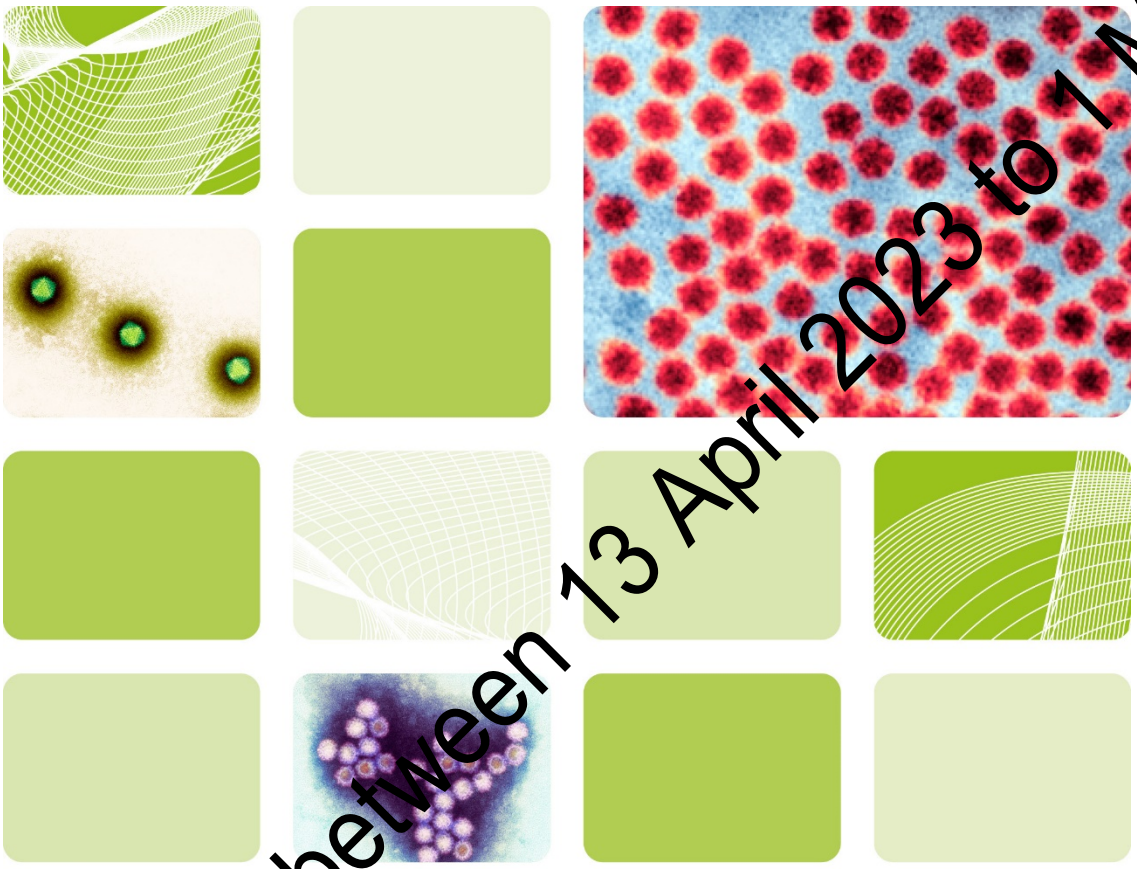
UK Health Security Agency

UK Standards for Microbiology Investigations

HIV screening and confirmation



National Institute for Health and Care Excellence (NICE) has renewed accreditation of the process used by the **UK Health Security Agency** to produce **UK Standards for Microbiology Investigations (UK SMIs)**. The renewed accreditation is valid until **31 June 2026** and applies to guidance produced using the processes described in '**UK Standards for Microbiology Investigations Development Process' (2021)**. The original accreditation term began on 1 July 2011.

Issued by the Standards Unit, Specialised Microbiology and Laboratories, UKHSA

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UK Standards for Microbiology Investigations (UK SMIs) are developed under the auspices of UKHSA working in partnership with the partner organisations whose logos are displayed below and listed on the UK SMI website. UK SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see the Steering Committee page on GOV.UK).

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Amendment table

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Any alterations to this document should be controlled in accordance with the local document control process.

