Australian Government
Department of Health
Therapeutic Goods Administration

Proposed performance requirements and risk mitigation strategies for HIV tests

Version 1.0, November 2014

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.

- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Devices Authorisation	November 2014

Contents

1. Purpose

Since the restriction on the supply of HIV self-tests has now been lifted, consideration needs to be given to acceptable performance requirements for all forms of HIV testing including self-testing. A balance is required between the need for high quality tests that are fit for purpose and improving access to HIV testing.

This paper proposes a model for the evaluation of antibody/antigen-based HIV tests depending on their intended purpose, the experience of the operator/user and the specimen type. The performance expectations for HIV point of care tests (PoCTs) and self-tests that have already been approved in overseas jurisdictions (e.g. Canada, USA, Europe, see Attachment 1) were taken into consideration when developing this approach. This paper will be used to develop guidance that will provide advice to industry, health care professionals and the community on TGA expectations when undertaking an evaluation of a HIV test, particularly if it is intended for use as a PoCT or for self-testing.

This paper does not directly consider the performance requirements for HIV nucleic acid tests (NAT).

2. Proposed performance requirements and risk mitigation strategies

A stratified model is proposed (summarised in Table 1) that suggests performance requirements and risk mitigation strategies, including conditions of approval. This model accepts that a HIV PoCT, and particularly a HIV self-test, may be considered fit for purpose at a lower level of sensitivity and specificity if the risks associated with using the test are mitigated and the benefits from use of the test outweigh the risks.

All tests for HIV should demonstrate the highest possible standard of performance relative to the intended purpose of the test. Different performance requirements are applicable depending on the nature of the test and take into consideration:

- the intended purpose of the test (e.g. presumptive screening test versus donor screening or confirmatory testing)

- the format of the test (e.g. simple rapid versus automated tests)

- the intended user of the test (e.g. whether it is laboratory-based, a PoCT or a self-test) and the environmental conditions under which the test would be conducted

- the specimen type (e.g. oral fluid versus finger-stick whole blood).

Overall acceptability of any test for the purposes of inclusion in the ARTG depends on compliance of the test device with the essential principles and in particular, a demonstration that the test does not compromise health and safety, is suitable for the intended purpose and the benefits of the test outweigh any residual risks associated with its use (essential principles 1, 3 and 6).

2.1 Laboratory tests

There are already a large number of laboratory tests available in Australia that have been approved for supply after taking into consideration their compliance with the European Union (EU) Common Technical Specifications (CTS).[1]

TGA will continue to be guided by the EU CTS standards for laboratory-based screening tests. This reflects the importance of these tests in relation to screening the blood supply and diagnostic testing strategies. Laboratory-based HIV tests intended for donor or diagnostic screening are required to have the following performance characteristics in relation to the detection of HIV antibodies:

- 100% sensitivity and 99.5% specificity for confirmed HIV positive samples based on a direct comparison with an established state-of-the-art device (e.g. a fourth-generation enzyme immunoassay (EIA)) or an established reference test (e.g. western blot);[2]

- 100% sensitivity and 99.5% specificity for HIV seroconversion samples (EU CTS ≥ 99% for rapid tests) based on a direct comparison with an established state-of-the-art device.[3,4]

The EU CTS provides further guidance on other parameters such as appropriate specimen numbers and additional requirements are outlined with regard to the detection of HIV-1 antigen in combined antibody/antigen tests (i.e. fourth generation EIA).

It is desirable that HIV reference tests (e.g. western blot) have a demonstrated high level of clinical sensitivity, but it is recognised that these tests may not necessarily perform to the same standard as established screening tests particularly for the detection of HIV during seroconversion.

HIV antibodies are generally detectable in serum, whole blood or oral fluid by weeks 3–12 of infection for 99% of cases but may take up to 6–12 months to form. Third-generation EIA screening tests can detect HIV antibody as early as 20 to 30 days following exposure while fourth-generation EIAs (which detect antigen and antibody) can reduce the window period (i.e. time between exposure and production of detectable HIV antibodies) further to approximately 15 to 20 days.[5,6] The western blot detects only IgG antibodies (and confirms their antigenspecificity) but does not detect antigen and can lag behind a reactive third or fourth-generation EIA assay by as much as 3 weeks.[7]

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[1] Commission Decision 2002/364/EC of 7 May 2002 on common technical specifications for in vitro-diagnostic medical devices.

