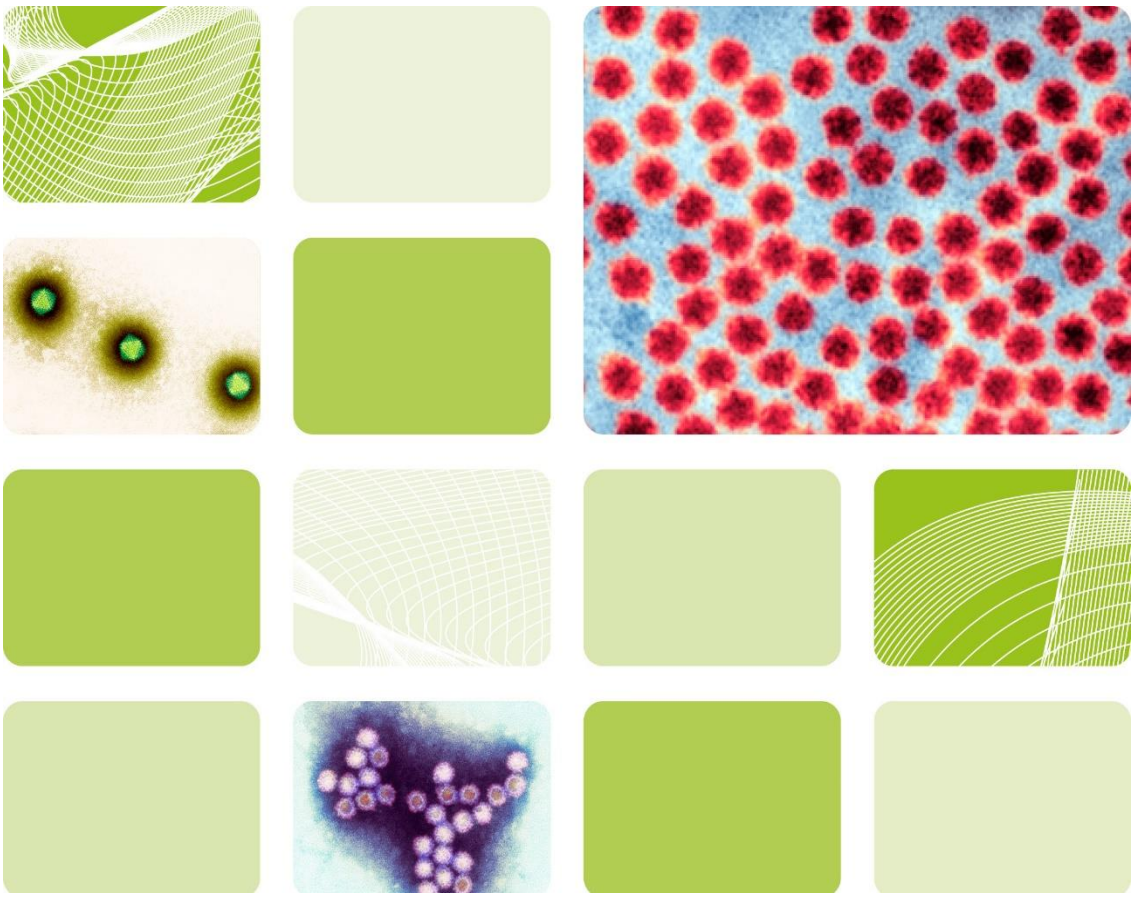
UK Health Security Agency

UK Standards for Microbiology Investigations

Laboratory diagnosis of HIV infection



Issued by the Standards Unit, UK Standards for Microbiology Investigations, UKHSA

Acknowledgments

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The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the medical editors for editing the medical content.

UK SMIs are produced in association with:

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Amendment table

Each UK SMI document has an individual record of amendments. The amendments are listed on this page. The amendment history is available from standards@ukhsa.gov.uk.

