European AIDS Treatment Group

EATG Position Paper
Inclusion of people living with HIV
in non-HIV clinical trials - September 2022

Why people living with HIV must be included in non-HIV clinical trials

BELONG: Inclusion of people living with HIV in non-HIV clinical trials

Contents

Key messages

- Where HIV treatment is available and accessible, people living with HIV are living longer lives and are developing illnesses seen in the general population.
- People living with HIV often experience multiple illnesses that can strongly impact their quality of life. At the same time, they are still marginalised and do not receive the same level of healthcare as the general population.
- People living with HIV are frequently and arbitrarily 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.
- 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 treatment.
- People living with HIV should not be arbitrarily excluded from non-HIV clinical research. European national and supranational regulatory authorities should adopt consensus guidelines supporting their participation in non-HIV clinical research.
- Meaningfully engaging people living with HIV in clinical research is paramount to building a trusting relationship between patients, researchers and healthcare personnel while aiming for equitable access to treatment and healthcare for all.
- Advocating that people living with HIV are included in non-HIV clinical research contributes to a global patient empowerment effort and democratisation of the research process.

1. Why is EATG advocating that people living with HIV be included in non-HIV clinical trials?

The European AIDS Treatment Group (EATG) is a member-led network of more than 150 volunteer activists, mostly people living with HIV, based in 45 countries across Europe and Central Asia. EATG members represent different communities coming together to strengthen the voices of people living with or at risk of acquiring HIV in clinical research, as well as in the design, implementation and evaluation of policies, laws and programmes that affect their lives. EATG members come from a diverse range of backgrounds. They include community and patient activists, social workers, researchers, medical doctors, service providers, counsellors, and community-based peer workers. All are linked to national, regional and sub-regional organisations.

As people living with HIV live longer lives, they may experience non-HIV-related health conditions and illnesses that affect the general population but that can affect them more than the general population[1,2].

However, there is a lack of safety and efficacy data on the treatment for these ailments in people living with HIV, which can limit their access to appropriate healthcare. This information is missing because people living with HIV have historically been excluded from clinical research of potentially life-extending or life-saving drugs and treatments for these illnesses and comorbidities.

Patients, researchers and research sponsors recognise that patients should be actively involved in the design, conduct and dissemination of clinical research. Participation in research is essential for patient empowerment and it benefits all stages of clinical investigation. Studies have shown that it is feasible and beneficial to involve patients in the planning, implementation and dissemination of clinical research[3]. Participation in research is also important as it gives patients a sense of control over healthcare decisions. In a survey conducted in the UK[4], research participants said they wanted to be part of the wider picture; they felt that their participation was valued and that they had an impact on the research.

There is increasing evidence that the participation of people living with HIV in clinical research is safe and benefits product development. This underlines the urgent need to advocate against the systematic exclusion of people living with HIV and for their increased participation in non-HIV clinical trials.

With this position paper, EATG aims to:

(1) Inspire all people living with a health condition to fight for their right to be part of clinical research whose outcomes may benefit their treatment and care.
(2) Support the development and implementation of inclusive clinical research guidelines toward improving health outcomes for people living with HIV.
(3) Advocate that eligibility criteria, similar to those developed by the US Food and Drug Administration (FDA), be adopted by European countries and regulated by national and supranational regulatory agencies (such as the European Medicines Agency, EMA).
(4) Contribute to discussions in Europe and elsewhere towards the revision of Good Clinical Practice (GCP) Guidelines.

2. Comorbidities in people living with HIV

Antiretroviral therapy (ART) has revolutionised HIV treatment. However, an estimated 650,000 people died from AIDS-related illnesses globally in 2021, adding to the 40.1 million who have died from AIDS-related causes in the past four decades[5].

Today, when diagnosed early and ART is available, HIV is considered a chronic and manageable condition. There is a growing population of people ageing with HIV. In 2021, 38.4 million people were living with HIV and 1.5 million acquired HIV. Nearly 41% of people living with HIV in Western and Central Europe and North America are over 50 years old[6].

Although people living with HIV are living longer lives, they do not necessarily live better than the general population due to comorbidities related to HIV and ageing. These include cardiovascular disease and cancers, the leading causes of death in over-50s. People living with HIV are also at higher risk of developing certain illnesses from an earlier age and having poorer outcomes. These include cardiovascular disease, chronic kidney disease, osteopenia, osteoporosis, hepatic diseases, diabetes and cancers[7-9]. Other health conditions, including other infectious diseases, neurocognitive disorders and mental health-related conditions, are also more common among people living with HIV.

