2019

Accelerating a Cure for HIV:

The NL4Cure research agenda

NL4Cure is a Dutch initiative to advance an HIV cure and consists of representatives of people with HIV, researchers from Dutch universities, HIV nurses and physicians and the HIV Monitoring Foundation. It is initiated and coordinated by aidsfonds

Objectives of the NL4Cure research agenda

This NL4Cure research agenda seeks to accelerate the development of an HIV cure for all people with HIV utilizing the unique opportunities and strengths afforded by Dutch infrastructure. NL4Cure prioritizes and outlines the ambitions for cure research for the next five years. The research agenda was developed through the active participation of scientists from several institutions, people with HIV, HIV nurses and physicians and others. This collaborative foundation and involvement of all key stakeholders puts this agenda on a strong footing to sustain broad support and accelerate progress towards a cure. For more background information on the process used to develop the agenda, see Appendix 1.
The NL4Cure agenda reflects the priorities of people with HIV and the strengths of the Netherlands and encourages others to participate in the initiative. This agenda serves as a guiding document for those currently in the field and as a recruitment tool for disciplines not yet active in HIV research. Importantly, this plan will not be carried out in national isolation: it fits within the international context formulated by the Global Scientific Strategy Towards an HIV Cure created by the International AIDS Society.[4]

The NL4Cure agenda contains four main sections. However, none of these can be addressed in isolation: each section impacts the others.

The four sections are:

1. Social engagement
2. Identifying and understanding the viral reservoir
3. Developing cure strategies
4. Clinical investigation and implementation

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Introduction

Importance of an HIV cure

To date, there are 37 million people worldwide living with HIV.[1] Although antiretroviral therapy is lifesaving, it requires lifelong adherence, which is, in turn, associated with drug-related toxicity, persistent stigma and costs. Perhaps most importantly, therapy will not lead to a cure and its cascading benefits for people with HIV: an end to drug therapy, relief from stigma and a future free of HIV. An HIV cure is one of three pillars to end the global HIV epidemic: prevention, treatment and cure.[2]

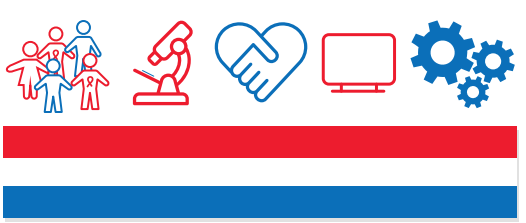
Strengths of the Dutch enterprise

The Netherlands is a global leader in the fight against HIV and AIDS. The "Dutch approach" has been successful in integrating basic, epidemiological, clinical and social sciences, and in engaging with all stakeholders, most importantly people with HIV. This has laid the foundation for an efficient and nationally-organized infrastructure for prevention and care that can now be harnessed for the development of a comprehensive cure research agenda and program.

One critical achievement in the Netherlands is the long-standing national cohort of people with HIV, coordinated by the HIV Monitoring Foundation.[3] Since 1998, clinical and epidemiological data and blood samples have been continuously collected and are available from over 20,000 individuals with HIV. Given the size and growth of this cohort, this collection offers a valuable tool for national and international HIV research. The information it yields contributes to an array of investigations into HIV and could be particularly useful for HIV cure research worldwide.

Similarly beneficial is the highly supportive and collaborative scientific infrastructure in the Netherlands. The Dutch system of academic medical centers with integrated clinical care, diagnostic services and research relies on an integrated approach that allows disciplines to collaborate and exchange knowledge efficiently. Active public-private collaborations have resulted in a strong portfolio of both basic science and clinical studies. Community participation is also strong. In the Netherlands, people with HIV have participated in prevention, care and policy making since the early 1980s, beginning with the Amsterdam Cohort Studies. In addition, Aidsfonds has served as a strong partner and an involved funder for more that 30 years.

NL4Cure, a Dutch initiative to advance an HIV cure, consists of representatives from the population of people with HIV, researchers from Dutch universities, HIV nurses and physicians, the HIV Monitoring Foundation and Aidsfonds. These parties have created this agenda jointly in order to guide cure research in the Netherlands.



The combination of a well-organized infrastructure for care and research, highly-skilled professionals, the involvement of people with HIV and a collaborative culture makes the Netherlands a unique and high-impact environment to accelerate the HIV cure agenda globally.