Amendment number/date	x/dd.mm.yy
Issue number discarded	
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Anticipated next review date*	dd.mm.yy
Section(s) involved	**Amendment**

*Reviews can be extended up to 5 years where appropriate

1 UK SMI scientific and general information

This standard should be read together with the general information and scientific information related to the UK Standards for Microbiology Investigations (UK SMI).

2 Introduction

Early detection of HIV infections enables prompt initiation of antiretroviral therapy and thereby has benefits for the individual (better preservation of immunological function, and avoidance of morbidity and mortality), their partners (quicker viral load suppression and avoidance of transmission by having an undetectable viral load), and public health (reduced community viral load and HIV transmission).

The UK government action plan to achieve zero new HIV infections, AIDS, and HIV related deaths in England by 2030 considers the implementation of a combination prevention approach focussing on prevent, test, treat and retain. Testing should be made available in all healthcare settings and community testing, self-testing, and self-sampling should be easily accessible to specific groups at high risk.

The WHO recommends that screening strategies for HIV infection using laboratory-based assays should allow the detection (diagnosis of infection) or exclusion of infection with a 99% level of certainty. Modern laboratory HIV assays have improved in sensitivity, specificity, and turnaround times but their capacity to correctly diagnose HIV infection continues to depend on the correct selection of the assay and interpretation and reporting of results, the frequency of testing, local prevalence, and the window period for chosen tests.

This standard, reviews existing laboratory-based assays and provides an HIV testing strategy/algorithm with three consecutive reactive tests for the definitive HIV-positive diagnosis. This strategy is in line with the WHO recommendations and other public health organisations and serves to maintain at least a 99% positive predictive value (that is, less than one false positive per 100 people diagnosed with HIV) and avoids the chances of misdiagnosis.

3 Scope of document

This standard provides a detailed review of initial and supplemental laboratory-based tests for the detection and exclusion of HIV infection using serological assays and nucleic acid amplification tests (NAAT). The document also addresses special situations that confound HIV testing, including the diagnosis of acute and recent HIV infection and initial and supplemental testing in those receiving Antiretroviral Treatment (ART), Post-Exposure Prophylaxis (PEP) or Pre-Exposure Prophylaxis (PrEP). In addition, the algorithms aim to assist clinicians and laboratories in their decision making providing a framework for additional testing and the interpretation of results. Furthermore, reporting criteria for commonly obtained test results are also provided.

This standard is intended for use in the laboratory diagnosis of HIV infection in the health care setting and does not address methods or strategies for the investigation

of potential mother to child transmission of HIV in children under 18 months of age; The Children's HIV Association CHIVA has issued separate guidance and recommendations for the HIV testing in children. Nor does this standard address testing of blood prior to organ or blood donation; refer to the SaBTO Guidance on the microbiological safety of human organs, tissues and cells used in transplantation.

Furthermore, this standard is not intended for use outside the clinical setting and does not address testing methods or strategies commonly used in community testing such as POC-T testing, self-sampling, or self-testing.

Testing of specimens other than blood, plasma and serum obtained by venepuncture, such as oral fluid and saliva is not covered by this UK SMI.

Refer to UK SMI Q 7 - Good practice when undertaking serology assays for infectious diseases for information regarding good laboratory practice in serological testing.

4 Background

4.1 Human immunodeficiency virus

Human immunodeficiency virus (HIV) is a retrovirus that causes a chronic infection in the cells of the immune system. It is transmitted via exposure to body fluids containing free virus particles. Without treatment, most persons with HIV develop acquired immunodeficiency syndrome (AIDS) within 10 years of infection, which is associated with substantial morbidity and premature death (1).

There are two recognised HIV types – HIV-1 and HIV-2.

HIV-1 is found largely throughout the world including UK, USA and the rest of Europe. It is divided into four groups based on differences in the envelope region, HIV-1 major group HIV1-M, outlier HIV1-O, HIV1-N group and HIV1-P group. The HIV1-M major group can be classified further into 9 subgroups designated A through to K excluding E and I. They differ in geographical distribution, biological characteristics and major mode of transmission etc. HIV-1 groups O and N are more distant to all other HIV-1 subgroups (but less so compared to HIV-2) and therefore are classified under HIV-1 only, with a limited distribution in West Africa (2).

HIV-2 is found largely in West Africa and also comprises of a heterogeneous group of viruses that has been divided into 5 subgroups designated A through to E (2,3).

