TIMELINE

Past, present and future: 30 years of HIV research

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Abstract | This year marks the thirtieth anniversary of the publication of the study that first reported the isolation of HIV-1. In this Timeline article, we provide a historical perspective of some of the major milestones in HIV science, highlighting how translational research has affected treatment and prevention of HIV. Finally, we discuss some of the current research directions and the scientific challenges ahead, in particular in the search for a cure for HIV.

During the early 1980s, the world was suddenly confronted with a devastating new epidemic when the first cases of AIDS were observed[1]. The epidemic — which was initially associated with men who have sex with men, then with drug users, people who had received blood transfusions and finally the general population — was rapidly spreading across the world, urging the scientific and medical community to react promptly and investigate the origin and causes of this deadly disease. The sudden spread of cases led epidemiologists to establish surveillance activities, and within a couple of years the groups at the highest risk of infection and modes of transmission of the disease had been identified. The isolation of the retrovirus[2] in 1983, later to be known as HIV-1, led to three decades of intense research on the virus itself, its interplay with the host and its pathogenesis, as well as on the development of approaches to test, treat and prevent HIV infection.

In this Timeline article, we look back over the past 30 years of HIV research, providing a brief overview of some of the key milestones that have been achieved since the isolation of HIV-1 (FIG. 1 (TIMELINE)). We also discuss some of the main current research directions and key goals for the future, with an emphasis on novel biomedical prevention tools and a look ahead towards a cure for HIV.

Milestones in HIV research: a historical view

Understanding the basics. The long story of HIV research began in 1981, when clinical observations of what would later be known as AIDS were reported in the United States and then quickly elsewhere across the world. The global medical and scientific community was initially powerless against this disease and rapidly joined forces to mobilize efforts into gaining some insight.

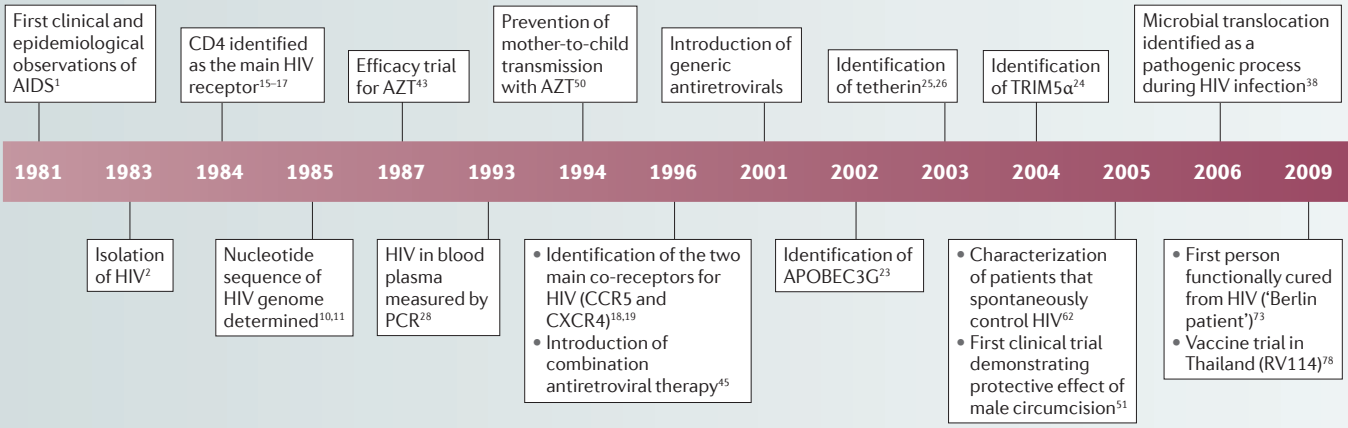
In early 1983, a new human retrovirus, at the time coined lymphoadenopathy-associated virus (LAV), was isolated at the Institut Pasteur, Paris, France, from a culture derived from a lymph node biopsy sample of a patient with generalized lymphadenopathy, which was provided by French clinicians[2] (BOX 1). Within a year, similar viruses had been isolated from patients with AIDS[3,4], and a serological test had been developed to carry out large sero-epidemiological studies, which confirmed that HIV causes AIDS. Importantly, this research was the basis of the first diagnostic test for HIV infection[5,6].