What do we mean by "cure"?

When talking about a cure, we refer to a situation in which someone with HIV no longer has measurable replicating virus without the aid of antiviral therapy. As a result, they cannot transmit the virus and do not experience virus-related complications or disease progression. Cure can mean either a "functional" or "sterilizing" cure. A functional cure is also called "remission", since the virus is fully suppressed but not eliminated. Therefore, replicating virus may rebound, and so this is considered the first - but not the last - step on the road to a permanent cure. A more traditional definition of cure is sterilization, meaning the elimination or permanent silencing of the virus. It is not clear which strategy is more likely to succeed. Therefore, research must investigate both possibilities.

Collaborating for success

This ambitious agenda cannot be pursued solely by the Dutch cure enterprise or by research groups in isolation. Building successful collaborations and eliminating silos provides for a greater efficiency toward our common goal. International collaborations are key in pursuing the aims described above, e.g., by Dutch representation on the HIV Cure advisory board of the International AIDS Society. Moreover, as discussed at various places throughout this agenda, scientific progress made outside of the HIV field will be important in the development of an HIV cure. Indeed, developments in oncology and autoimmune diseases may be of particular value. The HIV research community will reach out to these disciplines to determine whether collaboration might shorten the route to an HIV cure. We will also actively pursue collaboration with partners outside of the Netherlands in areas where we lack expertise or critical mass. Finally, additional stakeholders and private parties such as pharmaceutical companies, insurance companies and local and national governments are essential partners for the development and implementation of an accessible and globally applicable cure for HIV.
We call on all parties and stakeholders to join us and make these aims a reality.

1. Social Engagement

Social engagement research is primarily concerned with questions regarding the views, experiences and support of people with HIV, their partners, key populations and other stakeholders. The Dutch and international cure fields need to make significant advances in this area. The knowledge, attitude and perceptions of cure among people with HIV and other stakeholders will play a crucial role in advancing these investigations. In order to sustain meaningful progress, more insight is needed on these views, particularly as different cure strategies are developed and clinically tested. Dutch research will focus on four interlinked aspects of HIV cure research and the following research questions:

1. Views of people with HIV
2. Ethical and practical aspects
3. Views of other stakeholders
4. Health and economic impact

1.1 Priorities of the social engagement research agenda

1.1.1 Views of people with HIV and key populations

HIV cure strategies are intended to benefit the health and well-being of people with HIV and others affected by HIV and should respond to their needs and preferences.[5,6] These populations shape the acceptability and success of HIV cure strategies. The NL4Cure social engagement agenda specifies the following questions to advance knowledge in this area:

Importance and meaning: What is the importance of an HIV cure for people with HIV, their partners and other key populations? What meaning do they attach to a cure? What are their views regarding the benefits, risks and acceptability of specific HIV cure strategies, and what factors influence these views? What do people with HIV expect and hope for in a cure, and to what extent can specific HIV cure strategies meet these expectations?

Awareness and support: To what extent are people with HIV, their partners and other key populations aware of the global pursuit of an HIV cure and the early successes and obstacles that have been identified in that pursuit? To what extent is there support for the pursuit of an HIV cure within these communities?

Communication and decision-making: How do people with HIV, their partners and other key populations prefer to receive information about this research? How should information be framed to best inform decision-making? How can the uncertainty of cure research be communicated best to manage expectations, including the timeframe for developing a cure?

HIV-related stigma: Does the possibility of an HIV cure contribute to a potential reduction in HIV stigma, including self-stigma and structural stigma? Might reduced stigma allow for increased HIV testing in key populations? Is it possible that new HIV-related stigma may arise, affecting people with HIV who remain uncured, continue to test positive or become infected again?

Impact of HIV cure on HIV prevention: Does the possibility of an HIV cure affect attitudes regarding HIV risk and prevention?

1.1.2 Ethics and practice of meaningful involvement of people with HIV (MIPA)

Ensuring appropriate participation: The Dutch Association of People with HIV strongly believes in the MIPA principles[7]: a Meaningful Involvement of People with HIV on all levels within the field of HIV, including research. It is essential to address how people with HIV, key populations and other stakeholders are involved in HIV cure research. It is also important to study the extent to which the involvement of people with HIV in HIV cure research reflects the best practices contained in guidelines such as MIPA. How can MIPA be strengthened in HIV cure research?

