European
AIDS Treatment
Group

STEPS8: A Community Initiative to Design the Pathway to a Longer-Term Remission of HIV Infection

Summary Report

Glasgow, 23 October 2022

In Memory of Giulio Maria Corbelli

Interoffices | Avenue des Arts 56-4c, 1000 Brussels, Belgium | +32.2626.9640 | office@eatg.org eatg.org

Highlights

- Investing in HIV cure research is not a curiosity exercise but aims to solve many unanswered issues faced by people living with HIV.
- The strengthening of community involvement in HIV cure research is essential to the development and implementation of clinical trial strategies.
- The implementation of HIV cure-related trials remains complicated, even with strategies considered safe.
- A life-long remission (functional cure) is a more realistic objective than a sterilising cure. It is also easier to implement and safer.
- Researchers in the HIV cure field must work collaboratively.
- The impact of participation in cure-related research on individuals is something to consider fully before designing studies.
- Also, to consider, is the fact that some people with HIV perceive long-acting drugs almost as a cure.
- More effort on communication about why cure-related research is important is needed.

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Background

In recent years, there has been a renewed scientific focus on therapeutic strategies for long term drug-free remission from HIV infection. This research is widely supported by both the scientific and advocacy communities. However, it raises critical issues such as minimising risk for analytical treatment interruptions and restarting therapy, assessing benefit-risk balance, managing expectations from clinical trial participants, providing update and reliable information accessible to participants and to the community at large.

The STEPS workshops, initiated by **Giulio Maria Corbelli** in 2014 and organised annually ahead of the main European HIV scientific events, are an opportunity to expand the dialogue among community members, researchers and other relevant stakeholders, such as peer educators, community journalists, advocates, industry partners and healthcare professionals, in order to promote the share of knowledge, information, experiences from different perspectives, as well as community engagement in research on the HIV cure and related topics.

The 8th STEPS HIV Cure Community-led Workshop took place on Sunday October 23, 2022 in Glasgow (Scotland). Coordinated by **Sean Hosein** and chaired by **Brian West**, the workshop addressed approaches for HIV cure research, provided updates on therapeutic vaccination and highlighted the significance of the contributions of the community.

The present report was prepared by **Alain Volny-Anne** and provides an overview of key messages from the workshop.

HIV Cure - Where do we stand?

Overview of HIV cure/remission research with different approaches

Dr. Casper Rokx, Erasmus University Medical Centre Rotterdam (The Netherlands)

To access the slides, click here.

"Can I ever get rid of it? Can I stop my pills one day? What's new out there? Do you think there will be a cure in my lifetime? Will my children live to see that?" are questions asked by people with HIV to their physicians, either at the beginning of their care pathway or along the road – questions that scientists should focus on, if an HIV cure is to be found.

Casper Rokx highlights the significance of team work around the search for an HIV cure.

Antiretroviral therapy (ART) reduces the HIV viral load to undetectable levels, considered as a good proxy for survival, since this contributes to preventing the development of AIDS and improving people's general health. However, HIV is never out of the body. This can be seen directly in the HIV reservoir, but also indirectly through the host-response (a response to HIV by the individual's immunity). This residual immune activation can be found in blood and tissues in almost all people living with HIV, and should not be neglected since it has an accelerating and/or enhancing impact on the ageing process, which includes the potential development of comorbidities.

"Do we need an HIV cure?" is a question heard once in a while within the scientific community, because HIV is now well-treated with ART and has become a chronic disease. However, investing in HIV cure research is not a curiosity exercise but aims to solve many unresolved issues faced by people living with HIV:

- Despite its increase thanks to ART, many people with HIV have a life expectancy that is still not equal to that of the general population.
- inflammation-driven comorbidities that people with HIV can experience often result in a reduced quality of life.
- The costs of treatment and care.
- The risk of the emergence of HIV variants of concern (mutations that could lead to HIV resistance to ART).
- HIV stigma.

In essence, an HIV cure should control HIV reservoir cells (which are latent, after being infected by HIV). There is one major challenge: these cells are hard to find (at least as rare as one in a million cells, depending on the tissue studied) and can be found dispersed in different tissues, including the brain, testicles, spleen, lymph nodes and so on.

Extremely rare are cases of individuals who were cured of HIV thanks to a stem cell transplant (stem cells lacking the HIV entry co-receptor CCR-5). Another major challenge is to find a matching donor without the CCR-5 receptor. Moreover, a stem cell transplant is far from being without risk for a patient.

