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HIV TESTING SERVICES
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Web Annex I. In vitro diagnostics for HIV diagnosis

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I.1. Formats of HIV assays

Manufacturers design their products for one of the following test purposes:¹

- screening – testing people without apparent signs or symptoms;
- diagnosis – testing people with signs and symptoms to give a definitive result;
- aid for diagnosis – testing people with signs and symptoms to help provide supplemental information;
- staging – to determine the stage of infection;
- monitoring – to monitor disease or response to treatment;
- prognosis – to measure factors linked to clinical outcome, irrespective of treatment.

Serology assays for HIV diagnosis are categorized by generation, based on the composition of the antigen and what the assay detects (Table I.1a).

Table I.1a. Generations of HIV serology assays, inclusive of RDTs, simple assays and immunoassays (1)

Generation	Antigen source	Attributes of the assays
First generation	Crude viral lysate	Comparatively lacking sensitivity and specificity – detects IgG only
Second generation	Recombinant proteins and synthetic peptides	Improved specificity and sensitivity – detects IgG only (IgG sensitive)
Third generation	Recombinant proteins, with same antigen conjugated to enzyme (antigen sandwich)	Further improved sensitivity and specificity – detects IgM and IgG antibodies (IgM/IgG sensitive)
Fourth generation	Recombinant proteins as antigen and monoclonal antibody	Detects IgM and IgG antibodies and HIV p24 antigen (antigen/antibody combination)

Fourth generation serology assays that detect both HIV p24 antigen and HIV-1/2 antibodies can potentially identify HIV-infected individuals during acute infection. Typically, the clinical utility of fourth generation serology assays is highest when used for screening, such as for screening blood and tissue donations. Some fourth generation serology assays produce test results that indicate whether the specimen is reactive to *either* HIV p24 antigen and/or reactive to HIV-1/2 antibodies rather than combined detection to both. Thus, theoretically, it is possible to identify individuals with acute infection.

However, recent data show that HIV p24 antigen detection for many fourth generation RDTs lacks analytical and diagnostic sensitivity (2). Furthermore, if HIV infection is insufficiently treated or not treated at all, the individual's immune response wanes and levels of HIV-1/2 antibodies may decrease. Therefore, rising titres of HIV antigen may be observed as the antigen/antibody complex disintegrates (detectable HIV antigen but no HIV-1/2 antibodies) in late established HIV infection.

The sensitivity and specificity of assays are important, but their clinical utility is a critical determinant of their overall impact on the programme. Table I.1b describes different assay formats of HIV in vitro diagnostics (IVDs) and their operational characteristics.

¹ Other test purposes, of predisposition, prognosis, prediction and determination of physiological status, are not relevant in the context of HIV testing.

Table I.1b. Assay formats of HIV in vitro diagnostics and their operational characteristics

Type	Format	Number of hands-on steps	Time to result	Through-put	Specimen type	Storage conditions	Testing location
Rapid diagnostic tests (RDTs)	Immunofiltration (vertical flow)	3–4	<3 minutes	5 per 5 minutes ^b	Serum, plasma, venous/ capillary whole blood	~2–30 °C or 2–8 °C	All levels including community (level 0)
	Immunochromatographic (lateral flow)	1–2	15–30 minutes	10 per 15 minutes ^b	Serum, plasma, venous/ capillary whole blood, oral fluid	~2–30 °C	All levels including community (level 0)
Simple assays	Indirect solid-phase enzyme immunoassays (for example, comb or bead assays)	3–4 ^a	<30 minutes	8 per 30 minutes ^b	Serum, plasma	2–8 °C	Levels 1 ^c , 2
	Agglutination	2 ^a	2 hours	15 per 2 hours ^b	Serum, plasma	2–8 °C	Levels 1, 2
Immuno-assays (IAs)	Enzyme immunoassay (microtitre plate)	Manually loaded ^a	2–3 hours	90 per hour ^b	Serum, plasma	2–8 °C	Levels 2, 3, 4
	Enzyme immunoassay (simple immunoanalysers)	Moderately automated ^a	2 hours	50 per hour	Serum, plasma	2–8 °C	Levels 3, 4
	Random access chemiluminescence and electrochemiluminescence immunoanalysers	Highly automated	2 hours	100 per hour, no need to batch	Serum, plasma	2–8 °C	Levels 3, 4

^a Precision pipette required. ^b If batched in one run. ^c If electricity is available.