Advancing HIV cure research: It is insightful to know who is sharing information, setting agendas and initiating advocacy, and to what effect: What actions are required to increase political and policy support?

Normative and salient ethical concerns: What are the ethical challenges of HIV cure, its possible research and its possible future implementation? What ethical issues and concerns are most salient to people with HIV, HIV care providers, purchasers, policy makers and medical research ethics committees, and what support and information do ethics committees need to address them?

1.2 Additional considerations for social engagement research

These questions are considered a priority. In addition, important questions arise regarding the involvement of people with HIV in research and the views of other stakeholders with regard to the costs and health impact of cure research.

1.2.1 Involvement of people with HIV in HIV cure research

Willingness to participate in HIV cure research: To what extent and in what circumstances are people with HIV willing to participate in HIV cure research? What information and support will help them make this decision? What do people with HIV understand to be the benefits and harms of HIV cure research?

Inclusiveness of HIV cure research: How equitable are opportunities for participation in research in the Netherlands and globally? Are studies open to people with HIV of all genders, ages and key populations? What are the inclusion and exclusion criteria?

1.2.2 Other stakeholder perspectives

Familiarity with and support for pursuing HIV cure: To what extent are HIV care providers and policy makers aware of progress in HIV cure research? What do they know about HIV cure strategies? To what extent do they consider an HIV cure to be important?

Willingness to support HIV cure research: To what extent and under what conditions are clinicians willing to recruit participants into research, and is this support dependent on the HIV cure strategy under investigation? To what extent are funders and donors willing to support HIV cure research? How likely are shifts in funding priorities, and what might be their implications?

1.2.3 Health and economic impacts

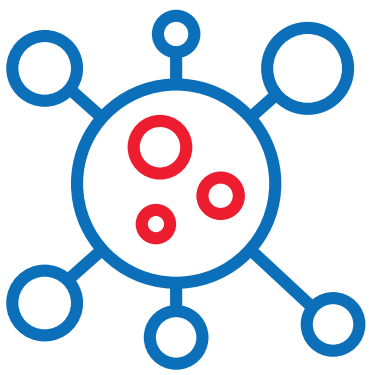
Population health benefits: What does mathematical modelling show to be the epidemiological impact - across a range of scenarios for implementation - for each strategy under investigation? This includes both strategies that result in remission and those that lead to a sterilizing cure.

Health expenditure impacts: What are the costs, benefits and savings related to various scenarios of implementation of specific HIV cure strategies?

What value can the Netherlands add?
Social research on HIV-related topics in the Netherlands is robust and draws from a long-standing collaboration between scientists and people with HIV. Collaboration across disciplines facilitates the objectives of HIV cure research by way of the development of a cross-infrastructural platform.

2. Identifying and Understanding the Viral Reservoir

The lifelong persistence of HIV in various cells and organs in the body, despite antiviral therapy, represents the major barrier for cure. No methods exist yet to accurately determine the nature and number of cells carrying viruses in an individual infected with HIV ("reservoir"). To develop effective cure strategies and monitor their impact, it will be essential to analyze the size and nature of the reservoir as a starting point for insights into how to control or eliminate it. The following three areas of research will address those needs:



1. Defining the "relevant" viral reservoir
2. Molecular mechanisms underlying viral latency
3. Identifying correlates of immune protection

2.1 Defining the "relevant" viral reservoir

Not all cells containing HIV are capable of producing new virus, and not all virus is capable of replication. For a cure, only virus able to replicate or reactivate into infectious virus and negatively impact health - the "relevant reservoir" - needs to be controlled or eliminated. This research involves establishing the size, the cellular composition and the anatomical location of the viral reservoir as well as the characterization of the cells that are capable of producing replication competent viruses.

2.1.1 Size of the relevant viral reservoir

Several assays are available to measure the reservoir, but they do not accurately determine the total size of the relevant reservoir. Further investigation is imperative, since measuring the relevant reservoir is a foundational step in testing an HIV cure.