For the recently reported "New-York City case", researchers used umbilical cord blood cells. This scientific step is huge: cord blood cells have less potential to cause graft versus

host disease, are more available and can adapt to a new host. Of note, no single HIV reservoir cell in 100 million blood cells has so far been found in the tissues of the woman from New-York City.

Casper briefly describes the two current approaches of cure research. The sterilising approach or eradication of HIV from the body approach, is now known to be

i) almost impossible to reach with the currently available medicines; and
ii) very rarely possible with the host's own immunity.

Beyond stem cell therapy, gene therapy might be an option in the future:

a) CD4s would be taken out of the body (ex vivo), genetically manipulated to become rid of the CCR-5 receptor, then reinfused in individuals); or
b) The HIV DNA that is integrated in people's genomes would be excised.

Among the challenges to consider is the off-target effect of genetic manipulation, that could lead to a risk of oncogenic developments.

The background principle of the functional cure is that HIV will remain in the body, on a "sleeping mode" (low amounts, inactive or immunity-controllable). The cure could be reached by passive immunisation (ex vivo manipulation to increase T-cell potency towards attacking HIV, or use of broadly neutralising antibodies (bNAbs)), active immunisation (therapeutic vaccination to either induce antibodies or anti-HIV T-cells, but in a better way than biology does with a constant immunisation process), or "shock and kill".

Finding the reservoir cells requires an assay that is sensitive and a large amount of blood in which to look for them. The assay must have some discriminatory power to distinguish between dead and live cells. Other reservoir sites might exist that need to be identified. Also, having a validated biomarker (everywhere in the blood, easily measurable) for a cure would be a key step.

Current approaches to HIV Cure Research are built around two main priorities: understand (HIV cure, reservoir, hurdles) and intervene. Among the focus areas of this programme are the necessity to personalise approaches to cure as early as possible and to include understudied populations in cure research. Casper highlights the need to synergise intellect within a network such as those that he has been collaborating with: the EHEG.

Focus areas

1) Which drugs (clinical translation of cure drugs) – basically what the EHEG is working on is a cure drug pipeline, starting with the targeted screening of compounds potentially capable of purging the HIV reservoir and the characterisation of host-responses. The LUNA clinical trial illustrates this strategy.

   LUNA was a 6-week randomised proof-of-concept clinical cure trial looking at one compound identified over ten years ago: pyrimethamine (already used in HIV against toxoplasmosis). The drug can target the reservoir, manipulate it, shock it (by which there is hope that these latently infected cells will produce antigens, to become visible to the immunity and destructible).

The study has shown that pyrimethamine can reactivate the HIV reservoir. The drug did not lead to a measurable HIV reservoir decline, but it should be noted that this is a very first step in the research on this compound towards an HIV cure.

2) Personalise the approaches (find the right drugs for the right people) – it is important to stratify and study potential cure drugs as per key characteristics of people that usually influence responses to therapy, namely sex, therapy duration, disease stage and HIV subtypes. Then, the next step is to identify which of these drugs will be the most promising in a cure clinical trial.

   Such a trial will probably require an analytical treatment interruption (ATI) for the observation of efficacy. It will also be important to keep adding new products from the pipeline in the trial – this is the principle of an adaptive trial platform.

3) Prioritise understudied populations – the EU2cure consortium is planning to launch a research project on HIV subtypes, the most studied one in the HIV cure field being subtype B (the most prevalent in Western countries, but unfortunately not in parts of the world that bear the brunt of the HIV pandemic). Casper explains that since HIV subtypes behave differently and can affect clinical outcomes, it is important to look into this as early as possible.

4) European Network – Casper presents the many complementary studies performed so far in HIV cure and reiterates that it is essential to synergise efforts around specific goals in the field of HIV cure research.

Casper concludes his presentation by stating that the strengthening of community involvement in HIV cure research is essential to the advancement of clinical trial strategies in the field.

Q&A Session

- From what specific stage of this research could the most concrete results be expected within the next ten years?

  Scientists involved in HIV cure research know towards which phenotypes they want to move: elite controllers (with a very engaged immune system to control HIV) and post-treatment controllers (with a very latent HIV and very small amounts of virus).

  It is easier to talk about what will not be achieved on a large scale within the next ten years. Stem cell transplant will remain very difficult to perform and gene therapy will not yet be ready for the clinic (although clinical trials are underway).