In some cases, ART reduces the risks of some of these comorbidities and leads to better outcomes. For example, ART lowers the risk of AIDS-defining cancers that are usually linked to viral infections (especially Kaposi sarcoma and non-Hodgkin lymphoma), although the risk remains higher for people living with HIV than the general population. ART does not generally reduce the risk or incidence of non-AIDS-defining cancer; on the contrary, as people on effective ART are no longer dying of AIDS-related illness, they are developing illnesses common in older age[10].

Overall, risk and severity of comorbidities in people living with HIV are often higher with poorer clinical outcomes. Stigma further complicates access to care[11].

3. Our concerns about the exclusion of people living with HIV from non-HIV clinical research

Stigma and discrimination against people living with HIV have been a regular feature of the HIV response since the first cases of AIDS were reported in 1981. Discrimination can affect all aspects of life for people living with HIV. Healthcare often marginalises people living with HIV, in both access to care services and treatment.

Given the higher life expectancy and risk of HIV-related illnesses and other comorbidities for people living with HIV today, it is a priority to ensure that they can easily access appropriate care.

Lack of diversity in clinical research, including HIV research, is well documented, with women, minorities and older patients being underrepresented[12-14]. Regulatory authorities, mainly in the USA, have engaged in an effort to improve diversity in clinical research with consensus guidelines and recommendations to ensure that trial populations are representative of target patient populations[15]. Study sponsors broadly acknowledge the issue, and some pharmaceutical companies are committed to increasing diversity and representation in their studies[16].

However, systematic data on the participation and contribution of people living with HIV in non-HIV clinical research remains limited. Clinical trials of non-HIV investigational drugs frequently exclude people living with HIV, solely based on their serological status, from research they could benefit from. This occurs even if their HIV is well controlled with an undetectable viral load and a normal CD4 count. Scientific or medical justifications for exclusion are often lacking.

Common exclusion criteria for people with HIV from non-HIV clinical trials:

- Use of live vaccines
- Use of immunosuppressive therapies
- Drug-drug interactions
- Lack of safety information

For example, the development of immune checkpoint inhibitors (ICIs) has transformed cancer treatment, but people living with HIV have been historically excluded from ICI trials. Research shows that 74% of 809 ICI trials starting in 2019-2020 excluded people living with HIV[17].

A 2015 study reported the exclusion of people living with HIV in 70% of interventional clinical trials on lymphoma in the UK[18]. Exclusion was based on positive serostatus and occurred for a range of drugs and treatments and in all phases of clinical research. Reviewing the nine study protocols available, investigators found only one biologically valid reason in one study and one potentially valid reason in another study that could have been circumvented. Overall, there were no scientific or safety rationales provided to exclude people living with HIV from these studies.

A 2020 study assessing trends in inclusion of people living with HIV in ICI studies between 2014 and 2019 observed that only 14 out of 87 studies included people living with HIV at the letter of intent stage[19]. However, following an advocacy effort led by the Cancer Therapy Evaluation Programme, a US National Cancer Institute initiative[20], people living with HIV were included in 61 out of 87 trials that had initially excluded them from the research. Improved inclusion was observed at all stages of clinical research and for a range of ICIs. Inclusion was possible through the creation of HIV-specific eligibility criteria that included baseline CD4 count, minimal to undetectable viral load (VL) and clinical stability on ART.

Exclusion of people living with HIV from ICI trials occurs despite evidence that these drugs are safe and effective for people living with HIV [21-23]. It occurs despite consensus guidelines backed by the American Society of Clinical Oncology and the FDA[24] that recommend the inclusion of people living with HIV with adequate immune function in cancer trials.

In many cases, the decision to exclude people living with HIV is arbitrary. When there is a potentially viable biological explanation for exclusion, efforts to address safety concerns are rarely made. If people living with HIV are regularly excluded from research, it will never be possible to know if their exclusion is warranted.

The exclusion of people living with HIV from important non-HIV clinical studies leads to a lack of safety data for old and new treatments and prevents people living with HIV from receiving effective treatment.

4. EATG supports what is proven to benefit people living with HIV

Clinical research plays a crucial role in the development of new drugs and treatments by providing the necessary

evidence (for example, efficacy and safety) to support clinical management policies and practice. Appropriate and comprehensive research evidence is central to effective patient care. It is equally critical to engage and empower patients so that they can shape the research process, as well as choose how to be involved in it.

The conduct of clinical trials relies on rigorous and universal standards enshrined in international, regional and national clinical trial legislation[25]. Defining eligibility criteria for a study population is paramount to the relevance of the study results. Different people may have different responses to the same treatment, based on their age, gender, ethnicity, and other factors.

Eligibility criteria should be developed taking into consideration: the mechanism of action of the drug; 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 to meet the objectives of the clinical trial (Source: FDA[15]).