The molecular cloning of HIV[7–9] and the subsequent nucleotide sequencing of the virus in 1985 (REFS 10–12) was later instrumental in developing viral load and resistance tests to monitor patients who were infected with HIV. The genomic information of HIV was also the basis for the identification of the diversity, origin and evolution of HIV, and was crucial in providing evidence that both HIV-1 and HIV-2 are the result of cross-species transmissions of simian immunodeficiency virus (SIV)[13,14].

Soon after the isolation of HIV-1, the CD4 cell surface molecule was identified as the main receptor for HIV[15–17]. This discovery, together with the knowledge that HIV was cytopathic, reinforced the rationale for monitoring $CD4^+$ cell counts in the clinical follow-up of patients who were infected with HIV. Several years later, in the mid-1990s, research groups identified the main co-receptors of HIV: CXC-chemokine receptor 4 (CXCR4) and CC-chemokine receptor 5 (CCR5)[18,19]. Binding to these chemokine receptors was found to lead to the conformational changes that are necessary for entry of X4-tropic HIV-1 (which uses CXCR4) and R5-tropic HIV-1 (which uses CCR5). Around the same time, the scientific community identified rare individuals with a homozygous *CCR5* deletion who were resistant to HIV-1 infection[20–22]. As the transmitted virus is R5-tropic, the *CCR5Δ32* mutation blocks viral entry, therefore conferring resistance to HIV infection.

By the end of the twentieth century, we had obtained insights into the life cycle of HIV and, subsequently, had identified the targets of antiretroviral drugs that had been used since the mid-1990s to efficiently prevent and treat HIV infection. Even in the new millennium, the scientific community is still acquiring new information about the interplay between the host and the virus, which complements our existing knowledge of the HIV replication cycle (FIG. 2). Several studies have offered a better understanding of the delicate balance between the viral and host factors that promote or impede viral replication; for example, in 2002 APOBEC3G — a cytidine deaminase — was shown to prevent HIV-1 replication but is counteracted by the viral Vif protein[23]. The identification of other restriction factors and the corresponding counteraction mechanisms of HIV followed: tripartite motif-containing 5α (TRIM5α)[24]; tetherin (also known as BST2)[25,26], which is counteracted by Vpu, and the deoxynucleoside triphosphate triphosphohydrolase SAMHD1, which is counteracted by Vpx[27]. Although HIV has evolved to evade the restriction mechanisms of each of these factors, current research focuses on identifying means to exploit these proteins and to block the viral antagonists.

Timeline | **Key moments in HIV research**



AZT, azidothymidine; TRIM5α, tripartite motif-containing 5α; CCR5, CC-chemokine receptor 5; CXCR4, CXC-chemokine receptor 4; iPrex, initiative for pre-exposure prophylaxis.

Insights into HIV and SIV pathogenesis. With the wealth of information about the virus itself, the past three decades have seen important advances in understanding the complexity of HIV and SIV transmission and pathogenesis. In 1993, a PCR technique used to measure plasma viral levels during the early phase of HIV infection detected up to 20 million RNA copies per ml of plasma[28]. Following this initial burst of viral replication in the periphery, HIV disease is active and progressive in lymphoid tissues even when only minimal viraemia is detectable in plasma[29]. In 1998, studies in rhesus monkeys showed that, during the acute phase, within just a few days of SIV infection, there is significant $CD4^+$ T cell depletion in the gastrointestinal tract[30]. Subsequent studies provided further insights into the mechanisms of $CD4^+$ T cell depletion in the gastrointestinal tract during both HIV and SIV infection[31–33]. For many of the above-mentioned studies, and indeed for other HIV research areas, non-human primate models have been instrumental, and SIV infection in non-human primates so far remains the best model for the study of HIV transmission, pathogenesis and control. The comparison between pathogenic and non-pathogenic simian models was crucial in determining that viral replication is not the only factor involved in disease progression[34–36].

