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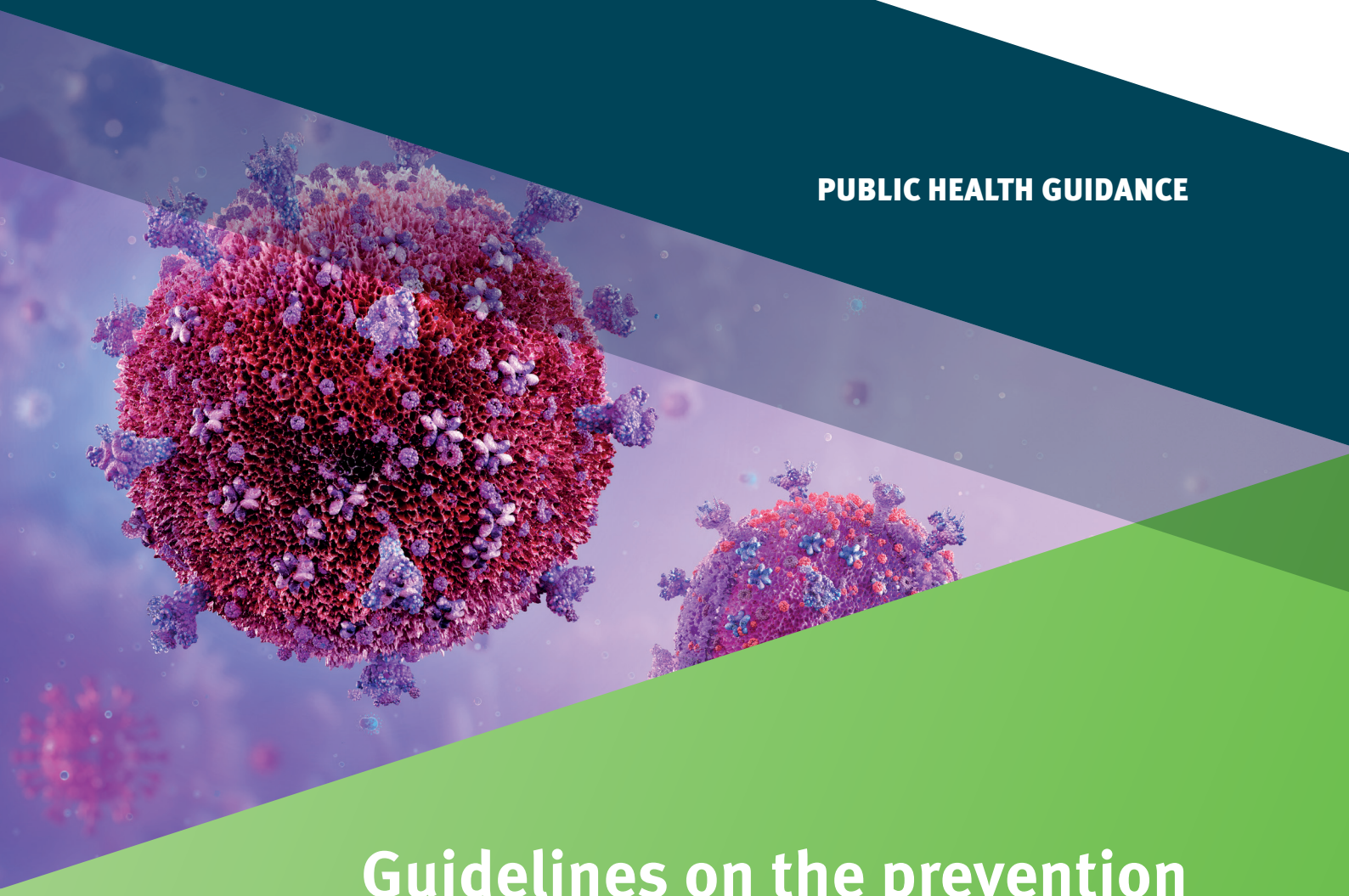

PUBLIC HEALTH GUIDANCE

Guidelines on the prevention of HIV transmission through substances of human origin

Technical guidelines supporting the regulation on standards of quality and safety for substances of human origin intended for human application

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Acknowledgements

We would like to thank the following members of the ECDC ad hoc scientific panel for their insightful input supporting with evidence and expertise, reviewing the pathogen data sheet and meeting minutes, and providing statements to the guidelines:

Alessandra Alteri, IRCCS San Raffaele Scientific Institute; Italy, Alexandra Hartmann, Cells and Tissue bank, Austria; Aliénor Xhaard, Hopital St-Louis, France, Ana Avellón, National Center of Microbiology Carlos III Institute of Health, Spain; Andreas Lind, Oslo University Hospital, Norway; Anna Vilarrodona, Banc de Sang i Teixits, Spain; Anthi Gafou, Hospital of Kifisia "Oi Agioi Anargyroi", Greece; Branka Golubić Ćepulić, University Hospital Center Zagreb, Croatia; Danica Valkovicová Staneková, Slovak Medical University, Slovakia; Dominique Challine, Henri Mondor Hospital, France; Dragoslav Domanovic, European Blood Alliance, international organisation; Jaana Mättö, University of Helsinki, Finland; Paolo Grossi, ASST-Sette Laghi, Italy; Piotr Grabarczyk, Institute of Haematology and Transfusion Medicine, Poland; Ruth Offergeld, Robert Koch Institute, Germany; Ryanne W Lieshout-Krikke, Sanquin Blood Supply Foundation, Netherlands; Silvia Sauleda, Banc de Sang i Teixits, Spain; Syria Laperche, Etablissement Français du Sang, France.

We would also like to thank the observers of the expert panel for their valuable input:
Rada Grubovic Rastvorceva, European Directorate for the Quality of Medicines and Healthcare (EDQM), Jacinto Sanchez, EDQM (delegated), Richarde Forde, EDQM.

Suggested citation: European Centre for Disease Prevention and Control. Guidelines on the prevention of HIV transmission through substances of human origin. Stockholm: ECDC; 2025.

Stockholm, September 2025

ISBN 978-92-9498-823-2
doi: 10.2900/6503189
Catalogue number TQ-01-25-053-EN-N

Contents

Abbreviations

Ab	Antibody
AIDS	Acquired immunodeficiency syndrome
Ag	Antigen
ART	Antiretroviral therapy
ECDC	European Centre for Disease Prevention and Control
EDQM	European Directorate for the Quality of Medicines and Healthcare
EEA	European Economic Area
EIA	Enzyme immunoassay
ESHRE	European Society of Human Reproduction and Embryology
EU	European Union
HIV	Human Immunodeficiency virus
IU	International Units
IVDR	Regulation (EU) 2017/746 on in vitro diagnostic medical devices
LOD	Limit of Detection
mL	Millilitre
NAT	Nucleic Acid Test
MAR	Medically Assisted Reproduction
NCA	National Competent Authorities
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
RNA	Ribonucleic acid
SoHO	Substances of human origin (excluding solid organs)[1]
U=U	Undetectable Equals Untransmittable
WHO	World Health Organization

[1] As per the Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC.

Glossary

These guidelines use the definitions of key terms as laid out in Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC [1]. The main key terms used from the Regulation are as follows:

Allogeneic use	The human application of SoHO collected from a person other than the SoHO recipient.
Autologous use	The human application of SoHO collected from a person to the same person.
Blood component	A constituent of blood, such as red blood cells, white blood cells, platelets and plasma, that can be separated from it.
Deceased SoHO donor	A deceased person who has been referred to a SoHO entity with a view to SoHO collection, and from whom consent had been granted in that respect or from whom SoHO collection is permitted, in accordance with national legislation.
Human application	Being inserted, implanted, injected, infused, transfused, transplanted, ingested, transferred, inseminated or otherwise added to the human body in order to create a biological interaction with that body.
Living SoHO donor	A living person who has volunteered to a SoHO entity, or has been presented by a person granting consent on their behalf, in accordance with national legislation, with a view to making a donation of SoHO, for the purpose of use in a person other than themselves, and other than in situations of within-relationship use.
Medically assisted reproduction	Any laboratory or medical intervention, including any preparatory steps, that involves the handling of reproductive SoHO for the purpose of the facilitation of pregnancy or for preservation of fertility.
Offspring from medically assisted reproduction	Children born following medically assisted reproduction.
Reproductive SoHO	Human sperm, oocytes, ovarian and testicular tissue intended to be used for the purpose of medically assisted reproduction or restoring endocrine function; for the purposes of this definition, embryos are considered reproductive SoHO even though they are not collected from the human body. For these guidelines, for clarity, reproductive SoHO are referred to as 'reproductive tissues and cells'.
SoHO donation	A process by which a person voluntarily and altruistically gives SoHO from their own body for persons in need, or authorises the use of such SoHO after their death; it includes the necessary medical formalities, examination and treatments and monitoring of the SoHO donor, irrespective of whether that donation is successful or not; it also includes, where applicable, the consent given by an authorised person in accordance with national legislation. For simplicity, for these guidelines, SoHO donations are referred to as 'donations'.
SoHO donor	A living or deceased SoHO donor.
SoHO entity	An entity legally established in the Union that carries out one or more of the SoHO activities referred to in Article 2(1), point (c) in the Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024. For simplicity, for these guidelines, "'SoHO entity' is referred to as 'entity'.
SoHO recipient	The person to whom SoHO are applied or the human application of SoHO is envisaged, whether by allogeneic, autologous or within-relationship use. "Recipient" means a SoHO recipient or any person receiving a product manufactured from SoHO, regulated by other Union legislation. For simplicity, for these guidelines, 'SoHO recipients' are referred to as 'recipients'.
Substance of human origin or SoHO	Any substance collected from the human body, whether it contains cells or not and whether those cells are living or not, including SoHO preparations resulting from the processing of such substance.
Third-party donation	A donation of reproductive SoHO to be used for medically assisted reproduction in a SoHO recipient with whom the SoHO donor does not have an intimate physical relationship.
Within-relationship use	The use of reproductive SoHO for medically assisted reproduction between persons with an intimate physical relationship

Executive summary

These guidelines support adherence to the European Union (EU) Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application. They provide evidence-based recommendations for assessing SoHO donors within the EU and European Economic Area (EEA) with the aim of preventing transmission of the human immunodeficiency virus (HIV) to recipients and offspring from medically assisted reproduction (MAR). HIV poses a significant risk to the safety of SoHO due to its potential transmission through blood, tissues, cells, and organs, as well as the lifelong consequences and severity of the disease. The sustained incidence of HIV in EU/EEA countries underscores the need for a strategic approach to prevent the transmission of HIV from donors via SoHO.

The guidelines are divided into three main sections corresponding to different types of SoHO: blood and blood components, tissues and non-reproductive cells, and reproductive cells. Solid organs and SoHO intended for industrial manufacturing are excluded from the scope, as is the protection of SoHO recipients and offspring from MAR other than from transmission of communicable diseases through SoHO.

The guidelines were developed by the European Centre for Disease Prevention and Control (ECDC) with the support of a panel composed of experts from EU/EEA countries. These experts provided specific technical and scientific advice to the ECDC. Expert meetings, supported by evidence synthesis, were conducted to inform guideline recommendations. To develop the statements in these guidelines and to support the expert panel, evidence synthesis based on structured literature searches was provided in a pathogen data sheet. This pathogen data sheet contains microbiological and clinical information on HIV, including virus and disease descriptions, epidemiology, test characteristics and testing approaches, and evidence of transmission through SoHO.

Key requirements

Blood and blood components

(For additional information and recommendations, please refer to 'Requirements and recommendations: Blood and blood components')

Testing requirements	Donor screening tests	Outcome of test results		
		Screening test results	Confirmatory test results	Actions

All donors, at each donation[a]
• Assessment of recent risks of exposure to HIV is required.
• Donors should not be tested in the context of donor evaluation before a period of at least eight weeks since the last event with a risk of exposure to HIV except for:
  • Oral PrEP or PEP: at least 12 weeks since last event
  • Injectable PrEP: at least 24 months since last event
	Anti-HIV-1/2 + HIV-1 RNA NAT	Both NAT and serological tests reactive	Any	• Do not release donation for clinical use.
				• Inform donor and refer to relevant clinical care.
				• Permanent deferral.
				• Initiate look-back procedures.

		Either NAT or serological test reactive	Positive	
		NAT reactive and serological test negative	Not confirmed positive	• Do not release donation for clinical use. • Inform donor and refer to relevant clinical care based on risk assessment. • Donor re-entry possible after eight weeks. • Initiate look-back procedures based on risk assessment.
		NAT negative and serological test reactive	Indeterminate	
		NAT negative and serological test reactive	Negative	• Do not release donation for clinical use. • Re-entry possible without a deferral period.

HIV: human immunodeficiency virus; NAT: nucleic acid testing; PrEP: pre-exposure prophylaxis; PEP: post-exposure prophylaxis; RNA: ribonucleic acid
[a] Approaches to confirm screening test results should rely on nationally established algorithms.

Tissues and non-reproductive cells – living and deceased donors

(For additional information, requirements and recommendations, please refer to 'Requirements and recommendations: Tissues and non-reproductive cells')

Testing requirements	Donor screening tests	Outcome of test results		
		Screening test results	Confirmatory test results[c]	Actions

All donors, at each donation[a]
• Assessment of recent risks of exposure to HIV is required.
• Donors should not be tested in the context of donor evaluation before a period of at least eight weeks since the last event with a risk of exposure to HIV except for:
  • Oral PrEP or PEP: at least 12 weeks since last event
  • Injectable PrEP: at least 24 months since last event
	Anti-HIV-1/2 + HIV-1 RNA NAT
	• A 95% LOD of 100 IU/mL or below should be used for the NAT detecting HIV-1[b].
		Both NAT and serological test reactive	Any	• Do not release donation for clinical use.
				• Inform the donor or the transplant coordination team.
				• Living donors: refer to relevant clinical care.
				• Initiate look-back procedures if relevant.

		Either NAT or serological test reactive	Positive	
		NAT reactive and serological test negative	Not confirmed positive	• Do not release donation for clinical use. • Inform the donor or the transplant coordination team based on risk assessment. • Living donors: refer to relevant clinical care based on risk assessment. • Initiate look-back procedures if relevant, based on risk assessment.
		NAT negative and serological test reactive	Indeterminate	
		NAT negative and serological test reactive	Negative	• Release donation for clinical use.

HIV: human immunodeficiency virus; IU: international unit; LOD: limit of detection; NAT: nucleic acid testing; PrEP: pre-exposure prophylaxis; PEP: post-exposure prophylaxis; RNA: ribonucleic acid

[a] Should be understood as close as possible to donation, and test results should be available before transplantation.

[b] A higher LOD can be considered if justified by a risk assessment considering the endemicity of the disease.

[c] Approaches to confirm screening test results should rely on nationally established algorithms.

Reproductive cells – third party donations

(For additional information and recommendations, please refer to 'Requirements and recommendations: Reproductive cells')

Testing requirements and recommendations	Donor screening tests	Outcome of test results		
		Screening test results	Confirmatory test results[c]	Actions

All donors, at each donation[a]
• Assessment of recent risks of exposure to HIV is required.
• Donors should not be tested in the context of donor evaluation before a period of at least eight weeks since the last event with a risk of exposure to HIV except for:
  • Oral PrEP or PEP: at least 12 weeks since last event
  • Injectable PrEP: at least 24 months since last event
	Anti-HIV-1/2 + HIV-1 RNA NAT
	• A 95% LOD of 100 IU/mL or below should be used for the NAT detecting HIV-1[b].
	• In case of donations quarantined for >180 days: only anti-HIV-1 and -2 serological test is required.
		Both NAT and serological test reactive	Any	• Do not release donation for clinical use.
				• Inform donor and refer to relevant clinical care.
				• Permanent deferral.
				• Initiate look-back procedures.

		Either NAT or serological test reactive	Positive	
		NAT reactive and serological test negative	Not confirmed positive	• Do not release donation for clinical use. • Inform donor and refer to relevant clinical care based on risk assessment. • Donor re-entry possible after eight weeks. • Initiate look-back procedures based on risk assessment.
		NAT negative and serological test reactive	Indeterminate	
		NAT negative and serological test reactive	Negative	• Do not release donation for clinical use. • Re-entry possible without a deferral period.

HIV: human immunodeficiency virus; IU: international unit; LOD: limit of detection; NAT: nucleic acid testing; PrEP: pre-exposure prophylaxis; PEP: post-exposure prophylaxis; RNA: ribonucleic acid

[a] For oocyte donation, the donation could be considered as the starting date of stimulation, and the testing can hence be performed at the time of stimulation. When using fresh sperms, the testing of the donor should be performed as close as possible to donation, ideally, the day before collection. In the case of serial donations, testing of the donor should be performed at the initial donation and prior to the release of a donation, at least 16 days after the last donation.

[b] A higher LOD can be considered if justified by a risk assessment considering the endemicity of the disease. [c]Approaches to confirm screening test results should rely on nationally established algorithms.

Reproductive tissues and cells – within partner use

(For additional information and recommendations, please refer to 'Requirements and recommendations: Reproductive cells')

Testing requirements and recommendations	Screening tests	Outcome of test results		
		Screening test results	Confirmatory test results	Actions
All partners • Less than three months before collection. • Maximum of 24 months between tests.	Antigen-antibody combination tests for HIV-1/2	Serological test reactive	Positive or indeterminate	• Procedures should be implemented to prevent the risk of infection to the partner and to their offspring. • Refer to ESHRE guidelines on medically assisted reproduction in patients with a viral infection/disease [2].

ESHRE: European Society of Human Reproduction and Embryology; HIV: human immunodeficiency virus.

