

29/10/2025

CLINICAL TRIAL ELIGIBILITY CRITERIA FOR PATIENTS WITH HIV: GUIDANCE ON IMPROVING INCLUSION IN NON-HIV TRIALS

A proposal led by the European AIDS Treatment Group as part of the
Belong Project

Version 1

Background

The [Belong project](#) advocates for European regulatory authorities to adopt clinical guidelines that facilitate and support the inclusion of people living with HIV in trials for other illnesses and medical conditions affecting them.

To achieve this objective, the European AIDS Treatment Group (EATG) first developed [a position paper](#) in 2022 entitled “*Why people living with HIV must be included in non-HIV clinical trials*”. This paper describes the ongoing challenges in recruiting people living with HIV to non-HIV trials and outlines the rationale for their inclusion in these studies.

The present document builds on that foundation and describes the clinical guidance developed in collaboration with a broad range of stakeholders between July and October 2025.

Contents

Background.....	2
Introduction	3
1. Principles of Eligibility Criteria in Clinical Research	4
2. Exclusion of people living with HIV from clinical research.....	5
Recommendations	6
1 Eligibility of people living with HIV must be based on sound scientific or clinical rationale	7
2 Characteristics of the investigational product	7
3 Relevance of the condition under investigation for people living with HIV	8
4 Diversity of people living with HIV	8
5 HIV status and testing	8
6 Clinical status	9
6.1 History of AIDS-defining illness	9



6.2 Immune functions	10
6.3 Timing, type and effectiveness of antiretroviral therapy	10
6.4 Comorbidities	11
7 Product development stage.....	12
8 Clinical design	12
9 Engaging with communities of people living with HIV	13
10 Training and Capacity Building for Product Developers and End-Users.....	13
Funding and Independence Statement.....	14
References	14

Introduction

This guidance provides recommendations on defining eligibility criteria for clinical trials of drugs and biologics for the prevention and treatment of a range of non-HIV related medical conditions that affect people living with HIV. It is intended to assist clinical research stakeholders, including sponsors from industry and not-for-profit sectors, investigators, ethics review committees, regulatory authorities, and community representatives, in the design, conduct, and oversight of clinical trial.

The inclusion of people living with HIV in non-HIV trials must be guided by sound scientific and clinical reasoning, taking into account the nature of the intervention, the medical condition under study, the participant’s clinical status, and any factors that may affect either individual safety or the ability of the study to achieve its objectives.

This guidance promotes an evidence-based approach that avoids the arbitrary exclusion of people living with HIV from clinical research that may provide them with potential benefit.



This guidance recognises that increasing participation of people living with HIV in individual studies may not always be sufficient to draw definitive conclusions for this population. Dedicated studies may still be required. However, the early inclusion of people living with HIV, where appropriate, can help reduce delays in access to new treatments and ensure that research more accurately reflects the diversity of populations affected by these medical conditions.

1. Principles of Eligibility Criteria in Clinical Research

Appropriate representation in clinical research is essential to evaluate the safety and effectiveness of new therapeutics, improve the generalisability of trial results, ensure the equitable distribution of research benefits, and foster trust in the research process.¹

Eligibility criteria for participation in clinical research should comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, specifically E6(R3) and E8(R1).^{2,3} These guidelines note that “When appropriate, the participant selection process should be representative of the anticipated population who are likely to use the medicinal product in future clinical practice. When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations.”²

Sponsors, researchers, regulatory authorities, research ethics committees and other stakeholders must ensure a fair and equitable distribution of research benefits. This requires that research does not disproportionately focus on the health needs of a limited group of people; instead, it should aim to address diverse health needs across different groups.

According to ICH-GCP, appropriate eligibility criteria are essential for selecting trial participants in a way that ensures the study population can support the trial objectives and that the results are relevant and beneficial to those who may need the intervention. These criteria should be clearly documented in the clinical study protocol.³ The study population may be narrowly defined for safety or sensitivity or broadly defined to reflect the target population. Important, the participants selected for the research should reflect the population groups for whom the investigational product is intended once approved.



2. Exclusion of people living with HIV from clinical research

As people living with HIV live longer, they increasingly experience non-HIV-related health conditions common in the general population, often at earlier ages and with poorer outcomes.^{4,5} These include cardiovascular disease, chronic kidney disease, liver diseases, diabetes, non-AIDS cancers, osteopenia and osteoporosis, among others. People living with HIV are also more likely to face mental health issues, neurocognitive disorders, and other infectious diseases. These differences are driven by factors such as chronic immune activation, antiretroviral drug effects, co-infections, and health care disparities.

