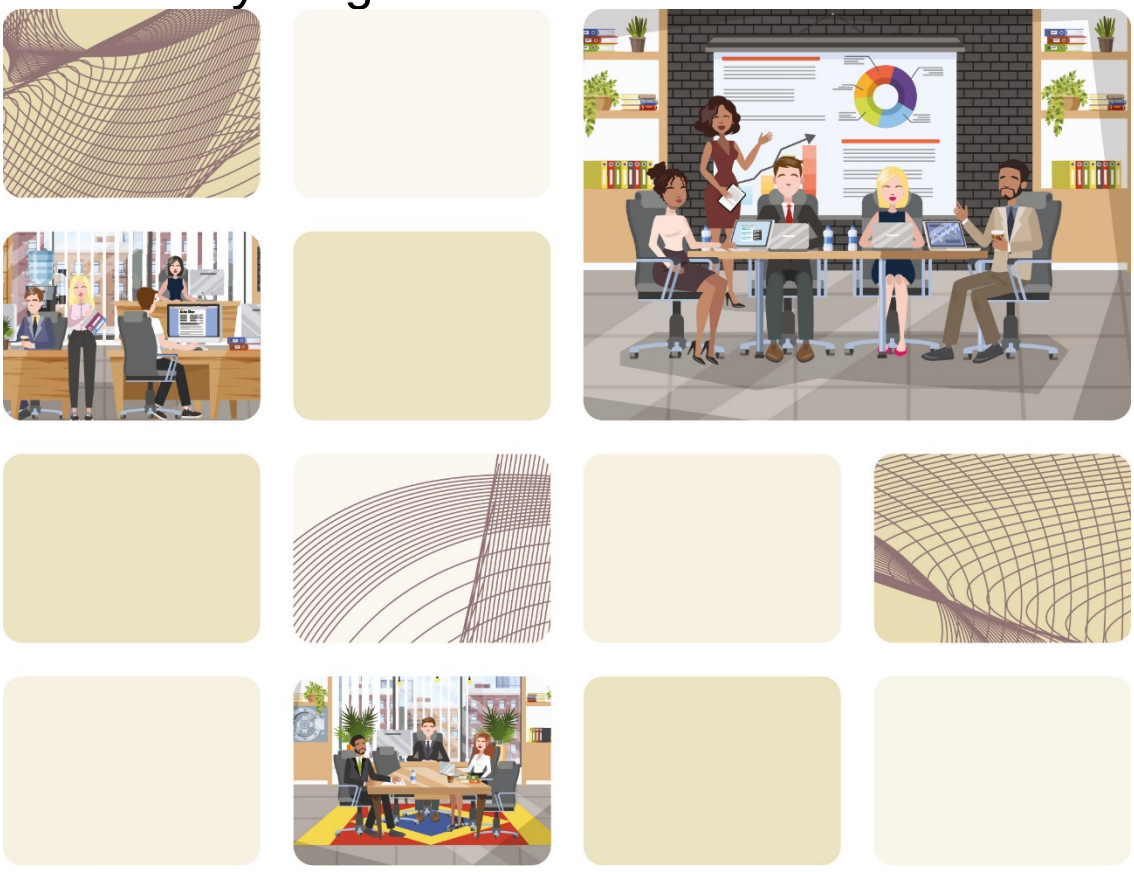
UK Health Security Agency

UK Standards for Microbiology Investigations

Review of users' comments received by Working group for microbiology standards in clinical virology/serology

Laboratory diagnosis of HIV infection



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 **30 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.

This publication was created by UK Health Security Agency (UKHSA) in partnership with the partner organisations.

Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

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

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Version of document consulted on: df+

3.0 Scope of document

Comment number: 1

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Editorial- no need for the comma after 'This standard.....' in paragraph 4 page 5

Recommended action

1. Accept: amendment made

Comment number: 2

Date received: 19/04/2023
Laboratory or organisation name: Salisbury NHS Foundation Trust

I think that this section should include reference to the antenatal screening handbook and additional requirements may be indicated as per national screening guideless and regulatory requirements.
Propose adding the statement:
'Additional requirements may be applicable in relation to the national antenatal screening programme and this SMI should be used in conjunction with other standards as per the requirements of the service user. Please refer to the guidance on antenatal screening available from gov.uk'.