Introduction

These guidelines support adherence to the European Union (EU) Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application, henceforth referred to as the Regulation [1]. They aim to prevent communicable disease transmission from donors through SoHO in the European Union and European Economic Area (EU/EEA). Following these guidelines should be considered as a means to demonstrate compliance with the standards laid down in the Regulation to ensure a high level of quality and safety. For more information on the legal context, see the Legal background in the Annex.

In this document, SoHO are divided into three categories:

- Blood and blood components (e.g. whole blood, red blood cells, platelets, platelet-rich plasma, and plasma not intended for industrial manufacturing).
- Tissues obtained from deceased or living donors and non-reproductive cells (e.g. corneas, cardiovascular tissues, bones, tendons, skin, amniotic membrane, and hematopoietic progenitor cells), including reproductive tissues when used for allogeneic purposes.
- Reproductive cells (i.e. sperms and oocytes) and tissues, including embryos and reproductive tissues when used for autologous purposes.

These SoHO are used in medical procedures and treatments such as blood transfusions, transplantation therapy or medically assisted reproduction (MAR). They play a pivotal role in enhancing the quality of life and even saving the lives of patients suffering from severe medical conditions or injuries. Despite the life-saving potential of SoHO, the transmission of pathogens through SoHO could lead to infections in recipients and offspring from MAR, compromising their health and potentially leading to severe complications or even death. Ensuring that these substances are safe and free from avoidable risks, including the transmission of infectious agents, is paramount to protect the health and wellbeing of patients who receive them.

Objectives and scope

These evidence-based guidelines provide technical requirements and recommendations for evaluating SoHO donors, focusing on the risk of transmitting HIV to recipients and the offspring from MAR. These guidelines provide the minimum SoHO safety requirements to meet the standards in the Regulation. Countries may, however, apply more stringent measures.

These guidelines aim to provide:

- Requirements and recommendations on laboratory testing methods for screening donors for HIV.
- Requirements and recommendations on testing strategies for HIV.
- Recommendations on events to consider in donor assessment that may lead to laboratory testing limitations.

The content of these guidelines covers SoHO for allogeneic use (meaning the human application of SoHO collected from a person other than the SoHO recipient), as described in the Regulation.

The SoHO Regulation does not apply to solid organs; therefore, organs are outside the scope of these guidelines. Faecal microbiota and breast milk are not included in this iteration of the guidelines. SoHO for autologous use (meaning the human application of SoHO collected from a person to the same person) except for reproductive tissues for autologous use, SoHO for industrial manufacturing, such as plasma for fractionation, pre-analytical considerations, laboratory quality requirements, storage and detailed tests and algorithms for confirmatory testing, are also out of the scope of this iteration of the guidelines.

The current guidelines will be adapted at a later stage to cover the prevention of HIV transmission from donors through SoHO intended for industrial manufacturing, such as plasma for fractionation. The risk of HIV transmission through faecal microbiota and breast milk will be addressed separately. The plans for these adaptations will be published on the ECDC website[ii].

[ii] https://www.ecdc.europa.eu/en/infectious-disease-topics/related-public-health-topics/substances-human-origin/technical-guidelines

Protection of SoHO recipients and the offspring from MAR other than from transmission of communicable diseases through the application of SoHO, quality requirements for the preparation, use and quality control of blood components, tissues, and cells are not covered in these guidelines. Instead, the European Directorate for the Quality of Medicine and Healthcare (EDQM) Guide to the preparation, use and quality assurance of blood components [3] and Guide to the quality and safety of tissues and cells for human application [4] should be followed.

Target audience

The target audience for the guidelines are professionals in the EU/EEA working in SoHO entities, as well as other professionals involved in the selection of blood, tissues, and cells donors. These guidelines may also serve as a reference for National Competent Authorities (NCA) for blood, tissues and cells, and MAR.

Structure of the document

These guidelines are structured into three main sections for the following types of SoHO:

- Blood and blood components;
- Tissues and non-reproductive cells (living and deceased donors);
- Reproductive cells and embryos, and reproductive tissues for autologous use.

Preceding the SoHO-specific sections, the guidelines outline general requirements and recommendations that apply to all SoHO, which provides a common framework for the subsequent sections. Each SoHO-specific section is subdivided into subsections, addressing requirements and recommendations concerning testing of donors, consequences of test results, risk of exposure to HIV, and other aspects to consider for the described SoHO type. Each set of requirements and recommendations is accompanied by evidence, including expert opinion and justification to support the statements provided. Some of the statements are repeated in the 'Evidence and justification' sections but are included for clarity and are consistent with the list of statements in the 'Requirements and recommendations' sections.

Prior to the general and SoHO specific requirements and recommendations, the guidelines offer an overview of considerations for HIV which is relevant to SoHO safety, as well as a summary of the guideline development process applicable to all SoHO within these guidelines. A summary table outlining key requirements and recommendations is included in the 'Executive summary'.

Detailed information on the guidelines development process, including methods for evidence collection and synthesis, as well as details on the ad hoc scientific expert panel, can be found at the end of this document in the Annex.

The statements in these guidelines are supported by evidence compiled in a pathogen data sheet for HIV (Pathogen data sheet, Annex). Additional details and references are available in the corresponding sections of the pathogen data sheet, as indicated in the guidelines.

In this document, requirements including the term 'should' describe technical requirements to meet the standards set out in the SoHO regulation. Recommendations and practical considerations including the terms 'advised' or 'is advised' or 'considered' are used to describe additional recommendations or suggestions to consider, but that are not required to meet these standards.

Guidelines development

Overall guidelines development

The development of the technical guidelines on the prevention of HIV transmission from donors through SoHO was coordinated by ECDC with the support of an expert panel convened for this activity. The panel included experts in infectious diseases, donor selection, and donor testing for blood, tissues and reproductive and non-reproductive cells from different EU/EEA countries.

Three expert panel meetings were hosted virtually between September 2023 and February 2024, addressing the topics covered by the present guidelines:

- Laboratory testing methods for screening of donors;
- Testing strategies for screening of donors;
- Events to consider in donor assessment that may lead to laboratory testing limitations.

Discussions with the expert panel were supported by a pathogen data sheet for HIV developed by ECDC. This document served as an evidence base for the expert panel and was intended to support statements agreed upon with the expert panel.

Conclusions from the expert panel meetings, including discussions on the provided evidence and agreements reached during the meetings, were used to draft these guidelines. The guideline text clarifies when statements rely on the expert opinion expressed during the meetings rather than on the evidence synthesised in the pathogen data sheet. For additional information on the guideline development and the ad hoc expert panel work procedures, see the Annex.

Evidence synthesis

Evidence synthesis supporting the expert panel discussions was provided in the pathogen data sheet for HIV (Pathogen data sheet), containing information on the following topics:

- Description of the virus;
- Description of the disease;
- Epidemiology in the EU/EEA, including risk factors for HIV infection;
- Laboratory testing approaches;
- Current testing requirements in EU/EEA countries;
- Recommendations from other organisations;
- Evidence of transmission through SoHO;
- Pathogen reduction/inactivation methods.

The evidence for all sections relied on structured but non-systematic literature searches. Quantitative descriptive analysis (range and median values) was performed for laboratory testing approaches and pathogen reduction/inactivation methods; qualitative synthesis was used for all other sections. No assessments for risk of bias were performed. This approach was considered acceptable for HIV as the risk for SoHO is well established, as are the measures to prevent transmission (testing and deferral strategies).

The expert panel had the opportunity to critically review the evidence provided before each meeting and request or offer additional evidence to support discussions and decision-making.

Expert meetings

Prior to each meeting, anonymous surveys were sent to the panel, and results were used as a basis to reach agreement during the meeting. The surveys covered the following topics:

- Which SoHO donors should be tested for HIV?
- When should SoHO donors be tested for HIV?
- Which laboratory screening tests should be used to test SoHO donors for HIV?
- What limit of detection (LOD) should be applied for nucleic acid tests (NAT) detecting HIV-1 ribonucleic acid (RNA)?
- What actions should be performed in case of reactive screening tests, including the deferral of donors?
- Which risks of exposure to HIV are considered relevant for SoHO safety and need to be considered in the SoHO donor assessment?
- What deferral period should be considered for donors with events with a risk of exposure to HIV to ensure reliable test results?

Where survey results indicated a general agreement on a question, ECDC proposed a corresponding statement to the expert panel for formal agreement. Formal agreement was defined as the absence of major disagreement by the participants. In addition to statements proposed by ECDC, agreements reached with the expert panel could rely on expert opinions expressed during the meeting. Summaries of discussions and agreements reached in meetings were detailed in meeting minutes and sent for review to the panel after each meeting. All discussions conducted with the panel were inclusive of all SoHO types considered within the scope of these guidelines. Panel members who could not participate in a specific meeting were encouraged to provide written input. If the panel deemed evidence insufficient to reach an agreement on a specific topic, the topic was reconsidered in the subsequent pre-survey and rediscussed in the following meeting, supported by additional evidence in the pathogen data sheet, if available. Approved agreements in the final meeting minutes were a reference for drafting the guidelines.

In cases of major disagreements that could not be resolved, the option to submit the subject to the ECDC SoHO network for consultation was available. Throughout the panel discussions on the development of the HIV technical guideline, there have been no major disagreements. For additional information on the guidelines development process and methods, see the Annex.

HIV and the considerations for SoHO safety

Description of HIV infection and disease

HIV is a single-stranded positive-sense enveloped RNA virus belonging to the family of retroviruses. Based on genetic characteristics and differences in viral antigens, it is subdivided into two major types: HIV type 1 (HIV-1) and HIV type 2 (HIV-2) [5,6].

HIV infection is typically classified into three distinct stages with progressive severity: acute HIV infection, chronic HIV infection, and acquired immunodeficiency syndrome (AIDS). Without treatment, HIV infection progresses through these stages, worsening over time. Untreated HIV infection is characterised by active viral replication, progressive immunodeficiency, and significant clinical consequences. The infection can manifest with a wide range of symptoms and lead to oral, cutaneous, renal, ocular, pulmonary, gastrointestinal, neurological, metabolic, endocrine, and cardiac diseases. Without appropriate treatment, AIDS is fatal [7,8].

In the initial stage of HIV-1 infection, the virus infects the immune cells and spreads rapidly through the lymphoid system, resulting in a rapid increase in plasma viremia. HIV RNA levels in the blood become detectable approximately six to ten days after infection, considering a LOD of 50 HIV-1 copies/mL. Viraemia levels increase exponentially, with an average doubling time of 20 hours, reaching peak viraemia levels of up to 10^7 HIV RNA copies/mL a few weeks later. At this point, the adaptive immune system responds, resulting in partial control of the virus and a set level of viraemia (known as the 'set point') is then established. When left untreated, viraemia levels remain high throughout the course of the disease [8,9].

HIV-2 mainly circulates in West Africa. Though epidemiological information is lacking, it is considered to represent less than 1% of all HIV infections in Europe. However, dual infection with HIV-1 can occur where both viruses circulate. HIV-2 infections present a longer asymptomatic stage and slower declines of CD4-positive T-cell counts compared to HIV-1 infections, though progression to AIDS and death will also occur in the majority of individuals affected by this subtype [10].

Antiretroviral therapy (ART) is available for patients with an HIV infection, significantly prolonging the median survival of treated patients with manageable side effects. All ARTs reduce the capacity of HIV to replicate. While therapy can reduce and even suppress blood viral load, the virus persists in tissue reservoirs in a quiescent state, necessitating lifelong treatment [8,11-13].

The primary mode of transmission for HIV is through contact with infected bodily fluids, particularly blood, semen, pre-seminal fluid, rectal secretions, cervicovaginal secretions, and breast milk, during unprotected sexual contact, sharing of contaminated needles or injection equipment, and mother-to-child transmission during pregnancy, childbirth, or breastfeeding. HIV can also be transmitted through transfusion of infectious blood or blood components and plasma-derived medicinal products, transplantation of different tissue types, as well as non-reproductive and reproductive cells, and human solid organ transplantations [7,8].

Antiretroviral drugs for pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for HIV have emerged as highly effective preventive measures when taken consistently and according to prescription. PEP entails the use of antiretroviral medications to prevent infection after potential exposure to HIV, such as unprotected sex, needle sharing, or occupational exposure [14]. PrEP involves the intake (either daily or on-demand) of antiretroviral medication by individuals who are HIV-negative but at high risk of contracting the virus [15]. Long-acting injectable PrEP regimens have been approved for use in the EU/EEA [16]. Another potential intervention for the prevention of HIV infection is anti-HIV vaccination. Clinical trials evaluating the efficacy of anti-HIV vaccines are ongoing or have been completed, with active sites in EU/EEA countries [17].

The risk of HIV infection through SoHO

Transmission of HIV through SoHO has previously been reported for blood and blood components, cells (except for oocytes), and tissues [18-22]. The 50% minimum infectious dose, defined as the dose that infects 50% of recipients, is low and estimated to be approximately 830 to 918 HIV-1 RNA copies [19,23]. Considering the low infectious dose and the viral dynamic progression of the infection, transmission of HIV can occur relatively early after exposure, as a viraemia level leading to a unit of blood containing the 50% infectious dose can be reached between 5 to 10 days after exposure.

As a likely result of effective donor screening processes in the EU/EEA, there has been no HIV transmission through SoHO reported in the period from 2017 to 2022 in the serious adverse reactions and events reports published by the European Commission [24,25]. Screening processes include a combination of thorough donor assessment, considering risks of recent exposure to HIV, and the use of sensitive laboratory testing methods. These laboratory testing methods encompass a range of serological assays detecting antibodies towards HIV-1 and HIV-2, or the HIV p24 antigen, as well as nucleic acid testing (NAT) for HIV-1 and/or HIV-2 RNA.

The window period, i.e. the minimal time from infection to a positive test result, varies depending on the test method, with highly sensitive NAT associated with the shortest window period. The time from infection to detection by available test methods for HIV-1 is described in Table 1.

Table 1. Time from infection to positive results by test methods in the HIV-1 acute stage

Test method	Target	Approximate time to positive result
Enzyme Immunoassays – 3rd generation (antibodies only)	IgM and IgG antibodies	20 days [26]
Enzyme Immunoassays – 4th generation	IgM and IgG antibody p24 antigen	15–16 days [26]
NAT [26-28]	HIV RNA	95% LOD 5 IU/mL: less than 5 days 95% LOD of 100 IU/mL: 6–10 days 95% LOD 875 IU/mL: 14 days

NAT: nucleic acid test. LOD: limit of detection. IU ≈ 0.5–0.6 copies [19,23].
Adapted from Sax [27].

A small fraction of individuals with an HIV infection, so-called elite controllers, maintain an undetectable viral load, typically below 50 HIV RNA copies/mL, while still testing positive for HIV antibodies [29]. Similarly, effectively treated HIV infection can lead to undetectable viral levels from three to 12 months after treatment initiation, depending on individual characteristics. While the 'Undetectable Equals Untransmittable' (U=U) paradigm has been accepted as an important public health message to prevent HIV infection through sexual contact [30], it should be noted that, considering the infectious dose for HIV, the amount of HIV virions potentially transferred through SoHO application, and the route of administration, this paradigm cannot be considered applicable to transmission through SoHO [31].

Although the number of reported HIV diagnoses in the EU/EEA has been declining in the last decade, trends of notification rates at the national level vary substantially between countries and range from 2.1 to 21.0 cases per 100 000 population in 2023 [32]. In EU/EEA countries, the proportion of people living with HIV who are diagnosed is estimated to be approximately 90% in 2023, with important variations across countries [33]. Compared to HIV-1, HIV-2 infections are less common, accounting for around 5% of all HIV infections and are thought to affect one to two million individuals worldwide, predominantly in West Africa [10]. Recent data on HIV-2 are lacking in most EU/EEA countries. Still, the number of individuals with HIV-2 is considered limited in most countries, comprising less than 1% of all HIV infections [34-38].

The overall prevalence of HIV and the varying proportion of people living with HIV that remain undiagnosed in EU/EEA countries warrant a strategic approach to prevent HIV transmission from donors via SoHO. The standards for the prevention of HIV transmission through SoHO in the EU/EEA were established in Directive 2002/98/EC for blood and blood components and Directive 2006/17/EC for tissues and cells [39-41]. Following the application of the SoHO regulation and the repeal of these directives, and considering the life-long consequences of an HIV infection, the severity of the disease, and its sustained incidence in EU/EEA countries, guidelines addressing the prevention of transmission of HIV through SoHO remain relevant for SoHO safety in the EU/EEA.

General requirements and recommendations applicable to all SoHO

These guidelines follow the definitions of SoHO donors described in the Regulation, referred to as 'donors' in these guidelines. For these guidelines, donors are defined as individuals presenting for donation, irrespective of whether that donation was successful or not.

Donations from donors who do not meet the requirements outlined in these guidelines may be considered for human application, subject to a positive risk-benefit assessment, which should be justified and traceable. Prior to application, specific informed consent should be obtained from the recipient or the recipient's legal representative when necessary. An appropriate follow-up procedure for the recipient should be considered, and adverse outcomes (e.g. transmission) of using such SoHO should be reported through a dedicated national system (e.g. haemovigilance and biovigilance systems) [3,42].

Testing should be performed on the type of specimen required in the manufacturer's instructions for use.