HIV infection was linked to immune activation in the early days of research, after a 1983 study reported the hyperactivation of B cells[37]. Over time, we have increased our knowledge of the generalized immune activation state that is caused by HIV infection, in particular how pro-inflammatory cytokines and chemokines contribute to the chronic activation of the immune system. One of the causes of this chronic immune activation was more recently shown to be the translocation of microbial products from the gastrointestinal tract into the circulation[38].

Although much is known about adaptive (that is, cytotoxic T cell- and antibody-mediated) immune responses to HIV-1, the role of innate immunity has only recently become evident. In 2011, a report showed that natural killer (NK) cells can contribute to the control of HIV through viral recognition by killer-immunoglobulin receptors (KIRs), thus placing immunological pressure on HIV[39]. The same study showed that the virus evades such responses by selecting for sequence polymorphisms in KIRs[39].

Over the years, numerous studies have shown the link between host genetics and variations in HIV infection, treatment

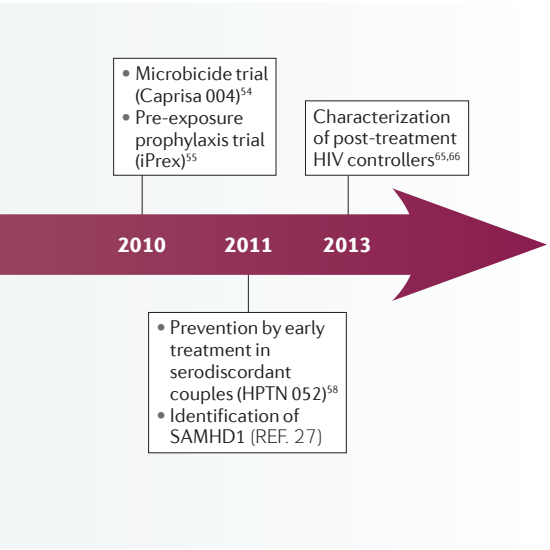
Box 1 | **Isolating HIV — the beginning of a translational research partnership**

Isolating HIV-1 would have been impossible without productive interactions between basic scientists and clinical researchers. The importance of translational research has been an unequivocal driving force for HIV research over the past three decades.

In the early days of the epidemic, researchers and clinicians were faced with the human tragedy of AIDS and the intense conviction of the necessity to act as rapidly and effectively as possible. The sense of extreme urgency encouraged virologists, immunologists, molecular biologists, epidemiologists and clinicians to rise to the challenge and to form a united front that allowed each group to benefit from the other's experience. This cross-disciplinary partnership was a crucial element in isolating HIV-1 in 1983, when virologists at the Institut Pasteur, Paris, France, worked closely with French clinicians who were treating patients with AIDS and individuals with generalized lymphadenopathy.

In the 1980s, many basic research scientists were brought into contact for the first time with clinicians and, occasionally, even with the patients themselves, which opened new perspectives on both sides and connected the two worlds. Moreover, many clinicians dedicated to the treatment and care of individuals infected with HIV felt compelled to undertake research for the first time. As a result, the response to the HIV epidemic was the first opportunity for many young clinicians to work in a multidisciplinary manner and to create new international collaborations. Clinical observations were essential in guiding basic research; the findings of laboratory research were fundamental in the development of key clinical tools for diagnosis and for the improved clinical care and follow-up of patients with HIV.