Recommended action

1. Accept: suggested wording with the reference to antenatal screening added.

4.1 Human immunodeficiency virus

Comment number: 3

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Page 6: Mentions HIV 1 is found largely in..... HIV is more prevalent in Africa so why single out the UK, USA, Europe? If because this is a UK guideline, then leave out USA and Europe and just say worldwide.

Recommended action

1. Accept: amendment made

4.2 HIV diagnostic approaches and measures of test performance

Comment number: 4

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. 'Screening for HIV is done using serological assays or enzyme immunoassays (EIAs)'
   An EIA is a serological assay, isn't it?
2. '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.'
   Consider 'The other main diagnostic test that can be used.....'
   Also note there are proviral DNA tests.

Recommended action

1. Accept: amendment made
2. Accept: amendment made

4.3 Types of HIV diagnostic tests and markers of infection

Comment number: 5

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. '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' Consider 'HIV 1 p24 antigen becomes detectable in blood using 4th gen.....' It is sort of expressed, as there can be more than expected per virion, I suppose.
2. Mention HIV 2 homologue is p25 which is detected in most p24 assays I think, but not reliably.
3. Suggest mention IgM is not used as a separate assay in routine diagnostics.

Recommended action

1. Accept: amendment made
2. Accept: appropriate wording added with a reference
3. Accept: amendment made

Comment number: 6

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. Page 8 and 9: I know it is standard to request laboratories select the most sensitive assay to screen and a more specific one to confirm, however, this is not achievable in modern HIV diagnostics.
   Almost all screening assays conform to the required standard and head to head comparisons demonstrate very little statistically significant benefits. Anyway, how would you define the following mathematically? 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.' In effect that means you ought to use it as the screening assay aside from operational or cost issues.
   Please recognise the convergence of screening assay performance.
2. Finally, selecting the screening assay on the basis of sensitivity criterion alone is too simplistic- what if assay A was 0.05% more sensitive than assay B, but the specificity of B was 5% less than A? Would that be the best outcome for the tested population?
3. Finally, I don't find the interpretation recommendations at the bottom of p9 helpful- it avoids mentioning clot testing if not initially done from primary tube, and the information should naturally fall out of the algorithms and tables.

Recommended action

1. Accept: amendment made
2. Accept: amendment made
3. Accept: section on ‘Test interpretation recommendations’ removed

5 Methodology

Comment number: 7

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. Page 11: 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).
   Should be permissible to test before 45 days, and that reference 3 is titled HIV2- is it applicable?
2. '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.'
   I would rephrase this- the words in brackets are unnecessary and it implies you cannot diagnose infection without chatting to the trial team- you can with NAAT or seroconversion.

Recommended action

1. Accept: appropriate wording added
2. Accept: amendment made

Comment number: 8

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Page 11: (end)
Issue interim 'HIV-indetermined' report and repeat test if p24 or
NAAT are not conclusive.
I am undetermined as to whether I like 'indetermined', anyway, I feel it would be more appropriate to use 'HIV infection status inconclusive'

Recommended action

1. Accept: amendment made

5.1 Pre-screening considerations

Comment number: 9

Date received: 19/04/2023
Laboratory or organisation name: Salisbury NHS Foundation Trust

I feel this section should include reference to local validation of sample types for the assay deployed at the testing site in question and as per the instructions for use. There is reference to use of DBS samples in resource limited countries but it should be clarified that use of samples other than plasma and serum are subject to local verification and accreditation requirements. This is important when selecting assays and verifying their sensitivity and specificity compared to manufacturer claims, and other factors such as false positivity rate of initial screening assay on local populations and the sample types used.
Propose adding the statement:
'Use of sample types in selected assays is subject to local verification requirements, associated literature, and instructions for use provided by the manufacturer'

Recommended action

1. Accept: amendment made

5.2 HIV screening and confirmation

Comment number: 10

Date received: 21/04/2023

Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. There is a confirmation box which needs to state that the EIA done there is not the same EIA as done in the screening box- it could be if retesting from same assay plus a second assay.
   This box is called confirmation but has an embedded box stating go to confirmation algorithm- confusing.
   How would you define the difference between acute infection (=NAAT) and recent infection (=retest 14 days)?
2. What evidence are you using to define the retest interval of 14 days? If second window (antigen clearance but inadequate antibody levels to detect), whilst this has been described, it is very rare and doesn't sit well with the earlier statement that IgM appears no more than 5 days after antigen. 14 days is however precautionary and practical- if those are factors, consider adding to narrative.