4.2 HIV diagnostic approaches and measures of test performance

Screening for HIV is done using serological assays or enzyme immunoassays (EIAs) on venous whole blood, plasma, or serum, which detect HIV antibodies and/or antigens. Other key group of diagnosis assays that can be used in HIV screening, are molecular assays or nucleic acid amplification tests (NAAT) that can detect viral nucleic acid (RNA) and can provide quantification of the virus.

Key attributes of laboratory tests are their sensitivity (the extent to which a test correctly identifies those with infection – true positives) and specificity (the ability to identify those without infection – true negatives). Latest generations of HIV EIAs have improved considerably showing high sensitivity and specificity (Appendix 1). However, the performance of these test varies between populations where the

prevalence of the disease may vary. This means that the probability that when a person's test result is positive, they truly have the infection (positive predictive value – PPV), and that those whose test is negative truly do not have the infection (negative predictive value – NPV) will vary between groups of population, with higher PPV and lower NPV in high prevalence populations. When a test is applied to a population with low prevalence of HIV, unless the test has 100% specificity, the number of false positive results will be higher than when testing a population with a high prevalence. Therefore, high sensitivity tests should be recommended for first line testing, and these should be followed with further confirmatory tests with a high specificity before confirming diagnosis. As the sensitivity of EIAs has increased, the window period (the time from infection with the virus to the appearance of measurable virus antigen or antibody) has decreased.

4.3 Types of HIV diagnostic tests and markers of infection (4)

Following HIV infection, untreated individuals will go through stages of the disease which are characterised by clinical symptoms and biological markers that offer the opportunity for use in diagnosis and monitoring using laboratory testing:

- **HIV RNA** becomes detectable by NAAT in plasma approximately 10 days after infection. Most NAAT assays detect HIV-1 RNA, though HIV-2 RNA testing is available at a few laboratories in the UK. HIV NAAT assays offer very little advantage over fourth generation assays in terms of earlier detection of acute infection and are not recommended for initial HIV screening as they may also give false positive results. NAAT assays can be used as supplementary test when a patient gives persistently indetermined immunoblot/immunoassay results, or in suspected primary HIV infection but should only be performed with specialist input.
- **HIV-1 p24 antigen** is expressed and quantities rise to levels that can be detected by 4th generation immunoassays within 4 to 10 days after the initial detection of HIV-1 RNA and before HIV antibody detection during acute infection. However, p24 antigen detection is transient because, as antibodies begin to develop, they bind to the p24 antigen and form immune complexes that interfere with p24 assay detection. Conversely, p24 antigenemia can last 3 to 5 months depending on the host's immune response and other viral regulatory factors. Thus, the window period for these tests is around 2 to 4 weeks. However, p24 antigen can become detectable again in advanced HIV infection due to the prolonged immunosuppression of HIV antibodies by the virus
- **Immunoglobulin M (IgM) antibodies** are expressed 3 to 5 days after p24 antigen is first detectable and can be detected by 3rd and 4th generation immunoassays 10 to 13 days after appearance and detection of viral RNA.
- **Immunoglobulin G (IgG) antibodies** emerge after IgM and persist throughout the course of HIV infection. These are detected by 1st 2nd, 3rd and 4th generation immunoassays 18 to 38 days or more after the initial detection of viral RNA, with high variability.

The WHO recommends the use of rapid diagnostic tests which can be used at the point of care (POCTs), and EIAs for HIV diagnostics (1). A positive HIV POCT test should be followed by laboratory testing using the algorithmic approach for screening and confirmation as described in this standard.

The first test in an HIV testing strategy and algorithm should have the highest sensitivity, followed by a second and third test of the highest specificity (1). These tests should be used with consideration to the window period of infection which is defined by the time of exposure and the ability of the test to detect the infection markers in peripheral blood. BHIVA recommends that clinical policies and patient information regarding the HIV test window period should be based on 99th percentile estimates when tests are able to detect 99% of HIV infections; where a test is undertaken sooner than this time interval, window period data should be used to counsel patients as to the likelihood of a false-negative result and on the need for future testing (5).

Table 1: The following table shows the estimated window period and the 99th percentile for HIV immunoassays (5) – based on two studies that specifically addressed window periods for different HIV screening tests and the implications for interpreting results and counselling patients.