However, people living with HIV are frequently excluded from clinical research of potentially life extending or life-saving drugs and treatments for illnesses and comorbidities that affect them more than the general population.⁶⁻⁸

In many cases, the decision to exclude people living with HIV is arbitrary. When there is a potentially physiological rationale for exclusion, efforts to address safety concerns are rarely made. Yet, research has proved that it is possible for people living with HIV to contribute to the development of safe and effective treatment other than HIV therapy.^{9,10}

The exclusion of people living with HIV from key clinical studies has resulted in a lack of safety and efficacy data for this population and limits their access to new treatments. When not scientifically justified, such exclusion restricts the evidence base for prevention and treatment, and can contribute to, or worsen, health disparities and unequal access to treatment.

Expanding clinical trials eligibility to be more inclusive of people living with HIV has been shown to be safe in many cases and may accelerate the development of effective therapies for this group of people. Designing clinical trials that avoid the systematic exclusion of people living with HIV, and reflecting their inclusion in product labelling, also promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice. It is therefore imperative to develop evidence-based guidance specific to non-HIV related medical conditions that disproportionately or specifically affect people living with HIV.



Recommendations

This guidance is part of a global effort to promote greater diversity and representativeness in clinical research, with the aim of improving the generalisability of study findings and, ultimately, access to medicines for those who need them.^{11,12} This guidance is intended to complement existing guidelines and does not restate recommendations or best practices already detailed in ICH-GCP or other applicable clinical trial regulations. It is intended for use by industry, not-for-profit organisations, and other relevant stakeholders.

The guidance is intended to apply to both the prevention and treatment of a range of non-HIV related medical conditions that disproportionately affect people living with HIV. It covers all investigational products (e.g., drugs, biologics, vaccines, Advanced Therapy Medicinal Products such as cell and gene therapies, and drug-device combinations where relevant) across all disease areas, with particular emphasis on conditions that disproportionately affect people living with HIV.

Careful consideration should be given to the inclusion and exclusion of people living with HIV in non-HIV clinical trials. This requires that eligibility criteria be intentionally developed to avoid the arbitrary exclusion of people living with HIV from research that may offer them potential benefit. In this regard, existing guidance about eligibility criteria from the US Food and Drug Administration and the European Medicine Agency note that eligibility criteria should be developed taking into consideration: the mechanism of action of the investigational products; the targeted disease or patient population; the anticipated safety of the investigational drug; the availability of adequate safety data; and the ability to recruit trial participants from the patient population.

For people living with HIV, additional factors to consider include immune function, clinical status, and the potential for drug–drug interactions.

The following recommendations aim to support a holistic approach to defining eligibility criteria.



1 Eligibility of people living with HIV must be based on sound scientific or clinical rationale

Eligibility criteria, particularly those used to exclude people living with HIV from non-HIV clinical trials, should be carefully and proactively formulated and evaluated. Standardised protocol eligibility templates should not be used without justification.

People living with HIV should be appropriately represented in clinical studies, especially in disease areas where they are disproportionately affected, to allow for meaningful safety and efficacy analyses. Decisions on inclusion or exclusion should be guided by the considerations outlined in this document, and any exclusion of people living with HIV must be clearly documented and justified with a sound scientific and clinical rationale.

Risk assessments should be performed to ensure the safe and appropriate inclusion of all people living with HIV in trials. Where concerns exist and whenever feasible, study protocols should prioritise risk-mitigation strategies over exclusion (e.g. enhanced monitoring, temporary adjustment of antiretroviral therapy (ART), or management of potential drug–drug interactions). The participation of people living with HIV should be systematically recorded as part of the trial dataset. Data collection and reporting should adhere to ethical and regulatory standards, with particular attention to confidentiality and sensitivity, given the persistent stigma associated with HIV.

2 Characteristics of the investigational product

When evaluating the eligibility of people living with HIV in non-HIV clinical trials, the properties of the investigational drug should be considered from multiple perspectives.

These include drug’s mechanisms of action, existing safety data about the investigational drug or other class-related drugs, the potential or suspected drug–drug interactions with ART and concurrent treatment for comorbidities, and whether a temporary treatment switch may be feasible and appropriate (see Recommendations 6.3 and 6.4).

Protocols must explicitly state whether the investigational drug has a known or potential immunosuppressive effect, which may in some cases justify the exclusion of people living with HIV.



3 Relevance of the condition under investigation for people living with HIV

Where a medical condition poses an increased risk or disproportionately affects people living with HIV, their inclusion in clinical trials should be encouraged, provided participation does not compromise individual safety or the study meeting its objectives. Any exclusion of people living with HIV due to safety concerns or conflicts with study objectives must be clearly documented in the study protocol.