In these guidelines, the term 'screening test' refers to tests used for 'the detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration' in accordance with the classification of class D devices in the Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) [43]. The results from screening tests used to detect HIV in SoHO donors are considered to be reactive or negative. Serological screening tests are typically designed to have a low threshold for detecting possible cases, which carries a risk of false-reactive results. It is advised to retest initially reactive samples from serological tests in duplicate, using the same sample and the same assays to validate the result and minimise variability during testing. If the sample volume is too low for retesting in duplicate, another sample collected at the same time point as the reactive sample could be considered. If any of the repeat tests are reactive, the sample is considered repeatedly reactive. If both retests are negative, the sample is considered negative for the serological test. These guidelines assume that initially reactive serological screening tests are repeated in duplicates. Hence, the term 'reactive' when used in the context of serological tests can be understood as 'repeatedly reactive' results if these tests are repeated in duplicates. The retesting of samples in duplicates with the same assays only applies to serological tests. For NAT, a reactive result is defined as a reactive result at the individual sample level. This reactive result in an individual sample may be obtained either through the testing of samples individually, or through individual testing performed during resolution of a reactive pool. It is advised to establish algorithms at a national level to investigate and consistently resolve reactivity in the screening assay.

Testing of SoHO donors

Requirements and recommendations

Required:

- All tests should comply with class D devices in Regulation (EU) 2017/746 on in vitro diagnostic medical devices.
- All tests should be used according to the manufacturer's specifications and their defined intended purposes.
- Reactive screening test results should lead to further testing to confirm the screening test result. Confirmatory testing should be performed as soon as possible following reactive screening test results.
- The confirmatory testing should be performed by an authorised, licensed, or accredited laboratory according to national standards.
- Approaches to confirmation of screening test results should rely on nationally preestablished algorithms. These may differ according to the screening strategy in place.

Advice and practical consideration:

- Concordant reactive serology and NAT tests would very likely exclude false-reactive results and may be considered equivalent to positive confirmatory testing.
- In the case of a positive confirmatory test result, when possible, it is advised to obtain a further sample to reconfirm the test result and to confirm the identity of the donor.

Evidence and justification

Class D in vitro diagnostic medical devices cover general life-threatening conditions and, more specifically, transmissible agents in blood, blood components, cells and tissues intended to be transfused, transplanted or administered to the body [43]. Such transmissible agents may also present a high risk to the wider population.

It is essential to adhere to the manufacturer's specifications when using tests to ensure accuracy, reliability, regulatory compliance, safety, and reproducibility of results, and the use of tests should strictly comply with the conditions of use provided by manufacturers [43]. Deviating from these specifications may compromise the quality of testing and the validity of results and constitute misuse of the device.

In the case of reactive screening test(s), the test result should be confirmed to confirm the presence of markers of HIV infection in the donor. For these guidelines, the term 'reactive' is used for screening tests and 'positive' is used for confirmatory test results. Confirmation of the markers of HIV infection is essential to guide appropriate actions to ensure the safety of the SoHO supply as well as the donor's safety and appropriate referral to clinical care, and it should be performed by an authorised, licensed, or accredited laboratory according to national standards.

There are no approved tests to confirm a reactive NAT. However, additional tests (e.g. a different NAT assay) can be performed to verify a NAT that tested reactive in screening. For these tests, approaches to confirmation of screening test results should rely on nationally preestablished algorithms. For these guidelines, the term 'positive confirmatory test results' will include these additional test results verifying NAT reactivity. However, negative results from these additional tests cannot rule out an infection in the donor with a reactive NAT in screening. The initial reactive NAT may reflect a sample with a very low viral load that is not detected by an additional NAT, and serological tests may also yield negative results if seroconversion has not yet occurred (Pathogen data sheet, Section 2). In rare cases, initial NAT reactivity can be due to amplification anomalies or laboratory errors [44]; in these situations, a pre-established validation algorithm can confirm inaccurate NAT results, and the sample could be considered negative for NAT.

Considering the overall high performance of HIV screening tests and based on expert opinion, concordant reactive results from both HIV RNA NAT and anti-HIV tests on the same sample could be considered equivalent to a confirmed positive test result.

Based on good practice principles, in the case of a positive confirmatory test result, if possible, it is advised to call back the individual for a second sample and further confirmatory testing to reconfirm the test result and confirm the identity of the donor.

Requirements and recommendations: blood and blood components

Testing of blood donors for HIV

Requirements and recommendations

All blood and blood components

Testing requirements

Required:

- All donors, at each donation, should be tested for HIV.

Screening tests

Required:

- Donors should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2.

Advice and practical consideration:

- It is advised to base the LOD for HIV RNA NAT on a documented risk assessment, considering the estimated residual risk. An update of the risk assessment and the residual risk could be performed in case of significant changes to the epidemiology of the disease or a transmission event from donor to recipient.
- The use of NAT detecting both HIV-1 and HIV-2 RNA is advised.
- Antigen-antibody combination tests can be used instead of antibody-only tests.

Outcome of test results

Required:

- Donations from donors with a reactive serological test and/or NAT should not be released for clinical use.
- In case of a positive confirmatory test result, or where both the serological test and NAT are reactive in screening:
  - The donor should be notified and referred to relevant clinical care.
  - The donor should be deferred permanently.
  - Look-back procedures of previous, potentially infectious donations should be initiated.
- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result:
  - The decision to notify and refer the donor to clinical care should be based on the likelihood of an infection based on available information, including other available test results obtained during screening and confirmation procedures.
  - The decision to initiate look-back procedures of previous, potentially infectious donations should be based on a risk assessment considering available information, including other available test results obtained during screening and confirmation procedures.

Advise and practical consideration:

- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result, it is advised to call back the donor for an additional test on a follow-up sample.

Criteria for re-entry

Required:

- In the case of a negative confirmatory test result, and provided a negative NAT in screening, the donor can re-enter screening procedures without a deferral period.
- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result: the donor can re-enter donor screening procedures but should not re-enter before a minimum period of eight weeks from the last donor testing.

Look back procedure

Required:

- The extent of the look-back procedure should be based on a risk assessment to determine which previous donations are at risk of transmitting HIV.
  - A residual sample of the last donation that tested negative in screening should be retested using a highly sensitive NAT detecting HIV. Exemption from retesting previous donations can be considered if the previous donation was tested with a highly sensitive NAT and was negative.
  - If the last donation is positive in the retest, the retesting of archived samples of previous donations should be performed sequentially until a donation is negative. No further testing of prior archived samples is required if the previous sample is negative in the retest. Recipients who received a donation found positive in the retesting of archived samples should be tested for HIV infection.
  - In case of a sample with a positive confirmatory test result, and if no archived samples are available for look-back procedures, the institution that performed the transfusion should test the recipients of the previous potentially infectious donation. The results should be reported to the entity where the donation was performed.

Advice and practical consideration:

- A 95% LOD of 100 IU/mL or below could be considered for the retesting of the residual sample of the last donation.
- If archived samples test negative upon retesting, additional measures, such as testing recipients who received a potentially infectious donation, could be taken following a risk assessment considering other relevant information.

Evidence and justification

Testing requirements

Because of the documented severity of the disease and the significant consequences on the recipient in case of HIV transmission, the experts agreed that all donors should be tested at each donation to reduce the risk of transmission through SoHO (Pathogen data sheet, Section 2).

Screening tests

The safest way to detect an HIV infection is to test donors with a combination of NAT for HIV RNA and serological tests detecting antibodies against HIV. This is based on existing evidence and expert opinion, considering the performance of HIV screening tests and window periods. NAT provides high specificity, and when tests with high sensitivity (low LOD) are used, HIV RNA can be detected relatively early after infection, hence shortening the window period compared to serological tests (Pathogen data sheet, Section 4). There are risks of mutation in the HIV RNA, and if the mutation is in the target region, an HIV mutant may escape detection by NAT [45]. If the NAT assay targets two separate regions in the HIV genome, as specified for class D devices in the IVDR and its implementing acts [46,47], the risk of not detecting escape mutants is reduced [28].

In rare cases, individuals with an HIV infection may have a low viral load that is undetectable by NAT but where the infection is detectable by testing for HIV antibodies. Such cases would cover individuals effectively treated with ART who are well-controlled and have an undetectable viral load and may present for a donation, as well as the so-called elite controllers, individuals who naturally control viraemia below 50–75 HIV RNA copies/mL [29]. The use of serological tests detecting antibodies against HIV would allow for the identification of such individuals with an HIV infection.

As both HIV-1 and HIV-2 are present in EU/EEA countries (Pathogen data sheet, Section 3), based on evidence and expert opinion, donors should be tested for both HIV-1 and HIV-2. In EU/EEA countries, HIV-2 infections remain limited in most countries, with less than 1% of HIV-2 infections among all HIV infections, though this proportion may reach 3% in a few countries. According to the expert panel and available evidence, the requirement for NAT is mainly supported for HIV-1. Hence, the expert opinion is to require only NAT detecting HIV-1 RNA and serological tests detecting antibodies against HIV-1 and HIV-2. However, using a NAT detecting both HIV-1 and HIV-2 RNA is advised, and detection of both viruses is a specification for class D devices in the IVDR and its implementing acts [46,47].

It is estimated a NAT with a 95% LOD of 85-100 IU/mL, or 50 HIV-1 RNA copies/mL, considering 1.7-2.0 IU per HIV copy [19,23,48], would detect an infectious dose in 20 mL of plasma (considering an infectious dose of 1 000 HIV RNA copies). A 95% LOD of 100 IU/mL is estimated to correspond to a window period between six and ten days (Table 1). However, according to expert opinion, increasing sensitivity of NAT may come with an increase in healthcare resource use costs and limit the possibility of performing pooled donation testing. It should also be noted that HIV transmission through transfusion of blood and blood components is rare in the EU/EEA and has not been reported in the period 2017–2022 (Pathogen data sheet, Section 7), including in countries relying on less sensitive NAT, allowing for pooled donation testing. Donor selection through a donor health questionnaire assessing the risk of recent exposure to HIV is considered to significantly reduce the risk of donors presenting with a recent HIV infection associated with a low viral load and undetectable antibodies (Pathogen data sheet, Sections 3; expert opinion). Considering these elements and based on expert opinion, it is advised to base the 95% LOD for NAT on a risk assessment considering estimated residual risk. The risk assessment should be documented to ensure transparency in case of exchange of blood components to other regions or countries. An update of the risk assessment and the estimated residual risk could be performed in case of significant changes to the HIV epidemiology (as defined by the NCA) or in case of an HIV transmission event from donor to recipient.

There is no available evidence suggesting that using serological tests detecting both antigens and antibodies against HIV in combination with NAT reduces the risk of transmission of HIV compared to using tests only detecting antibodies in combination with a sensitive NAT if the NAT relies on two targets in the HIV genome. When NAT is used, antigen-antibody combination tests are as safe as antibody-only tests and antigen-antibody combination tests can be used instead of antibody-only tests.

Outcome of test results

Given the high performance of the HIV screening tests, reactive screening test results indicate a high likelihood that the donor has an HIV infection, with a high risk for HIV transmission to the recipient if the donation is used for transfusion (Pathogen data sheet, Section 4). While false-reactive results of serological screening tests are possible, the expert panel agreed that donations from donors with reactive serological tests should not be released for clinical use due to the severe impact of an HIV transmission on the recipient. Hence, based on evidence and expert opinion, the donation from a donor with reactive HIV screening tests should not be released for clinical use.

In the case of a positive confirmatory test result or in the case both the serological test and NAT are reactive in screening, as well as in other situations where an HIV infection cannot be ruled out and is considered likely considering other available information (including other test results), the donor should be informed and referred to relevant clinical care. Due to the risk of transmission of HIV through blood and blood components (Pathogen data sheet, Section 7), based on good practice and considering expert opinion, in case of a positive confirmatory test result or where both the serological test and NAT are reactive in screening in a repeat donor, look-back procedures to identify previous potentially infectious donations should be performed to identify and follow up on recipients who may be at risk of infection. In other cases where HIV infection cannot be definitively ruled out, such as when test results are inconclusive or indeterminate, the decision to initiate look-back procedures should be based on a risk assessment, considering other available information, including other test results.

The extent of the look-back procedure should be guided by a risk assessment considering other available test results and relevant information to identify which previous donations may pose a risk of transmitting HIV, and therefore which samples and recipients require testing. Although samples from previous donations were found negative in screening, it is possible the donation was made at a moment prior to seroconversion and with a viral load below the LOD defined for NAT in routine screening. Using a highly sensitive NAT for look-back procedures would support the identification of low viral loads and a 95% LOD of 100 IU/mL or below could be considered for the retesting of the residual sample of the previous donation. To ensure the safety of recipients, based on expert opinion, recipients who received a donation positive in retesting should be tested for HIV infection. Testing recipients who received a donation negative in retesting could also be considered following a risk assessment, and considering other relevant information, since the negative result could reflect a very low viral load. If no archived samples are available for testing in the context of look-back procedures, according to expert opinion, the recipient(s) of the previous potentially infectious donation should be tested for an HIV infection. As a single individual may donate several different SoHO, where it is possible, look-back procedures may also consider donations of other SoHO types.

Criteria for donor re-entry

Due to the risk of HIV transmission (Pathogen data sheet, Section 2), a donor with a positive confirmatory test result, or where both NAT and the serological screening tests are reactive or where an infection cannot be ruled out, taking into account all information available, should be permanently deferred.

A negative confirmatory test following a reactive serological test and a negative NAT in screening is very likely indicative of a false-reactive result for the serological test. Therefore, if the confirmatory test is negative, and provided the NAT is negative in screening, the donor is not considered to have an HIV infection, and the donor can be allowed to re-enter donor screening procedures without a deferral period.

It is advised to call back the donor for further testing on a follow-up sample, in case of discordant results between a reactive NAT in screening and the results of additional tests performed to confirm the initial NAT results. A higher viral titre may be detected in the follow up sample. This procedure is also advised in case of an indeterminate confirmatory test result, where only the serological test is reactive in screening. For these donors, there should be a minimum period of eight weeks from the last donor testing before re-entry to formally exclude potential seroconversion (Pathogen data sheet, Section 2) [49].

According to ECDC's opinion, HIV infection is highly likely in donors where both the serological test and NAT are reactive, regardless of the confirmatory test result. The concordance of the screening tests significantly reduces the likelihood of a false-reactive screening result. These donors should be deferred permanently and referred to relevant clinical care (i.e. treated as donors with positive confirmatory test results).

Limitations

The evidence is based on studies evaluating individual test performance and not the comparison of a combination of test methods. There are a limited number of studies on the window period and correlation with the standardised measures of the LOD for NAT. There are also a limited number of studies on the comparison of the accuracy of antibody-only tests with a combination of antigen-antibody tests for HIV when used in combination with NAT.

Risk of exposure to HIV and testing limitations in case of recent exposure to be considered for each donation

Requirements and recommendations

Donors should receive accurate and understandable information about HIV transmission and risk of exposure to HIV, as well as the risks to recipients posed by communicable disease transmission through transfusion, as detailed in the latest version of the EDQM guide to the preparation, use, and quality assurance of blood components [3]. Donors should be given the opportunity to self-defer.

These guidelines follow the definition of Estcourt et a. for 'a new partner', 'one-off partner and 'casual partners' [50]. Condom failure should be understood as any instance in which a condom breaks, leaks, or slips off during sexual activity.

Injection of non-prescription drugs refers to the use of any drug or other substance not prescribed by a registered healthcare professional and self-administered via injection. This includes both illicit drugs (e.g. heroin, methamphetamine) and performance enhancing drugs (e.g. testosterone) when injected and which can be associated with needle sharing.

The events listed below are provided to support entities in developing their donor eligibility assessment strategies but are not intended to be the exact questions asked, or physical examination performed, during the donor assessment.

All blood and blood components

Risk of exposure to HIV

Required:

- All donors, at each donation, should be assessed for recent risks of exposure to HIV when assessed for donor eligibility.

Advice and practical consideration:

The following events are considered risks of exposure to HIV. It is advised to consider the occurrence of these events in the past eight weeks (12 weeks for oral PrEP or PEP and 24 months for injectable PrEP use) when assessing donor eligibility:

- Condomless* anal sex with a new partner, one-off partner, or a casual partner;

- Condomless* anal sex with more than one partner;
- Sexually transmitted infection;
- Needle sharing and/or injection of non-prescription drugs;
- Use of injectable PrEP;
- Use of oral PrEP or PEP;
- Condomless* sex with a person living with HIV;
- Condomless* sex with a partner with sexually transmitted infection(s);
- Condomless* sex with a partner who injects non-prescription drugs;
- Condomless* sex with a partner using PrEP or PEP;
- Condomless* sex in exchange for money, drugs, or other payments.

** Condomless should be understood as a situation where no condom was used or situations where it was used incorrectly (e.g. condom failure).*

Testing limitations in case of recent risk of exposure to HIV

Required:

- Donors should not be tested in the context of donor evaluation before a period of at least eight weeks since the last event with a risk of exposure to HIV.
- Exceptions:
  - Oral PrEP or PEP use, for which a period of 12 weeks since the last event should be considered.
  - Injectable PrEP use, for which a period of 24 months since the last event should be considered.

Evidence and justification

Risk of exposure to HIV

Based on evidence and expert opinion, the above-described events include the major risks of exposure to HIV, relevant for SoHO safety, in EU/EEA countries (Pathogen data sheet, Section 3).