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

Amendment number/date	7/08.05.25
Issue number discarded	5
Insert issue number	5.1
Section(s) involved	**Amendment**
Whole document	**This is an administrative point change.** **The content of this UK SMI document has not changed.** **The last scientific and clinical review was conducted on 19.12.2023.** Hyperlinks throughout document updated to Royal College of Pathologists website. Public Health England replaced with UK Health Security Agency throughout the document, including the updated Royal Coat of Arms Partner organisation logos updated. Broken links to devolved administrations replaced. References to NICE accreditation removed. Scope and Purpose replaced with General and Scientific information to align with current UK SMI template.
Section 10: Public health responsibilities of diagnostic laboratories	This section has been added to UK SMI templates to highlight the public health responsibilities that diagnostic laboratories have as part of their duties.

Amendment number/date	6/19.12.2023
Issue number discarded	4.1
Insert issue number	5
Anticipated next review date*	19.12.2026

Section(s) involved	Amendment
Title	The title has been changed from ‘HIV screening and confirmation’ to ‘Laboratory diagnosis of HIV infection’
Whole document	Amended the entire document with up-to-date information and references
Flowcharts	Both flowcharts updated and presented in a new style

*Reviews can be extended up to 5 years where appropriate

1 General information

View general information related to UK SMIs.

2 Scientific information

View scientific information related to UK SMIs.

3 Scope of document

This UK SMI provides a detailed review of initial and supplemental laboratory-based serological and Nucleic Acid Amplification (NAAT) tests for the detection and exclusion of Human Immunodeficiency Virus (HIV). The document addresses special situations that may confound HIV diagnostic testing, including acute and recent HIV infection and 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, by providing a framework for additional testing and the interpretation of results. Reporting criteria for commonly obtained test results are also provided.

This UK SMI is intended for use in the laboratory diagnosis of HIV infection in the healthcare setting. It is not intended to cover:

- 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 HIV testing in children)
- 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)
- testing methods or strategies commonly used in community testing such as POCT testing, self-sampling, or self-testing
- testing of specimens other than blood, plasma and serum obtained by venepuncture, such as oral fluid and saliva
- ongoing monitoring tests used for those with a confirmed diagnosis of HIV

Additional requirements may be applicable in relation to the national antenatal screening programme. Please refer to the guidance on antenatal screening available from GOV.UK and the corresponding devolved administration website.

This UK SMI should be used in conjunction with other associated UK SMIs and standards.

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

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 burden and HIV transmission).

The UK government action plan to eradicate new HIV infections, AIDS diagnoses, and HIV related deaths in England by 2030 proposes a multi-faceted approach focusing on four strategies: “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 high-risk groups.

The World Health Organization (WHO) recommends that screening protocols using laboratory-based assays should allow the detection (diagnosis of infection) or exclusion of HIV infection with a 99% level of certainty. Modern laboratory HIV assays have improved in sensitivity, specificity, and turnaround times but accurate diagnosis will always be influenced by assay selection, the interpretation and reporting of results, the frequency of testing, the prevalence of infection in those being screened, and the window period for the chosen tests.

This UK SMI reviews existing laboratory-based assays and recommends that a sample should yield reactive tests in three different assays for a HIV-positive result to be issued. This strategy, which accords with recommendations from the WHO and other public health organisations, aims to maintain at least a 99% positive predictive value (that is, less than one false positive per 100 people diagnosed with HIV) in order to minimise the chances of misdiagnosis.

4.1 Human Immunodeficiency Virus (HIV)

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, known as HIV-1 and HIV-2.

HIV-1 is the most prevalent strain globally. 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 subtypes designated A through to K (excluding E and I). They differ in geographical distribution, biological characteristics, and common modes of transmission. HIV-1 groups O and N are more genetically distant to other HIV-1 groups (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 comprises a heterogeneous group of viruses that has been divided into 5 groups designated A through to E (2,3).

4.2 HIV diagnostic approaches and measures of test performance

Screening for HIV is done using enzyme or chemiluminescent immunoassays (EIAs or CLIAs) which detect HIV antibodies and/or antigens in venous whole blood, plasma, or serum. Molecular assays, that can detect and quantify viral nucleic acid (RNA) or proviral DNA, may sometimes be used as supplementary tests in certain clinical scenarios (see section 5.5).