2.1.2 Cellular composition of the viral reservoir

Latent HIV resides in various cell populations. Most important are the long-lived CD4+ resting memory T cells. However, other CD4+ T-cell subsets and cells of the myeloid lineage (monocyte/macrophage, microglia and dendritic cells) can also carry virus. Mechanisms of viral latency likely depend on cell type and epigenetic factors that trigger the expression of different cellular proteins (e.g., host dependency or restriction factors). It is vital that we understand the mechanism for latency, determine the effect that latent HIV has on its host cell and discover whether HIV latency induces the expression of specific cellular proteins (for instance, to maintain their latent state). This knowledge can then be used to target the viral reservoir.

2.1.3 Location of the viral reservoir

HIV-infected cells, including macrophages, microglia and dendritic cells, can persist in tissue, thus contributing to the viral reservoir. In addition to the cell type, the specific immediate tissue environment of the infected cell may play an important role in the molecular pathways involved in viral latency. Furthermore, the viral

reservoir may contain different variants of virus at different sites in the body (anatomical locations) as a result of selective pressures associated with either the cell type that has been infected or the immediate tissue environment. The identification of the anatomical location of the viral reservoir is of great importance for the design of cure treatment strategies, since a given strategy may work in one kind of tissue or at one location in the body, but not in another.

2.2 Molecular mechanisms underlying viral latency

The viral reservoir consists of cells that contain HIV in a "dormant or latent" status, referred to as the HIV provirus. These proviruses persist but do not produce new virus. Cells carrying proviruses are not recognized by the immune system. Several factors contribute to this viral latency, such as the HIV integration site in the human DNA, epigenetics, transcriptional silencing and differential expression of (unknown) cellular proteins. In order to achieve remission or cure of HIV, it is helpful to understand the mechanisms for latency induction or control. Currently, the role of the mechanisms that establish or maintain viral latency and control the size of the viral reservoir are incompletely understood, and the identities of the key molecular players involved remain unknown.

2.3 Identifying correlates of immune protection

Biomarkers that indicate that a person is able to control their HIV once therapy has stopped have yet to be discovered. At this time, the only way to know if HIV replication is under control is to stop therapy and then measure viral load. Yet so-called "treatment interruption" carries several potential disadvantages (e.g., the risk of developing resistant virus, enlargement of the reservoir and the potential of viral transmission). There are three approaches we will pursue to gain insight into in biomarkers for viral control.

2.3.1 Elite controllers

A small group of people with HIV can control their HIV without therapy from the beginning of their infection. They are referred to as 'elite controllers', and they represent a unique resource for identifying immunological, virological, and genetic predictors. Once the field has a better understanding of which predictors correlate with controlling the virus, investigation can advance into the mechanisms of immune control, including some known factors such as HLA-B57. Strategies to boost the immune system to control or eliminate infected cells can then be developed and tested.

2.3.2 Post-treatment controllers

These are individuals who have initiated antiviral therapy shortly after they became infected (i.e., within weeks or months) and are able to control, to varying degrees, HIV replication without therapy. Identifying the genetic, immunological or virological predictive biomarkers in this group will similarly advance the field's knowledge of viral control.

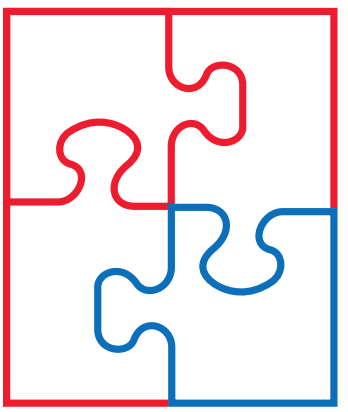
2.3.3 Treatment interruption

Learning more about the difference between those who experience viral rebound after treatment interruption and those who do not may also reveal relevant biomarkers for control of HIV. Immune-based approaches can be adapted and optimized before treatment interruption for those without the right biomarkers. Therefore, understanding post-treatment control is critical for designing HIV cure clinical trials.

What value can the Netherlands add?
The expertise and history of interdisciplinary and translational collaboration in genetics, immunology and virology, among other fields, uniquely positions the Netherlands to advance cure research on these critical questions. In addition, a wealth of biobank material from cohorts of treated/untreated participants and cohort studies focused on the initiation of early treatment and treatment interruptions will be instrumental in this research.