[2] Western blot is traditionally used as a confirmatory test (Australasian Society for HIV Medicine (ASHM) 2011, *National HIV Testing Policy*, <http://www.ashm.org.au/>).

[3] The currently accepted state-of-the-art is the 'fourth-generation' enzyme immunoassay (EIA) which simultaneously detects p-24 antigen as well as HIV-1/2 IgG and IgM antibodies (Branson, MB 2007, 'State of the Art for Diagnosis of HIV Infection', *Clinical Infectious Diseases*, vol. 45, supplement 4 pp S221-225).

[4] Centres for Disease Control and Prevention 2014, *Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations*, available at < http://www.cdc.gov/>.

[5] Busch, MP and Satten G A 1997, 'Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure' *American Journal of Medicine* vol. 102(5B):117-124; discussion 125-126.

[6] Branson, BM and Stekler JD 2012, 'Detection of Acute HIV Infection: We Can't Close the Window' *Journal of Infectious Disease* 205:521-4

[7] Cornett, JK & Kirn, TJ 2013, 'Laboratory Diagnosis of HIV in Adults: A Review of Current Methods', *Medical Microbiology* vol. 57, no. 5, pp. 712-718.

Therefore reference tests, such as the western blot, will be evaluated primarily on the basis of test specificity which reflects the key role these tests have in confirming true positive status by distinguishing true from false reactivity.

For laboratory-based rapid tests intended for screening or confirmatory diagnosis, the performance requirements would be the same as for HIV PoCT described below.

Risk mitigation strategies

Although laboratory tests are required to perform to the highest possible standard, it is recognised that no test is necessarily 100% sensitive in all circumstances and these tests should be evaluated in the context of:

- their performance in a population equivalent to the Australian population (i.e. similar prevalence rate as that in Australia);

- whether the benefits of performing the test outweigh any potential risks.

The National Pathology Accreditation Advisory Council (NPAAC) document, *Requirements for Laboratory Testing for Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV),* sets out specific standards and guidelines for laboratory based testing.

In the laboratory setting, residual risks associated with use of the product are mitigated by the fact that these tests are performed by qualified staff in medical testing laboratories accredited by the National Association of Testing Authorities (NATA) or laboratories that hold a TGA issued Good Manufacturing Practice (GMP) licence with appropriate quality control and quality assurance procedures in place to continually monitor the performance of the test and quality of the results.

2.2 HIV Point of Care Tests (PoCTs)

HIV PoCTs are presumptive screening tests intended to aid in the diagnosis of HIV. Confirmation of positive results is required using a diagnostic laboratory test.

Rapid HIV diagnostic testing in the point-of-care setting is an important strategy to expand access to HIV testing and enable appropriate referral for confirmatory testing and follow-up treatment. HIV PoCTs have been shown to increase HIV testing rates leading to:

- a reduction in morbidity due to increasing detection rates earlier in the course of disease, enabling earlier use of antiretrovirals

- a reduction in ongoing HIV transmission through self-identification and resultant behaviour modification.

It is desirable that HIV PoCTs have a demonstrated high level of clinical sensitivity and specificity, but it is recognised that these tests may involve the use of alternative specimen types that are more convenient to the user in a point-of-care setting (e.g. fingerstick whole blood, oral fluid) and may not necessarily perform to the same standard as laboratory tests that are

intended for professional use (e.g. fourth-generation EIA[8] on serum/plasma). Consequently, there are grounds for a more flexible approach where it can be demonstrated that:

- the manufacturer has clearly identified the limitations of the test and provided acceptable evidence of risk mitigation; and

- the benefits of the test outweigh any potential risks associated with use of the product.

HIV PoCTs are required to demonstrate the following minimum performance requirements in relation to the detection of HIV antibodies (in the context of their performance in a population equivalent to the Australian population):

- a sensitivity of at least 99.5% for whole blood and 99% for oral fluid;[9]

- a specificity of at least 99% for detection of HIV infection.[10]

This would reflect the expected performance of the test for confirmed HIV positive samples based on a direct comparison with a currently accepted state-of-the-art device (e.g. third or fourth generation EIA)[11] when used under controlled conditions. A direct comparison to western blotting is of limited value due to the relatively poor sensitivity of a western blot compared to a third or fourth generation EIA, particularly during early seroconversion. However, it would be expected that any western blot positive samples would also test positive on a rapid test.