Key attributes of laboratory tests are sensitivity (the extent to which a test correctly identifies those with infection – true positives) and specificity (the ability to correctly identify those without infection – true negatives). HIV immunoassays have evolved since the first assays were developed in the 1980s, and the latest generations of HIV immunoassays now have high sensitivity and specificity (see Appendix 1). However, the overall performance of these tests varies according to the prevalence of the disease. 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 different target groups, with higher PPV and lower NPV in high prevalence populations. When the same test is applied to a population with low prevalence of HIV, unless the test has 100% specificity, the PPV falls and 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 the result for a particular sample. A second sample should also then be tested to confirm the diagnosis for that patient. As the sensitivity of immunoassay has increased, along with advances in the types of marker(s) targeted, the window period (the time from infection with the virus to the appearance of measurable virus antigen or antibody in the peripheral blood) has decreased.

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

Following HIV infection, untreated individuals will develop a range of biological markers (and sometimes clinical symptoms) that can be used in laboratory testing for diagnosis and monitoring:

- **HIV RNA** becomes detectable in plasma approximately 10 days after infection. Most NAAT assays are specific for 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. They are not recommended for initial HIV screening as, in common with all NAAT tests they are prone to give false positive results. NAAT assays may be appropriate as a supplementary test when a patient gives persistently indeterminate immunoblot/immunoassay results, or in suspected primary HIV infection, but should only be performed with specialist input.
- **HIV-1 p24 (capsid) antigen** rises to detectable levels within 4 to 10 days after the earliest measurement of HIV-1 RNA and before HIV antibody detection. They can be detected by 4th generation immunoassays. 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. Thus, the window period for these tests is generally considered to be around 2 to 4 weeks. However, p24 antigenemia can sometimes last for 3 to 5 months depending on the host's immune response and other viral regulatory factors; it can also become detectable again in advanced HIV infection due to the suppression of antibody production by the virus.

- **Immunoglobulin M (IgM) antibodies** are detectable 3 to 5 days after p24 antigen is first detectable and 10 to 13 days after appearance and detection of viral RNA. IgM is detected by 3rd and 4th generation immunoassays, but IgM-specific assays are not used for routine diagnostic tests.
- **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, becoming measurable around 18 to 38+ days after the initial detection of viral RNA, with high variability.

The WHO recommends the use of rapid diagnostic tests which can be used at Point of Care Testing (POCT) (1). A positive HIV POCT test should be followed by laboratory testing using the algorithmic approach for screening and confirmation as described in this document.

The first test in a 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 between exposure and the ability of the test to detect the infection markers in peripheral blood. British HIV Association (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-testing 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 in hard-to-reach populations.

Use of specific sample types in individual assays is subject to local verification and validation requirements, alongside the manufacturer's instructions.

Specimen collection

Collect specimens in appropriate CE-marked, leak-proof containers and transport in sealed plastic bags (7).

Compliance with postal, transport and storage regulations is essential.

Safety

The section covers specific safety considerations related to this UK SMI, and should be read in conjunction with the general safety considerations on the UK SMI website (8-27).

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

HIV is a hazard group 3 organism but in most cases it has a derogation for handling at containment level 2.

This guidance should be supplemented with local COSHH and risk assessments.

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

Laboratories should follow manufacturer's instructions and validate or verify all methods used, as appropriate.