I.2. Verification of HIV testing algorithms

National regulatory authorities assess the performance, safety and quality of a product for use within their jurisdiction only. WHO assesses the quality, safety and performance of products for use in resource-limited settings through its prequalification procedure. WHO ensures that the prequalification status of products is up to date, especially as and when the assay manufacturer makes changes to the product – those that affect the quality, safety and performance as well as other types of changes. When a product is well-regulated² and the performance claims made by the product's manufacturer have been thoroughly assessed, the probability of detecting an additional quality or performance issue during a field evaluation study is low.

If a product is WHO prequalified, clinical evidence has already been submitted and assessed by WHO; therefore, there is little additional benefit in repeating clinical performance studies to reconfirm sensitivity and specificity.

WHO does recommend that HIV testing algorithms be verified, i.e. the selection of specific products for use within the testing strategy. The purpose of verification is to provide objective evidence that a combination of products in a particular sequence can be used to accurately diagnose HIV infection before widespread roll-out. This means that the products selected do not have overlapping false-reactive results that may lead to misdiagnosis, i.e. a person is diagnosed as HIV-positive when indeed HIV-negative.

Given that studies are resource intensive, WHO recommends that the verification of testing algorithms be coordinated by a level IV laboratory or other facility designated by national authorities. The verification study may be carried out in a laboratory setting and/or at the point of use (testing site). A national taskforce (or existing technical working group) comprising diagnostic and programmatic experts should adapt the study protocol, devise a list of candidate assays, conduct the verification study and analyse and disseminate the results. To preserve harmonization and standardization, programmes should inform any implementing partners about the verification study and seek agreement on implementing its outcomes.

If a stock-out occurs, which requires a switch to a new product, even temporarily, the testing algorithm should be reverified.

There are three phases for verification prior to widespread roll-out.

Phase 1. Preparing for the verification study

The objective of the study is to determine which products have the highest rate of **common false-reactivity** between each other and are therefore not suitable for use within the same testing algorithm.

a. Shortlist candidate products to be considered

It is suggested that no more than 6–10 products be considered for the verification study.

Quality criteria

Select products from the following lists of quality-assured in vitro diagnostics (IVDs) and in accordance with national requirements:

- List of nationally registered IVDs; and/or

² WHO prequalification or stringent assessment by a founding member of the Global Harmonization Task Force.

- WHO list of prequalified IVDs; and/or
- List of products eligible for procurement by donors/implementing partners.

Performance criteria

Any product that is WHO prequalified is expected to meet the following performance characteristics as a minimum. The manufacturer should also make a statement about the claimed performance in the instructions for use. For WHO-prequalified products, the data claims in the instructions for use have been verified as correct.

- Consider the type of detection that the products should have:
 - combined detection of antibodies to HIV-1/2 (HIV-1/2);
 - discriminatory detection of antibodies to HIV-1 and antibodies to HIV-2 (HIV-1/HIV-2);
 - combined detection of antibodies to HIV-1/2 and HIV-1 antigen;
 - discriminatory detection of antibodies to HIV-1/2 and HIV-1 antigen, etc.

Operational criteria

Depending on the testing setting, certain operational aspects may be more important than others. In that case, apply criteria for operational characteristics:

- hands-on processing time, including time to result (reading times);
- other factors – items required but not provided, nature of internal quality control;

Also see *WHO Guidance for procurement of in vitro diagnostics and related laboratory items and equipment (3)*.

Table I.2a. Criteria for selection of candidate products

Performance characteristics
For rapid diagnostic tests (RDTs), as per the manufacturer’s instructions for use: minimum sensitivity 99% minimum specificity 98%
For immunoassays (IAs), as per the manufacturer’s instructions for use: minimum sensitivity 100% minimum specificity 98%
Detection type – for example, combined HIV-1/2 antibodies, discriminatory HIV-1/HIV-2 antibodies, discriminatory HIV-1/2 antibodies/HIV antigen, subtype O
Operational characteristics – see also WHO <i>Guidance for procurement of in vitro diagnostics and related laboratory items and equipment</i>
Hands-on processing time – for example, number of precision steps, time to result (minimum and maximum reading times)
Other factors – for example, items required but not provided (specimen transfer devices, lancets, alcohol swabs, etc.), nature of internal quality control (specimen addition control or not).

