testing with the clinic's standard HIV test: venepuncture with serum forwarded to the Victorian Infectious Diseases Reference Laboratory for testing by third generation enzyme immunoassay. Subsequent HIV tests were also conducted using serology. <u>Men were required to return to the clinic one week after the test to be given their results in person.</u> Testing for HIV and other STIs was according to national guidelines – annual screening for HIV, syphilis, pharyngeal and rectal gonorrhoea, and urethral and rectal chlamydia, with three to six monthly screening of men at higher risk	<u>Primary:</u> The frequency (incidence rate) of HIV testing over 18 months, expressed as the number of tests per person year. HIV testing included those performed at the study clinic (rapid or conventional), and including tests conducted at other sites (given rapid testing was not approved at that time, all testing at other clinics would have been conventional). <u>Secondary:</u> The frequency (incidence rate) of testing for syphilis, gonorrhoea and chlamydia to determine if rapid HIV testing would result in a fall in testing for other STIs.

Appendix E   Excluded studies

Incorrect intervention

(Not a fourth generation Ag/Ab combo test or not conducted POC)

Abbate, I., Pergola, C., Pisciotta, M., et al. (2014). Evaluation in a clinical setting of the performances of a new rapid confirmatory assay for HIV1/2 serodiagnosis. *Journal of Clinical Virology, 61*(1), 166-169.

Aghokeng, A. F., Mpoudi-Ngole, E., Dimodi, H., et al. (2009). Inaccurate diagnosis of HIV-1 group M and O is a key challenge for ongoing universal access to antiretroviral treatment and HIV prevention in Cameroon. *PLoS ONE [Electronic Resource], 4*(11), e7702.

Aguirre, D., Mares-DelGrasso, A., Emerson, C., et al. (2007). Rapid HIV testing in outreach and other community settings - United States, 2004-2006. *Morbidity and Mortality Weekly Report, 56*(47), 1233-1237.

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Incorrect comparator

(Not a compared with laboratory-based EIA/ELISA and/or Western Blot)

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Appendix F   Economic evaluation search strategy

		Embase	Medline	EBM
1	exp Human immunodeficiency virus infection/di [Diagnosis]	27783	0	0
2	exp HIV infections/di [Diagnosis]	27783	23694	141
3	exp "cost utility analysis"/	5884	61357	0
4	(cost-util* or (cost adj util*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	8897	2771	4107
5	exp "cost effectiveness analysis"/	103835	61357	0
6	(cost-effect* or (cost adj effect*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	160663	82622	26218
7	exp "cost benefit analysis"/	66752	61357	16001
8	(cost adj study).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	330	183	160
9	(mathematical adj model).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	96584	21046	328
10	1 or 2	27783	23694	141
11	3 or 4 or 5 or 6 or 7 or 8 or 9	309847	137696	30471
13	10 and 11	**735**	**522**	**92**

Embase: 1974 to 2015 February 23
Medline: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present
EBM: Cochrane Database of Systematic Reviews 2005 to January 2015, EBM Reviews - ACP Journal Club 1991 to February 2015, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2015, EBM Reviews - Cochrane Central Register of Controlled Trials January 2015, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 1st Quarter 2015, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2015

Inclusion criteria:
Modelled analysis; comparing Conventional HIV (EIA/WB) testing versus Rapid testing algorithms; for HIV detection.

Exclusion criteria:
Testing of blood donations, other organ or tissue donations, or routine serology during pregnancy.

To identify as many potentially relevant models in the literature, (i) population, (ii) type of screening and (iii) country economic status were not specified as inclusion/exclusion, for example selective testing in "high-risk" patients in high income countries as expected in Australia. The search identified a total of 1,349 citations. Of 1,006 unique citations, 38 full text publications were retrieved. Six unique models were identified.

Glossary and abbreviations

Ab   antibody

Ag   antigen

AIDS   Acquired Immune Deficiency Syndrome

CI   confidence interval

DHC   Determine HIV Combo test (HIV-1/2 Antigen/Antibody)

EIA   Enzyme ImmunoAssay

ELISA   Enzyme-Linked ImmunoSorbent Assay

GBM   gay, bisexual and other men who have sex with men

GP   General Practitioner

GMSM   gay and other men who have sex with men

G/MSM   gay and other men who have sex with men

HAART   highly active anti-retro viral therapy

HIV   human immunodeficiency virus

HTA   health technology assessment

ICER   incremental cost-effectiveness ratio

LR   likelihood ratio

MBS   Medical Benefits Schedule

mL   millilitre

MSAC   Medical Services Advisory Committee

MSM   men who have sex with men

mths   months

NATA   National Association of Testing Authorities

NHMRC   National Health and Medical Research Council

NHS   National Health Service

NPV   negative predictive value

OR   odds ratio

pg   picogram

POC   point-of-care

POCT   point-of-care test

PPV   positive predictive value

Prob.   probability

QAP   quality assurance program

RCT   randomised controlled trial

RNA   ribonucleic acid

STI   sexually transmitted infection

TGA   Therapeutic Goods Administration

UAIC   unprotected anal intercourse with casual partners

WB   Western Blot

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