3. Developing Cure Strategies

Within the global HIV community there is no consensus regarding the most promising cure strategy. Several approaches are being explored in parallel, and they may one day be combined to arrive at a successful cure. Here, we have organized three approaches into two categories: "controlling HIV replication" ("lock and block") and "reducing or eliminating HIV" (including "kick and kill"). These approaches are non-exclusive and can be complementary. For instance, after reduction of the viral reservoir, it may be easier to control the remaining viruses. Since it is unknown which approach will be most successful, additional "out of the box" approaches will also be considered.



3.1 Approaches to controlling virus replication

Controlling virus replication is one of the more promising approaches to a cure. Several strategies are under investigation. "Lock and block" induces cellular and/or humoral immunity to stop virus replication. Another strategy uses human gene editing to manipulate the cells that are targeted by HIV. Through this approach, the altered cells will not be susceptible to HIV infection.

3.1.1 Identify molecular targets to control viral replication

Research on the molecular mechanisms for viral latency, mentioned in section 2.2, will increase the understanding of the molecular mechanisms that control HIV replication.
The next step to translate this knowledge into clinical applications is to identify and test new pharmacological interventions that target these pathways. These could consist of newly designed molecules or already known molecules that currently have other application and will allow for the control of latent cells.

3.1.2 Immune control

Although in natural HIV infections the immune system is unable to fully control the virus without medication, boosting the immune system could lead to control of viral replication and prevent the infection of target cells. To achieve this sort of therapeutic vaccine, potential strategies include using broadly neutralizing monoclonal antibodies, engineered antibodies or nanobodies.
These strategies may neutralize free virus or redirect or activate immune cells (natural killer cells, macrophages and complement) to kill HIV-infected cells.

3.1.3 Protecting target cells

An alternative approach is to protect target cells against HIV infection. This would prevent newly produced virus from infecting target cells. Strategies that are being explored are cell and gene therapy to modify immune cells and render them unsusceptible to HIV infection. More studies are needed, however, to understand how to enhance the delivery of gene therapy to the appropriate cells, to learn more about the functionality of modified cells and to gain knowledge about the underlying mechanisms and other effects.

3.2 Approaches to reducing or eliminating HIV-infected cells

Another approach is to reactivate the virus out of latency ("kick") followed by approaches that either "kill" infected cells or induce intrinsic cell death. This can be done by activating the immune system to kill infected cells, a strategy known as "kick and kill", or by targeting pathways within the cell that cause it to self-destruct, bypassing the need for killing the infected reactivated cells. Both approaches target cells emerging out of latency. There is as yet no accepted approach for effective viral reactivation or the cells' subsequent elimination, pointing to the need for new approaches and suggesting that the most effective methods will likely be a combination of different approaches.

3.2.1 Reactivation of the virus (kick)

Molecules known as "latency reversal agents" have been identified and tested in clinical settings and can reactivate (or kick) HIV-infected cells. Thus far, there has been limited efficacy in vitro, yet this remains a potentially effective approach. In the Netherlands, several parties are in the process of identifying new reactivators and improving the activity of existing and potentially succesful molecules.

3.2.2 Stimulating the immune system to kill infected cells

It is critical that we understand the molecular mechanisms that induce immune cells to kill HIV and how these mechanisms burn out and become exhausted or dysfunctional. Strategies need to be developed to stimulate immune cells to kill HIV, prevent exhaustion or restore cell-kill-ing capacity in order to reduce HIV-reactivated cells. In order to develop innovative approaches, this requires the use of knowledge from other research areas such as cancer therapeutics. Examples of strategies include checkpoint blockade or a therapeutic vaccine. Additionally, antibodies that recognize HIV-infected cells can be engineered to kill infected cells. Cell and gene therapy can be applied to enhance the immune system to control or eliminate HIV-infected cells. One example of a strategy being explored is the engineering of T cells to make them (more) efficient or specific as a means of clearing or controlling HIV. This engineering could alter their function, resistance to exhaustion and penetrance in tissues.

3.2.3 Elimination of the virus-infected cells through cell or gene therapy

Cell and gene therapy may completely eliminate infected cells. Development of DNA-nuclease-based (e.g., CRISPR-Cas9) gene therapy approaches are being explored to permanently inactivate the viral reservoir. In addition, stem cell transplants were involved in the two known cases of a cure.[8] Although not widely applicable (yet), this has potential and is being pursued in the Netherlands.