This approach promotes equity and accelerates the generation of evidence that is directly relevant to people living with HIV.

4 Diversity of people living with HIV

The literature on comorbidities associated with HIV is substantial, yet it has significant limitations. Much of the existing research focuses on narrow demographic groups, often over-representing specific regions, genders, or age brackets. As a result, there are gaps in understanding how comorbidities vary, and potentially interact, across gender, age, geography and other factors such as social determinants of health and life circumstances.

Consequently, the ICH-GCP recommendations and sponsor commitment to ensuring diversity and appropriate representation in clinical research should extend to all people living with HIV, considering factors such as gender and age, particularly when medical conditions may affect these subpopulations differently.

5 HIV status and testing

HIV testing should not be mandated as part of general trial eligibility for non-HIV studies; however, if there is a suspected risk specifically associated with enrolling a person living with HIV in a non-HIV trial, testing should be offered (See Recommendation 2).

To minimise the risk of stigma and ensure comprehensive participant safety, study protocols should, where appropriate, offer testing for other major blood-borne infections that may influence the conduct or interpretation of clinical research (e.g. hepatitis B and C).

In trials addressing conditions for which people living with HIV may be at increased risk, or that disproportionately affect them, HIV testing should be offered as an option when a prospective



participant's HIV status is unknown. This ensures that participants are not placed at risk due to unrecognised HIV infection, while also supporting appropriate medical study oversight and data interpretation and providing an opportunity to expand access to testing.

When HIV-positive status is not an exclusion criterion, the study protocol should explicitly state that people living with HIV are eligible to participate in the research.

In all cases, HIV testing must be performed in accordance with existing guidelines and best practices.

6 Clinical status

The following clinical parameters should be considered when assessing the eligibility of people living with HIV for participation in non-HIV clinical trials. These parameters inform eligibility decisions, as well as clinical monitoring and management throughout the trial.

- History of AIDS-defining illnesses.
- Immune functions.
- Timing, type and effectiveness of antiretroviral therapy.
- Comorbidities.

6.1 History of AIDS-defining illness

The participant's history of AIDS-defining illnesses such as opportunistic illnesses should be evaluated in the context of the timing of the illness, the intervention under study in the clinical trial and the medical condition being investigated.

- People living with HIV who do not have a history of AIDS-defining opportunistic illnesses should be considered eligible for participation in non-HIV clinical trials.
- For those with a prior history of such illnesses, eligibility should be determined based on a study-specific risk assessment. Decisions to include or exclude people living with HIV should consider the timing and control of the AIDS-defining opportunistic illnesses, and their relevance to the medical condition under clinical investigation.



- Uncontrolled AIDS-defining illnesses are a valid reason to exclude an individual from a clinical trial. However, participation may be reconsidered once the illness is adequately controlled.
- When an illness occurred in the distant past and has been fully resolved, it should not generally preclude participation. The appropriate duration for defining an infection as ‘controlled’ may vary; in general, a 12-month period since the illness has been resolved may be reasonable, depending on the type of illness, risk of recurrence, and effectiveness of available treatment. Shorter window periods may be considered if the illness is clinically controlled and prophylaxis is adequate.

6.2 Immune functions

CD4⁺ T-cell count and CD4⁺/CD8⁺ T-cell ratio, as surrogates of immune function, are important factors to consider when relevant to the clinical investigation. However, CD4⁺ T-cell thresholds should not be used as systematic exclusion criteria without an appropriate, study-specific risk assessment.

CD4⁺ T-cell count should be evaluated in the context of the investigational product, the stage of the clinical research, the medical condition under study, and the potential of the intervention to prevent, cure, or mitigate the medical condition.

- Patients with sustained CD4⁺ T-cell counts of ≥ 350 cells/ μ L should generally be considered eligible for any study provided they are on suppressive ART.
- For participants with CD4⁺ T-cell < 350 , eligibility may be considered based on other immune surrogate markers such as CD4:CD8 ratio, concomitant medical conditions, ART history, etc.

6.3 Timing, type and effectiveness of antiretroviral therapy

Eligibility criteria may specify a minimum duration since initiation of ART or exclude patients on a specific antiretroviral drug or drug regimen. Requirements must be justified and documented. People living with HIV should provide input into the study design, and adequate training should be provided to the trial team if they lack experience in managing ART.



Time on ART should be set in relation to the investigational product, the stage of the clinical research, the medical condition under study, and the potential of the intervention to prevent, cure, or mitigate the medical condition.