Manufacturers are also required to provide studies that demonstrate the performance of the test with seroconversion panels and establish the limitations of the tests with regard to the detection of HIV antibodies (and, if applicable, antigen) in the window period.

These performance requirements ensure that tests used at the point-of-care are of a high quality while also reflecting the fact that PoCTs are intended for presumptive screening for HIV rather than as part of a laboratory-based diagnostic/confirmatory testing strategy.

Risks

Additional false negatives are likely to occur if a lower level of sensitivity is accepted (i.e. less than 100% sensitivity). There would be a greater 'window period' resulting in a higher number of false negative results if testing is performed during the acute phase of infection, and prior to seroconversion.

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[8] Note however that several studies have reported that rapid HIV tests have performance characteristics that are comparable with first-, second- or third- generation EIA, (Cornett, JK & Kirn, TJ 2013, 'Laboratory Diagnosis of HIV in Adults: A Review of Current Methods', *Medical Microbiology* vol. 57, no. 5, pp. 712-718).

[9] It has been reported that rapid testing using oral fluid has a lower sensitivity compared with whole blood and that this may be attributable to a lower quantity of HIV antibodies in oral fluid rather than a variation in the inherent performance characteristics of the test itself, (Pai, NP et al 2012, 'Head-to-Head Comparison of Accuracy of a Rapid Point-of-Care HIV Test with Oral Versus Whole-Blood Specimens: A Systematic Review of Meta-Analysis' *Lancet Infectious Disease*, vol. 12, no. 5, pp. 373-380).

[10] This requirement is guided by the EU CTS.

[11] Third-generation EIA detect HIV-1/2 IgM and IgG antibody and are the relevant performance benchmark for antibody only rapid tests. Fourth-generation EIA simultaneously detect p-24 antigen as well as HIV-1/2 IgG and IgM antibodies and serve as the relevant performance benchmark for antigen/antibody combination rapid tests, (Cornett, JK & Kirn, TJ 2013, 'Laboratory Diagnosis of HIV in Adults: A Review of Current Methods', *Medical Microbiology* vol. 57, no. 5, pp. 712-718).

Despite this limitation it has been accepted by comparable regulatory jurisdictions that the benefits to be gained from the use of HIV PoCT (i.e. increased testing rates) at sensitivities below 100% outweigh any undesirable effects arising from its use (i.e. false negative results).

Mitigation strategies

HIV PoCTs differ from laboratory tests and self-tests in that a health professional is responsible for performing or supervising all aspects of the testing process from sample collection to test interpretation. Unlike a self-test, a health professional is available to provide pre- and post-test counselling including information on the limitations of the test, the risk of false positives and the risk of false negative results, particularly if testing is done soon after possible exposure to the virus.

The overall acceptability of a HIV PoCT would depend on the mitigation strategies the sponsor has in place to offset any potential risks associated with the use of the product. For example:

- the test must be easy to perform with minimal operator intervention or procedural steps

- the instructions for use (IFU) must be clear and easy to understand

- the sensitivity and specificity of the test must be clearly identified

- the IFU must clearly state the limitations of the procedure, that:

    - negative results obtained within three months of a high risk event should be repeated at three months to confirm the initial negative result (i.e. false negative results can be obtained if testing is performed during the 'window period')

    - positive results require confirmation using another test method; and

    - all results should be evaluated in light of the overall clinical evaluation before a diagnosis is made

- evidence must be provided that demonstrates the stability and reliability of the product across a range of operational and environmental conditions.

Depending on the performance of the test and the information provided in the IFU and robustness of the test, TGA may place conditions on the supply of a particular PoCT to ensure that the product is only supplied in an appropriate point-of-care setting. These could include that the sponsor:

- supply the device only for use by:

    - accredited laboratories; or

    - specified health care professionals or appropriately trained staff under the supervision of a health care professional (eg, medical practitioners, registered nurses)

- make available training in the correct use of the device

- provide the TGA with regular reports on the distribution of the product and numbers of any false positive or false negative results or problems with the test.