The use of HIV prophylaxis, PrEP or PEP, does not in itself pose a risk for HIV infection, but this preventive treatment is indicated for individuals who are at high risk of exposure to HIV (Pathogen data sheet, Section 3). Due to the risk of breakthrough infections (e.g. due to adherence issues [51]) and interference with laboratory test results (Pathogen data sheet, Section 3), the use of PrEP or PEP should be considered when assessing donor eligibility. Similarly, the risk for donors having condomless sex with individuals living with HIV with suboptimal adherence to ART should be considered, as breakthrough infections are rare but may occur (Pathogen data sheet, Section 3). People living with HIV and effectively treated with ART, with repeatedly undetectable viral loads, are shown not to transmit HIV through sexual contact [52,53]. In the specific circumstances of donors in a monogamous relationship with a person living with HIV, with optimal ART adherence and undetectable viral loads in consecutive evaluations, countries may choose to consider such donors eligible, as the risk of HIV transmission to the partner is considered negligible. While condom use reduces the risk of exposure to HIV (Pathogen data sheet, Section 3), condoms may be used incorrectly or may break, leak, or slip off during the sexual act [54,55].

Based on expert opinion, it is advised to consider all the above risk events when assessing donor eligibility, noting that these events can be challenging to identify through interviews, particularly in the context of risk events concerning a partner, as well as the correct usage of condoms, as condom failure is not always recognised [54].

Testing limitations in case of risk of exposure to HIV

Given the high performance of the HIV screening tests required in these guidelines, the risk for transmission through SoHO is related to potential donors who are newly infected with HIV tested during the window period (Pathogen data sheet, Section 2). To avoid window period transmissions from donors newly infected with HIV, donors with recent risk of exposure to HIV should not be tested in the context of donor evaluation until the test results are considered reliable. Based on expert opinion, applying a multiplication factor to the window period would ensure a safe period before testing to reduce the risk of a window period transmission.

A period of eight weeks after an event with a risk of exposure to HIV covers more than three times the maximum window period of a NAT, including when considering testing in pools. Eight weeks is also expected to fully cover the seroconversion period in individuals with an HIV infection [49,56].

Due to the risk of delayed seroconversion in PrEP or PEP users, a more extended period before testing should be considered for these individuals. A period of 12 weeks is expected to cover three times the worst-case assumptions

for delayed seroconversion following oral PrEP or PEP use (Pathogen data sheet, Section 3). For injectable PrEP, a period of 24 months from the last PrEP injection is based on FDA recommendations [57] in the absence of evidence on the impact of injectable PrEP on test reliability.

During donor assessment, the possibility of exposure to HIV-2 may be considered, either through sexual contact with a partner who is living with HIV-2 or in other events where a risk of exposure to HIV-2 could be envisaged, e.g. during travels to countries with increased HIV-2 circulation, mainly West African countries [10]. If a NAT detecting HIV-1 but not HIV-2 is used, it should be noted that the detection of an HIV-2 infection will rely solely on the serological tests detecting antibodies to HIV-2, which have a longer window period than NAT. A period of eight weeks is considered sufficient to observe seroconversion in individuals infected with HIV-1 or HIV-2.

Limitations

The events with increased risk of exposure to HIV are based on targeted literature searches and not on systematic literature reviews and may not be comprehensive. There are also limited and conflicting data available on the association between PrEP and PEP use and an increase in risk behaviours. The interval between potential exposure to HIV and testing to be considered to ensure reliability of the test results is based on an arbitrary multiplication factor of the window period; however, it is consistent with the deferral periods currently used in several EU/EEA countries, where no HIV transmissions have been reported in the 2017–2022 period (Pathogen data sheet, Section 7).

Donor eligibility is assessed for all pathogens at once, and the list of events in the current guidelines only covers HIV. The list of events with an increased risk of exposure to other pathogens will be completed by ECDC as new guidelines are published. Pending these updates, the EDQM guides can be used as a resource for additional events to consider in the assessment of donor eligibility [3].

Affected individuals and other situations to consider

Requirements and recommendations

All blood and blood components

Required:

- Individuals with a prior diagnosis of HIV or using ART should be deferred permanently.
- Individuals with prior participation in an HIV vaccine trial or who received an HIV vaccine should be deferred permanently.

Evidence and justification

HIV treatment is not curative, and it is not known if treated individuals may transmit the infection through SoHO. The 'undetectable equals untransmittable' (U=U) paradigm cannot be applied to SoHO donors, and an infectious viral load in 20 mL of plasma (considering an infectious dose of 500 virions) would be below the threshold of 200 HIV RNA copies/mL used to define well-controlled individuals in the U=U paradigm [30]. In addition, in treated individuals, there is a risk of viraemia due to recent adherence issues or resistance (Pathogen data sheet, Section 2). Based on evidence and expert opinion, considering the severity and long-term consequences of the disease, the route of transmission, and the low infectious dose of HIV, all individuals with a prior diagnosis of HIV or antiretroviral use for HIV should be deferred permanently to reduce the risk of transmission.

HIV vaccination is expected to lead to inconsistencies in test interpretation (Pathogen data sheet, Section 3) and trials preferentially recruit participants who are at a high risk of HIV infection. Based on this, individuals who have participated in an HIV vaccine trial or received an HIV vaccine should be deferred permanently.

Limitations

The effectiveness of anti-HIV vaccination is currently unknown, and the eligibility of vaccinated individuals may be reconsidered when further evidence is available.

Requirements and recommendations: tissues and non-reproductive cells

Testing of tissues and non-reproductive cells donors for HIV

Reproductive tissues used for allogeneic purposes should be considered as tissues.

In the context of the evaluation of deceased children, the birth mother should be understood as the person who carried and gave birth to the child. The person breastfeeding the child should be understood as the person who feeds the child with their own breast milk, either directly or by milk expression.

Donations should be understood as distinct procurement or collection events. Multiple units of SoHO collected at a single time point are considered a single donation for the purpose of these guidelines.

For these guidelines, 'at donation' should be understood as close as possible to donation, and test results should be available before transplantation and the conditioning regimen of hematopoietic progenitor cells recipients. The timing of sampling should be in accordance with the latest EDQM guidelines for tissues and cells [42].

The potential impact of haemodilution and haemolysis on screening test results should be considered, according to the recommendations of the EDQM guidelines for tissues and cells [42].

Requirements and recommendations

Living donors

Testing requirements

Required:

- All donors, at each donation, should be tested for HIV.

Screening tests

Required:

- Donors should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2. A 95% LOD of 100 IU/mL or below should be used for the NAT detecting HIV-1 RNA.
- A higher LOD can be considered if justified by a documented risk assessment, considering the endemicity of the disease. An update of the risk assessment should be performed in case of significant changes to the epidemiology of the disease or a transmission event from donor to recipient.

Advice and practical considerations:

- The use of NAT detecting both HIV-1 and HIV-2 RNA is advised.
- Antigen-antibody combination tests can be used instead of antibody-only tests.

Outcome of test results

Required:

- Donations from donors with a reactive NAT, or with a reactive serological screening test in the absence of a negative confirmatory test result, should not be released for clinical use.
- In the case of a negative confirmatory test result and provided a negative NAT in screening, the donation can be released for clinical use.
- In case of a positive confirmatory test result, or where both the serological test and NAT are reactive in screening:
  - The donor should be notified and referred to relevant clinical care.
  - The donor should be deferred permanently.
  - A risk assessment should be performed to determine if any previous donations are at risk of transmitting HIV for repeat donations and if look-back procedures should be initiated.

- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result:
  - The decision to notify and refer the donor to clinical care should be based on the likelihood of an infection based on available information, including other available test results obtained during screening and confirmation procedures.
  - A risk assessment should be performed to determine if any previous donations are at risk of transmitting HIV and if look-back procedures should be initiated.

Advice and practical considerations:

- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test, it is advised to call back the donor for an additional test on a follow-up sample.

Criteria for further donations

Required:

- In the case where only the NAT is reactive in screening and is not confirmed positive in testing, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test, donor screening procedures for future donation(s), if relevant, should not be considered before a period of at least eight weeks from the last donor testing.

Deceased donors

Testing requirements

Required:

- All donors, at donation, should be tested for HIV.

Screening tests

Required:

- Donors should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2. The NAT detecting HIV-1 RNA should have a LOD of 100 IU/mL. If the sample needs to be diluted prior to testing, and the threshold of 100 IU/mL cannot be achieved, the dilution factor should be documented.
- A higher LOD can be considered if justified by a documented risk assessment considering the endemicity of the disease. An update of the risk assessment should be performed in case of significant changes to the epidemiology of the disease or a transmission event from donor to recipient.

Advice and practical considerations:

- The use of NAT detecting both HIV-1 and HIV-2 RNA is advised.
- Antigen-antibody combination tests can be used instead of antibody-only tests.

Outcome of test results

Required:

- Donations from donors with a reactive NAT, or with a reactive serological test in the absence of a negative confirmatory test result, should not be released for clinical use.
- In the case of a negative confirmatory test result and provided a negative NAT in screening, the donation can be released for clinical use.
- In case of a reactive NAT, or a reactive serological test in the absence of negative confirmatory test results, the transplant coordination team(s) should be informed. A risk assessment should be performed based on available information, including other available test results to determine if other or previous donations are at risk of transmitting HIV and if look-back procedures should be initiated. Recipients who received potentially infectious donations should be tested for HIV. As a single individual may donate several different SoHO, where it is possible, look-back procedures may also consider donations of other SoHO types.

Deceased donors: specific requirements -neonates and young children

Children 18 months of age or less

Testing requirements and recommendations

Required:

- The birth mother and the person who has breastfed the child in the past six months (if applicable) should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2.
- If it is not possible to test the mother or the person breastfeeding, but an HIV infection can be ruled out through other means in the birth mother or in the person who has breastfed the child in the past six months (if applicable), the child can be tested with a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2 from three months of age, in place of the birth mother or the person who has breastfed the child in the past six months (if applicable).

Advice and practical considerations:

- The use of a NAT detecting both HIV-1 and HIV-2 RNA is advised.

Outcome of test results

- Donations from children should not be released for clinical use if either the child, the birth mother, or the person who has breastfed the child in the past six months has reactive NAT, a reactive serological test in the absence of a negative confirmatory test result, or a known HIV infection.
- In the case of a negative confirmatory test result, and provided a negative NAT in screening, the donation can be released for clinical use.

Children older than 18 months of age who have been breastfed in the past six months

Testing requirements and recommendations

Required:

- The person who has breastfed the child in the past six months should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2.
- The child should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2.
- If it is not possible to test the person breastfeeding in the past six months, but an HIV infection can be ruled out through other means, the child alone can be tested.

Advice and practical considerations:

- The use of NAT detecting both HIV-1 and HIV-2 RNA is advised.

Outcome of test results

Required:

- Donations from children who have been breastfed in the past six months by a person with reactive NAT, a reactive serological test in the absence of a negative confirmatory test result or a known HIV infection, or donations from breastfed children with a reactive NAT or a reactive serological test in the absence of a negative confirmatory test, should not be released for clinical use.
- In the case of a negative confirmatory test result and provided a negative NAT in screening for the child and the person breastfeeding the child (if applicable), the donation can be released for clinical use.

Evidence and justification

Testing requirements

All tissue donors and donors of non-reproductive cells

Because of the documented severity of the disease and the significant consequences on the recipient in case of HIV transmission, the experts agreed that all tissue donors and donors of non-reproductive cells should be tested at each donation to reduce the risk of transmission through SoHO (Pathogen data sheet, Section 2).

Screening tests

All tissue donors and donors of non-reproductive cells

Based on existing evidence and expert opinion, considering the performance of HIV screening tests and window periods, the safest way to detect an HIV infection is to test donors with a combination of NAT for HIV RNA and serological tests detecting antibodies for HIV. NAT provides high specificity, and when tests with high sensitivity (low LOD) are used, HIV RNA can be detected relatively early after infection, hence shortening the window period compared to serological tests (Pathogen data sheet, Section 4). There are risks of mutation in the HIV RNA, and if the mutation is in the target region, an HIV mutant may escape detection by NAT [45]. If the NAT assay targets two separate regions in the HIV genome, as specified for class D devices in the IVDR and its implementing acts [46,47], the risk of not detecting escape mutants is reduced [28]

In rare cases, individuals with an HIV infection may have a low viral load that is undetectable by NAT but where the infection is detectable by testing for HIV antibodies. Such cases would cover individuals effectively treated with ART who are well controlled and have an undetectable viral load, and who may present for donation [58], as well as the so-called elite controllers, individuals who naturally control viraemia below 50–75 HIV RNA copies/mL [29]. The use of serological tests detecting antibodies against HIV would allow for the identification of such individuals with an HIV infection.

As both HIV-1 and HIV-2 are present in EU/EEA countries (Pathogen data sheet, Section 3), based on evidence and expert opinion, donors should be tested for both HIV-1 and HIV-2. In EU/EEA countries, HIV-2 infections remain limited in most countries, with less than 1% of HIV-2 infections among all HIV infections, though this proportion may reach 3% in a few countries. According to the expert panel and available evidence, the requirement for NAT is mainly supported for HIV-1. Hence, the expert opinion is to require only NAT detecting HIV-1 RNA and serological tests detecting antibodies against HIV-1 and HIV-2. However, using NAT detecting both HIV-1 and HIV-2 RNA is advised, and detection of both viruses is a specification for class D devices in the IVDR and its implementing acts [46,47].

Tissues and cells may be transferred across countries depending on clinical need, increasing the importance of harmonised safety requirements in the EU/EEA. In addition, the assessment of recent risks of exposure to HIV in deceased donors, and for some living donors, may be limited, increasing the risk associated with the window period. The window period of NAT can be reduced by increasing sensitivity (lowering the LOD). It is estimated a NAT with a 95% LOD of 85-100 IU/mL 95% LOD, or 50 HIV-1 RNA copies/mL considering 1.7-2.0 IU per HIV copy [18,22,47], would detect an infectious dose in 20 mL of plasma (considering an infectious dose of 1000 HIV RNA copies). A 95% LOD of 100 IU/mL is estimated to correspond to a window period between six and ten days (Table 1).

Based on these elements and according to expert opinion, a 95% LOD of 100 IU/mL or lower should be used for tissue donors and non-reproductive cell donors. However, according to expert opinion, increasing sensitivity may increase healthcare resource use costs, which may not be justified in settings where the epidemiology of the disease would be associated with a very low residual risk. It should also be noted that HIV transmission through transplantation of tissues and cells is rare in the EU/EEA and has not been reported between 2017–2022 (Pathogen data sheet, Section 7). Additionally, the selection of living donors through thorough donor assessment relying on a health questionnaire assessing the risk of recent exposure to HIV can significantly reduce the risk of donors presenting with a recent HIV infection associated with a low viral load and undetectable antibodies (Pathogen data sheet, Sections 3; expert opinion).

Considering these elements, and based on expert opinion, a higher LOD can be considered if justified by a risk assessment that follows national recommendations, if available, considering the endemicity of the disease. The risk assessment should be documented to ensure transparency in case of exchange of tissues or cells to other regions or countries. An update of the risk assessment should be performed in case of significant changes to the HIV epidemiology (as defined by the NCA) or in case of an HIV transmission event from donor to recipient.

Due to the presence of inhibitory substances in post-mortem samples following death by circulatory criteria, some NAT may require a dilution of the sample to ensure valid test results [59,60]. As a result, the required 95% LOD may not be achievable in the diluted sample. In these situations, the dilution factor should be documented to facilitate the interpretation of the results.

There is no available evidence suggesting that using serological tests detecting both antigens and antibodies against HIV in combination with NAT reduces the risk of transmission of HIV compared to using tests only detecting antibodies in combination with a sensitive NAT if the NAT relies on two targets in the HIV genome. When NAT is used, antigen-antibody combination tests are as safe as antibody-only tests and antigen-antibody combination tests can be used instead of antibody-only tests.

Specific requirements for deceased donors: neonates and young children

HIV can be vertically transmitted to a child from women with low viral load and on antiretroviral therapy, irrespective of mode of delivery [2,61]. To exclude vertical HIV transmission in children below 18 months of age, the birth mother should be tested for HIV in the same way as living donors. Similarly, the individual who breastfed the child with their own milk, either directly or by expressed milk, should also be tested for HIV to rule out transmission through this route.

Serological antibody testing alone is not recommended for children below 18 months of age due to potential interference from maternal antibodies [62,63]. Although virologic testing performance increases rapidly after two weeks of age [62-65], reaching 100% sensitivity and specificity by three months of age [65], the current evidence considers that a single time-point NAT is not sufficient for conclusively excluding HIV infection in children under 18 months of age with known or suspected exposure to HIV [63,66]. Virological tests (NAT detecting HIV RNA or DNA, reverse transcribed from HIV RNA) can be used in children above three months of age to assess the presence of HIV [65]. Testing for antibodies to HIV-1 and HIV-2 is usually not recommended in children below 18 months of age since children may not mount an immune response that results in sufficient antibodies for detection by serological tests [62,63]. However, these serological tests could be used in addition to virological tests to identify passive transfer of antibodies from the mother or the person breastfeeding and eventually rule out vertical transmission if testing the mother or the person breastfeeding is not possible. Hence, if it is not possible to test the mother or the person breastfeeding, but an HIV infection can be ruled out through other means in the birth mother or in the person who has breastfed the child in the past six months (if applicable) the child can be tested with a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2 from three months of age, in place of the birth mother or the person who has breastfed the child in the past six months (if applicable). As the evidence on the accuracy of NAT to screen for HIV in young children has mainly been established after three months of age, if it is not possible to test the birth mother and the person breastfeeding (if applicable), children aged below three months of age should not be screened for HIV, and donation from these children should not be considered.