  Many teams are using this approach: a targeted activation of the immune system, either passively or actively, as well as the improvement of antigen presentation in reservoir cells. That is, to teach the immune system to recognize and attack HIV-infected cells. This would allow for a more durable HIV control.

  Importantly, the first step in this strategy would be to identify patients whose reservoirs could be reactivated “easily”, while they still have a preserved immunity, such as people who are going through an acute phase of HIV infection.

Approaches to remission and European research in therapeutic vaccines

Prof. Jean-Daniel Lelièvre, Inserm/APHP/UPEC (France)

The EHVA T02/ANRS VRI 07 Clinical Trial

To access the slides, click here.

By way of introduction, Jean-Daniel tells the meeting that he wants to provide a feedback on the implementation of the EHVA T02/ANRS VRI 07 (therapeutic vaccine) trial, but also on scientific expectations and reality on the ground.

He introduces the EHVA consortium: 39 partners from 11 countries in Europe, 4 in sub-Saharan Africa and the US, with leading scientists and community experts in the fields of molecular and structural biology, vectors, adjuvants, delivery, immunology, clinical science and biostatistics – all necessary expertise to build clinical trials. Launched in Paris in 2016, the consortium's objective is to set up HIV prophylactic and therapeutic vaccines, as well as cure trials. It also intends to develop new vaccines.

The EATG is a partnering organisation of the EHVA consortium.

Referring to the previous talk, Jean-Daniel addresses the two ways to think in terms of cure strategies. The first is the eradication of HIV from the body, for which there are only four known models. There are more models (elite controllers…) for the second, which is the functional cure. It is now widely accepted that:

- Cure strategies will require combined therapies.
- A life-long remission (functional cure) is a more realistic objective than a sterilising cure. It is also easier to implement and safer.
- Functional cure approaches need to combine therapeutic vaccination and immune-based therapies.

An analytical treatment interruption (ATI) is typically followed by a viral rebound within two months. However, in some cases, the control of HIV lasts longer (post-controllers). In elite controllers (who never received ART) HIV control is constantly associated with T-cell control. People on ART tend to not have a high number of antiviral CD8 cells as their viral load is controlled by the medicines. In contrast, elite controllers' specificity is that they maintain a high count of CD8 lymphocytes that are able to detect HIV-infected cells and attack them. Consequently, they have a low level of viral replication. Notably, in elite controllers, the CD4 qualitative defect observed in other people with HIV is not found.

HIV therapeutic vaccines developers want to mimic what is going on in elite controllers with, for example, products that will try to increase the quantity and the quality of the T-cell response.

Among the several issues encountered on this pathway is the fact that inducing CD8 responses requires endogenous protein expression. This target has been found to be achievable, but that was with live-attenuated vaccines, which are not recommended for people with HIV. Therefore, different platforms have been developed to allow for the

presentation of HIV epitopes (as protein expression) to CD8 T cells through vaccination: viral vectors, RNA and DNA vaccines (some being widely used in other fields such as COVID-19).

These products are based on the same principle: integrate the nucleic acid fragment into cells that will code for the proteins of interest delivered from the vaccine platform. It is also essential to choose the part of HIV to include in this type of vaccine. Generally, sequences coding for Gag, Pol and Nef are the ones chosen because it is known that CD8 cell responses against them are associated with viral load control, for example in elite controllers.

Finally, the combined use of vaccine platforms that, although different, express the same viral antigens (heterologous vaccination strategy) can also increase the CD8 cell count.

The EHVAT01 trial (the first trial of the series, designed in 2017): the choice of vaccines is shown (against a subtype B as the trial was run in Europe), as well as the trial design. The objective was to compare the efficacy of the two chosen products (DNA/MVA vaccines) to a placebo. Following the immunisation phase, there was a 24-week ATI.

The significance of combining different strategies – e.g a vaccine and an immunomodulator - in a search for a cure is highlighted again. It brought investigators in EHVAT02, designed in 2018, to combine vedolizumab (a monoclonal antibody) with their candidate therapeutic vaccine, in light of previous studies showing a potential synergy of the two.

Following the bankruptcy of the company making the DNA vaccine, the investigators decided to use only the MVA (which is a good immune response inducer).

Jean-Daniel addresses the restart (after an ATI) criteria. It was decided that the viral rebound could reach levels as high as 100.000 copies in the trial (which would not have been allowed in other countries like the US). This decision was based on results from the ANRS VRI 02 LIGHT trial showing no individual risk with a prolonged ATI even with a very high viral rebound, if patients had fulfilled the inclusion criteria (notably the CD4 nadir >350 CD4s and the CD4 baseline count of >500).