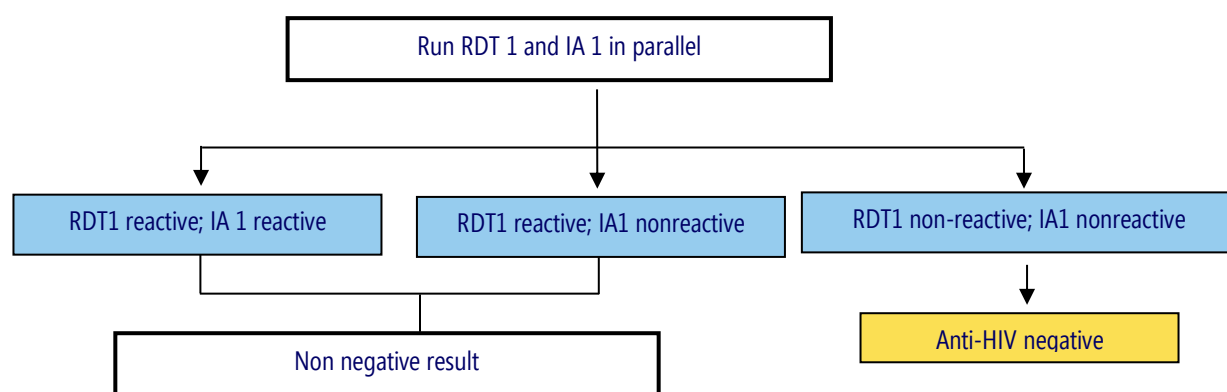
b. Request test kits

Obtain a sufficient number of tests from two lots of each product from the manufacturer (or in-country distributor). Test kits should be stored in conditions stated in the manufacturer’s instructions for use. Any additional consumables that are required to perform each of the assays must be available.

c. Establish the verification panel

The specimen types that have been validated by the manufacturer are listed in the product’s instructions for use. If listed among validated specimen types, serum or plasma is recommended for verification studies of this nature as these specimens can be collected and stored in larger volumes and are more easily handled. If claimed, the panel may include capillary and/or venous whole blood specimens. However, collecting a sufficient volume of capillary whole blood to test all candidate assays with the requisite number of replicates may be difficult to coordinate.

Ensure that the panel specimens have been adequately characterized for the absence of HIV, i.e. the diagnostic accuracy criteria³ have been established for each specimen. An example for characterization of verification specimens is given below.



If the candidate testing algorithm contains fourth-generation IVDs, a fourth-generation assay should be used for the characterization of verification panel specimens.

Specimens may be collected from clinical settings, antenatal care clinics, or otherwise commercially acquired. The verification panel may be collected, processed and then stored at –20 °C before use.

Table 1.2b. Verification specimen panel

Type of specimen	Number of specimens	Number of replicates
Negative for HIV-1/2 antibodies	100 clinical specimens	Test duplicates of each specimen on each of 2 different lots

d. Select study site(s)

The verification study may be conducted in any setting (laboratory or at point of use), as designated by national authorities.

e. Train study staff

³ The diagnostic accuracy criteria is defined by CLSI as the “best currently available criteria for establishing the presence or absence of the condition, event or characteristic of interest using a single method or combination of methods, including laboratory tests, imaging tests, pathology, and clinical information including follow-up” (5).

All test operators should be trained on the relevant study standard operating procedures (SOPs), including on how to handle specimens, how to perform each assay, and how to read and record test results. Training should be documented in the training records. All test operators should be able to demonstrate proficiency before participating in the study.

f. Implement data quality practices

Accurate record-keeping is crucial, and it should be emphasized that transcription errors are common. Individual-run worksheets and the consolidated worksheet should be in place for overall data analysis. Data entry should be double-checked.

Phase 2: Conducting the verification study

a. Test each product using the verification panel

Each specimen of the verification panel should be labelled with a specimen identification number that does not reveal the expected result (diagnostic accuracy criteria). Each test operator should be blinded to the expected reference result for each of the specimens. Aliquots should be removed from storage only on the day when they need to be tested to protect their integrity.