Type of tests	**Median (IQR), days**	**99th percentile, days**	**Recommended window period, days**
Antibody/antigen (4th generation laboratory tests)	17.8 (13.0-23.6)	44.3	45
IgG/IgM-sensitive (3rd generation laboratory tests)	23.1 (18.4-28.8)	49.5	60
IgG-sensitive rapid tests (3rd generation POCT)	31.1 (26.2-37.0)	56.7	90
Western blot (lysate)	36.5 (31.0-43.2)	64.8	90

5 Methodology

5.1 Pre-screening considerations (6)

Specimen type

Whole blood, serum, or plasma

Note: Venous blood is the preferred specimen for HIV testing. Dried blood, dried plasma spots and capillary blood samples, have been validated and are commonly used for HIV testing and monitoring of hard-to-reach groups.

Specimen collection

Collect specimens in appropriate CE marked leak proof containers and transport in sealed plastic bags. In resource limited countries, dried blood spots (DBS) on filter paper for sample collection are used rather than blood samples because the storage conditions in these settings are impractical. DBS has been shown to keep the viral nucleic acid in good condition during transportation (7).

Compliance with postal, transport and storage regulations is essential.

Safety

Refer to the general safety considerations on GOV.UK.

Refer to current guidance on the safe handling of all organisms documented in this UK SMI.

The above guidance should be supplemented with local COSHH and risk assessments (8-27).

Test selection

As a minimum, the first assay used for screening should be a 4th generation assay with the highest sensitivity.
As a minimum, the second assay used to confirm the screening result, should be a 4th generation assay with similar sensitivity to the first assay but higher specificity.
For typing, 3rd generation assays with the highest specificity should be used.