Why was it important to allow this high viral rebound? Because for clear comparisons between the vaccine efficacy and a placebo, a viral setpoint is needed. This setpoint cannot be met without a viral replication that is going on for a while. Indeed, there is no correlation between the slope of the viral load rebound and the setpoint, while there is a strong one between the setpoint and a normalised area under curve (nAUC).

EHVAT02 was launched in 2019, a couple of months before the COVID-19 pandemic. The investigators had to develop COVID-19 mitigation strategies. Among them was the requirement to have all participants having a complete COVID-19 vaccination scheme. A second launch took place in 2021. However, the project was confronted with a new problem: the monkey pox (Mpox) epidemic.

Jean-Daniel describes the potential impact of the Mpox vaccination on the EHVAT02 trial and the questions raised around the use of an MVA vaccine against that disease. Other major challenge: difficulties in recruiting patients in the trial. The target population number was 69, but four months into the trial, only 3 patients had been recruited. The

investigators decided to stop the trial (which also had time constraints, such as the future loss of European funding and the vaccine expiry).

The reasons why people with HIV would not join the EHVAT02 trial are currently being explored.

In his conclusion, Jean-Daniel emphasises the high interest in trials aimed at studying cure strategies in the course of HIV infection, both in patients and in the scientific community (there are many ongoing trials). However, he says that the implementation remains complicated even with strategies considered safe. It will be crucial to understand the reasons that led to the failure of the EHVAT02/ANRSVRI07 trial and take these lessons into account when planning other trials in the future.

Question and comment from the floor

- How easy is it today to study elite controllers, while guidelines recommend prescribing ART to anyone with HIV?

  It is important to differentiate elite controllers from post-treatment controllers, in whom immune correlates are quite different. In the former, the main immune actors are the CD8 cells, while in the latter, it is probably a combination of CD8 cells and Natural Killer (NK) cells, plus some other factors. A lot of research is going on to identify these mechanisms, for example in the context of an ATI – to answer the question: what will control HIV?

- It is striking that an HIV vaccine trial has had to be stopped due to two outbreaks of other viruses.

  It is equally important to acknowledge that the development of COVID-19 vaccines could not have been so fast without the knowledge accumulated over the years from the HIV vaccine field.

A Community Initiative to Design the Pathway to a Long-Term Remission of HIV Infection

Simon Collins, i-base (United Kingdom) and EATG

To access the slides, click here.

Simon Collins says that he wants to share informal comments from a community perspective about cure research. Over the last ten or fifteen years, there has been a huge interest in “cure-related research”. But words matter and using “cure research” may be misinterpreted by people with HIV as “research to be cured of HIV”. No matter how much an informed consent form explains that the study is NOT a cure study, one individual might think that whatever, they might be the only lucky one to be cured in that study.

This non-ethical disconnect could be difficult to overcome, as even with more cautious terms such as “cure-related research” this risk could exist. The good news is that cure-related research has been funded and that researchers working in this field have done so collaboratively.

Simon highlights the incredible every-five-year work done by the International AIDS Society (IAS): a review of what happened in the field in the previous five years, and design of a sort of roadmap based on the scientific questions that should be answered within the next five years. He also says that the report language may be difficult to understand to some readers (the last one, published in Nature Medicine on World AIDS Day 2021, covers 170 new studies, showing how significantly the field is moving on).

A summary of the paper is published for medical journalists in a slightly less technical language, and there are translations into Spanish, Portuguese and French. Another tool was developed, in very easy-to-read language, by people from the community who were involved in the IAS working groups *(Hand-outs are circulated in the audience)*.

From the IAS technical report, one of the easy things to explain is the HIV reservoir, which gets talked about as this "tiny reservoir". But by tiny, one should understand a reservoir where, for example, HIV is found in two million cells. Therefore, the reservoir can be "smaller" but is not "small". In one case, after the patient with a "tiny reservoir" decided to stop ART, viral load rebounded. This demonstrates that HIV is there, in significant quantities, after years of ART.

As a matter of fact, the reservoir is very diverse, with HIV-infected cells resting in many different tissues of the body – which explains why the eradication of HIV is difficult to even imagine (not to mention the word "sterilisation" that should be avoided).