Test selection

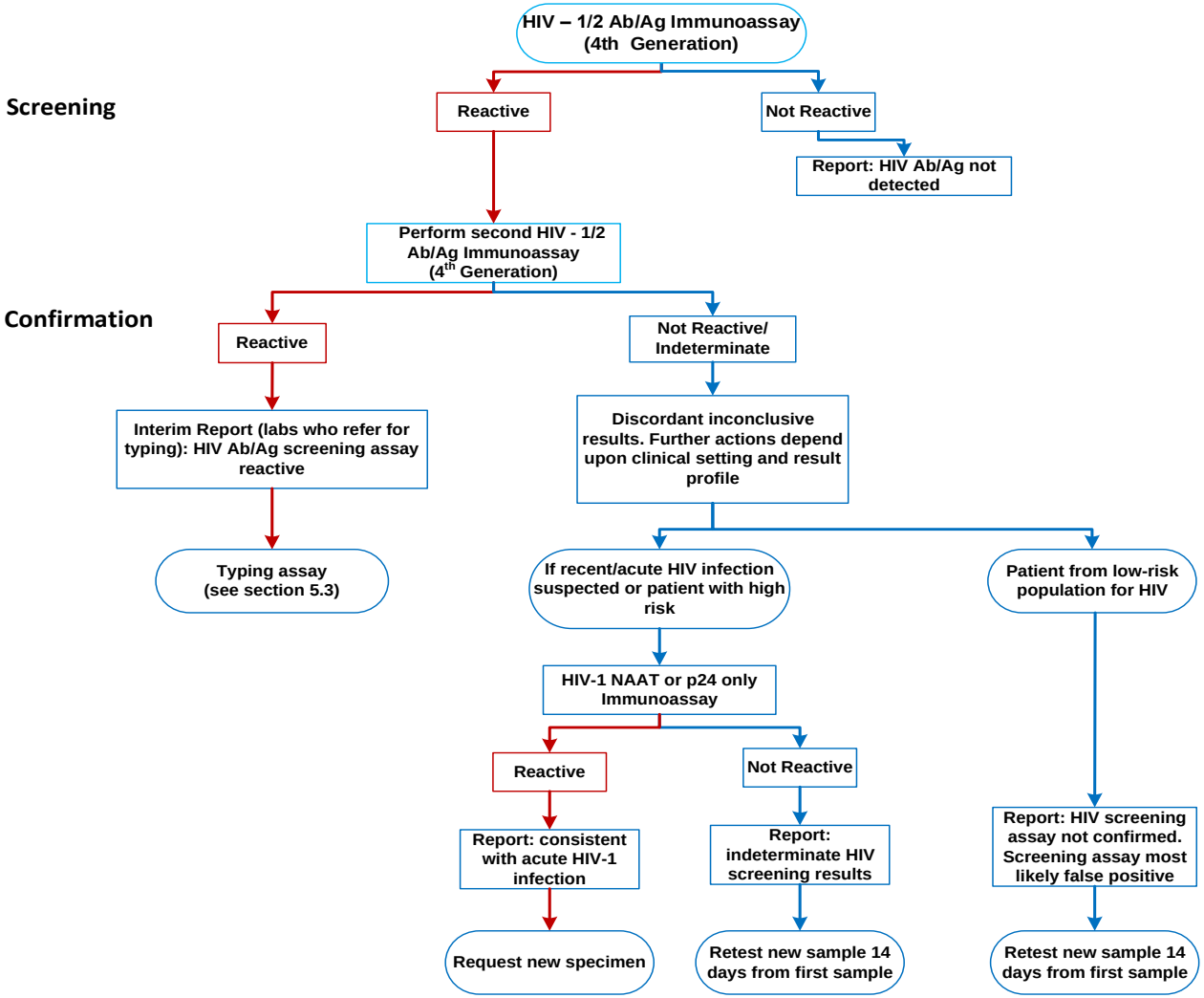
The initial screening assay should be a 4th generation assay, and a second 4th generation assay should be used to confirm any reactive screening results. Ideally, the screening test should have the highest sensitivity, while the subsequent assay should have similar sensitivity to the first assay but higher specificity.

However, it is recognised that modern 4th generation assays typically have nearly identical technical performance, therefore it may not be possible to identify an assay that is equally sensitive and more specific than the screening assay.