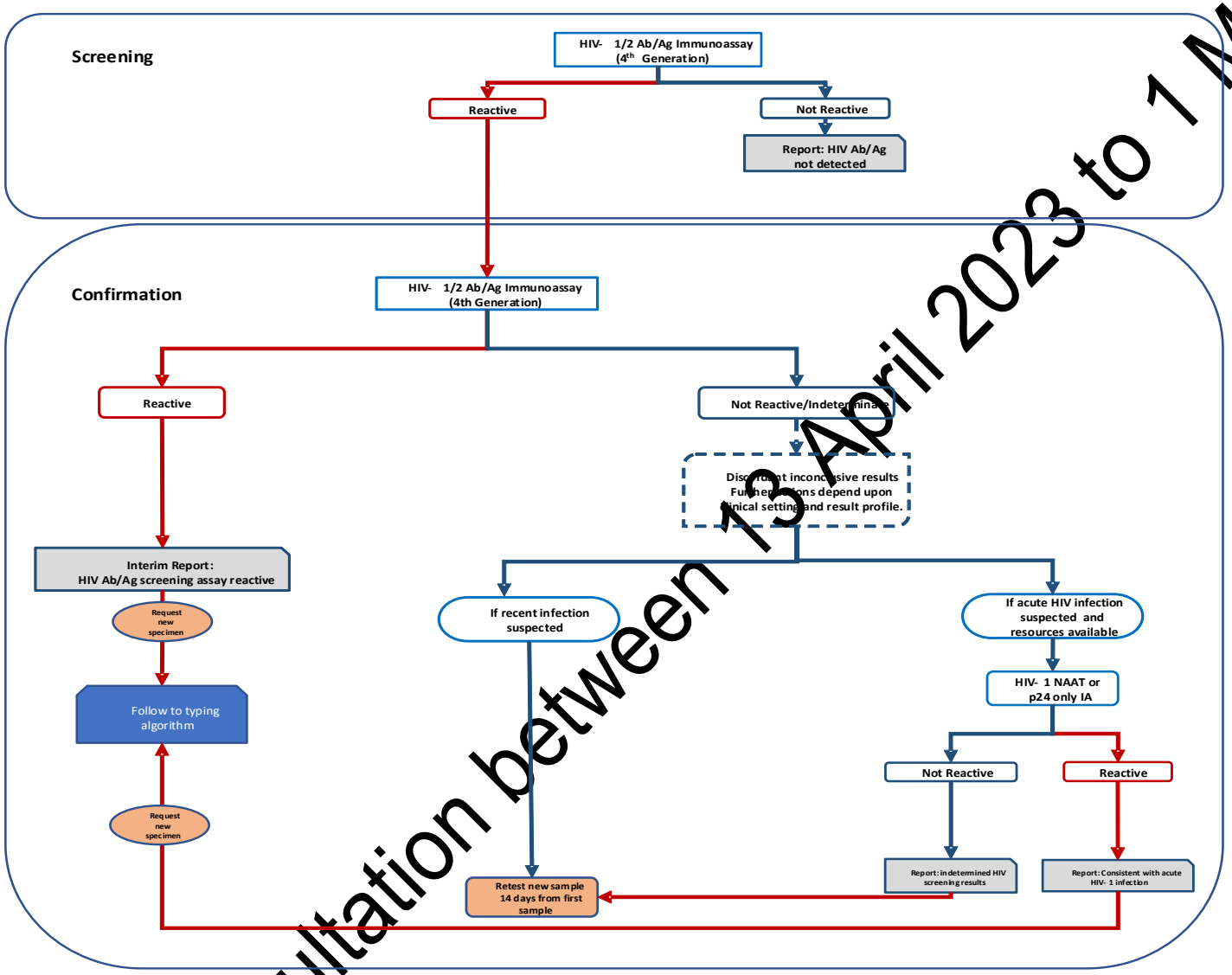
Test interpretation recommendations

If the result from the first assay is reactive or undetermined, laboratories should consider repeating the first assay before proceeding to confirmatory testing, using the following interpretation and reporting if results are discordant:

- Assay 1 (+) or undetermined / Repeat Assay 1 (-) / Assay 2 (-): report HIV negative
- Assay 1 (+) or undetermined / Repeat Assay 1(+) / Assay 2 (-): report HIV inconclusive, retest in 14 days (possible acute infection?)

Individuals who are confirmed to be HIV-positive, should be requested to submit another sample for identity confirmation.

5.2 HIV screening and confirmation



The 4th generation assay used to screen individuals for HIV will detect HIV-1 and HIV-2 Antibodies (Ab) and Antigens (Ag). These assays should have the highest sensitivity which will allow to rule in most individuals with active infection. Refer to the manufacturer information for more details on the specific sensitivity of the test.

Screening assay not reactive:

For non-reactive results on the screening assay, report “HIV Ab/Ag not detected”.

For individuals with history of recent exposure with no HIV related signs or symptoms, it is advised to test 45 days post exposure (3).

For individuals with suspected signs or symptoms related to primary HIV infection request a new sample for retesting within 14 days.

Screening assay reactive

All specimens that are reactive on the screening test should undergo confirmatory testing with a separate and distinct 4th generation test of equivalent sensitivity to the screening test but higher specificity which will allow to rule out false-positive results.

Laboratories who need to send specimens for typing, can issue an interim report “HIV Ab/Ag screening assay reactive” at this stage.

HIV vaccine recipients (having an HIV test) with reactive immunoassay results are encouraged to contact a vaccine trial site for specialised testing to determine their HIV infection status.

Discordant or inconclusive results

Specimens with a non-reactive or indeterminate result at confirmation testing constitute discordant or inconclusive results and further action should be taken depending on the clinical setting and the result profile.

In this scenario, it is important to repeat the screening assay if not done before. This will determine if the individual is repeatedly reactive on the assay that has the highest sensitivity (where reduced specificity is expected). Discordant results are driven by the specificity of the product chosen for the screening assay.