Testing should be done using only those materials provided with the test kit (e.g. instructions for use [IFU], labels and other instructional materials) by test operators who are representative of the intended users, and who are unassisted. If test kit controls are available, within the test kit or separately, these should be used in accordance with the manufacturer’s instructions for use.

Both lots of each product should be tested on the same verification panel.

Recording results for visually read assays (e.g. RDTs)

The test band intensity should be recorded on the following scale as it is critical to distinguish between weak and strong test lines.

0	non-reactive
1+	weakly reactive
2+	moderately reactive
3+	strongly reactive

b. Interpret the results

Results for visually read assays (e.g. RDTs)

A second reader should make a blinded rereading of any visually read assay after the first reader (the test operator) has read and recorded the test result. In addition, the intensity of the test line/band should be recorded, so that variability due to faint test lines may be quantified.

- If the two readers interpret the test results the same way, then the status of the specimen is recorded as is.
- If the two readers do not agree, a third reader should adjudicate on the reading. The result that has the majority, i.e. two of three readers, should be taken.

If a result cannot be conclusively reached, the result should be recorded as inconclusive and the specimen retested on a new test device from the same lot. These results should be included in the data analysis as a misdiagnosed specimen.

Results for instrument-based assays (e.g. IAs)

Certain IAs display an optical density-to-cut-off (OD/CO) ratio that is within the grey zone, according to the manufacturer's instructions for use (usually 0.90–1.10). These specimens should be repeated in duplicate on the same lot. These should be included in the data analysis as a misdiagnosed specimen.

Invalid results

For visually read assays such as RDTs, test results are said to be invalid typically when the control line does not appear, irrespective of whether the test line appears or not, or when a high background colour completely obscures the result window. Other anomalies should also be recorded such as streaking across the membrane, non-migration of specimen, debris on the membrane, etc.

For instrument-based assays such as IAs, chemiluminescence immunoassays and electro-chemiluminescence immunoassays, invalid results or invalid runs occur when the internal and/or external test kit controls (HIV negative, HIV positive) are not within the acceptance range specified in the manufacturer's instructions for use.

The rate of invalid test results/run should be recorded in the data analysis as a proportion of invalid results/run of the total tests/runs performed.

c. Conduct data analysis

Calculate the rate of common false reactivity between the candidate products. It may not be possible to choose a combination of products that has no false-reactive results shared, so choose the combination that has the least common false-reactive results.

Expiry date of study results

The results of the verification study should remain valid for a period of three to five years.

Phase 3: Monitoring implementation of the testing algorithms and post-market surveillance

Testing algorithms must be continually monitored for effectiveness, including any adverse events of HIV misdiagnosis.

It is suggested to run the new testing algorithms in parallel with the existing testing algorithm for a period of two weeks for high-throughput testing sites or four weeks for low-throughput testing sites. A discrepancy rate of >1% between the new and existing algorithms is noteworthy and requires investigation of the root cause. After this initial familiarization period, the testing algorithms may be rolled out more widely.

Data should be collected on the rate of HIV-inconclusive status and the rate of invalid test results (no more than 5% is acceptable). Any observations related to test procedure or other operational characteristics that do not appear to meet the manufacturer's claims should be documented and reported according to WHO guidance on post-market surveillance of IVDs.

Any complaints related to the products themselves can be reported to the assay manufacturer as part of post-market surveillance.

I.3. Infection, detection and definitive diagnosis of HIV

For people over two years of age, HIV is diagnosed through the detection of antibodies to HIV and/or HIV-1 p24 antigen (serological markers of HIV) rather than detection of the virus itself (virological marker of HIV).

