European AIDS Treatment Group

STEPS9: A Community Initiative to Design the Pathway to a Durable ART-Free Control of HIV Infection

Summary Report

Warsaw, 18 October 2023

In Memory of Giulio Maria Corbelli

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

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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 type of research is very important and 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 the expectations of the participants, providing update and reliable information accessible to the participants and the community at large.

The STEPS workshops, organised annually since 2014 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 and promote community engagement in research on the HIV cure and related topics from the very earliest phases of the development of the scientific research for the long-term drug-free remission of HIV infection.

The 9th STEPS HIV Cure Community-led Workshop took place on Wednesday October 18, 2023, in Warsaw, Poland). The workshop, coordinated by **Sean Hosein** and chaired by **Brian West**, discussed approaches for HIV cure research, provided updates on upcoming trials on therapeutic vaccination and stressed the importance of the contributions of the community. This year's theme was "***STEPS towards a cure for everyone – dedicated to Giulio Maria Corbelli***".

The present report was prepared by **Gus Cairns** and provides an overview of key messages from the workshop.

Highlights

- **NOVA study** proves that starting ART during acute HIV infection substantially **reduces transmissions**.
- **EU2CONTROL** cohort study will enrol post-treatment controllers in collaboration with EATG.
- Researchers are designing personalised therapeutic vaccines based on **similarly successful ones used to cure cancer.**

Erasmus Medical Centre HIV Elimination Group (EHEG): Cure Studies

Kate Hensley & Henrieke Prins, Erasmus Medical Centre (The Netherlands)

In the first half of the workshop, Kate Hensley and Henrieke Prins of the Erasmus Medical Centre HIV Eradication Group (EHEG) in Rotterdam, Netherlands, presented their work and results for six completed, ongoing and planned HIV cure strategy studies: CHRONO, LUNA, NOVA, EX VIVO, ORBIT and EU2CONTROL.

These studies are part of the work of the **EU2CURE Consortium**, a multidisciplinary European collaboration towards a cure for HIV, which was launched in 2021 under the leadership of the late Charles Boucher (1958-2021), another figure keenly missed by the HIV community.

The basis of these studies involves the so-called 'reservoir' of long-lived immune-system cells (largely central-memory CD4 cells) that contain integrated HIV genetic material (proviral DNA). These cells are invisible to the immune system and are not eliminated by it but give rise to a new wave of productive HIV infection when ART is stopped and also contribute to low-level replication even when ART is taken. Their existence is the reason HIV infection is life-long, and their elimination is a core aim of most HIV cure strategies.

Completed Studies

LUNA: This is a completed study which looked at two investigational Latency Reversing Agents (LRAs) – drugs that can 'kick' reservoir cells out of their dormant or 'latent' stage. The hope then was that they would thus become visible to the immune system, which could then kill them off and reduce the size of the reservoir. Research has shown that while many drugs can reverse latency, this does not result in reservoir reduction through immune processes alone. However, latency reduction may still form an important aspect of a cure strategy that might also use therapeutic vaccines (*see below*) to induce a more effective immune response.

LUNA randomised 28 volunteers to receive one, both or neither of the two candidate LRA drugs valproic acid and pyrimethamine. It found that valproic acid had little effect and no synergy with pyrimethamine, and there were also issues of tolerability when the two drugs were combined.

However, pyrimethamine alone led to a twofold increase in the production of unspliced HIV rRNA by reservoir cells, which is a measure of reactivated HIV gene transcription, and that this activity persisted for at least two weeks after dosing. However, it did not lead to an increase in the overall size of the HIV reservoir in volunteers, as measured by DNA assays, so it would need to be combined with another immunotherapy.

NOVA: This study, which took place between 2015 and 2020, looked at people who were diagnosed with early HIV infection (infected no more than a few months previously, and ideally in the last month). There is evidence to suggest that very early ART can result in a much smaller HIV reservoir and in some cases, this could result in durable ART-free control of HIV infection ('Post treatment control').

One issue with starting ART immediately upon diagnosis is that if the person has acquired HIV with drug resistance mutations, ART that is not optimised to overcome resistance could lead to treatment failure and worse resistance. But genotypic resistance tests may take four weeks to report. NOVA dosed 140 volunteers diagnosed in early infection with boosted darunavir and dolutegravir, two drugs with very high barriers to the development of resistance, and even gave the dolutegravir twice daily. Once resistant test results came back, patients reverted to a normal dolutegravir-based regimen.

The study found that there was no synergy between the two drugs and that drug levels with twice-daily dolutegravir were not raised enough over one-daily to make two pills a day necessary.

However, NOVA did produce a significant result in terms of implications for prevention. In phylogenetic analysis that reveals the genetic similarity between viruses in different people, 'clusters' of infection are often discovered that are evidence of rapid-fire transmission within a group of people that may be connected sexually or via needle sharing. But phylogenetic analysis of NOVA subjects found very few clusters, proving that very early treatment and thus viral suppression does indeed have a significant role in reducing HIV incidence, especially if combined with PrEP. Although we already knew this from HIV surveillance and cohort studies, it is good to have confirmation on the molecular level.

Ongoing and Future Studies

CHRONO: This is a prospective cohort study with people who are diagnosed or who start antiretroviral therapy (ART) while in the chronic phase of HIV infection.

The object is to develop a prospective cohort for in-depth characterisation of the HIV reservoir and study how its characteristics, and the host immune response, evolve over time. It will last at least ten years from 2021.

Volunteers joining CHRONO will have blood draws 0, 4, and 12 weeks after starting ART and then undergo leukapheresis – the filtration of blood to remove a sample of leukocytes (white blood cells) six months and then one, three and ten years into the study. The cells will be analysed for sub-studies.