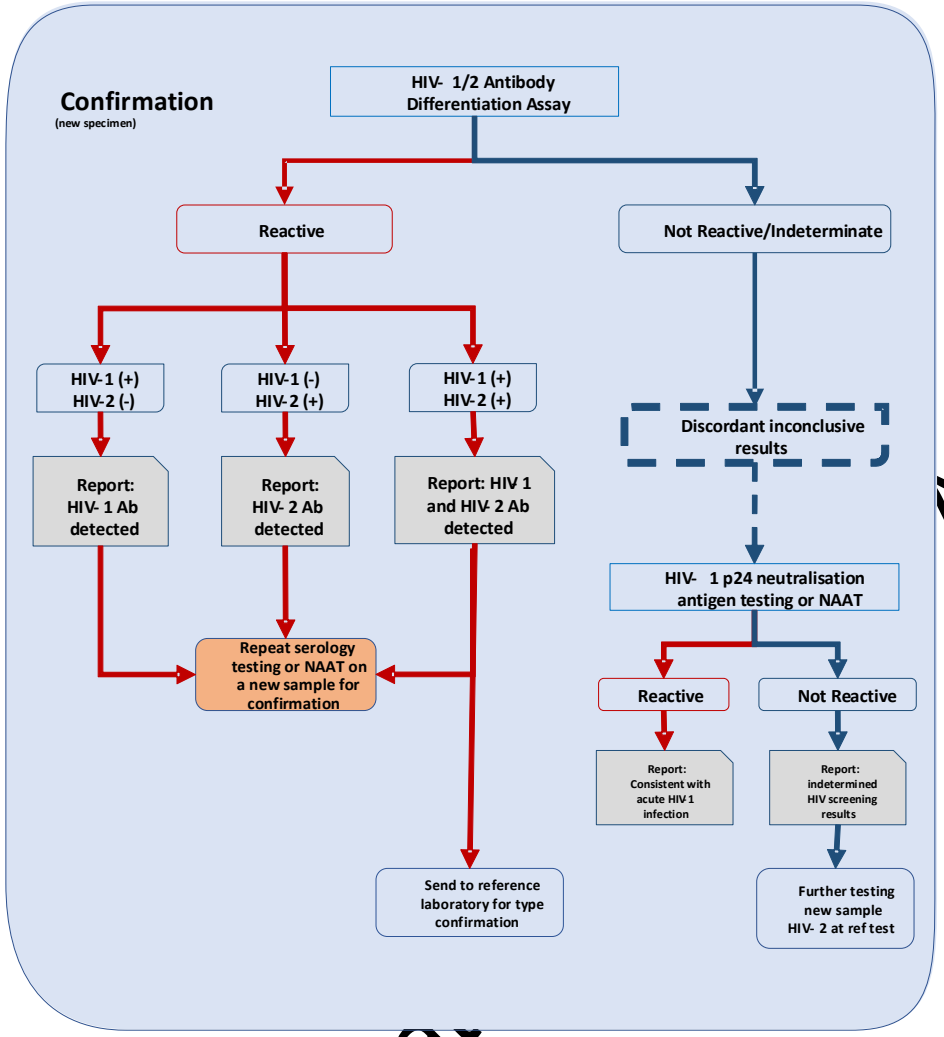
There is no need to repeat the confirmation assay after a reactive result, as this assay is chosen for its specificity, and both repeatedly reactive and non-reactive test results on confirmation would lead to an HIV-inconclusive status.

There is no added value in testing individuals with discrepant results (screening test reactive, confirmation test non-reactive) with the third typing assay, as the result would be HIV-inconclusive, irrespective.

For individuals with suspected acute infection, repeat screening test after 14 days. Consider requesting a new sample for HIV-1 NAAT (HIV-1 RNA) or p24 only immunoassay (IA) if resources are available. Report “consistent with acute HIV-1 infection” for NAAT or p24 positive/reactive results and request a new sample for the confirmation stage. Issue interim “HIV-indetermined” report and repeat test if p24 or NAAT are not conclusive.

For individuals with a history of recent exposure request a new sample and retest 14 days from first sample.

5.3 HIV typing and differentiation



HIV typing is done using HIV-1/2 antibody differentiation assays. Attention should be paid to the final diagnosis, whether HIV-1, HIV-2 or both as it has important treatment implications. Test results with both HIV-1 and HIV-2 antibodies reactive results should be referred to the appropriate reference laboratory for further HIV testing and typing. Although very rare, HIV-1 and HIV-2 coinfections are possible.

Conclusive results

Reactive assays should be able to provide results that are conclusive of the type of infecting HIV (HIV-1 or HIV-2).

It is recommended to repeat the serological screening on a new sample to rule out mislabelling and to confirm patient identity. This requirement can be fulfilled with a NAAT positive result. Where viral load is undetectable or below the detection limit of the assay, a further sample should be collected for serological testing.

Discordant or inconclusive results

Non-reactive or indeterminate results on differentiation assays constitute discordant or inconclusive results and further testing is required. Consider HIV-1 p24 neutralisation antigen testing or NAAT for HIV-1 RNA detection. Individuals with a reactive NAAT or p24 neutralisation antigen test should be issued with a report “consistent with acute HIV-1 infection”. Individuals with a non-reactive test result are issued with an “indeterminate HIV screening result” and requested to submit a new sample for further testing. Results should be interpreted along with patient history. Consider HIV-2 specific testing and send EDTA sample to the appropriate reference laboratory.