These conditions would ensure that high quality tests are used at the point-of-care and are conducted under the supervision of a health care professional in an environment where the individual can be provided with appropriate counselling and follow-up testing and treatment if required. Additional conditions may be considered on a case-by-case basis and would depend on the individual product.

There is a concern that the placement of strict conditions on HIV PoCTs may adversely impact the uptake of point of care testing and result in an increased reliance on HIV self-testing. The TGA has already received feedback from some stakeholders that the conditions placed on the supply of a HIV PoCT that is currently registered in the ARTG are too restrictive (see Attachment 2) and have hampered the uptake of HIV point of care testing in Australia.

The TGA does not regulate clinical practice however, it is expected that any services providing point of care testing would comply with best practice guidelines such as the guidelines currently being developed by the National Pathology Accreditation Advisory Committee (Guidelines for Point of Care Testing) when finalised.

2.3 HIV self-tests

Based on international experience it is expected that HIV self-testing will improve access to testing and result in increased rates of testing which in turn has the potential to improve the detection of HIV, facilitate earlier access to treatment and reduce transmission rates. It provides an alternative testing option for those individuals who are not accessing current testing services.

Because HIV self-tests and HIV PoCTs are both presumptive screening tests (and generally the technology is the same), the expected "benchmark" level of sensitivity and specificity for a self-test across the relevant specimen types such as whole blood (fingerstick) and oral fluid would be the same as that expected for HIV PoCTs. That is (in relation to the detection of HIV antibodies):

- a sensitivity of at least 99.5% for whole blood and 99% for oral fluid

- a specificity of at least 99% for detection of HIV infection.

This would reflect the expected performance of the test for confirmed HIV positive samples based on a direct comparison with a currently accepted state-of-the-art device (e.g. third or fourth generation EIA) when used by an experienced user under controlled conditions.

However, it is then recognised that the same level of performance may not be achieved in a self-testing environment (i.e. in the hands of an inexperienced user under less than idealconditions). As self-tests would predominantly be performed by inexperienced users, usability studies would be required to establish adequate performance in this setting, including:

- evidence that the effective sensitivity of the test is suitable in a self-testing environment (e.g., a significant reduction in sensitivity in the hands of inexperienced users would imply that the device may not be easy to use or may be difficult to interpret resulting in an increased rate of false negative results)[12]

- a low inter-reader variability

- an invalid test result of < 2% of the total tested (this includes defective tests or components).

The suitability of these studies would be assessed on a case-by-case basis and would depend on how well the manufacturer has mitigated any risks and demonstration that the overall benefits of the product outweigh any residual risks associated with its use. The manufacturer would not

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[12] A lower limit of effective sensitivity has not been specified as this may be variable depending on the product. The manufacturer's risk mitigation strategies wound need to be taken into consideration and whether the overall benefits outweighed any potential risks.

be required to provide Australian specific usability studies, but it is expected that studies would reflect the performance of the test in a comparable setting and population.

Risks

As is the case for HIV PoCTs, false negative results are more likely to occur if a test has a lower level of sensitivity and if testing is performed during the 'window' period. Although these limitations also apply to PoCTs, they are exacerbated in a self-testing environment due to individual user variability in the correct performance and interpretation of the test (i.e., the risks are predominantly user focussed). Additionally, pre- and post-test counselling may not be immediately available in the self-test environment, nor is follow up testing as easily able to be encouraged or implemented.

Mitigation strategies

The proposed mitigating strategies recognise that self-tests differ from laboratory based tests and PoCT in that the user is responsible for all aspects of the testing process from sample collection to test interpretation, and product information is used and the user may not elect to have pre- and post-test counselling.

Some of the mitigation strategies for HIV PoCTs are equally relevant to self-tests, that is:

- The specimen collection process must be straightforward and the specimen able to be collected safely in the home testing environment.

- The test must be easy to perform with minimal operator intervention or procedural steps. Extensive usability studies would be expected (e.g. device interpretation study, label comprehension study and observed self-testing studies).

- The stability of the product should be demonstrated across a range of operational and environmental conditions.