Studies should enrol virologically suppressed patients unless there is a clear potential benefit for including a patient with unsuppressed HIV that outweighs the risks. In such cases, appropriate risk management, clinical monitoring, and oversight must be implemented.

Transient viraemia (“viral blips”) should not automatically lead to exclusion without adequate clinical assessment. Similarly, nadir CD4+ count should not be used as an eligibility criterion, as it may unfairly exclude people living with HIV from participation in non-HIV trials.

Based on known or potential drug–drug interactions and overlapping cytotoxicity between HIV therapy¹, the investigational product, and treatments for other comorbidities, mitigation strategy such as switching to an alternative effective ART regimen during administration of the investigational drug should be considered.

Exclusion of participants receiving specific ART should be considered only when there is a known or theoretical risk of toxicity and switching to an alternative effective ART regimen is not feasible during treatment with the investigational product.

The study protocol may allow short interruptions of antiretroviral therapy to manage existing or emerging drug–drug interactions between ART and the investigational product, provided this does not compromise individual safety, or to meet the study objectives.

Treatment interruption should be exceptional and only considered when the potential benefit of the investigational product clearly outweighs the risks to the participant. Any treatment interruption must be supported by a thorough risk assessment and appropriate management plan, including clinical monitoring and oversight. Decisions should always involve the study participant and HIV specialists, particularly in non-HIV research settings.

6.4 Comorbidities

In non-HIV clinical trials, HIV should be considered and managed like any other comorbidity that may affect a study participant. This includes recognising that HIV may contribute to polypharmacy and increase the risk of drug–drug interactions. Accordingly, HIV should be evaluated as part of the participant’s overall medical history and clinical management.

¹ For example, using the Liverpool Drug Interactions resources <https://www.hiv-druginteractions.org/>



Appropriate clinical monitoring, specialist consultation, and risk mitigation strategies should be implemented as needed, rather than using HIV status as an exclusion criterion.

Switching to an alternative effective treatment regimen for comorbidities during the clinical trial should be considered when there is a clear potential benefit that outweighs the risks, with appropriate risk management, clinical monitoring, and oversight in place.

When comorbidities can be effectively managed or prevented (e.g., hepatitis B vaccination), standard-of-care interventions should be applied to enable the safe participation of people living with HIV in non-HIV trials.

7 Product development stage

Eligibility criteria should consider the stage of development of the investigational product or intervention.

- In early-phase trials, where the primary focus is on assessing investigational product safety, the exclusion of people living with HIV from non-HIV trials may be justified.
- However, from Phase 2 onwards, people living with HIV should be considered eligible provided they meet other relevant eligibility criteria as outlined above.

Regardless of the stage of clinical development, people living with HIV should be engaged in research preparedness activities from an early stage (see Recommendation 9).

8 Clinical design

Although exclusion of people living with HIV may be justifiable on sound scientific or clinical grounds, it is valuable to explore innovative trial designs that allow for a phased or stepped approach to enrolment. These include staggered inclusion, HIV stratification, subgroup estimands, sensitivity analyses.

Flexibility can be built into eligibility criteria so that, once the safety of the product or intervention is established, people living with HIV may begin to be included in the study population.



9 Engaging with communities of people living with HIV

It is important to proactively and meaningfully involve communities of people living with HIV as early as possible in the clinical development process, even if inclusion in the earliest trial phases is not feasible.

Early engagement of people living with HIV in clinical research offers an opportunity to build trusted relationships between patients, researchers, and health professionals.^{13,14} It also strengthens research at every stage, from clinical protocol development to product implementation and policy-making, by improving the relevance, acceptability, and effectiveness of a medical intervention (See the principles of Meaningful Involvement of PLHIV and Affected Communities, MIPA).¹⁵

Collaboration between people living with HIV, regulatory agencies, and trial sponsors should be actively fostered throughout the drug development process, building on good participatory practices as previously established for HIV biomedical research.¹⁶ The HIV community has been a key stakeholder in clinical research with a long-standing record of engagement and it should be given opportunities to contribute meaningfully to the design and implementation of non-HIV clinical research.

Engagement with both commercial and non-commercial trial sponsors is essential to emphasise the benefits of developing products that are safe and effective for use across a broader patient population, including people living with HIV.

10 Training and Capacity Building for Product Developers and End-Users

The HIV response has a long history of educating both affected communities and health professionals, fostering meaningful engagement between people living with HIV or at risk of HIV and those involved in research and care. However, similar levels of engagement of people living with HIV in other medical fields are less common.