The interdisciplinary nature that characterized the early period of HIV research did not always apply to work done in the years that followed; however some of the most important recent discoveries in the field underscore the benefits of collaborative research. In the true tradition of Louis Pasteur, who advocated the value of interaction between the laboratory and the public health clinic, the HIV scientific partnership has expanded to include social scientists, health economists and global health specialists, among others, creating a uniquely rich and multidisciplinary research environment.



response, resistance development and disease progression. The variations in the immunological and virological outcomes depend on a complex balance of viral and host factors, including human leukocyte antigen (HLA) variants, which can modulate both innate and adaptive immune responses. Several HLA-B alleles (including HLA-B*57, HLA-B*27 and HLA-B*13) have been consistently associated with viral control, including in interaction with KIR genotypes[40–42].

The treatment revolution. From a clinical perspective, the outcome of HIV infection over the past three decades has been revolutionized by considerable progress in the therapeutic options available, which has transformed HIV infection from a fatal to a manageable chronic disease that has little effect on life expectancy.

At the time of the first reports of AIDS, clinicians could only treat the opportunistic infections associated with the disease with limited success. Only when HIV was identified as the virus responsible for the disease, and its life cycle was characterized, were the medical and scientific communities able to start investigating antiretroviral approaches.

The first step in HIV therapy was made in 1987, when a clinical trial showed that azidothymidine (AZT; also known as zidovudine) decreased mortality and opportunistic infections in patients with AIDS[43]. AZT, which had been originally synthesized as an anticancer treatment, was found to also block the reverse transcription step of the HIV-1 life cycle[44]. However, viral resistance quickly developed, and so new drugs had to be developed on the basis of insights into the HIV replication cycle and how to target it.

Indeed, almost a decade later, a major breakthrough was made with the introduction of a therapy that combined several drugs to limit the development of resistance. Studies showed that the introduction of a protease inhibitor alongside two nucleoside reverse transcriptase inhibitors (NRTIs) in combination antiretroviral therapy (ART) markedly reduced morbidity and mortality[45–47].

Clinical research continues to improve the therapeutic options available, with the aim of successfully controlling viral replication with minimal side effects and manageable treatment regimens. Several studies have shown that starting ART early after