In addition, the manufacturer/sponsor of a HIV self-test is also expected to clearly outline the limitations of the test and provide clear advice, in the IFU and/or other information provided with the test, including the following:

- clear and simple instructions on how to perform and interpret the test (including the provision of instructions in multiple languages).

- the 'effective' sensitivity and specificity of the test (i.e. in a self-testing environment)

- clear warnings on the risk of false negative results if testing is performed in the 'window period' (and a clear explanation of what the window period is)

- the need to consult a medical practitioner for confirmatory testing of positive results by a laboratory test

- information on behaviour that may place an individual at an increased risk for HIV infection, including a warning that a negative result does not indicate that engaging in high risk behaviour is safe

- how to contact support and counselling services.

An expected condition on the supply of a self-test would be that the sponsor would be required to provide the TGA with regular reports on the numbers of any reported false positive or false negative results or problems with the test. Additional conditions would be applied on a case-by-basis and would depend on the evaluation of an individual product, the overall benefits and how

well any risks have been mitigated. Conditions may potentially include a requirement that the Australian sponsor provide additional support for users of the test through provision of an on-line support service and/or 24 hour phone line.

The overall acceptability of a HIV self-test would depend on the manufacturer/sponsor demonstrating that any benefits gained from use of the test (i.e. increased testing rates) would outweigh any risks associated with use of the product (i.e. false negatives).

3. Summary of proposed performance requirements

Table 1: Comparison of Proposed Performance Criteria for HIV Tests

	Stratified Operational Performance Criteria for the Detection of HIV antibodies
Laboratory testing	All specimen types 100% sensitivity (known positives) ≥ 99.5% specificity 100% seroconversion sensitivity
HIV PoCT	Whole Blood ≥ 99.5% sensitivity (known positives) ≥ 99.0% specificity Oral Fluid ≥ 99.0% sensitivity (known positives) ≥ 99.0% specificity
HIV Self-tests	Same performance requirements as HIV PoCT when used in controlled laboratory conditions with additional usability studies to demonstrate the effectiveness of the test in inexperienced hands, including: • Effective sensitivity (in the hands of inexperienced user) • low inter-reader variability • invalid/error rate of < 2%.

Attachment 1

Examples of HIV PoCT & Self-Tests Approved For Use by TGA and Overseas Jurisdictions

PoCTs			
Test Name	**Antibody Sensitivity**	**Antibody Specificity**	**Regulatory Approval**
Alere Determine HIV 1/2 Ag/Ab Combo	99.9-100%	99.8%	FDA, TGA
INSTI HIV-1 Antibody Test Kit	99.8%	99.0-99.5%	FDA, Canada
SURE CHECK HIV 1/2	99.3-99.7%	99.9-100%	FDA, EU
HIV 1/2 STAT-PAK	99.7%	99.9%	FDA, EU
Chembio DPP HIV 1/2	99.8% 98.9% (oral fluid)	100% 99.9% (oral fluid)	FDA
OraQuick Advance Rapid HIV 1/2 Antibody Test	99.6-100% 99.3-100% (oral fluid)	99.9%	FDA, EU
Self-Tests			
OraQuick In-Home HIV	91.7% (oral fluid)	99.9% (oral fluid)	FDA

Attachment 2

Summary of current product specific conditions for a HIV PoCT registered in the ARTG

1. The person (the sponsor) in relation to whom the device is registered 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. health professionals working for an organisation that:

        i.   has an established relationship (in relation to the referral and testing of specimens) with a NATA accredited medical testing laboratory; and

        ii. participates in an HIV point of care quality assurance program; and

        iii. provides a declaration to the sponsor every 12 months that all health professionals 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 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 TGA a post market surveillance report for each period of 6 months (for a period of 3 years) 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 for a period of three years.

5. The sponsor must provide to the TGA a report and documents for each period of 12 months commencing on the date of inclusion of the device in the ARTG. Information about the distribution of the product and evidence of compliance with the conditions of registration 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 an HIV point of care quality assurance program;

    b. in relation to each organisation for whom health professionals using the device in that period have worked in that period:

        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 an HIV point of care quality assurance program;

    c. documented evidence that condition 2 has been complied with by the sponsor during the period;

    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 the user, date of training and provider of the training; and

        ii.   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.

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