5.4 HIV monitoring - Avidity testing

HIV avidity testing distinguishes recent infections from established infections and is primarily used for monitoring at a population level. Only HIV-1 avidity testing is available as a public health surveillance tool at UKHSA Colindale, London Edinburgh and in Glasgow, West of Scotland. In England, Wales and Northern Ireland, clinics and laboratories can have specimens tested for evidence of recent HIV infection by antibody avidity testing through agreeing a memorandum of understanding with UKHSA, Colindale. Specimens for HIV avidity testing should be the first confirmed anti-HIV positive specimen from the patient if available, however where not available, the laboratory should ask for another specimen. Clinicians should be aware that the avidity test is not diagnostic, and the result should be considered with clinical and other laboratory data. The avidity test can be affected by infecting HIV subtype, current or previous treatment with ARV’s and declining immune status such as found in patients with AIDS.

5.5 Atypical results on ART, PEP and PrEP

Guidance on testing healthcare workers who are exposed to HIV infection in an occupational setting and other groups who require pre-exposure or post-exposure prophylaxis is available in BHIVA/BASHH adult HIV testing guidelines. The guidelines include recommendations on the frequency of HIV testing for various groups of individuals including those on antiretroviral therapy and those at risk of HIV acquisition. It is recommended that a follow up HIV test is performed a minimum of 45 days after cessation of PEP course thus a minimum of 10.5 weeks post exposure when using a 4th generation laboratory test.

Post-exposure prophylaxis (PEP), Pre-exposure prophylaxis (PrEP) and early initiation of antiretroviral therapy (ART) in acute infection can blunt the HIV antibody response yielding non-reactive, atypical or non-progressive HIV serology results in a scenario where HIV viral load is likely to be undetectable (28). HIV breakthroughs on PrEP are difficult to diagnose and may involve multiple tests including western blot, RNA and proviral DNA molecular assays. Where there is an increase in reactivity in repeat samples below or above the assay cut off these should be considered suspicious and monitored (29). Repeat testing at 4 and 8 weeks after PrEP cessation is recommended for anyone with atypical HIV results. Table 2 outlines atypical result profiles to be considered for further testing when interpreting test results from people who are on ART, PrEP or PEP.

Table 2: Atypical HIV result profiles (BHIVA/BASHH adult HIV testing guidelines)

1	Low signals near to cut-off in screening assays (including either just below or below cut-off)
2	Seroreversion on follow-up specimens
3	Discrepant results between assays
4	Slow development of antibody/antigen signals in subsequent samples
5	Weak and/or incomplete banding patterns on line immunoassay or western blot

5.6 Interpreting and reporting laboratory results

The table below is a summary of the combinations of typing results that may occur and require individual comments based upon profile and clinical setting, along with a further sample. Note: Two fourth generation tests have already been performed in the screening stage.
Further testing of HIV screening test reactive samples by using HIV-1/HIV-2 antibody differentiation immunoassay or a further immunoassay followed by a typing assay.

	HIV-1	HIV-2	Report and interpretative comment	Notes
1	Detected	Not Detected	HIV- 1 antibodies detected. Evidence that HIV-1 infection is present. Please send a repeat sample to confirm.	Repeat serology testing or NAAT on a new sample to confirm results
2	Not Detected	Detected	HIV- 2 antibodies detected. Evidence that HIV-2 infection is present. Please send a repeat sample to confirm.	Repeat serology testing
3	Detected	Detected	HIV- 1/HIV-2 antibodies detected. Evidence that HIV infection is present. HIV antibodies could not be differentiated as HIV-1 or HIV-2. Please send a repeat sample to confirm.	Repeat serology testing. If result consistent (both HIV1 and HIV-2 antibodies detected), suggest sending sample to reference laboratory for further testing.
4	Not Detected/ Indeterminate	Not Detected/ Indeterminate	No report issued	HIV antibodies are not confirmed, and further testing required. Issue report if results from p24 antigen or NAAT are conclusive and request a repeat sample to confirm results • HIV-1 RNA detected and/or p24 antigen neutralised – report: Consistent with acute HIV-1 infection. Please send a repeat serum sample to confirm.