3.3. Translation to the clinic

Given the current limitations in clinical cure research due to the difficulties in measuring the size and nature of the viral reservoir, developing systems that remain as close as possible to the human ("in vitro" and/ or "ex vivo") models will be fundamental to progress from the lab to the clinic. These include mathematical and laboratory-based models. Several model systems that are being developed and used in the Netherlands are models for single- or multi-cell systems which can provide platforms for drug screens (as, for example, for novel agents to reverse latency). Molecules or strategies that are shown to be successful in single/multi-cell systems need to be tested in larger models before they can be tested in humans. These include animal and human models, such as human/patient-derived organoid models (including lymph node and brain organoids). These models should resemble the human setting as closely as possible and need to be continuously improved for HIV cure research. These models will allow for proof-of-concept, bioavailability, toxicity and safety studies, which are needed before advancing to clinical studies.

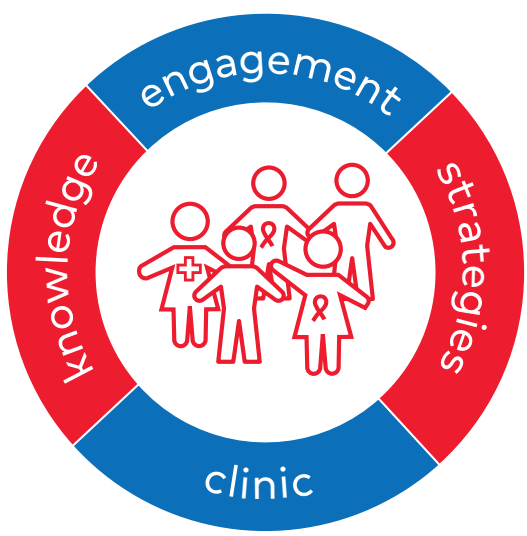
What value can the Netherlands add?
All of these approaches hold significant potential, and some are currently being explored in the Netherlands. Researchers in the Netherlands are at the forefront of the following areas of inquiry: developing models to understand CD8+ T cell exhaustion, identifying and (preclinically) testing compounds that may play a role in HIV latency reversal and cure, examining the potential of microRNAs and CRISPR-Cas9 for HIV cure, identifying factors that restrict viral function as potential targets for genetic modification, identifying novel broadly-neutralizing antibodies and developing vaccine strategies. Dutch enterprise in all of these areas has established a broad and innovative foundation for cure research. This community of researchers is poised to lead an accelerated effort in the field and is focused on translating potentially successful strategies in human and animal models to the clinic.

4. Clinical Investigation and Implementation

A translational cure platform is of key importance in applying the results of fundamental research into clinical HIV curative strategies. This platform will draw from the existing network of Dutch treatment centers and will connect with all relevant scientific disciplines. Innovative patient-focused studies will also prioritize the meaningful involvement of people with HIV. The core feature of this platform will be strong communication between clinical peers and the HIV community.

All clinical studies will observe the medico-ethical adage "primum non nocere" ("first do no harm") as a central governing principle of the overall research agenda and of clinical studies in particular. Several translation/preclinical studies are currently underway in the Netherlands. Together, they are investigating the size and composition of the viral reservoir in relation to disease stage and the effect of different combinations of curative interventions. These interventions target different aspects of HIV infection as mentioned in Section 3's discussion of Cure Strategies: reactivating latency (with latency reactivating agents or immune activating agents), locking the reservoir (immunological interventions that provide potent neutralizing antibodies, therapeutic vaccines) or gene therapy. So far, these interventions have exhibited broad individual variation in their responses. This indicates that preclinical studies need designs that better acknowledge differences in virus and host factors among individuals. Patient-centered clinical studies are essential in the development of appropriate "personalized" approaches for reducing the viral reservoir with strategies that are safe and globally expandable.

Realistic perceptions and expectations of cure might be different for various stakeholders involved (e.g., patients, physicians, nurses). Open communication should be a prominent factor in translating findings from bench to bedside. Cure strategies must reflect the vision and expectations of people with HIV and their caregivers and must include their consideration of acceptable risks and treatment burdens, as mentioned in Section 1's discussion of social engagement.