EX VIVO study: This is a cross-sectional 'snapshot' study of the nature of the latent reservoir, and especially whether there are differences in reservoir characteristics in a) people with non-B HIV subtypes b) people with HIV-2 and c) so called long-term non-progressors, who maintain good immune function off ART. These may also be elite controllers (people who have always maintained viral control off ART) or post-treatment controllers.

The importance of studying the reservoir in non-B subtypes and in HIV-2 is that the majority of cure research so far has been done in subtype B, the predominant strain in the high-income world, but that the majority of the world's infections are of subtype C. Non-B subtypes may respond differently to Latency Reversing Agents and need different cure strategies. Studying HIV-2 will involve the characterisation of this cousin of HIV-1 that has a less virulent course of infection and will look at whether its more indolent nature is due to viral characteristics or the evolution of immune defences.

ORBIT: This study will start enrolling Dutch subjects in the first quarter of 2024. Building on the findings of the LUNA study, it is a phase I/II study looking at the activity of a variety of Latency Reversing Agents, by themselves and in combination.

EU2CONTROL: This multi-partner, Europe-wide study answers a need long expressed by HIV cure researchers and activists, for a large, pan-European cohort study of post-treatment controllers (PTCs) and their characteristics: there are national ones like CODEX in France but because PTCs are hard to find and don't all have the same immune responses, we need a large cohort to explore how they control HIV and whether what they do could be induced in non-controllers. EATG are working as partners to the EU2CURE consortium to publicise the study, identify PTCs and encourage them to join the cohort.

Devising a Personalised Therapeutic Vaccine

Mario Ostrowski, University of Toronto (Canada)

In the second half of the workshop, Mario Ostrowski of the University of Toronto talked about immunotherapies which, as mentioned above, may be needed in combination with Latency Reversing Agents to reduce the size of the HIV reservoir or even eliminate it.

He talked first of the necessity for a cure. A lifetime's ART may cost from thousands to nearly a million dollars depending on where someone is, and although mortality in people with HIV has been decreasing steadily since the 1990s, it is still twice that in HIV-negative people.

He outlined the size of the task involved in shrinking the HIV reservoir to nothing. There are probably 200 to 400 million reservoir cells in people on ART and they are so long-lived that their number only shrinks by two-thirds in forty years. Existing approaches aiming to shrink the reservoir have been ineffective and the only approach that has produced cures, stem-cell transplant, is very expensive and so dangerous it is only ethically justified in people who need transplants for cancer. Viral rebound has been observed in people with as few as one infected lymphocyte per 1.7 billion cells sampled.

However, there are quite a number of examples of people who are able to take prolonged breaks off ART before HIV viral loads rebound, and presumably some kind of immune control of the virus, probably by CD8 cells (also called cytotoxic T-lymphocytes) is happening during those times.

Why can't CTLs keep on controlling viral reactivation? There are three possible explanations, which may all play their art:

- HIV's unmatched ability to mutate away from immune control, so it is not recognised by CTLs,
- CTL exhaustion: 'immune checkpoint' receptor molecules either eventually kill off senescent CTLs or force them into latency,
- 'Original antigenic sin': this means that CTLs are sensitised to parts of HIV (epitopes) whose control does not curb viral replication instead of to less immunogenic 'conserved' areas that are vulnerable to CTL control.

The third possibility is illustrated by the fact that some varieties of human HLA genes, which detect foreign pathogens and expose them to the immune system, are better at reacting to conserved regions of HIV than others.

In short, no person's HIV is the same as another's, and no person's immune response is the same as another's. This suggests that immunotherapies for HIV are only likely to be effective if they are *personalised* – an approach that has already produced promising results in cancer.

How this would work is that a person's HIV and their CTLs would be sampled to see what epitopes their CTLs do target and what sections of the virus seem to be changing in order to evade immune surveillance. This epitope-mapping would then be fed into an AI system for computational analysis to find out what are the best regions of the virus to target, including regions that the immune system has not yet targeted.

mRNA vaccine technology has made this personalised approach possible because it is fast: an individualised vaccine that could have taken years could now be made within 60 days, and an Analytical Treatment Interruption (time off ART) could be started within four to five months of the first vaccination, if immune responses are promising.

This idea, of "vaccinating someone against their own virus", has already been used to vaccinate people against their own cancer cells, but Dr Ostrowski warned that in the case of HIV cure there is probably no 'silver bullet' approach that might in itself lead to a cure: a personalised vaccine, for instance, might have to be combined with antibodies that target immune checkpoint receptors and prevent T-cell exhaustion. The post-treatment controllers also suggest that it may not be necessary to get rid of every single reservoir cell if we can engineer an immune response that stops the remaining from ever re-activating.

Afterword From a Polish EATG Activist

Grzegorz Jezierski, Buddy Polska Project (Poland) and European AIDS Treatment Group

Finally, EATG Member Grzegorz Jezierski spoke of his hopes for a cure. Aged 47, he was diagnosed fairly recently (in 2018), and his present state of good health was reached only through treatment for significant comorbidities ranging from bone cancer with lung metastases to drug dependency (he has been sober for two years). He described his involvement in AIDS activism as "probably one of the most meaningful activities in my life".

He said that witnessing the advancement of new treatments is encouraging, providing people living with HIV the freedom to choose, and that the concept of U=U, in particular, provided him with "immense relief". However, 22 people still died of AIDS in Poland, a low-prevalence country in 2022, and he felt, with his experience of them, that he longed to witness increased efforts in addressing comorbidities."

Lastly, he noted that he was one of a literal handful of people with HIV in his country who had dared to stand up and declare their status and that an unnecessary burden of death and treatment complexities would persist as long as few people were "willing to openly share their experiences living with HIV".

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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.

For more information, please visit www.eatg.org

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