By the age of 18 months, the child has usually cleared maternal antibodies and can initiate an independent immune response and be tested as other deceased donors with NAT and antibody tests, provided they have not been breastfed by a person with HIV in the past six months. At this age, an HIV antibody test will almost always be negative in a child without an infection from their mother due to sero-reversion and loss of maternal antibodies. However, in children born from mothers with an HIV infection, fourth-generation serological tests may still give a false-positive results by detecting maternal antibodies against HIV instead of the child's until up to two years of age, with negative results on third generation serological assays. Fourth-generation assays (antigen-antibody combination tests) are highly sensitive, capturing lower levels of maternal antibodies for longer periods than third-generation assays (antibody only tests) [67,68]. In these children, the fourth-generation tests are not recommended before 24 months of age because of the risk of false positive test results.

For children who are breastfed by a person with an HIV infection, the algorithm for excluding an HIV infection is not as well defined and requires a certain duration from the cessation of breastfeeding, including for older children [69,70]. As a negative test result in the child may not formally exclude an HIV infection, both the mother and the child should be tested in the context of donor evaluation if less than six months after cessation of breastfeeding. If it is not possible to test the person breastfeeding in the past six months, but an HIV infection can be ruled out through other means, e.g. with recent negative HIV test, performed for other reasons than the donor screening, the child alone can be tested with a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2.

If the milk has been procured from a milk bank with a donor selection procedure for the prevention of HIV transmission, the child, aged 18 months or older, can be tested following the general recommendations for deceased donors.

Outcome of test results

All tissue donors and donors of non-reproductive cells

Given the high performance of the HIV screening tests, reactive screening test results indicate a high likelihood that the donor has an HIV infection, with a high risk for HIV transmission to the recipient if the donation is used. (Pathogen data sheet, Section 4). Hence, based on evidence and expert opinion, the donation from a donor with reactive HIV screening tests should not be released for clinical use.

Due to the nature of screening tests and based on expert opinion, if false-reactive serological screening results are ruled out with confirmatory testing, donations with negative confirmatory test results, provided a negative NAT in screening, can be released for clinical use [71].

Living donors

In the case of a positive confirmatory test result, or in the case of an indeterminate confirmatory test result and where an HIV infection is considered likely, taking into account other available information, including other test results, the donor should be informed through any means available and referred to relevant clinical care.

Due to the risk of transmission of HIV through tissues and cells (Pathogen data sheet, Section 7), based on good practice and considering expert opinion, in case of a positive confirmatory test result, or where both the serological test and NAT are reactive in screening, look-back procedures to identify previous potentially infectious donations should be performed to identify and follow up on recipients who may be at risk of infection. In other cases where HIV infection cannot be definitively ruled out, such as when test results are inconclusive or indeterminate, the decision to initiate look-back procedures, in the case of previous donations, should be based on a risk assessment, considering other available information, including other test results. To ensure the safety of recipients, based on expert opinion, recipients who received a potentially infectious donation should be tested for HIV infection. As a single individual may donate several different SoHO, where it is possible, look-back procedures may also consider other donations of other SoHO types.

Based on evidence and expert opinion, due to the risk of HIV transmission (Pathogen data sheet, Section 2), a donor with a positive confirmatory test result, or where both the serological test and NAT are reactive in screening, or where an infection cannot be ruled out, taking into account all information available, should be permanently deferred.

It is advised to call back the living donor for further testing on a follow-up sample, in case of discordant results between a reactive NAT in screening and the results of additional test(s) performed to confirm the initial NAT result. A higher viral titre may be detected in the follow up sample. This procedure is also advised in case of indeterminate confirmatory test results, where only the serological test is reactive in screening. There should be a minimum period of eight weeks from the last donor testing before these donors should be considered for donor screening for future donations, to exclude potential seroconversion transmission (Pathogen data sheet, Section 2) [49,56].

According to ECDC's opinion, HIV infection is highly likely in donors where both the serological test and NAT are reactive, regardless of the confirmatory test result. The concordance of the screening tests significantly reduces the likelihood of a false-reactive screening result. These donors should be deferred permanently and referred to relevant clinical care (i.e., treated as donors with positive test results).

Deceased donors

Based on good practice and expert opinion, in the case of a reactive NAT, or a reactive serological test in the absence of a negative confirmatory test result, the transplant coordination team(s) should be notified to inform all entities which received SoHO of the donor. Due to the risk of transmission of HIV through tissues and cells (Pathogen data sheet, Section 7), based on good practice and considering expert opinion, in case of a reactive NAT or a reactive serological test in the absence of negative confirmatory test in a multi-tissues and organs donor a risk assessment should be performed, including other available test results to determine if there are other potentially infectious donations and if look-back procedures should be initiated. Recipients who may be at risk of infection should be identified and tested for HIV. As a single individual may donate several different SoHO, where it is possible, look-back procedures may also consider donations of other SoHO types.

Specific requirements for deceased donors: neonates and young children

Due to the risk of HIV vertical transmission and lack of reliable testing strategies for children less than 18 months of age [62,63], a donation from a child less than 18 months of age and where an HIV infection cannot be ruled out, or in case of reactive NAT, or a reactive serological test in the absence of a negative confirmatory test result in the birth mother or the child, should not be released for clinical use. Similarly, a donation from a child less than 18 months of age who has been breastfed in the past six months and where an HIV infection cannot be ruled out, or in the case of reactive NAT, or in the case of a reactive serological test in the absence of a negative confirmatory test result, in the person breastfeeding [69,70] or the child, should not be released for clinical use.

Breastfeeding with an HIV infection is not recommended in Europe because transmission of HIV is still possible, even if the person breastfeeding is on ART and has a low viral load [2,61]. Because of the risk of transmission, if the HIV infection cannot be excluded in the person who breastfed the child below 18 months of age in the past six months, the child should not be accepted as a donor, and the donation should not be released for clinical use. If the birth mother and the person who breastfed the child (if applicable) are negative in screening or in the case of negative confirmatory test results, and provided a negative NAT in screening, and no other exposure to HIV is suspected, the donation can be released for clinical use without additional testing of the child. Alternatively, if the child has been tested from three months of age, with negative confirmatory test result, and provided a negative NAT in screening and if an HIV infection in the birth mother and the person who breastfed the child can be ruled out by other means, e.g. by other recent test results, the donation can be released for clinical use.

For the same reason, donations from children older than 18 months of age who have been breastfed in the past six months by a person with a suspected or known HIV infection should not be released for clinical use, due to the lack of reliable testing strategies to exclude an HIV infection in these children [69,70].

A child of 18 months of age or older who has not been breastfed, or if the person who has breastfed is HIV negative, should be tested and assessed for HIV similar to other deceased donors.

Limitations

The evidence is based on studies evaluating individual test performance and not comparing a combination of test methods. There are a limited number of studies on the window period and correlation with the standardised measures of the LOD for NAT. There are also a limited number of studies on the accuracy of antibody-only tests compared with a combination of antigen-antibody tests for HIV when used in combination with NAT.

Risk of exposure to HIV and testing limitations in case of recent exposure to be considered for each donation

Requirements and recommendations

These guidelines follow the definition of Estcourt et al. for 'a new partner', 'one-off partner', and 'casual partners' [50]. Condom failure should be understood as any instance in which a condom breaks, leaks, or slips off during sexual activity.

Injection of non-prescription drugs refers to the use of any drug or other substance not prescribed by a registered healthcare professional and self-administered via injection. This includes both illicit drugs (e.g. heroin, methamphetamine) and performance enhancing drugs (e.g. testosterone) when injected and which can be associated with needle sharing.

The events listed below are provided to support entities in developing their donor eligibility assessment strategies but are not intended to be the exact questions asked, or physical examination performed, during the donor assessment.

All tissue donors and donors of non-reproductive cells

Risk of exposure to HIV

Required:

- All donors, at each donation, should be assessed for recent risks of exposure to HIV when considered for donor eligibility.

Advice and practical consideration:

The following events are considered risks of exposure to HIV. It is advised to consider the occurrence of these events in the past eight weeks (12 weeks for oral PrEP and PEP and 24 months for injectable PrEP use) when assessing donor eligibility:

- Condomless* anal sex with a new partner, one-off partner, or a casual partner;
- Condomless* anal sex with more than one partner;
- Sexually transmitted infection;
- Needle sharing and/or injection of non-prescription drugs
- Use of injectable PrEP;
- Use of oral PrEP or PEP;

- Condomless* sex with a person living with HIV;
- Condomless* sex with a partner with sexually transmitted infection(s);
- Condomless* sex with a partner who injects non-prescription drugs;
- Condomless* sex with a partner using PrEP or PEP;
- Condomless* sex in exchange for money, drugs, or other payments.

** Condomless should be understood as a situation where no condom was used or situations where it was used incorrectly (e.g., condom failure).*

Testing limitations in case of recent risk of exposure to HIV

Required:

- Donors should not be tested in the context of donor evaluation before a period of at least eight weeks since the last event with a risk of exposure to HIV.
- Exceptions:
  - Oral PrEP or PEP use, for which a period of 12 weeks since the last event should be considered.
  - Injectable PrEP use, for which a period of 24 months since the last event should be considered.

Evidence and justification

Risk of exposure to HIV

All tissue donors and donors of non-reproductive cells

Based on evidence and expert opinion, the above-described events include the major risks of exposure to HIV, relevant for SoHO safety, in EU/EEA countries (Pathogen data sheet, Section 3).

The use of HIV prophylaxis, PrEP or PEP, does not in itself pose a risk for HIV infection, but this preventive treatment is indicated for individuals who are at high risk of exposure to HIV (Pathogen data sheet, Section 3). Due to the risk of breakthrough infections (e.g. due to adherence issues [51]) and interference with laboratory test results (Pathogen data sheet, Section 3), the use of PrEP and PEP should be considered when assessing donor eligibility. Similarly, the risk for donors having condomless sex with individuals living with HIV with suboptimal adherence to ART should be considered, as breakthrough infections are rare but may occur (Pathogen data sheet, Section 3). People living with HIV and effectively treated with ART, with repeatedly undetectable viral loads, are shown not to transmit HIV through sexual contact [52,53]. In the specific circumstances of donors in a monogamous relationship with a person living with HIV, with optimal ART adherence and undetectable viral loads in consecutive evaluations: countries may choose to consider such donors eligible as the risk of HIV transmission to the partner is considered negligible. While condom use reduces the risk of exposure to HIV (Pathogen data sheet, Section 3), condoms may be used incorrectly or may break, leak, or slip off during the sexual act [54,55].

Based on expert opinion, it is advised to consider all the above risk events when assessing donor eligibility, noting that these events can be challenging to identify through interviews, particularly in the context of risk events concerning a partner, as well as the correct usage of condoms, as condom failure is not always recognised [54].

While vertical transmission of HIV and transmission through breastfeeding has been demonstrated [2,61], the consequences of vertical transmission or transmission through breastfeeding are described and considered in the 'Testing of tissues and non-reproductive cells donors for HIV' section.

Testing limitations in case of risk of exposure to HIV

All tissue donors and donors of non-reproductive cells

Given the high performance of the HIV screening tests required in these guidelines, the risk for transmission through SoHO is related to potential donors newly infected with HIV tested during the window period (Pathogen data sheet, Section 2). To avoid window period transmissions from donors newly infected with HIV, donors with recent risk of exposure to HIV should not be tested until the test results are considered reliable. Based on expert opinion, a multiplication factor of the window period should be considered to ensure reliability of the test results and reduce the risk of a window period transmission.

A period of eight weeks after an event with a risk of exposure to HIV covers more than three times the maximum window period of a NAT, including when considering testing in pools. Eight weeks is also expected to fully cover the seroconversion period in individuals with an HIV infection [49,56]. Due to the risk of delayed seroconversion in PrEP or PEP users, a longer period should be considered for these individuals. A period of 12 weeks is expected to cover three times the worst-case assumptions for delayed seroconversion following oral PrEP or PEP use (Pathogen data sheet, Section 3). For injectable PrEP, a period of 24 months from the last PrEP injection is based on FDA recommendations [57] in the absence of evidence on the impact of injectable PrEP on test reliability.

During donor assessment, the possibility of exposure to HIV-2 may be considered, either through sexual contact with a partner who is living with HIV-2 or in other events where a risk of exposure to HIV-2 could be envisaged, e.g. during travels to countries with increased HIV-2 circulation, mainly West African countries [10]. If a NAT detecting HIV-1 but not HIV-2 is used, it should be noted that the detection of an HIV-2 infection will rely solely on the serological tests detecting antibodies to HIV-2, which have a longer window period than NAT. A period of eight weeks is considered sufficient to observe seroconversion in individuals with an HIV-1 or HIV-2 infection.

Limitations

The events with increased risk of exposure to HIV are based on targeted literature searches and not on systematic literature reviews and may not be comprehensive. There is also limited and conflicting data available on the association between PrEP and PEP use and an increase in risk behaviours. The interval between potential exposure to HIV and testing to be considered to ensure reliability of the test results is based on an arbitrary multiplication factor of the window period; however, it is consistent with the deferral periods currently used in several EU/EEA countries, where no HIV transmissions have been reported in the 2017-2022 period (Pathogen data sheet, Section 7).

Donor eligibility is assessed for all pathogens at once, and the list of events in the current guidelines only covers HIV. The list of events with an increased risk of exposure to other pathogens will be completed by ECDC as new guidelines are published. Pending these updates, the EDQM guides can be used as a resource for additional events to consider in assessment of donor eligibility [42].

Affected individuals and other situations to consider

Requirements and recommendations

All tissue donors and donors of non-reproductive cells

Required:

- Individuals with a prior diagnosis of HIV or using ART for HIV should be deferred permanently.
- Individuals with prior participation in an HIV vaccine trial or who received an HIV vaccine should be deferred permanently.

Evidence and justification

All tissue donors and donors of non-reproductive cells

HIV treatment is not curative, and it is not known if treated individuals may transmit the infection through SoHO. The 'undetectable equals untransmittable' (U=U) paradigm cannot be applied to SoHO donors, and an infectious viral load for a donation could be below the threshold of 200 HIV RNA copies/mL used to define well-controlled individuals in the U=U paradigm [30]. In addition, in treated individuals, there is a risk of viraemia due to recent adherence issues or resistance (Pathogen data sheet, Section 2). Based on evidence and expert opinion, considering the severity and long-term consequences of the disease, the route of transmission, and the low infectious dose of HIV, all individuals with a prior diagnosis of HIV or antiretroviral use for HIV should be deferred permanently to reduce the risk of transmission.

HIV vaccination is expected to lead to inconsistencies in test interpretation (Pathogen data sheet, Section 3) and trials preferentially recruit participants who are at a high risk of HIV infection. Based on this, individuals who have participated in an HIV vaccine trial or received an HIV vaccine should be deferred permanently.

Limitations

The effectiveness of anti-HIV vaccination is currently unknown, and the eligibility of vaccinated individuals may be reconsidered when further evidence is available.

Requirements and recommendations: reproductive cells

Testing partners within relationship use and third-party donors

For these guidelines, embryo donors who contributed their reproductive cells to the embryo should be considered and tested as sperm or oocyte donors.

For embryo donation, partners within relationship use who contributed to the embryo with their reproductive cells should be tested as sperm or oocyte donors at the time of embryo donation or at the time of the procurement of partner gametes.

Reproductive tissues used for autologous purposes should be considered as within relationship use.

Donations should be understood as distinct procurement or collection events. Multiple units of SoHO collected at a single time point are considered a single donation for the purpose of these guidelines.

As described in the requirement below, all oocyte donors should be tested for HIV at each donation. For oocyte donation, the donation could be considered as the start of stimulation, and the testing can hence be performed at the time of stimulation.

To have the test result available before the treatment, when using fresh sperms, the testing of the donor should be performed as close as possible to donation, ideally, the day before collection.

For these guidelines, serial sperm donations are considered a process where a sperm donor donates sperm on multiple occasions in a frequent and repetitive manner during a limited time period. If two donations are separated by a period of 90 days or more, these should not be considered serial donations.

Requirements and recommendations

Reproductive cells: Third-party donation

Testing requirements

Required:

- All oocyte donors, at each donation, should be tested for HIV.
- All sperm donors should be tested for HIV at each donation, or in the case of serial donations, at the initial donation and at least 16 days after the last donation in the series. The second test should be done before release of any of the donations from the series of donations.

Screening tests

Required:

- Donors should be tested with both a NAT detecting HIV-1 RNA and serological test(s) detecting antibodies against HIV-1 and HIV-2. The NAT detecting HIV-1 RNA should have a 95% LOD of 100 IU/mL or below.
- A higher LOD can be considered if justified by a documented risk assessment considering the endemicity of the disease. An update of the risk assessment should be performed in case of significant changes to the epidemiology of the disease or a transmission event from donor to recipient.
- In case of donations quarantined for 180 days or more, and if the donor is retested after the quarantine period, the donor does not need to be tested with NAT at donation and after the quarantine period, and only the serological test(s) detecting antibodies against HIV-1 and HIV-2 is required.

Advice and practical considerations:

- The use of NAT detecting both HIV-1 and HIV-2 RNA is advised.
- Antigen-antibody combination tests can be used instead of antibody-only tests.

Outcome of test results

Required:

- Donations from donors with reactive serological test and/or NAT should not be released for clinical use.
- In case of a positive confirmatory test result, or where both the serological test and NAT are reactive in screening:
  - The donor should be notified and referred to relevant clinical care.
  - The donor should be deferred permanently.
  - Look-back procedures of previous, potentially infectious donations should be initiated.
- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result:
  - The decision to notify and refer the donor to clinical care should be based on the likelihood of an infection based on available information, including other available test results obtained during screening and confirmation procedures.
  - The decision to initiate look-back procedures of previous, potentially infectious donations should be based on a risk assessment considering available information, including other available test results obtained during screening and confirmation procedures.