				• HIV-1 RNA not detected and/or p24 antigen not neutralised, indeterminate HIV screening results. Results must be interpreted along with patient history. Consider HIV-2 and send EDTA sample to the appropriate reference laboratory for additional tests. Please send a second serum sample for further testing at least 14 days after the original sample. **Note:** HIV-2 RNA testing should be performed if clinically indicated.

6 Public health management

Early HIV screening and testing of patients helps in controlling the HIV epidemic and reducing late HIV diagnosis. Programmes that have been introduced to increase HIV testing have been shown to be cost-effective and provide a positive return on investment.

For information regarding notification to UKHSA (or equivalent in the devolved administrations), refer to the section for Notification to UKSHA or equivalent in the devolved administrations.

For more information on promotion of HIV testing, refer to the joint UKHSA and NICE guideline on HIV testing: increasing uptake among people who may have undiagnosed HIV and for a recommended testing approach refer to BHIVA/BASHH/BIA adult HIV testing guidelines (2020).

For further information on public health management of HIV, refer to UKHSA guidance on HIV: surveillance, data and management.

For information on healthcare workers who are exposed to blood borne viral infections in the occupational setting, refer to guidance on UK Advisory Panel for Healthcare Workers Living with Bloodborne Viruses (UKAP) and for information on post exposure prophylaxis, refer to HIV post-exposure prophylaxis: guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS.

Reporting

Laboratory reports of newly identified HIV positive individuals from clinics and laboratories in England and Wales should be forwarded to the HIV Reporting Section of Public Health England, Colindale. While new cases in Scotland should be reported to Health Protection Scotland. In Northern Ireland, new HIV diagnoses are reported via CoSurv to the Public Health Agency Northern Ireland.

A definitive diagnosis of HIV infection should not be reported to the relevant agency unless the full confirmatory testing algorithm has been completed with a positive result AND the results are confirmed by testing a second specimen.

7 Appendix 1: Evolution of serological assays used for HIV screening.

Only 3rd., 4th and 5th generation are used for laboratory screening, confirmation and typing of HIV in clinical settings.

	1st (1984)	2nd (1987)	3rd (1991)	4th (1997)	5th (2015)	p24 only tests
	Indirect ELISA (HIV-1)	**Indirect ELISA HIV-1/2**	**Sandwich ELISA HIV-1/2 IgG and IgM**	**Sandwich ELISA HIV-1/2 IgG and IgM + p24 Ag**		**Indirect ELISA p24 Ag**
Antigen (Ag) source	Virus Infected Cell Lysate	Lysate and recombinant	Recombinant and Synthetic peptides	Recombinant and Synthetic peptides	Recombinant and Synthetic peptides	Recombinant and Synthetic peptides
Specificity	98%	>99.5%	>99.5%	>99.5%	>99.5%	
Sensitivity	99%	>99.5%	>99.5%	>99.5%	100%	
Widow period	8-10 weeks	4-6 weeks	2-3 weeks	2 weeks	2 weeks	2-4 weeks
99th percentile window period (where 99% of cases are detected)	65 days	58 days	50 days	45 days	-	-
Antibody (Ab) and Ag detected	IgG Anti-HIV-1	IgG Anti-HIV-1 IgG Anti-HIV-2	IgG and IgM Anti-HIV-1, HIV-2 and Group O	IgG and IgM Anti-HIV-1, HIV-2, and Group O HIV-1 p24 Ag	IgG and IgM Anti-HIV-1, HIV-2, and Group O HIV-1 p24 Ag	HIV-1 p24 Ag
Results	Single result	Single result	Single result	Single result without differentiation between Ab and Ag	Separate HIV-1 and HIV-2 Ab and Ag results	Single result

confirmatory tests	HIV-1 western blot (WB) or immunofluorescence (IFA)	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1/2 differentiation Assay followed by P24 antigen neutralisation test or HIV-1 RNA PCR if differentiation assay is negative		P24 antigen neutralisation test or HIV-1 RNA PCR
Recommendation for use	not used	not used	Not first in line tests. May be used as supplementary test to differentiate Ab from Ag signals in samples reactive in 4th generation assay.	Used as first line choice tests in clinical settings		used acute or recently acquired infection

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