4.1 Clinical platform for cure research

This national platform will develop hypothesis-driven designs for preclinical studies. Clinicians, nurses and patient representatives, basic scientists and trial methodologists will work together to coordinate this research. This platform will also identify promising preclinical strategies for translation to clinical intervention studies. Existing and novel clinical cohorts, comprised of both acute and chronically HIV-positive patients, will provide a resource for identifying candidate strategies. Maintaining and expanding databases with patient-derived material can be of great value for basic and preclinical sciences. In collaboration with HIV caregivers and people with HIV in the Netherlands, the working group will explore how to successfully engage people with HIV in cure research, as mentioned in Section 1 's discussion of "social engagement".

4.2 Cohorts and repositories

Existing repositories and cohorts will be expanded to develop a sustainable platform for facilitating clinical and translational research. This platform aims to invest in studies that provide the basis for preclinical research (e.g., with a focus on the reservoir as well as on strategies). This platform consists initially of three existing prospective cohort studies: the national HIV Monitoring Foundation registry of people with HIV in care (SHM), the Netherlands Cohort Study on Acute HIV Infection (NOVA) and Biomarkers for the HIV Reservoir Cohort (CHRONO). Promising findings and strategies, knowledge about the reservoirs, and insights derived from social engagement will be translated to new cohort/interventional studies if they are sufficiently safe and likely to be beneficial to people with HIV. Additionally, studies will be conducted that focus on exceptional patients who exhibit an unusual phenotype or disease course of relevance for cure studies (e.g., viral controllers, as mentioned in Section 2.2 on immune control), including patients from underrepresented groups. Breakthroughs from other research groups will be evaluated and incorporated into studies using our well-characterized clinical cohorts. We will also identify and seek collaboration with experts in areas outside the field of HIV research (e.g., cancer immunology).

4.3 Patient-centered approach of preclinical trials

New opportunities and questions will arise with the transition to translational "proof of principle" trials. Trials addressing the safety and efficacy of cure strategies - including those directed towards people with HIV who started treatment during acute and chronic infection - will focus more on personalized approaches. These include clinical interventions that incorporate social engagement and trial designs that reflect collaboration with people with HIV. Clinical intervention studies will need to first assess the pros and cons to make a fair judgement. We will pursue well-powered clinical trials based on promising preclinical findings regarding strategies towards HIV cure, including:

- The validation and use of HIV reservoir assays
- New clinical technologies to aid in curing HIV
- Approaches to induce viral control
- Approaches to eliminate infected cells
- The achievement of post-treatment control in people with HIV who initiated treatment during acute or chronic stages of the HIV infection.

What value can the Netherlands add?
The Dutch infrastructure is well disposed to collect patient material to contribute to basic and preclinical science and to implement translational research. This can be used to study interventions that account for individual host variables, e.g., genetics and functional variation in immune responses. We will establish and integrate a robust infrastructure for analysis of in vitro and ex vitro responses before entering patients in clinical trials to increase these trials' capacity to predict individual responses to the intervention under investigation. If this strategy is successful, it will enable an individualized cure approach.

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Appendix 1: Process description

This Dutch HIV cure research agenda was developed through a collaboration between people with HIV, HIV cure researchers and other stakeholders in the Netherlands to design a Dutch road toward a global, accessible cure for all people with HIV. The current document is based on the scientific and social challenges currently faced by the field and has taken into account the possibilities and extraordinary opportunities provided by the Dutch HIV community and research infrastructure at large. The creation of this document was a first step in the collaboration between all Dutch HIV cure stakeholders and has been a valuable process to gain insight into the challenges and needs of this group.

In spring 2018, Aidsfonds brought together Dutch stakeholders involved in accelerating an HIV Cure to collaborate in a participatory, energizing and collective way. NL4Cure was created from this work as a collective effort by Dutch partners to accelerate an HIV cure. The partners include academic HIV cure research institutes, the Dutch Association of People with HIV, HIV nurses and physicians, the HIV Monitoring Foundation and Aidsfonds. A key goal of NL4Cure is to create a Dutch research agenda for HIV cure.

The creation of this research agenda has been an open, collaborative, inclusive process, with input from several disciplines within the HIV field. We would like to thank all participants of the workshops and our reviewers and writers for all their time and effort in creating this document.

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Attendees of the Dutch national conference "Congres Soa*Hiv*Seks" lunch session on 23 November 2018.

(Inter)national respondents to the open online consultation in December 2018/ January 2019, https://aidsfonds.nl/internetconsultation.

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