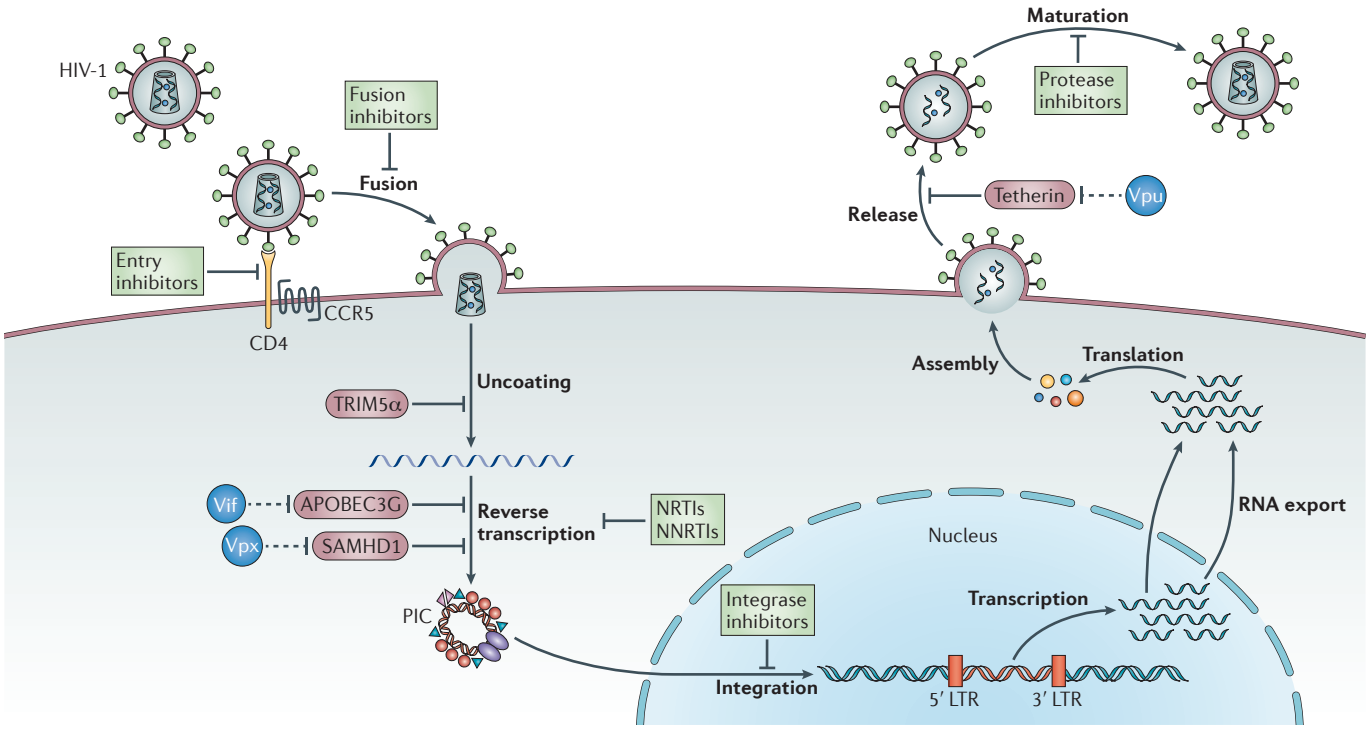


Figure 2 | **Schematic overview of the HIV-1 replication cycle.** The figure illustrates the main steps in the HIV-1 replication cycle: binding to the CD4 receptor and co-receptors; fusion with the host cell membrane; uncoating of the viral capsid; release of the HIV RNA and proteins into the cytoplasm; reverse transcription of HIV RNA to DNA; formation of the pre-integration complex (PIC); and translocation into the nucleus. Once in the nucleus the viral DNA is integrated into the host DNA and subsequently transcribed and translated to form new viral RNA and viral proteins that translocate to the cell surface to assemble into new immature virus forms. The new viruses bud off and are released. Finally, during maturation, the protease enzyme cleaves the structural polyprotein to form mature Gag proteins, resulting in the production of new infectious virions. The major families of antiretroviral drugs (green), and the step of the life cycle that they block, are indicated. Also shown are the key HIV restriction factors (tripartite motif-containing 5α (TRIM5α), APOBEC3G, SAMHD1 and tetherin; red) and their corresponding viral antagonist (Vif, Vpx and Vpu; blue). CCR5, CC-chemokine receptor 5; LTR, long terminal repeat; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors.

Box 2 | **The winding road of HIV vaccine research**

The discovery of the virus that causes AIDS led many, including politicians, activists and, indeed, several scientists, to believe that an effective vaccine could be made available within a few years. However, 30 years of research have taught us that HIV is able to mutate and evolve, which leads to very high diversity, and that the host is inefficient at mounting strong broadly neutralizing antibody (bNAb) responses against the conserved region of the HIV envelope. So far, a safe and effective HIV vaccine remains elusive.

A large number of scientists began working on a vaccine against HIV, and clinical trials started within 4 years of the isolation of the virus. The two VaxGen trials, the Phase IIb STEP trial[76] and its sister trial Phambili[77], were among a series of disappointing failures, both in preclinical trials in non-human primates and in clinical trials.

A glimmer of hope was provided in 2009 by the results of the RV114 trial in Thailand. The combination of two vaccines (canarypox ALVAC-HIVvCP1521 and AIDSVAX B/E gp120) administered in a prime-boost combination showed modest vaccine efficacy[78] and provided proof-of-concept that an effective vaccine against HIV acquisition could be developed. However, the vaccine research field was more recently confronted with a new set-back when the Phase IIb trial, HVTN 505 (which combined a DNA prime and a recombinant Ad5 boost) was stopped as interim results showed no difference in efficacy between the vaccinated and control patients.