Advice and practical considerations:

- In the case where only the NAT is reactive in screening and is not confirmed positive, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result, it is advised to call back the donor for an additional test on a follow-up sample.

Criteria for donor re-entry

Required:

- In the case of a negative confirmatory test result, and provided a negative NAT in screening, the donor can re-enter screening procedures without a deferral period.
- In the case where only the NAT is reactive in screening and is not confirmed positive in testing, or in the case where only the serological test is reactive in screening and followed by an indeterminate confirmatory test result, the donor can re-enter donor screening procedures but should not re-enter before a minimum period of eight weeks from the last donor testing.

Look back procedure

Required:

- The extent of the look-back procedure should be based on a risk assessment to determine which previous donations are at risk of transmitting HIV.
  - A residual sample of the last donation that tested negative in screening should be retested using a highly sensitive NAT detecting HIV. In case of a serial donation, the initial sample of the serial donation should be retested. Exemption from retesting previous donations can be considered if the previous donation was tested with a highly sensitive NAT and was negative.
  - If the residual sample is positive in the retest; the retesting of archived samples of previous donations should be performed sequentially until a donation is negative. In case of serial donation, testing of the initial and final sample of the previous series of donations should be performed sequentially until both samples are negative. No further testing of prior archived samples is required if the previous sample is negative in the re-test. Recipients who received a donation, positive in the retesting of archived samples, should be tested for HIV infection.
  - In case of a sample with a positive confirmatory test result, and if no archived samples are available for look-back procedures, the centre that performed the treatment should test the recipients of the previous potentially infectious donation. The results should be reported to the entity where the donation was performed.

Advice and practical considerations:

- A 95% LOD of 100 IU/mL or below could be considered for the retesting of the residual sample of the last donation.
- If archived samples test negative upon retesting, additional measures, such as testing recipients who received a potentially infectious donation, could be taken following a risk assessment considering other relevant information.

Reproductive cells and tissues: within relationship use

Testing requirements

Required:

- Partners within the relationship should be tested for HIV not more than three months before collection. For additional collection, testing should be repeated no later than 24 months after the first or previous testing or when a new risk is identified and according to national legislation.

Screening tests

Required:

- The partners should be tested with an antigen-antibody combination test detecting antibodies against HIV-1 and HIV-2.

Advice and practical considerations:

- The additional use of NAT detecting HIV-1 RNA or HIV-1 and HIV-2 RNA is advised. If NAT is used, the antigen-antibody combination test can be replaced with a serological test detecting antibodies against HIV-1 and HIV-2.

Outcome of reactive tests

Required:

- In the case of a positive confirmatory test result or of an indeterminate confirmatory test result that cannot be resolved:
- Proceeding with the within relationship use is to be discussed with the partners and the clinical team, including a specialist in HIV care; please refer to European Society of Human Reproduction and Embryology (ESHRE) guidelines [2].
- Procedures should be implemented to prevent the risk of infection to the partner and to the offspring; please refer to ESHRE guidelines [2].

Advice and practical considerations:

- In the case of a positive confirmatory test result, it is advised to obtain a further sample to reconfirm the test result.

Evidence and justification

Testing requirements

Third-party donations

Because of the documented severity of the disease and the significant consequences on the recipient in case of HIV transmission, the experts agreed that all donors should be tested at each donation to reduce the risk of transmission through SoHO (Pathogen data sheet, Section 1).

For oocyte donation, testing can be performed at the time of stimulation to avoid unnecessary stimulation of the donor in case of reactive screening test(s). When using fresh sperms, to have the test results available before the treatment, the testing can be performed before the actual donation. In this case, the testing of the donor should be performed as close as possible to the donation, ideally on the day before collection

Semen can be collected in a repetitive manner with short intervals between the donations during a limited period, so-called serial donations. In the case of serial donations for sperm, the donor should be tested for HIV at the initial donation and at least 16 days after the last donation in the series. The second test should be performed before release of any of the donations from the series of donations. Sixteen days corresponds to the upper limit of the NAT window period for a 95% LOD of 100 IU/mL. ECDC recommends that the maximum period for serial donations should be clearly defined at a national level, not exceeding a period of 90 days. ECDC has previously assessed a maximum period of 90 days between testing in the context of serial donations as a safe alternative to

testing at each donation. This assessment was conducted with an external expert panel, considering the estimated residual risk of HIV transmission through semen donation. The risk model used for this assessment took into account the incidence, prevalence, and the window period for HIV infection [72]. This is provided the donations are stored in a manner that mitigates cross-contamination risks and that the test results are negative before the release of any of the donations between the two periodically repeated screening tests. If the period of serial donations extends beyond 90 days, it is recommended to retest every 90 days for as long as the serial donations are ongoing. In addition, if two donations are separated by 90 days or more, then these should not be considered serial donations [72].

Within relationship use

Due to the risk of vertical transmission to the offspring and to protect the receiving partner within the relationship, all partners within the relationship use should be tested for HIV. It has been demonstrated that for MAR, within relationship use, testing the partners at entry and at fixed time intervals up to a maximum of 24 months would not diminish the level of safety of the cells concerned, compared to more frequent testing, as long as appropriate safety and quality systems are in place [73]. These requirements are based on the assumption that storage is performed in a manner that mitigates cross-contamination risks during cryopreservation, both to the material used within the relationship and to any other donations [2].

Screening tests

Third-party donations

Based on existing evidence and expert opinion, considering the performance of HIV screening tests and window periods, the safest way to detect an HIV infection is to test donors with a combination of NAT for HIV RNA and serological tests detecting antibodies for HIV. NAT provides a high specificity, and when tests with a high sensitivity (low LOD) are used, HIV RNA can be detected relatively early after infection, hence shortening the window period compared to serological tests (Pathogen data sheet, Section 4). There are risks of mutation in the HIV RNA, and if the mutation is in the target region, an HIV mutant may escape detection by NAT [45]. If the NAT assay targets two separate regions in the HIV genome, a specification for class D devices in the IVDR and its implementing acts [46,47], the risk of not detecting escape mutants is reduced [28].

In rare cases, individuals with an HIV infection may have a low viral load that is undetectable by NAT but where the infection is detectable by testing for HIV antibodies. Such cases would cover individuals effectively treated with ART who are well controlled and have an undetectable viral load and who may present for donation [58] as well as the so-called elite controllers, individuals who naturally control viraemia below 50–75 HIV RNA copies/mL [29]. The use of serological tests detecting antibodies to HIV would allow for the identification of such individuals with an HIV infection.

As both HIV-1 and HIV-2 are present in EU/EEA countries (Pathogen data sheet, Section 3), based on evidence and expert opinion, donors should be tested for both HIV-1 and HIV-2. In EU/EEA countries, HIV-2 infections remain limited in most countries, with less than 1% of HIV-2 infections among all HIV infections, where this proportion may reach 3% in a few countries. According to the expert panel and available evidence, the requirement for NAT is mainly supported for HIV-1. Hence, the expert opinion is to require only NAT-detecting HIV-1 RNA and serological tests detecting antibodies against HIV-1 and HIV-2. However, the use of NAT detecting both HIV-1 and HIV-2 RNA is advised, and detection of both viruses is a specification for class D devices in the IVDR and its implementing acts [40].

Reproductive cells may be transferred across countries depending on clinical need, increasing the importance of harmonised safety requirements in the EU/EEA. The window period of NAT can be reduced by increasing sensitivity (lowering the LOD). A 95% LOD of 100 IU/mL is estimated to correspond to a window period between six and ten days (Table 1). Based on these elements and according to expert opinion, a NAT with a 95% LOD of 100 IU/mL or lower should be used for third-party donors of reproductive cells in case the donations are not quarantined.

However, according to expert opinion, increasing sensitivity may increase healthcare resource use costs, which may not be justified in settings where the epidemiology of the disease would be associated with a very low residual risk. It should also be noted that HIV transmission through the application of reproductive cells is rare in the EU/EEA and has not been reported in the period 2017–2022 (Pathogen data sheet, Section 7). Additionally, the election of third-party donors through thorough donor assessment, relying on a health questionnaire assessing the risk of recent exposure to HIV, can significantly reduce the risk of donors presenting with a recent HIV infection associated with a low viral load and undetectable antibodies (Pathogen data sheet, Sections 3; expert opinion). Considering these elements, and based on expert opinion, a higher LOD can be considered if justified by a risk assessment that follows national recommendations, if available, considering the endemicity of the disease. The risk assessment should be documented to ensure transparency in case of exchange of cells with other regions or countries. An update of the risk assessment should be performed in case of significant changes to the HIV epidemiology (as defined by the NCA) or in case of an HIV transmission event from donor to recipient.

There is no available evidence suggesting that using serological tests detecting both antigens and antibodies against HIV in combination with NAT reduces the risk of transmission of HIV compared to using tests only detecting antibodies in combination with a sensitive NAT if the NAT relies on two targets in the HIV genome. When NAT is used, antigen-antibody combination tests are as safe as antibody-only tests; antigen-antibody combination tests can be used instead of antibody-only tests.

Donors whose donations are quarantined for 180 days or more, tested at each donation, and retested with serological tests detecting antibodies against HIV-1 and HIV-2 after the quarantine period, do not need to be tested with NAT at donation and after the quarantine period. The quarantine period allows sufficient time for seroconversion for HIV, but also for hepatitis B and C viruses, reducing the need for additional NAT.

Within relationship use

As the need for tests with short window periods to detect recent infections is less critical within relationship use, HIV-1 RNA NAT is not required for within relationship use. Based on existing evidence and expert opinion, individuals within a relationship should be tested through antigen-antibody combination tests detecting antibodies against HIV-1 and HIV-2. Combination tests are commonly used in the context of HIV screening and, in the absence of additional NAT use, provide increased safety compared to tests detecting antibodies only.

Based on expert opinion, it is advised to additionally test individuals within the relationship with NAT to further increase safety. If the NAT utilises two separate targets in the HIV genome, a specification for class D devices in the IVDR and its implementing acts [46,47], the antigen-antibody combination test can be replaced with a serological test detecting antibodies against HIV-1 and HIV-2, as there is no increase in safety using antigen-antibody combination tests when combined with NAT.

Outcome of test results

Third-party donors

Given the high performance of the HIV screening tests, reactive screening test results indicate a high likelihood that the donor is infected with HIV, with a risk for HIV transmission to the recipient if the donation is used for treatment (Pathogen data sheet, Section 4). Hence, based on evidence and expert opinion, the donation from a donor with reactive screening test(s) should not be released for clinical use. While false-reactive results of serological screening tests are possible, the expert panel agreed that donations from donors with reactive serological tests, even with a negative confirmatory test result, should not be released for clinical use due to the severe impact of an HIV transmission on the recipient. In the case of serial donations, this applies to both the initial and final donation in the series. For the initial donation, if the serological test or NAT is reactive, the donation should not be released for clinical use, and the serial donations should not proceed. If the NAT or the serological test is reactive in the final sample, none of the donations within that series, going back to the last (initial) negative donation, should be released.

In the case of a positive confirmatory test result, or if both the serological test and NAT are reactive in screening, as well as in other situations where HIV infection cannot be ruled out and is considered likely considering other available information (including other test results), the donor should be informed and referred to relevant clinical care.

Due to the risk of transmission of HIV (Pathogen data sheet, Section 7), based on good practice and considering expert opinion, in case of a positive confirmatory test result or where both the serological test and NAT are reactive in screening in a repeat donor, look-back procedures to identify previous potentially infectious donations should be performed to identify and follow up on recipients who may be at risk of infection. In other cases where HIV infection cannot be definitively ruled out, such as when test results are inconclusive or indeterminate, the decision to initiate look-back procedures should be based on a risk assessment, considering other available information, including other test results.

The extent of the look-back procedure should be guided by a risk assessment considering other available test results and relevant information to identify which previous donations may pose a risk of transmitting HIV, and therefore which samples and recipients require testing. Although samples from previous donations were found negative in screening, it is possible the donation was made at a moment prior to seroconversion and with a viral load below the LOD defined for NAT in routine screening. Using a highly sensitive NAT for look-back procedures would support the identification of low viral loads and a 95% LOD of 100 IU/mL or below could be considered for the retesting of the residual sample of the previous donation, or in case of serial donations, the initial sample in the series, and in case of a reactive test result, the initial and final sample in the previous series of donations. If either of the tests are reactive in the previous series of donations, all donations with the series are to be considered potentially infectious. To ensure the safety of recipients, based on expert opinion, recipients who received a donation positive in retesting should be tested for HIV infection. Testing recipients who received a donation negative in retesting could also be considered following a risk assessment and considering other relevant information, since the negative result could reflect a very low viral load. If no archived samples are available for testing in the context of look-back procedures, according to expert opinion, the recipient(s) of the previous

potentially infectious donation should be tested for an HIV infection. As a single individual may donate several different SoHO, where it is possible, look-back procedures may also consider donations of other SoHO types.

Within relationship use

A positive or an indeterminate confirmatory test result following a reactive serological test in screening or in other cases where an HIV infection cannot be ruled out, means a risk for HIV transmission to the partner or to the offspring. Based on good practice principles, in case of a positive confirmatory test result, it is advised to call back the individual for a second sample and further confirmatory testing to reconfirm the test result and confirm the identity of the individual. Based on evidence and expert opinion, in case of positive confirmatory test result, or in cases where HIV infection cannot be ruled out, assisted reproduction is to be discussed with the partners and the clinical team, including a specialist in HIV care. Procedures should be implemented to prevent the risk of infection to the partner and to the offspring following ESHRE's guidelines [2].

Criteria for donor re-entry

Third-party donors

Due to the risk of HIV transmission (Pathogen data sheet, Section 2), a donor with a positive confirmatory test result, or where both the NAT and serological screening tests are reactive, or where an infection cannot be ruled out taking into account all information available, should be permanently deferred.

A negative confirmatory test following a reactive serological test and a negative NAT in screening is very likely indicative of a false-reactive result for the serological test. Therefore, if the confirmatory test is negative, and provided the NAT is negative in screening, the donor is not considered to have an HIV infection, and the donor can be allowed to re-enter donor screening procedures without a deferral period.

It is advised to call back the donor for further testing on a follow-up sample in case of discordant results between a reactive NAT in screening and the results of additional test(s) performed to confirm the initial NAT result. A higher viral titre may be detected in the follow up sample. This procedure is also advised in case of indeterminate confirmatory test results where only the serological test is reactive in screening. For these donors, there should be a minimum period of eight weeks from the last donor testing before re-entry to exclude potential seroconversion (Pathogen data sheet, section 2) [49,56]. Similarly, donors with a reactive serological screening test and with indeterminate confirmatory test results that cannot be resolved can re-enter donor screening procedures if more than eight weeks from the last donor test have elapsed.

According to ECDC's opinion, HIV infection is highly likely in donors where both the serological test and NAT are reactive, regardless of the confirmatory test result. The concordance of the screening tests significantly reduces the likelihood of a false-reactive screening result. These donors should be deferred permanently and referred to relevant clinical care (i.e., treated as donors with positive confirmatory test results).

Limitations

The evidence is based on studies evaluating individual test performance and not the comparison of a combination of test methods. There are a limited number of studies on the window period and correlation with the standardised measures of the LOD for NAT. There are also a limited number of studies on the comparison of the accuracy of antibody-only tests compared with a combination of antigen-antibody tests for HIV when used in combination with NAT.

Risk of exposure to HIV and testing limitations in case of recent exposure to be considered for each donation

Requirements and recommendations

These guidelines follow the definition of Estcourt et al. for 'a new partner', 'one-off partner,' and 'casual partners' [50]. Condom failure should be understood as any instance in which a condom breaks, leaks, or slips off during sexual activity. Injection of non-prescription drugs refers to the use of any drug or other substance not prescribed by a registered healthcare professional and self-administered via injection. This includes both illicit drugs (e.g., heroin, methamphetamine) and performance enhancing drugs (e.g., testosterone) when injected and which can be associated with needle sharing.

The events listed below are provided to support entities in developing their donor eligibility assessment strategies but are not intended to be the exact questions asked, or physical examination performed, during the donor assessment.

Reproductive cells: third-party donors

Risk of exposure to HIV

Required:

- All donors, at each donation, should be assessed for recent risks of exposure to HIV when considered for donor eligibility.

Advice and practical considerations:

The following events are considered risks of exposure to HIV. It is advised to consider the occurrence of these events in the past eight weeks (12 weeks for oral PrEP and PEP and 24 months for injectable PrEP use) when assessing donor eligibility:

- Condomless* anal sex with a new partner, one-off partner, or a casual partner;
- Condomless* anal sex with more than one partner;
- Sexually transmitted infection;
- Needle sharing and/or injecting non-prescription drugs;
- Use of injectable PrEP;
- Use of oral PrEP or PEP;
- Condomless* sex with a person living with HIV;
- Condomless* sex with a partner with sexually transmitted infection(s);
- Condomless* sex with a partner who injects non-prescription drugs;
- Condomless* sex with a partner using PrEP or PEP;
- Condomless* sex in exchange for money, drugs, or other payments.

** Condomless should be understood as a situation where no condom was used or situations where it was used incorrectly (e.g., condom failure).*

Testing limitations in case of recent risk of exposure to HIV

Required:

- Donors should not be tested in the context of donor evaluation before a period of at least eight weeks since the last event with a risk of exposure to HIV.
- Exceptions:
  - Oral PrEP or PEP use, for which a period of 12 weeks since the last event should be considered.
  - Injectable PrEP use, for which a period of 24 months since the last event should be considered.