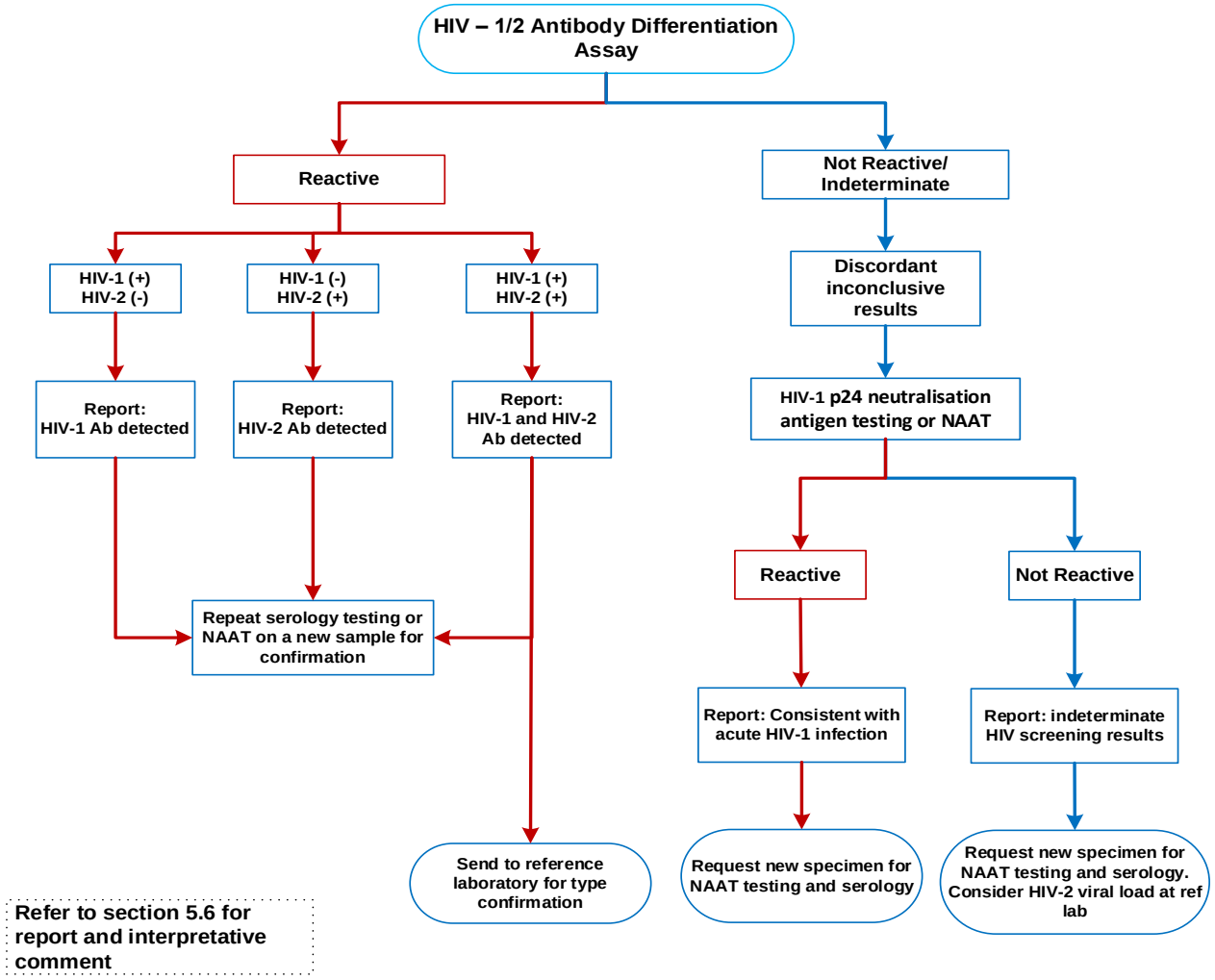
For typing, 3rd generation assays with high specificity should be used.

Refer to the manufacturer information for more details on the specific sensitivity and specificity of individual tests.

5.2 HIV screening and confirmation



5.3 HIV typing and differentiation



5.4 HIV epidemiological 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, Specialist Virology Centre Edinburgh and West of Scotland Specialist Virology Centre, Glasgow. 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 London. In Scotland, regional laboratories should send a specimen to their designated reference laboratory for HIV-1 avidity testing. Specimens for HIV avidity testing should be performed on the first confirmed anti-HIV-positive specimen from the patient, if sufficient volume is available however where not available, the laboratory should ask for another specimen. The avidity test is not a diagnostic assay, and the result should be considered with clinical and other laboratory data. The avidity test can be affected by HIV subtype, viral load, 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 individuals who require pre-exposure or post-exposure prophylaxis, is available in BHIVA/BASHH adult HIV testing guidelines. The guideline includes 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 4th generation HIV test is performed a minimum of 45 days after cessation of the 28-day PEP course, thus a minimum of 10.5 weeks post exposure.