Despite a series of discouraging results — a constant reminder of the challenges in the development of a vaccine against HIV — the field must continue to use both the positive and negative results to progress. A safe and effective vaccine will be the ultimate prophylactic option and, as such, should remain a priority for researchers worldwide. The detailed analysis of recent Phase IIb and III clinical trials, which should look at the immune responses elicited by the vaccines, and viral analysis of breakthrough infections will be crucial to determine the future directions and design of new clinical trials and to identify mechanisms of protection. In addition, we have gathered important insights into the structure of bNAbs and their specificities[79–83], which will be useful in the design of new vaccine candidates. For a preventive vaccine to ultimately induce these bNAbs, information from the fields of both structural biology and B cell biology will be necessary to develop specific immunogens that will stimulate B cells to produce effective protective antibodies. Interestingly, the use of bNAbs in passive immunization therapeutic approaches has also shown encouraging results in preclinical models[84,85]. Vaccine research is now looking beyond humoral and cell-mediated immunity and trying to harness the crosstalk between innate and adaptive responses by using innovative vaccine approaches, including targeting specific subsets of dendritic cells.

infection has beneficial effects, and the World Health Organization has recently updated its consolidated guidelines accordingly to recommend treatment initiation at 500 $CD4^+$ cells or fewer per mm^3 of blood[48]. The success of life-long ART is now clear on an individual basis, and a study in early 2013 showed that the adult life expectancy in South Africa increased by 11 years over the period between 2003 (just before ART became available in the public healthcare system) and 2011, which highlights the global health benefit and its cost-effectiveness[49].

The present age: the new era of prevention

For several years, and despite limited scientific studies to prove their efficacy, condom use together with education and behavioural changes were the only means of effective prevention against HIV infection.

The first milestone in terms of biomedical prevention was the proof that ART could be effective in the prevention of mother-to-child transmission of HIV. In 1994, the ACTG 076/ANRS 024 randomized clinical trial showed that ante- and intra-partum AZT treatment to the mother and infant significantly reduced the risk of HIV acquisition by the newborn[50]. More than a decade later, in 2005 and 2007, a series of major randomized clinical trials found that male circumcision provides a certain degree of protection from infection[51–53].

The first decade of the new millennium has been a period of renewed enthusiasm and interest in alternative biomedical prevention strategies, and there have been several important studies in the field. Following the failure of classic broad-spectrum microbicides in HIV prevention, the scientific community realized the importance of investigating the properties of specific antiretroviral microbicides in the prevention of HIV infection. For example, the South African Caprisa 004 clinical trial assessed the effectiveness and safety of a vaginal tenofovir disoproxil fumarate gel applied locally before and after coitus, which showed that HIV infection could be reduced by up to 54% depending on adherence levels[54]. Similarly, in 2010, the initiative for pre-exposure prophylaxis (iPrEX) trial showed that a once daily oral combination of two antiretrovirals (emtricitabine and tenofovir disoproxil fumarate) decreased HIV acquisition in men or transgender women who have sex with men by 44% (REF. 55); again, risk reduction strongly correlated with adherence. However, it is important to recognize the great disparity among the rates of transmission reduction (0–75%) in recent results and to note that other studies have reported no significant effect of pre-exposure prophylaxis in women in Africa, identifying a lack of adherence as a key factor for the negative outcome[56,57].

In 2011, a study applied the concept of using effective ART to render the viral load undetectable and thereby to limit infection via sexual transmission in serodiscordant couples (that is, couples in which one partner is HIV-positive and the other is HIV-negative). The results of the study were among the most important figures in HIV prevention: a 96% reduction in the transmission rate was shown[58].

Currently, the field of biomedical prevention research — in particular, Treatment as Prevention (TasP), to determine the effect of immediate ART on the population incidence rates, and Pre-Exposure Prophylaxis (PrEP) — is expanding, with ongoing randomized clinical trials to assess the efficacy of these interventions. It is probable that a combination approach, including several strategies, will prove the most fruitful.