Reproductive cells and tissues: within relationship use

Risk of exposure to HIV

Advice and practical considerations:

- It is advised to consider the risk of exposure to HIV for partners within relationship use.

Considerations for testing due to risk of exposure to HIV

Advice and practical considerations:

- It is advised to consider test results as not reliable before a period of at least eight weeks since the last event with a risk of exposure to HIV.
- If an event with a risk of exposure to HIV occurred within the above-described period, it is advised to test the individuals within the relationship after the corresponding period since the last event has passed.

Evidence and justification

Risk of exposure to HIV

Reproductive cells - third-party donors

Based on evidence and expert opinion, the above-described events include the major risks of exposure to HIV, relevant for SoHO safety, in EU/EEA countries (Pathogen data sheet, Section 3).

The use of HIV prophylaxis, PrEP or PEP, does not in itself pose a risk for HIV infection, but this preventive treatment is indicated for individuals who are at high risk of exposure to HIV (Pathogen data sheet, Section 3). Due to the risk of breakthrough infections (e.g. due to adherence issues [51] and interference with laboratory test results (Pathogen data sheet, Section 3), the use of PrEP and PEP should be considered when assessing donor eligibility. Similarly, the risk for donors having condomless sex with individuals living with HIV with suboptimal adherence to ART should be considered, as breakthrough infections are rare but may occur (Pathogen data sheet, Section 3). People living with HIV and effectively treated with ART, with repeatedly undetectable viral loads, are shown not to transmit HIV through sexual contact [52,53]. In the specific circumstances of donors in a monogamous relationship with a person living with HIV, with optimal ART adherence and undetectable viral loads in consecutive evaluations: countries may choose to consider such donors eligible as the risk of HIV transmission to the partner is considered negligible. While condom use reduces the risk of exposure to HIV (Pathogen data sheet, Section 3), condoms may be used incorrectly or may break, leak, or slip off during the sexual act [54,55].

Based on expert opinion, it is advised to consider all the above risk events when assessing donor eligibility, noting that these events can be challenging to identify through interviews, particularly in the context of risk events concerning a partner, as well as the correct usage of condoms, as condom failure is not always recognised [54].

Testing limitations in case of recent risks of exposure to HIV

Reproductive cells - third-party donors

Given the high performance of the HIV screening tests required in these guidelines, the risk for transmission through SoHO is related to potential donors newly infected with HIV tested during the window period (Pathogen data sheet, Section 2). To avoid window period transmissions from donors newly infected with HIV, donors with recent risk of exposure to HIV should not be tested in the context of donor evaluation until the test results are considered reliable. Based on expert opinion, applying a multiplication factor to the window period would ensure a safe period before testing to reduce the risk of a window period transmission. A period of eight weeks after an event with a risk of exposure to HIV covers more than three times the maximum window period of a NAT, including when considering testing in pools. Eight weeks is also expected to fully cover the seroconversion period in individuals with an HIV infection [49,56].

Due to the risk of delayed seroconversion in PrEP or PEP users, a more extended period before testing should be considered for these individuals. A period of 12 weeks is expected to cover three times the worst-case assumptions for delayed seroconversion following oral PrEP or PEP use (Pathogen data sheet, Section 3). For injectable PrEP, a period of 24 months from the last PrEP injection is based on FDA recommendations [57] in the absence of evidence on the impact of injectable PrEP on test reliability.

During donor assessment, the possibility of exposure to HIV-2 may be considered, either through sexual contact with a partner who is living with HIV-2 or in other events where a risk of exposure to HIV-2 could be envisaged, e.g. during travels to countries with increased HIV-2 circulation, mainly West African countries [10]. If a NAT detecting HIV-1 but not HIV-2 is used, it should be noted that the detection of an HIV-2 infection will rely solely on the serological tests detecting antibodies to HIV-2, which have a longer window period than NAT. A period of eight weeks is considered sufficient to observe seroconversion in individuals with an HIV-1 or HIV-2 infection.

Risk of exposure to HIV and considerations for testing

Within relationship use

Similarly to what is described for third-party donors, test results cannot be considered fully reliable before a minimum period of eight weeks after an event with a risk of exposure to HIV. If one of the partners within the relationship had an event with an increased risk of exposure to HIV less than eight weeks prior to testing for HIV, it is advised to re-test the individual for HIV after a minimum period of eight weeks from the event to ensure the reliability of the test results. It should be noted that, in the case of PrEP use, test reliability may be impaired for a longer period of time.

Limitations

The events with increased risk of exposure to HIV are based on targeted literature searches and not on systematic literature reviews and may not be comprehensive. There are also limited and conflicting data available on the association between PrEP and PEP use and an increase in risk behaviours. The interval between potential exposure to HIV and testing to be considered to ensure reliability of the test results is based on an arbitrary multiplication factor of the window period; however, it is consistent with the deferral periods currently used in several EU/EEA countries, where no HIV transmissions have been reported in the 2017–2022 period (Pathogen data sheet, Section 7).

Donor eligibility is assessed for all pathogens at once, and the list of events in the current guidelines only covers HIV. The list of events with an increased risk of exposure to other pathogens will be completed by ECDC as new guidelines are published. Pending these updates, the EDQM guides can be used as a resource for additional events to consider in assessment of donor eligibility [42].

Affected individuals and other situations to consider

Requirements and recommendations

Reproductive cells- third-party donors

Required:

- Individuals with a prior diagnosis of HIV using ART for HIV should be deferred permanently.
- Individuals with prior participation in an HIV vaccine trial or who received an HIV vaccine should be deferred permanently.

Reproductive cells and tissues- within relationship use

Advice and practical considerations:

Individuals with an HIV infection or those who are using ART for HIV:

- Proceeding with the within relationship use is to be discussed with the partners and the clinical team, including a specialist in HIV care; please refer to ESHRE guidelines [2].
- It is advised to implement procedures to prevent infection of the partner and the offspring; please refer to ESHRE guidelines [2].

Evidence and justification

Third-party donors

HIV treatment is not curative, and it is not known if treated individuals may transmit the infection through SoHO. The 'undetectable equals untransmittable' (U=U) paradigm cannot be applied to SoHO donors, and an infectious viral load in 20 mL of plasma (considering an infectious dose of 500 virions) would be below the threshold of 200 HIV RNA copies/mL used to define well-controlled individuals in the U=U paradigm [30]. In addition, in treated individuals, there is a risk of viraemia due to recent adherence issues or resistance (Pathogen data sheet, Section 2). Based on evidence and expert opinion, considering the severity and long-term consequences of the disease, the route of transmission, and the low infectious dose of HIV, all individuals with a prior diagnosis of HIV or antiretroviral use for HIV should be deferred permanently to reduce the risk of transmission.

HIV vaccination is expected to lead to inconsistencies in test interpretation (Pathogen data sheet, Section 3) and trials preferentially recruit participants who are at a high risk of HIV infection. Based on this, individuals who have participated in an HIV vaccine trial or received an HIV vaccine should be deferred permanently.

There is no evidence of transmission through oocyte MAR treatment (Pathogen data sheet, Section 7). However, as precautionary measures, and to contribute to the safety of healthcare worker, the requirements apply also to third-party oocyte donors.

Within relationship use

HIV can be vertically transmitted to a child from a person with low viral load and on ART [2]. There is also a risk for horizontal transmission even in treated individuals due to recent adherence issues or resistance (Pathogen data sheet, Section 2). To protect the partner and the offspring, it is recommended to implement procedures to prevent the risk of infection and follow ESHRE's guidelines for medically assisted reproduction in patients with a viral infection/disease, including individuals on antiretroviral therapy [2].

Limitations

The effectiveness of anti-HIV vaccination is currently unknown, and the eligibility of vaccinated individuals may be reconsidered when further evidence is available.

Next steps

ECDC will update these guidelines when significant new evidence becomes available or if the scope of the guidelines should be expanded to cover the needs of SoHO entities, such as considerations on pre-analytical requirements, or to cover additional SoHO currently not in scope of these guidelines.

An important step towards the harmonisation of SoHO safety in the EU/EEA could be accomplished by defining a common threshold for the residual risk of transmission of HIV through SoHO application, particularly blood and blood components. A common threshold for residual risk would ensure a similar level of safety in each country, considering the endemicity of the disease in the country, and the local organisation of donor screening. As such, a maximum required threshold for a residual risk of transmission would impact the content of the present guidelines and lead to an update of this document. Defining such as threshold would require an agreement across EU/EEA countries.

ECDC will follow significant developments in the epidemiology (e.g. changes in associated risks), in the prevention (e.g. vaccination against HIV infection), in the available laboratory screening test methods for SoHO donors, vaccine development and in the treatment (e.g. development of a curative treatment against HIV) that may significantly change the assessments in the current guidelines. During meetings of the ECDC SoHO network, and based on such developments, ECDC will evaluate, with the support of the SoHO Network, the need for an update of these guidelines.

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Annex

Legal background

On 14 July 2024, the new regulation on standards of quality and safety for substances of human origin intended for human application was published. After entry into force, in August 2027 for most provisions, the regulation will repeal the Blood Directive (2002/98/EC) and the Tissues and cells Directive (2004/23/EC).

Standards for the quality and safety of SoHO, including the prevention of communicable diseases transmission, are currently defined in the directives. In the SoHO regulation, guidelines for the implementation of standards for the prevention of communicable diseases transmission through SoHO are no longer listed. The regulation establishes the ECDC as an expert body for developing and updating technical guidelines on the safety and quality of SoHO from a communicable disease threat perspective. With regards to standards concerning donor, recipient and offspring protection, the regulation stipulates in the absence of Union legislation describing particular procedures to be applied and followed to meet the standards set out in this regulation, following the guidelines of the ECDC regarding communicable disease transmission through SoHO donation and EDQM for issues of quality and safety beyond the risks of communicable disease transmission should be considered as a means to demonstrate compliance with the standards laid down in the regulation to ensure high level of quality, safety and efficacy. SoHO entities should be permitted to follow other guidelines, provided that it has been demonstrated that those other guidelines achieve the same level of quality, safety and efficacy.

These guidelines support the regulation in the prevention of communicable disease transmission from donors through SoHO in the EU/EEA.

Detailed guideline development process and methods

Ad hoc expert panel

Selection of the panel

The ad hoc scientific expert panel members for this guideline were identified through the ECDC Expert Directory, suggestions from the ECDC Advisory Forum, ECDC experts and ECDC Coordinating Competent Bodies. A call for interest was sent through ECDC relevant networks (SoHO, Emerging and vector-borne diseases, HIV/AIDS, sexually transmitted infections and hepatitis B/C, and the Microbiology network) as well as SoHO professional associations (European Association of Tissue and Cell Banks (EATCB), European Blood Alliance (EBA), European Society of Human Reproduction and Embryology (ESHRE), International Society of Blood Transfusion (ISBT), International Plasma and Fractionation Association (IPFA), European eye bank association (EEBA), European Hematology Association (EHA), European Group for Blood & Marrow Transplantation (EBMT), International Council for Commonality in Blood Banking Automation (ICCBBA), International Haemovigilance Network (IHN), Nordic cryobank group, World Marrow Donor Association (WMDA)). The call for interest was also sent to the EU/EEA national competent authorities for SoHO.

The Expert Panel members were selected by ECDC based on their expertise in the technical field of the guidelines and their professional skills. Panel members were expected to have experience in evidence-based decision-making. The selected experts primarily come from the clinical field and public health institutes. Whilst selecting experts, ECDC has ensured sufficient representation for the different types of SoHO as well as geographical representativeness. The principles of diversity, equity, and inclusion, and absence of conflict of interests have been applied.

Following a selection based on the criteria described above, all panel members signed a declaration of interest, which has been reviewed by the ECDC expert responsible for the panel with the help of ECDC compliance office. One expert (Ana Avellón) received research funding from Diasorin, and one expert (Silvia Sauleda) received funding from Grifols. The following mitigation measures were proposed for these two experts: no participation in final advice related to the choice of test methods and careful monitoring of participation by ECDC.

The EDQM, also cited as an expert body establishing guidelines in the regulation, was represented by two observers selected by EDQM in the scientific expert panel.

The ECDC Advisory Forum was consulted regarding their opinion on the suitability of the proposed members of the panel, prior to formal appointment by the ECDC Director. The ECDC Advisory Forum had no objections to the proposed panel.

Terms of reference

The terms of reference of the ad hoc scientific panel, including a description of the requirements for the expert panel, are found in.

Work procedures

ECDC prepared guideline statements on screening strategies, test methods for donors, and circumstances for deferring donors. These statements were discussed with the scientific expert panel during three virtual meetings between September 2023 and February 2024. Pre-meeting surveys were sent prior to each meeting including questions on the following topics:

- Which SoHO donors should be tested for HIV?
- When should SoHO donors be tested for HIV?
- Which laboratory screening tests should be used for the testing of SoHO donors with regards to HIV?
- What LOD that should be applied for NAT detecting HIV-1 RNA?
- What actions should be performed in case of reactive screening tests, including the deferral of donors?
- Which risks of exposure to HIV are considered relevant for SoHO safety and need to be considered in the SoHO donor assessment?
- What deferral period should be considered for donors with events leading to a risk of exposure to HIV?

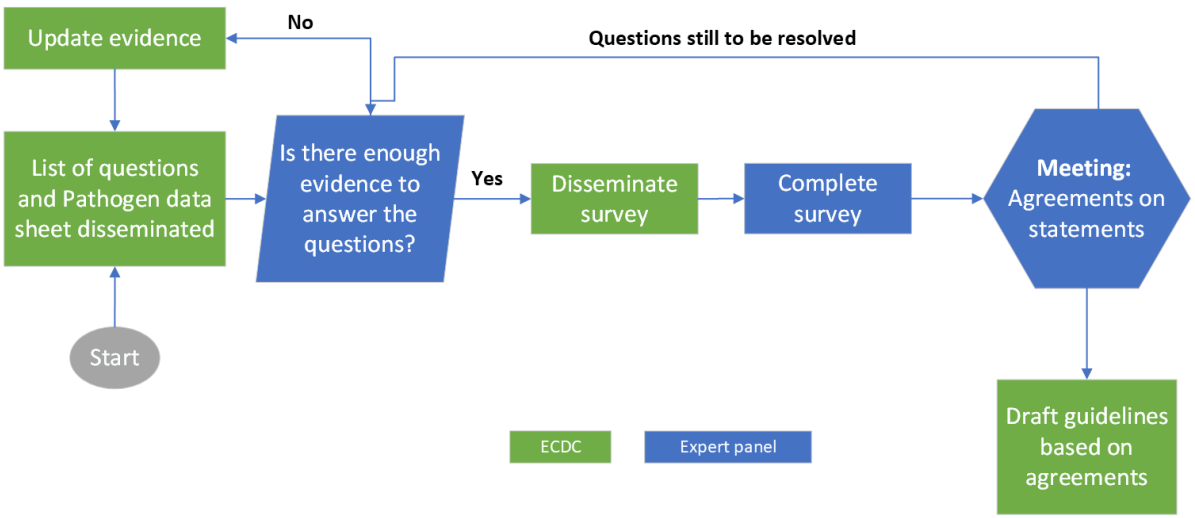
Supporting the development of these guidelines and discussions with the scientific expert panel, a 'pathogen data sheet' on HIV containing relevant epidemiological, microbiological, and clinical information was developed by ECDC based on methods detailed in the pathogen data sheet document (see Pathogen data sheet). For each question posed by ECDC, the panel assessed if there is sufficient evidence to support a reply to the question with the possibility of requiring additional evidence from ECDC prior to each meeting. Where no or limited evidence was available, this was communicated during meetings to the expert panel.

Pre-meeting survey results were presented and discussed during meetings, if results indicated a general consensus on a topic, corresponding statements were proposed by ECDC for agreement. Due to the limited number of experts per SoHO type, agreements were not reached through consensus voting but through the confirmation of the absence of major disagreements for a statement. All meetings with the scientific expert panel were virtual and audio-recorded for the purpose of drafting meeting minutes; recordings were deleted after the minutes were finalised. All experts have accepted the terms of reference, including an agreement to the audio recording of the panel meetings. Draft meeting minutes were circulated to the entire expert panel for comments and all members (including those who could not participate in the meeting) were invited to comment on the minutes and in particular on the agreed statements. The final minutes were then made available to the expert panel and to the observers.

The final meeting minutes served as reference documents for the drafting of the guidelines. In the case of serious disagreements that could not be resolved, the agreed process was to submit the subject to SoHO-Net for consultation. However, no unresolved disagreements were encountered during the development of the HIV statements.

Figure 1 describes the overall working procedures for agreements on statements with the expert panel.

Figure 1. Overall working procedures for agreements on statements



Responsibilities of ECDC, scientific panel members and of the observers during guideline development

Responsibilities of ECDC

During the guideline development, the responsibility of ECDC was to:

- Select and establish an independent ad hoc scientific expert panel to support ECDC in the development of the guidelines.
- Provide a 'pathogen data sheet' for HIV.
- Provide additional evidence upon request of the scientific expert panel.
- Provide technical and secretarial support to the meetings.
- Draft and finalise meeting minutes concluding on agreements reached by the scientific expert panel on donor testing and deferral strategies (including deferral periods) and testing methods for the group of pathogens covered by the terms of reference.
- Draft technical guidelines on the prevention of HIV transmission through SoHO and coordinate the review of the draft guidelines with the ECDC SoHO-Network.
- Coordinate the consultation of external stakeholders on the final draft of the technical guidelines on the prevention of HIV transmission of HIV through SoHO.
- Preparation of the final guideline document.