Recommended action

1. Accept: amendment made
2. None

Comment number: 11

Date received: 19/04/2023
Laboratory or organisation name: Department of Infection Sciences (microbiology and virology), Northern Care Alliance NHS Foundation Trust.

In the confirmation box, the flowchart suggests that if the second 4th generation assay is NOT reactive, further testing will be required either in the form of a repeat blood sample in 14 days or further tests (p24 Ag / NAAT). However, in most screening 4th generation HIV assays, low level reactivity / low signals near to cut-off values are seen in most HIV testing laboratories. If the second 4th generation assay is negative and there is no clinical information about the patient (such as in HIV opt-out testing in Emergency departments or other HIV screening tests), it will create a huge workload and cost pressure to either recall patient or do additional p24Ag / NAAT testing.

Recommended action

1. None: flowchart updated

Comment number: 12

Date received: 17/05/2023
Laboratory or organisation name: West of Scotland Virology

The main comment from us was around the interpretation of discordant screening tests in low-risk populations. The current guidance isn’t clear, the headings are confusing/hidden and the text seems to suggests that discordant screening samples should be reported as discordant with a request for follow up samples (We think the text suggesting this is actually relating to samples that don’t type but we were not sure). We think it needs to be re written more carefully, with clearer section headings and the algorithms needs to be clearer.

For the screening part, there needs to be some detail / wording around the fact that the risk of the group tested should be taken into account and that most discordant results are either very early acute infection or false. We agree with the SMI that if there is a risk of recent acute infection (inc those on PrEP) or clinical symptoms in keeping with acute HIV then NAAT or follow up should be considered. However, there is no detail around what to do in low-risk populations. In these the risk of acute illness if far less and therefore a negative follow up 4th gen should be good enough to rule out infection without the need for follow up samples.

We feel the algorithm should reflect this otherwise there will be a lot of discordant results and requests for follow up. This will cause unnecessary concern, additional testing and reduce the confidence in the tests being used.

Recommended action

1. Accept: patient from low-risk population added to the flowchart

5.3 HIV typing and differentiation

Comment number: 13

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. Algorithm. why is this called 'confirmation (new specimen)'. The typing can be done on the initial specimen if the two 4G assays are reactive and the second specimen only needs a single HIV screening test to confirm person identity. I think this is what you intend, so delete the 'new specimen'.
2. On right side of algorithm, is it possible that a p24 antigen assay might detect p25 HIV2?

Recommended action

1. Accept: wording ‘Confirmation and new specimen’ deleted
2. None

5.5 Atypical results on ART, PEP and PrEP

Comment number: 14

Date received: 27/04/2023
Laboratory or organisation name: Clinical Services Unit / Virus Reference Dept / UKHSA

BHIVA/BASHH guidelines on atypical HIV results in PrEP users (2018) recommend 'atypical testing cases should be discussed with a regional expert and investigated further for possible seroconversion. PHE [now UKHSA] Colindale should also be informed (via an email with non person identifiable information sent to

csuqueries@ukhsa.gov.uk), and will liaise with the regional expert, provide expert advice, and collate information on the frequency and details of these events.'

The BHIVA/BASHH/BIA Adult Testing Guidelines (2020) similarly state:
'Atypical results on ART
Post-exposure prophylaxis, PrEP and early ART initiation in acute infection can blunt the HIV antibody response [71] yielding non-reactive, atypical or non-progressive HIV serology in a setting in which the HIV viral load is likely to be undetectable. BHIVA/BASHH guidelines on the use of HIV PrEP [76] recommend that atypical test results in individuals taking, or after recent, PrEP should be discussed with a regional expert and investigated further for possible seroconversion and PHE [now UKHSA] Colindale should be informed (non-identifying information sent to csuqueries@ukhsa.gov.uk).'

1. Please consider adding some text in line with this BHIVA/BASHH/BIA guidance- many centres especially those lacking virology expertise have found the referral route helpful to access specialist advice and may not otherwise know who to approach.