A look ahead to the future

In late 2013, despite many successes, some key questions still need to be addressed. First, despite a decrease in the incidence rate, the global AIDS epidemic continues mainly unabated, particularly in the most at-risk populations. Second, although treatment provides successful viral control, HIV remains persistent and is not eradicated, and testing and treatment remain insufficiently implemented for many people in resource-limited settings. Third, ART does not fully restore the immune system and, consequently, health. In addition, it is associated with considerable side effects, and it remains a life-long commitment. Furthermore, AIDS is associated with chronic inflammation and immune activation, which probably result in immunosenescence and ageing, as well as with co-infections that frequently lead to complications. Finally, an effective vaccine against HIV is still elusive (BOX 2).

Indeed, a new scientific priority is the search for a potential cure for HIV, following some important scientific results suggesting that a cure, or at least a 'functional' cure (that is, permanently controlling HIV infection

Box 3 | **The role of civil society in shaping the response to the emergence of AIDS**

In parallel with the biomedical and scientific response to the emergence of AIDS in the early 1980s, and with equal rapidity, activists and members of civil society organized themselves in a powerful community. This led to one of the most definitive and efficient global civil society responses to a health issue and added a political dimension to the biomedical response. The civil society response initially involved a petition for enhanced human rights and rapidly evolved to a demand for better treatment and access to drugs. Over time, civil society became particularly engaged in scientific debates on drug developments and became a 'legitimate' group, monitoring ongoing scientific research on HIV and beyond.

The strength of the civil society response, which transcended national borders to form a coherent and synergistic global response, succeeded in placing HIV/AIDS on international political agendas and engaging in national governments and international organizations. The tangible outcome of this activism was particularly apparent in 2001, when an alliance of local and international non-government organizations (NGOs) succeeded in putting sufficient pressure on pharmaceutical companies to drop a legal case against South Africa for importing generic antiretroviral drugs.

Although the initial balance between activists and the biomedical community was fragile, the two groups soon found a way to work together, and civil society, NGOs and patient associations remain at the core of the global HIV response. Representatives are not only present in global health partnerships but are also members of scientific committees, partners of research organizations and are now players in community-based research.

without completely eradicating it), might be within reach.

Containing the infection — insights from controllers. A first key insight into the mechanisms by which the immune system could, in theory, control viral infection, was the identification of individuals who were infected with HIV but did not progress to AIDS, despite the absence of ART (these individuals were termed long-term non-progressors). These patients, representing a minority of individuals infected with HIV, were identified within the first years of the pandemic and in the early 1990s were found to maintain significant $CD4^+$ T cell levels for several years in the absence of treatment[59–61].

At the turn of the new millennium, researchers identified some even rarer individuals (0.1–0.5% of the total number of individuals infected with HIV) who remain asymptomatic and maintain normal $CD4^+$ T cell counts for over a decade. Further characterization showed that this subgroup of individuals infected with HIV, who were later termed HIV controllers, spontaneously control viral replication, which results in undetectable viral levels in the plasma[61,62]. We now have some detailed insights into the genetic predisposition and the immunological characteristics of these rare individuals that enable them to control viral infection; for example, these individuals have an over-representation of specific HLA-B alleles and potent $CD8^+$ T cell-mediated suppressive immune responses[41,63,64]. HIV controllers have been the focus of much scrutiny by the scientific community, with the hope that we may be able to reproduce their protective mechanisms in individuals who were infected with HIV who are not HIV controllers.