Responsibilities of scientific expert panel members

- Attend the meetings, according to availability, or provide their contribution by other means.
- Critically review evidence provided by ECDC in the pathogen data sheets.
- Provide additional evidence relevant to the discussion.
- Define the need for additional evidence, if required, to support panel discussions on specific pathogens.
- Provide expertise on donor selection, screening testing, and testing methods.
- Provide feedback as requested via surveys sent out by the ECDC SoHO team.
- Provide ECDC with expert advice on testing strategies and methods and deferrals (including deferral periods) for the pathogens under discussion.
- Help to develop and give opinions on proposals on testing and deferral strategies.
- Review draft meeting minutes covering discussions and agreements reached by the panel, to ensure alignment with the best practical in the field.
- Provide and keep up to date, at least on a yearly basis, declarations of interest throughout the guideline development process, including informing in a timely fashion ECDC of any potential conflict of interest that might affect their decisions and/or actions.

The expert panel also supported ECDC in the resolution of comments from external stakeholders.

Responsibilities of the observers

- Attend the meetings, according to availability, or provide their contribution by other means.
- Liaise with the EDQM guide working groups to avoid gaps and inconsistencies between the ECDC technical guidelines and the EDQM blood and tissues and cells guides.
- Treat in the strictest confidence and not make use of or divulge to third-party any information or documents which are linked to the tasks of the scientific expert panel. To continue to be bound by this undertaking after completion of the tasks unless it becomes public.
- Provide and keep up to date, at least on a yearly basis, declarations of interest throughout the guideline development process, including informing in a timely fashion ECDC of any potential conflict of interest that might affect their decisions and/or actions.

Review and stakeholder consultation

The draft guidelines were sent for review to the ECDC SoHO network and the comments from the ECDC SoHO network have been addressed. These guidelines were also sent to the list of stakeholders included in the list of

stakeholder organisations interested in participating in ad-hoc meetings with representatives of members of the Competent Authorities on Substances of Human Origin Expert Group. The guidelines were sent at the same time for consultation to third parties, e.g., EDQM, EMA, and WHO. The comments from the stakeholders and third parties have been addressed.

The final guidelines were sent for consultation regarding the scientific excellence and independence of activities and opinions to the ECDC Advisory Forum.

Methods of evidence collection and synthesis

The pathogen data sheet supporting the statements in the present technical guidelines consists of eight separate sections:

- Description of the pathogen.
- Disease description.
- Epidemiology of the disease.
- Laboratory testing approaches.
- Current testing requirements in EU/EEA countries.
- Recommendations from other organisations.
- Transmission through SoHO.
- Pathogen reduction.

Below is a description of how the evidence was systematically searched for and selected, including the different information sources used and criteria for inclusion or exclusion of the evidence found for the first seven sections in the pathogen data sheet.

Section 1: Description of the pathogen

Search questions and objectives:

- The objectives of this section are to describe the biological characteristics of HIV-1 and HIV-2 and to describe the pathogenesis of HIV-1 and HIV-2.

General search strategy:

- As this section aimed to provide a general overview of the pathogen, the search strategy was limited to a targeted review with pre-selected sources.

Section 2: Disease description

Search questions and objectives:

- The objectives of this section are to describe the disease, including severity, long-term outcomes, diagnostic possibilities, duration of infectivity and infectious dose, and treatment options.

General search strategy:

- As this section aimed to provide a general overview of the disease, the search strategy was limited to a targeted review with pre-selected sources.

Section 3: Epidemiology

Search questions and objectives:

- The objectives of this section are to describe the prevalence and incidence of HIV infections in EU/EEA countries in the general population and the SoHO donor population; to describe known risk factors for HIV; to describe any other relevant issue related to SoHO safety and HIV (e.g., pre-exposure and post-exposure prophylaxis).

General search strategy:

- As this section aimed to provide a general overview of the incidence and prevalence of HIV in EU/EEA countries and provide an overview of the risk factors of the infection and did not intend to answer a specific question, the search strategy was limited to a targeted review with pre-selected sources.

Section 4: Laboratory testing approaches

Search questions and objectives:

- To describe the characteristics and test accuracy properties of laboratory tests that are approved or used for the screening of HIV in SoHO donors (living and deceased donors).
- To describe the test accuracy properties of the NAT tests approved or used for the screening of HIV in blood donations according to pooled or individual donation use.
  - Population: SoHO donors.
  - Intervention: HIV tests used for screening in a SoHO context.
  - Comparators = reported reference standards.
  - Outcome: HIV-1/2 test accuracy metrics.

Search and eligibility:

- Searches were restricted from January 2001 (the start of 4th generation tests) to the present and covered MEDLINE only. Customised searches of grey literature using generic web search engines (e.g., Google) combined with searches in targeted websites were also conducted.
- Only publications available in English were considered eligible.
- Randomised controlled trials, non-randomised controlled trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies were considered eligible for inclusion, as well as systematic reviews reporting on HIV-1/2 test accuracy in the context of SoHO. Letters and commentaries, conference abstracts, case reports, and case series were excluded.

Index tests considered for inclusion were:

- Enzyme immunoassays (EIA);
- Enzyme-linked immunosorbent assay (ELISA);
- Indirect Fluorescent Antibody assay (IFA);
- Immunoblot (western blot);
- Chemiluminescent immunoassay (CMIA or ChLIA/CLIA);
- Nucleic acid amplification test (NAT).

No reference standard was prespecified.

- Additional eligibility criteria:
  - In-house (i.e. not commercial) tests were in scope if they were used in EU/EEA countries. In-house tests used outside EU/EEA were excluded as not considered relevant for the EU/EEA context.
  - Studies reporting accuracy metrics in the context of proficiency testing were excluded.
- Main outcomes:
  - Test type (e.g. antibody, antigen, NAT);
  - Test target (e.g. p24);
  - Manufacturer;
  - Test accuracy estimates: analytical sensitivity, clinical sensitivity, specificity (as reported);
  - Window period (as reported).
- Data extraction:
  - Studies were assessed for relevance, first by title/abstract and then by full text, excluding at each step studies which did not satisfy the inclusion criteria. The studies were assessed by a single reviewer. Data were extracted by a single reviewer using a standardised data extraction form, but the extracted data were reviewed by a second reviewer.
- Strategy for data synthesis:
  - The extracted data were described in a tabular format, no meta-analyses was conducted. The outcome data were presented by the type and target of the test. Test accuracy metrics that were not reported but could be calculated from the reported information were calculated.

No risk of bias assessment was performed.

Analysis of subgroups or subsets:

Donor type (living, deceased) sample

Keywords for the search (PubMed):

Concept	No.	Query	Results
All, >2001	6	#5 AND 2001:3000 [dp]	1 509
All	5	#1 AND #2 AND #3 AND #4	2 792
Accuracy metrics	4	"Sensitivity and Specificity"[Mesh:NoExp] OR "Predictive Value of Tests"[Mesh] OR "sensitiv*"[Text Word] OR "specific*"[Text Word] OR "npv"[Text Word] OR "ppv"[Text Word] OR "negative predictive value*"[Text Word] OR "positive predictive value*"[Text Word]	5 500 798
Test methods	3	"Polymerase Chain Reaction"[Mesh] OR "Enzyme-Linked Immunosorbent Assay"[Mesh] OR "Immunoblotting"[Mesh] OR "Immunoassay"[Mesh] OR "screen*"[Title/Abstract] OR "test*"[Title/Abstract] OR "serolog*"[Title/Abstract] OR "sero log*"[Title/Abstract] OR "assay*"[Title/Abstract] OR "antigen*"[Title/Abstract] OR "antibod*"[Title/Abstract] OR "PCR"[Title/Abstract] OR "nucleic*"[Title/Abstract] OR "polymerase*"[Title/Abstract] OR "ELISA"[Title/Abstract] OR "EIA"[Title/Abstract] OR "IFA"[Title/Abstract] OR "immunoblot*"[Title/Abstract] OR "immuno blot*"[Title/Abstract] OR "western blot*"[Title/Abstract] OR "immunoelectroblot*"[Title/Abstract] OR "electroimmunoblot*"[Title/Abstract] OR "CMIA"[Title/Abstract] OR "CLIA"[Title/Abstract] OR "ICT"[Title/Abstract]	7 303 130
SoHO	2	"Tissue Donors"[Mesh] OR "Tissue Transplantation"[Mesh] OR "Blood Transfusion"[Mesh] OR "donor*"[Title/Abstract] OR "donat*"[Title/Abstract] OR "transfus*"[Title/Abstract] OR "transplant*"[Title/Abstract] OR "tissue graft*"[Title/Abstract]	1 050 829
HIV	1	"HIV"[Mesh] OR "HIV Infections"[Mesh] OR "Human immune deficiency virus*"[tiab] OR "Human immunodeficiency virus*"[tiab] OR "Human immuno deficiency virus*"[tiab] OR "aids virus*"[tiab] OR "Immunologic Deficiency Syndromes"[Mesh:NoExp] OR AIDS[OT] OR "Acquired Immune Deficiency Syndrome*"[tiab] OR "Acquired Immuno-Deficiency Syndrome*"[tiab] OR "Acquired Immuno Deficiency Syndrome*"[tiab]	395 281

Section 5: Current testing requirements in EU/EEA countries

Search questions and objectives:

- The objectives of this section are to describe the laboratory testing procedures for blood donors and for tissue and cell donors in use in EU/EEA countries.

General search strategy:

- Data published by the European Directorate for the Quality of Medicines and HealthCare on the collection, testing and use of blood and blood components in Europe.
- Data published by the European Commission on the Mapping of More Stringent Blood Donor Testing Requirements (Mapping Exercise 2015).
- Input from the scientific expert panel.

Section 6: Recommendations from other organizations

Search questions and objectives:

- The objectives of this section are to describe the recommendations for the prevention of transmission of HIV through the application of SoHO from relevant organisations.

General search strategy:

- As this section aimed to describe recommendations published by recognised organisations and authorities in the field of SoHO, the search strategy was limited to a targeted review with pre-selected sources. The following organisations were considered:
  - European Commission
  - European Directorate for the Quality of Medicines & HealthCare (EDQM).
  - US Food and Drug Administration (FDA).
  - Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC).
  - World Health Organization (WHO).

Section 7: Transmission through SoHO

Search questions and objectives:

- The objectives of this section are to provide evidence of demonstrated transmission of HIV through SoHO and to describe the number of HIV transmissions through SoHO in the EU/EEA.

General search strategy

- As this section aimed to describe the possibility of transmission through SoHO rather than provide a comprehensive overview of all transmission events, the search strategy was limited to a targeted review, including a search on the Notify library (www.notifylibrary.org).
- The number of HIV transmissions through SoHO in EU/EEA was based on Serious Adverse Reactions and Events (SARE) data provided by the European Commission for the period from 2017 to 2021.

Section 8: Processing and pathogen inactivation approaches

Search questions and objectives:

- To describe the effectiveness properties, specific to HIV, of pathogen inactivation or reduction methods that are approved or used in each type of relevant SoHO: blood (including all blood products), tissues, or cells (including reproductive cells).
  - Population: SoHO.
  - Intervention: pathogen inactivation or reduction methods.
  - Comparator: not applicable.
  - Outcomes: pathogen reduction values reported for HIV.
- To describe the impact of specific SoHO processing steps on HIV levels in each type of relevant SoHO: blood (including all blood products), tissues, or cells (including reproductive cells).
  - Population: SoHO.
  - Intervention: processing steps:
  - Sperm wash;
  - Density gradient centrifugation;
  - Filtration;
  - Freezing;
  - Lyophilisation;
  - Glycerolization;
  - Vitrification.
  - Comparator: not applicable.
  - Outcomes: pathogen reduction values reported for HIV.

Searches and eligibility:

- Searches were restricted from January 2001 to the present and covered MEDLINE only. Customised searches of grey literature using generic web search engines (e.g., Google) combined with searches in targeted websites were also conducted.

Only publications available in English were considered eligible.

- Randomised controlled trials, non-randomised controlled trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies were considered eligible for inclusion, as well as any study type reporting efficacy/effectiveness measures of pathogen inactivation or reduction in the context of SoHO. Letters and commentaries, conference abstracts, case reports, and case series were excluded.

Main outcomes:

- Reduction/inactivation methods:
  - Qualitative assessment of effectiveness (e.g. pathogen no longer detectable);
  - Quantitative assessment of effectiveness (e.g. log reduction).

- Processing methods:
  - Qualitative assessment of impact on pathogen reduction;
  - Quantitative assessment of impact on pathogen reduction (e.g. log reduction).
- Data extraction
  - Studies were assessed for relevance, first by title/abstract and then by full text, excluding at each step studies which do not satisfy the inclusion criteria. The studies were assessed by a single reviewer. Data were extracted by a single reviewer using a standardised data extraction form.
- Strategy for data synthesis:
  - The extracted data were described in a tabular format and no meta-analysis was conducted. The data corresponding to the protocol outcomes were presented by the type of reduction/inactivation or processing method.

No risk of bias assessment was performed.

- Analysis of subgroups or subsets:

  SoHO type, processing method
- Keywords for the search (PubMed):

Search strategy – reduction or inactivation

Concept	No.	Query	Results
All, >2001	5	#5 AND 2001:3000 [dp]	768
All	4	#1 AND #2 AND #3	817
Virus, HIV	3	"retroviridae"[MeSH Major Topic] OR "retroviridae infections"[MeSH Major Topic] OR virus*[Title/Abstract] OR "viral"[Title/Abstract] OR "retrovir*"[Title/Abstract]	1 253 178
Pathogen reduction or inactivation	2	"pathogen"[Title/Abstract] AND ("reduction"[Title/Abstract] OR "inactivation"[Title/Abstract] OR "solvent-detergent"[Title/Abstract] OR "methylene blue"[Title/Abstract] OR "ultraviolet"[Title/Abstract] OR "amotosalen"[Title/Abstract] OR "alkylating agents"[Title/Abstract] OR "washing"[Title/Abstract] OR "riboflavin"[Title/Abstract] OR "uv light"[Title/Abstract]) AND (effect*[Text Word] OR effic*[Text Word] OR impact[Text Word])	8 377
Donors and SoHO	1	"Tissue Donors"[Mesh] OR "Tissue Transplantation"[Mesh] OR "Blood Transfusion"[Mesh] OR "donor*"[Title/Abstract] OR "donat*"[Title/Abstract] OR "transfus*"[Title/Abstract] OR "transplant*"[Title/Abstract] OR "graft*"[Title/Abstract] OR "soho*"[Title/Abstract] OR "mpho*"[Title/Abstract] OR "blood"[Title/Abstract] OR "cell*"[Title/Abstract] OR "tissue*"[Title/Abstract] OR "plasma"[Title/Abstract] OR "cornea*"[Title/Abstract] OR "bone*"[Title/Abstract] OR "tendon*"[Title/Abstract] OR "skin"[Title/Abstract] OR "islet*"[Title/Abstract] OR "valve*"[Title/Abstract] OR "rbc"[Title/Abstract] OR "platelets"[Title/Abstract] OR "sperm*"[Title/Abstract] OR "oocyte*"[Title/Abstract]	10 722 543

Search strategy – processing methods

Concept	No.	Query	Results
All, >2001	5	#4 AND 2001:3000 [dp]	1 438
All	4	#1 AND #2 AND #3	1 684
Virus, HIV	3	"retroviridae"[MeSH Major Topic] OR "retroviridae infections"[MeSH Major Topic] OR virus*[Text Word] OR "viral"[Text Word] OR "retrovir*"[Text Word] OR "hiv"[Text Word]	1 547 614
Processing methods	2	(("pathogen"[Title/Abstract] OR "safety"[Title/Abstract] OR "microb*"[Title/Abstract]) AND ("processing"[Title/Abstract] OR "wash*"[Title/Abstract] OR "density gradient centrifugation"[Title/Abstract] OR "filtration"[Title/Abstract] OR "freezing"[Title/Abstract] OR "lyophilis*"[Title/Abstract] OR "glyceroli"[Title/Abstract] OR "Vitrification"[Title/Abstract]))	41 640
Donors and SoHO	1	"Tissue Donors"[Mesh] OR "Tissue Transplantation"[Mesh] OR "Blood Transfusion"[Mesh] OR "donor*"[Title/Abstract] OR "donat*"[Title/Abstract] OR "transfus*"[Title/Abstract] OR "transplant*"[Title/Abstract] OR "graft*"[Title/Abstract] OR "soho*"[Title/Abstract] OR "mpho*"[Title/Abstract] OR "blood"[Title/Abstract] OR "cell*"[Title/Abstract] OR "tissue*"[Title/Abstract] OR "plasma"[Title/Abstract] OR "cornea*"[Title/Abstract] OR "bone*"[Title/Abstract] OR "tendon*"[Title/Abstract] OR "skin"[Title/Abstract] OR "islet*"[Title/Abstract] OR "valve*"[Title/Abstract] OR "rbc"[Title/Abstract] OR "platelets"[Title/Abstract] OR "sperm*"[Title/Abstract] OR "oocyte*"[Title/Abstract]	10 730 103

Supporting documents

Terms of reference - expert panel

The 'Terms of reference for the scientific expert panel convened for the development of the ECDC technical guidelines on the prevention of donor-derived transmission of communicable diseases through Substances of Human Origin' can be provided by ECDC upon request

Conclusions from the ad-hoc-expert panel meeting

Abridged versions of the meeting minutes containing only decisions reached during the meetings can be provided by ECDC upon request.

Pathogen data sheet

See the supporting document 'Data sheet to support the development of the ECDC technical guidelines on the prevention of HIV transmission through Substances of Human Origin (15 March 2024)'.

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