For example, during the COVID-19 pandemic, studies showed that people living with HIV have an increased risk of severe COVID-19 illness and an increased risk of dying from COVID-19. Nevertheless, people living with HIV were often not included in key COVID-19 vaccine studies[26]. Later studies showed that COVID-19 vaccines were safe and effective in people living with HIV, but observed weaker, poorer and shorter responses to vaccination[27-31]. This emphasises the importance of diversity during the recruitment of participants in the early stages of clinical research.

As certain groups and populations remain underrepresented in clinical research, regulatory authorities, such as the FDA, have developed guidance to increase enrolment of underrepresented populations in clinical trials and support new drug applications[15]. These guidelines have been extended further to define eligibility criteria for the inclusion of patients with HIV, hepatitis B virus or hepatitis C virus in cancer trial applications[24].

Appropriate representation in clinical research is essential to:

- Assess the safety and effectiveness of novel therapeutics.
- Increase the generalisability of clinical trial results.
- Ensure equitable distribution of the benefits of the research.
- Enable and foster trust in research.

EATG calls upon the EMA and other regulatory authorities in Europe to adopt clinical guidelines similar to those developed by the US FDA. It recommends that the scope of the guidelines includes other illnesses and health conditions that affect people living with HIV.

In addition, EATG believes that universal ethical principles provide a strong rationale for the recruitment of people living with HIV in non-HIV trials, especially the principle of equitable distribution of benefits and burden[32]. Sponsors, researchers, governmental 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.

The unjustified exclusion of certain groups of people from research limits information that is relevant to the prevention and treatment of diseases. It can result in, or exacerbate, health disparities and inequitable access to treatment.

EATG believes that the inclusion of people living with HIV is essential to accelerate the development of, and access to, effective therapies for pathologies affecting this population, whether they are related to HIV or not. Further, including safety and efficacy information specific to people living with HIV in the drug's label promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice.

The early engagement of people living with HIV in clinical research is an opportunity to build a trusted relationship between patients, researchers and health professionals. This contributes to addressing health disparities and fostering health equity.

5. Recommendations for stakeholders

EATG is committed to encouraging and supporting programme planning, implementation and evaluation processes that meaningfully involve people living with HIV. The adoption by the EMA and other European health regulatory authorities of guidelines mirroring those developed by the FDA is a first step towards better

representation of people living with HIV in non-HIV clinical research. Improving access of people living with HIV to the best healthcare available requires systematically addressing current research thinking and practice.

Specifically, EATG recommends that stakeholders:

- **Track the inclusion of people living with HIV in non-HIV clinical research in the model of the US Drug Trial Snapshots[33]. The snapshots provide consumers and healthcare professionals with concise information about who participated in clinical trials that supported FDA approval of new drugs.**
- **Ensure the rapid implementation by clinical research sponsors at the European level of the revised ICH-GCP General Considerations for Clinical Trials guidelines. The guidelines recommend the inclusion of participants representative of the diverse populations that will receive the intervention in clinical practice[34].**
- **Develop evidence-based guidelines specific to health conditions that disproportionally or specifically affect people living with HIV. These guidelines should consider stages of the research and include monitoring plans for the safe participation of people living with HIV.**
- **Further develop knowledge on drug interactions and encourage the use of the University of Liverpool HIV drug interaction resource[35] as a reference when defining eligibility criteria.**
- **Encourage national and supranational health regulators to assess exclusion criteria and require that investigators justify exclusion of people living with HIV.**
- **Uphold the ethical principles set forth in Guidance 3 of the International Ethical Guidelines for Health-related Research Involving Humans during the ethical review of research protocols.**
- **Emphasise the importance of diversity in non-HIV clinical trial recruitment, including transgender people and women living with HIV.**
- **Fostering collaboration between people living with HIV, regulatory agencies, and trial sponsors in the drug development process. The community of people living with HIV is an important stakeholder and must be given the opportunity to provide input into clinical research.**
- **Engage with commercial and non-commercial clinical trial sponsors to emphasise the benefit of developing products that can be safely used across a broader patient population.**
- **Engage clinical trial teams in educational programmes on the value of diversity and inclusiveness in clinical research (for example, increased generalisability of the study results and improved access to treatment).**

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About the European AIDS Treatment Group

The European AIDS Treatment Group (EATG) is a patient-led NGO that advocates for the rights and interests of people living with or affected by HIV/ AIDS and related co-infections within the WHO Europe region. Founded in 1992, the EATG is a network of more than 150 members from 45 countries in Europe. Our members are PLHIV and representatives of different communities affected by HIV/AIDS and co-infections. EATG represents the diversity of more than 2.3 million people living with HIV (PLHIV) in Europe as well as those affected by HIV/AIDS and co-infections.

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