Community members in the IAS working groups advocated for a broad awareness of cure-related research within the community of people with HIV, which can only be reached with simple language. They also recommended that researchers studying cure be more inclusive of sexuality, gender, race, regions of the world, age ("expand age criteria to include children and much older adults"), in studies. Looking at demographics of participants in 122 cure-related trials, TAG found that participants were overwhelmingly men and/or white people.

Social research in the clinical studies was also highlighted by them as essential (to collect data on motivations, experience, etc.), in a context of recent long-acting ART that may be perceived as getting closer to a life without HIV.

There was also a call from community representatives on the IAS panels for more global cure-related research, which should be understood not only in terms of involvement of national/regional scientists but also in terms of funding. Furthermore, the follow-up of post-treatment control cases must be extended.

The personal impact of participation in cure-related research is something to consider fully before designing studies. For instance, many cure-related studies often involve very intensive routines, while ATIs disrupt being stable and having an undetectable viral load, with all possible subsequent worries and risks – and in turn, a decrease in quality of life. Restarting ART after an ATI may be challenging to some. And what about you ending up being in a placebo arm, as some participants did in the RIO study?

Finally, taking into account the COVID-19 and mpox epidemic-driven challenges (such as those faced by the EHVAT02 trial), why not have cure-related trials designed in such a way that participants can be followed-up at home to reduce their risks?

What would an HIV cure mean for me?

Memory Sachikonye, UK Community Advisory Board and EATG

To access the slides, click here.

Memory Sachikonye introduces herself as a person living with HIV and shares some of her medical history. She highlights the positive impact of the care and treatment she has benefited from since she was diagnosed, including the decrease of the number of pills to take every day. She considers her quality of life as "generally quite good".

To her, the pros of an HIV cure might mean:

- A relief from a daily pill taking and from the polypharmacy (which she is experiencing for being a kidney transplant recipient and also ageing).
- A positive psychological impact on a possible lifestyle change (less clinic appointments etc.).
- On the whole, this could help relieve countries facing stock out issues.
- A way to avoid/combat stigma? (*Memory insists that this is a question)*.

What are the cons of an HIV cure?

- The process is complex.
- Memory's current treatment is effective and easy to take (why bother?).
- Where a cure becomes available in the UK, it will not be available, accessible or affordable to those who need it most.
- Stigma and discriminatory attitudes will always be there.
- The promise of a cure gives false hopes and might affect adherence to those already on treatment.
- You could still get re-infected!
- Is a cure roll out likely to happen in our lifetime? *(Memory adds that she does not think so)*.

In summary, the cons outweigh the pros of a potential HIV cure. Memory finds U=U quite liberating for not having to worry about passing HIV to someone else and is therefore happy to take her daily anti-HIV pills. She would actually focus more on making sure that everyone who needs treatment gets access to it. Finally, she finds long-acting therapy (every six months) more appealing than an HIV cure.

Discussion

The discussion starts with a comment by Brian West, regarding the concern he could personally have if he were asked to stop his antiretroviral therapy for a while in a cure-related clinical trial. He acknowledges that while saying that, he might be perceived as in contradiction with messages received by people with HIV for a very long time now.
Another delegate makes a similar comment but adds that messages inviting people to join cure-related research are too unclear. Why should he, at one point, stop taking his therapy and wait for a viral rebound, is a question that remains unanswered for him. Basically, he

explains his hesitancy to join a cure-related clinical trial. More communication efforts are needed!

There is consensus in the audience around the need to increase participation of understudied populations in HIV cure-related trial and to have better diagnostic tests. Referring to Simon Collins' presentation, the overlap between today's HIV treatments and an HIV cure possibly coming in is highlighted again.

Casper Rokx acknowledges the need for community and scientists to discuss and work together towards an HIV cure. He also agrees that current treatments, starting with long-acting drugs, are going into a direction that can be felt almost as a cure.

Clinical trial investigators should also keep in mind that one size does not fit all and consider all cultural approaches to science when designing scientific projects. Faith-based leaders who play an important role in certain communities should be included in discussions about clinical trials, treatment uptake, etc. in order to make sure that they pass on the appropriate messages to the communities that trust them.

The Chair of the meeting takes this opportunity to reiterate how significant it is to have all people with HIV informed, in simple language, about what is going on in the HIV cure field. He closes the meeting by inviting delegates to join the next STEPS Workshop in 2023.

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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 people living with HIV 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.

For more information, please visit www.eatg.org

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