2. We would also highlight that UKHSA offers a national clinical service jointly with Imperial College Healthcare NHS Trust and Imperial College London for individuals with difficult to interpret HIV test results, held at St Mary's Hospital, London. Trusts can refer individuals where they would like specialist consultation on complex cases (IDRIS clinic, imperial.idris@nhs.net).

Recommended action

1. Accept: wording from BHIVA/BASHH/BIA guideline added
2. None

Comment number: 15

Date received: 27/04/2023
Laboratory or organisation name: Clinical Services Unit / Virus Reference Dept / UKHSA

''Weak and/or incomplete banding patterns on line immunoassay of western blot.''
? Should this state 'or western blot'

Recommended action

1. None: table is from BHIVA/BASHH/BIA guideline and cannot be amended

5.6 Interpreting and reporting laboratory results

Comment number: 16

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

HIV- 1 antibodies detected. Evidence that
HIV-1 infection is present.
Seems unusual- most would state 'Evidence of HIV 1 infection'.

Recommended action

1. Accept: table updated

Title

Comment number: 17

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

HIV screening and confirmation is likely to be understood by most, but it isn't fully descriptive. HIV NAAT is mentioned but does not feature in the interpretation table. Consider whether this is 'Serological testing for HIV infection' or 'laboratory diagnosis of HIV infection'.

Recommended action

1. Accept: title of the document changed to 'laboratory diagnosis of HIV infection'.

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

Comment number: 18

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Nice educational tool.

Financial barriers

Respondents were asked: 'Are there any potential organisational and financial barriers in applying the recommendations or conflict of interest?'.

Comment number: 19

Date received: 19/04/2023
Laboratory or organisation name: Department of Infection Sciences (microbiology and virology), Northern Care Alliance NHS Foundation Trust.

Increased p24 Antigen testing or NAAT testing as per this UK SMI will add to the cost pressures /financial barriers.

Recommended action

1. None

Comment number: 20

Date received: 19/04/2023
Laboratory or organisation name: Salisbury NHS Foundation Trust

No

Comment number: 21

Date received: 21/04/2023
Laboratory or organisation name: Keith Shuttleworth and Associates Ltd

None to my knowledge

Comment number: 22

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

No CoI No barrier to implement in UK.

Comment number: 23

Date received: 27/04/2023
Laboratory or organisation name: Clinical Services Unit / Virus Reference Dept / UKHSA

No

Comment number: 24

Date received: 28/04/2023
Laboratory or organisation name: RCGP

Not from my perspective as a GP

Health benefits

Respondents were asked: 'Are you aware of any health benefits, side effects and risks that might affect the development of this UK SMI?'.

Comment number: 25

Date received: 19/04/2023

Laboratory or organisation name: Department of Infection Sciences (microbiology and virology), Northern Care Alliance NHS Foundation Trust.

No

Comment number: 26

Date received: 19/04/2023
Laboratory or organisation name: Salisbury NHS Foundation Trust

No

Comment number: 27

Date received: 21/04/2023
Laboratory or organisation name: Keith Shuttleworth and Associates Ltd

None to my knowledge

Comment number: 28

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

I anticipate this SMI will create a health benefit!

Comment number: 29

Date received: 27/04/2023
Laboratory or organisation name: Clinical Services Unit / Virus Reference Dept / UKHSA

No

Comment number: 30

Date received: 28/04/2023
Laboratory or organisation name: RCGP

No

Interested parties

Respondents were asked: 'Are you aware of any interested parties we should consider consulting with on the development of this document?'

Comment number: 31

Date received: 19/04/2023

Laboratory or organisation name: Department of Infection Sciences (microbiology and virology), Northern Care Alliance NHS Foundation Trust.

No

Comment number: 32

Date received: 19/04/2023
Laboratory or organisation name: Salisbury NHS Foundation Trust

United Kingdom Accreditation Service (UKAS)

Comment number: 33

Date received: 21/04/2023
Laboratory or organisation name: Keith Shuttleworth and Associates Ltd

None to my knowledge

Comment number: 34

Date received: 21/04/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

None that are not listed already.

Respondents indicating they were happy with the contents of the document

Overall number of comments: 1			
Date received	28/04/2023	**Lab name/Professional body (delete as applicable)**	RCGP