Education and capacity building among non-HIV healthcare professionals and researchers on comorbidities affecting people living with HIV are essential, as is raising awareness that HIV can coexist with other health conditions.

Study sponsors must take proactive steps to inform investigators and research staff that people living with HIV can safely participate in non-HIV trials. In addition, mandating the collection and



reporting of data on the inclusion of people living with HIV (see Recommendation 1) will help monitor progress and promote their meaningful participation in non-HIV research. All people living with medical conditions should be empowered to advocate for their right to participate in clinical research that may inform and improve their treatment and care.

Funding and Independence Statement

The Belong project was developed by the EATG with funding support from ViiV Healthcare, Gilead Sciences, and Novartis. EATG acknowledges that the sponsors had no influence over the structure or content of the project.

References

- 1 Schwartz, A. L., Alsan, M., Morris, A. A. & Halpern, S. D. Why Diverse Clinical Trial Participation Matters. *New England Journal of Medicine* 2023; 388, 1252–1254.
- 2 European Medicines Agency. Guideline for good clinical practice (GCP) E6(R3). 2025; published online July 23. <https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline>.
- 3 European Medicines Agency. ICH guideline E8 (R1) on general considerations for clinical studies. 2022; published online April 14. <https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies-scientific-guideline>.
- 4 Taiwo BO, Romdhani H, Lafeuille M-H, Bhojwani R, Milbers K, Donga P. Treatment and comorbidity burden among people living with HIV: a review of systematic literature reviews. *J Drug Assess*; 2023; **12**: 1–11.
- 5 Lerner AM, Eisinger RW, Fauci AS. Comorbidities in Persons With HIV: The Lingering Challenge. *JAMA* 2020; **323**: 19–20.
- 6 Vora KB, Ricciuti B, Awad MM. Exclusion of patients living with HIV from cancer immune checkpoint inhibitor trials. *Scientific Reports* 2021; **11**: 1–6.
- 7 Venturelli S, Pria AD, Stegmann K, Smith P, Bower M. The exclusion of people living with HIV (PLWH) from clinical trials in lymphoma. *British Journal of Cancer* 2015; **113**: 861–3.
- 8 Leone, A. G. *et al.* Inclusion of people living with HIV in Food and Drug Administration (FDA) oncology pivotal registration trials from 2020 to 2024. *Journal of Clinical Oncology* 2025; **43 (16_suppl)**:1517-1517.
- 9 Reuss JE, Stern D, Foster JC, *et al.* Assessment of Cancer Therapy Evaluation Program Advocacy and Inclusion Rates of People Living With HIV in Anti-PD1/PDL1 Clinical Trials. *JAMA Network Open* 2020; **3**: e2027110–e2027110.



10 Shah NJ, Al-Shbool G, Blackburn M, *et al.* Safety and efficacy of immune checkpoint inhibitors (ICIs) in cancer patients with HIV, hepatitis B, or hepatitis C viral infection. *Journal for ImmunoTherapy of Cancer* 2019; **7**: 1–8.

11 Department of Health and Human Services, United States. Food and Drug Administration, United States. Food and Drug Administration. Office of Medical Products and Tobacco. Oncology Center of Excellence, Center for Biologics Evaluation and Research (U.S.), Center for Drug Evaluation and Research (U.S.). Cancer clinical trial eligibility criteria : patients with HIV, hepatitis B Virus, or hepatitis C Virus Infections. Silver Spring, MD: United States Food and Drug Administration, Oncology Center of Excellence, 2020. <https://collections.nlm.nih.gov/catalog/nlm:nlmuid-9918227352206676-pdf> (accessed July 22, 2025).

12 Food, Administration D. Enhancing the Diversity of Clinical Trial Populations – Eligibility

Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. 2020.

<https://www.federalregister.gov/d/2020-24881>

13 Shakhnenko I, Husson O, Chuter D, van der Graaf W. Elements of successful patient involvement in clinical cancer trials: a review of the literature. *ESMO Open*. 2024; **9**(4):102947.

14 Gobat N, Slack C, Hannah S, *et al.* Better engagement, better evidence: working in partnership with patients, the public, and communities in clinical trials with involvement and good participatory practice. *The Lancet Global Health* 2025; **13**: e716–31.

15 UNAIDS. Policy Brief. The Greater Involvement of People Living with HIV (GIPA). 2007.

16 Good participatory practice: Guidelines for biomedical HIV prevention trials (2011). https://www.unaids.org/en/resources/documents/2011/20110629_JC1853_GPP_Guidelines_2011%20OK (accessed Nov 9, 2022).