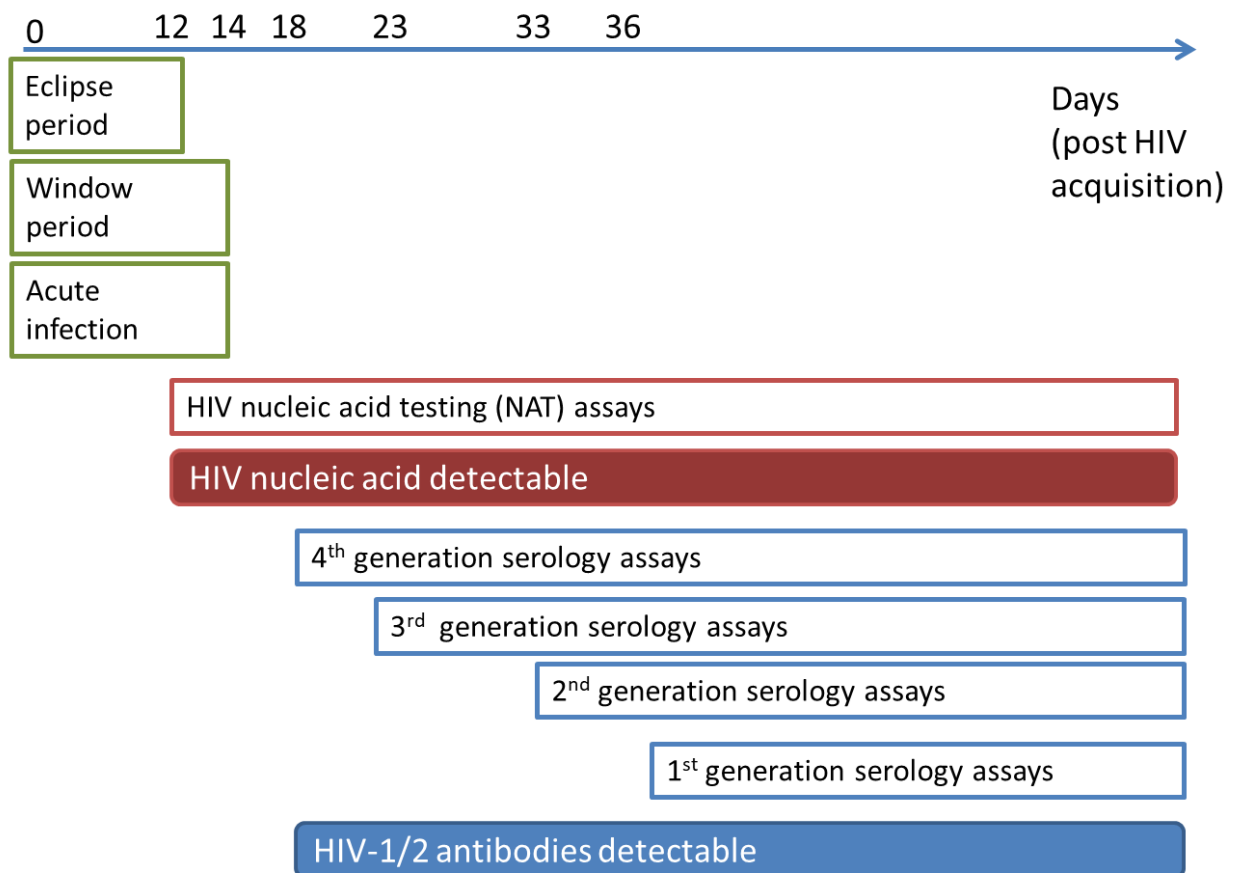
Where resources permit, other assays, such as assays that detect HIV p24 antigen only or assays that can detect specific types of HIV-1/HIV-2 antibodies, may be used to resolve atypical diagnoses.

Briefly, use of serology assays alone is insufficient to rule in HIV infection, as serological assays may detect maternal antibodies transferred to the infant during pregnancy, birth and breastfeeding. Virological testing, typically using nucleic acid testing (NAT), is recommended instead.

Natural history of HIV infection

Fig. I.3a shows when the various markers of HIV infection become detectable during the natural history of typical HIV infection.

Fig. I.3a. Detection of various markers of HIV over the natural history of typical HIV infection (7, 8)



The period immediately following HIV infection is the **eclipse period**. During the eclipse period no assay can detect HIV (neither serological nor virological markers), as the amount of nucleic acid from the virus is miniscule and antibodies are produced only in response to the presence of the virus. The eclipse period typically lasts approximately 10 days.