Post-exposure prophylaxis (PEP), Pre-exposure prophylaxis (PrEP) and early initiation of antiretroviral therapy (ART) in acute infection can blunt the HIV antibody response. This can cause HIV serology tests to yield non-reactive, atypical or non-progressive results, in a scenario where HIV viral load is also likely to be undetectable (28). HIV breakthrough infections 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, either below or above the assay cut off, these should be considered suspicious and monitored, see table 2 (29). Repeat testing at 4 and 8 weeks after PrEP cessation is recommended for anyone with atypical HIV results. See section 6: Public Health Management for information on atypical results on ART.

Table 2: Atypical HIV result profiles that should prompt consideration of further testing when interpreting test results from people who are on ART, PrEP or PEP (taken from 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

Table 3 is a summary of the combinations of typing results that may occur. Suggested report comments are indicated but many results will require individualised comments based upon the result profile and clinical scenario. A further sample should be requested for follow-up testing in all cases where a first sample has given a reactive screening result.

Note: Two fourth generation tests have already been performed in the screening stage.

	HIV-1	**HIV-2**	**Report and interpretative comment**	**Notes**
1	Detected	Not Detected	HIV-1 antibodies detected. Evidence of HIV-1 infection. Please send a repeat sample to confirm and EDTA blood for HIV-1 viral load.	Repeat serology testing or NAAT on a new sample to confirm results
2	Not Detected	Detected	HIV-2 antibodies detected. Evidence of HIV-2 infection. Please send a repeat sample to confirm and EDTA blood for HIV-2 viral load.	Repeat serology testing on new sample
3	Detected	Detected	HIV-1/HIV-2 antibodies detected. Evidence of HIV infection. HIV antibodies could not be differentiated as HIV-1 or HIV-2. Please send a repeat sample for further testing.	Repeat serology testing on a new sample. If result consistent (both HIV1 and HIV-2 antibodies detected), suggest send sample to reference laboratory for further testing.
4	Not Detected/ Indeterminate	Not Detected/ Indeterminate	No report issued until result of NAAT or p24 antigen, see notes	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 • If HIV-1 RNA detected and/or p24 antigen neutralised, report as consistent with acute HIV-1 infection. Request repeat samples for NAAT and confirmation of HIV type. • If HIV-1 RNA not detected and/or p24 antigen not neutralised, report as indeterminate. Results must be interpreted along with patient history. Consider the possibility of HIV-2 infection and send EDTA sample to the appropriate reference laboratory for additional tests, including HIV-2 RNA if clinically indicated. A second serum sample for further testing should be obtained at least 14 days after the original sample was collected.

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.

For information regarding public health notification, refer to the '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).

BHIVA/BASHH guidelines recommend that atypical test results in individuals who are taking (or have recently taken) PrEP should be discussed with a regional expert and investigated further for possible seroconversion; UKHSA Colindale should be informed (non-identifying information can be sent to csuqueries@ukhsa.gov.uk).

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 in this setting, refer to HIV post-exposure prophylaxis: guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS.

Reporting for epidemiological purposes

Laboratory reports of newly identified HIV positive individuals from clinics and laboratories in England, Wales, Northern Ireland and Scotland should be forwarded to the

Blood Safety, Hepatitis, Sexually Transmitted Infections (STI) and HIV Division, UKHSA, to be collated in the HIV and AIDS Reporting System (HARS).

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 Public Health responsibilities of diagnostic laboratories

Diagnostic laboratories have public health responsibility as part of their duties. Amongst these are additional local testing, or referral, to further characterise the organism, as required, primarily for public health purposes e.g. routine cryptosporidium detection; serotyping or microbial subtyping; and a duty to refer appropriate specimens and isolates of public health importance to a reference laboratory.

Diagnostic laboratory outputs inform public health intervention, and surveillance data is required to develop policy and guidance, forming an essential component of healthcare. It is recognised that additional testing and referral of samples may entail some costs that has to be borne by the laboratory but in certain jurisdictions these costs are covered centrally.

Diagnostic laboratories should be mindful of the impact of laboratory investigations on public health and consider requests from the reference laboratories for specimen referral or enhanced information.

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.
Table provided below draws inspiration from Alexander TS, see reference (30).

	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%	
Window 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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An explanation of the reference assessment used is available in the scientific information section on the UK SMI website.

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