The end of the eclipse period is marked by the detection of nucleic acid using nucleic acid testing (NAT) assays, approximately 12–14 days after infection. Shortly after detection of nucleic acid, immunoassays (IAs) can briefly detect HIV antigen. The amount of virus increases quite rapidly during this time; therefore, so does production of HIV-1/2 antibodies. As HIV-1/2 antibodies rise, levels of HIV antigen decrease as the antibodies and antigen bind together and, thus, hide HIV-antigen, so that antigen testing is no longer useful.⁴ The detection of HIV-1/2 antibodies – first immunoglobulin M (IgM) and then immunoglobulin G (IgG) – signals seroconversion and the end of the **window period**, when infection cannot be detected. This window period generally ends around 21 days after HIV infection. The period from HIV infection to the time when HIV-1/2 antibodies are detected is referred to as **acute infection**.

The duration of the diagnostic window period depends on four main factors:

- (1) genetic factors of the **virus**
- (2) genetics and immunocompetence of the **host**
- (3) **assay** target and detection type (antigen, IgM or IgG antibodies)
- (4) **specimen** type (serum, plasma, venous whole blood, capillary whole blood, oral fluid).

The earliest antibody detection is generally observed with fourth generation serology assays, followed by third generation serology assays, followed by second generation serology assays. First generation serology assays using viral lysate have the longest window period (see Table 1 for description of assay generations). Specifically, among RDTs those using oral fluid specimens have the longest window period, irrespective of their generation, but they are successfully used in many settings due to their great clinical utility (7).⁵

⁴ In the case of HIV-1 infection, HIV-1 p24 antigen appears briefly. In the case of HIV-2 infection, HIV-2 p26 antigen appears briefly.

⁵ Clinical utility is the usefulness of the results obtained from testing with the IVD and the value of the information to the individual being tested and/or the broader population (9).

I.4. Specimen collection for HIV testing

Specimen integrity is critical for assuring the accuracy of HIV testing. The manufacturer specifies in the instructions for use how to collect, process and store specimens for their assay. These instructions always take precedence, but, for a broad summary, see Table I.4a. When the assay's instructions for use do not include instructions for a certain specimen type, that means that the manufacturer has not validated that specimen type for use with that assay.

Table I.4a. Specimen types and processing requirements

Specimen type	Time to processing/storage/time to testing
<p>Venous whole blood Fresh whole blood collected by venepuncture</p>	Use the specimen immediately.
<p>Serum Freshly collected whole blood coagulates, and the serum fraction is collected away from the clotted red blood cells.</p>	Collect whole blood, mix by hand 4 or 5 times immediately and let stand for the clot to form. Process within 30 minutes of collection. Store at 2–8 °C. Test within 5 days or as specified by the instructions for the assay to be used.
<p>Plasma Freshly collected whole blood is added to the recommended anticoagulant, such as EDTA, heparin or citrate. After centrifugation the plasma is separated. Use only anticoagulants validated by the assay manufacturer.</p>	Collect whole blood, mix by hand 8–10 times immediately and centrifuge for up to 10 minutes. Process within 6 hours of collection or as specified by the manufacturer. (Most NAT assays permit 24 hours and some up to 72 hours.) Store at 2–8 °C. Test within 5 days or as specified by the instructions for the assay to be used.
<p>Capillary whole blood Capillary (finger-stick) whole blood is collected using a lancet and a specimen transfer device.</p>	Use the specimen immediately with the specimen transfer device recommended by the instructions for use. Note that the specimen transfer device may or may not include an anticoagulant. The hanging drop method, whereby blood is dropped directly from the fingertip onto the test device, is not recommended, as it does not ensure that the correct specimen volume is added.
<p>Oral fluid Oral mucosal transudate (not saliva) is collected from the gums using a collection device.</p>	Use the specimen immediately with the specimen transfer device recommended by the instructions for use.
<p>Dried blood spot (DBS) specimen Venous or capillary whole blood is applied to a filter paper by hanging drop or microcapillary. Whole blood is later eluted from the filter paper and used for the test procedure.</p>	Store at 4 °C for up to 3 months or at –20 °C for longer. The use of specific assays with DBS specimens should be validated by the manufacturer. When the manufacturer has not validated their assay for DBS specimens, the use of DBS specimens is considered “off-label”, or unauthorized for returning medical results to clients. <i>This includes use in the context of HIV surveillance.</i>

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