In addition to these spontaneous controllers, recent reports have indicated that early combination ART that is rapidly initiated after infection can limit the capacity of HIV to establish large viral reservoirs. In 2013, researchers published the VISCONTI (viro-immunological sustained control after treatment interruption) study report, which identified a group of patients who had initiated ART in the acute phase of HIV infection and subsequently controlled viral replication[65]. These patients, who underwent 3 years of prolonged and continued therapy, could still control viral replication 10 years on, even though treatment had been discontinued. The frequency of these post-treatment controllers seems to be higher than that of the very rare spontaneous HIV controllers. Moreover, they do not share the genetic background of most spontaneous HIV controllers, which suggests that early and prolonged therapy might enable some individuals to control viral infection even after treatment interruption and to achieve a functional cure. An additional report reinforced the idea of achieving a functional cure for HIV: an infant, who was born to an HIV-positive mother and infected with HIV, was treated within 30 hours of birth and, despite treatment discontinuation at 18 months of age, plasma HIV RNA levels remained undetectable[66]. Taken together, these results provide strong evidence that a functional cure for HIV may indeed be within reach.

Interestingly, controllers, both spontaneous and post-treatment, have extremely low HIV DNA reservoir levels, which even decrease over time in some post-treatment controllers.

Eliminating latent virus. The increased knowledge of HIV reservoirs and mechanisms of persistence has paved the way for the use of innovative approaches to attempt to eliminate latent virus. In the mid-1990s, a series of reports shed light on HIV reservoirs, showing the existence of provirus within latently infected resting life-long memory $CD4^+$ T cells[67] and that, even after successful ART, these reservoirs can produce infectious virus following cellular activation[68–70]. An example of innovative approaches that are currently being studied are reactivation strategies using histone deacetylase (HDAC) inhibitors. In 2005, a report provided proof-of-concept that the HDAC inhibitor valproic acid, together with intensified ART, aided the clearance of HIV in resting $CD4^+$ T cells[71]. Research has continued on reactivation strategies, and recent results show that the HDAC inhibitor vorinostat can induce HIV transcription, which results in higher levels of cell-associated unspliced RNA in more than 80% of patients in the trial[72]. However, total levels of HIV DNA did not decrease, which indicates that further research must be carried out to determine whether HDAC inhibitors are a beneficial approach to eliminate latent virus.

Stem cell transplant-based treatments. A report that caused a search for an HIV cure to be put back on the international scientific and advocacy agenda was the case of the so-called 'Berlin patient'. This patient had long-term aviraemia despite the absence of any ART following transplantation of stem cells from a donor carrying the protective *CCR5* mutation (see above)[73]. A more recent report found that HIV-1 DNA was undetectable in peripheral blood mononuclear cells and in the rectal tissue of individuals who were on ART but who had received allogeneic haematopoietic stem cell transplantation (HSCT) from donors with wild-type *CCR5* (the 'Boston patients'). Notably, the virus remained undetectable even a few weeks after ART was terminated, which suggests that the infection of donor cells (even potentially susceptible wild-type *CCR5* cells) had been prevented by previous ART[74]. The ongoing analytical treatment interruption studies will provide further insights into the effect of HSCT on HIV reservoirs. However, it is important to note that another recent study reported that autologous HSCT for HIV-related lymphoma did not result in

depletion of HIV, indeed HIV RNA was detected in nine out of ten study participants and HIV DNA was detected in all ten patients[75].

Although some of the strategies discussed in this section will not be applicable to the wider population, these studies have greatly contributed to re-invigorating global research to find a cure for HIV. The HIV scientific community needs to investigate several innovative approaches to achieve a potential HIV cure (be it functional or sterilizing), including immune-based treatment, therapeutic vaccines, gene therapy and bone marrow transplantation, and to approach other scientific disciplines, such as oncology, for new insights. Alongside the scientific discussion, there is an ongoing debate on the nomenclature of these strategies and whether it is appropriate to use the word 'cure' in the absence of complete viral eradication, which many think will not be possible to achieve.

Conclusion

The past three decades of HIV research have been marked by huge successes, but also severe disappointments. HIV-1 is undoubtedly one of the best characterized viruses, and we have accumulated a wealth of information regarding its biology, transmission and pathogenesis. The first responses to the epidemic were based on clinical reports, and today clinical observations still have a key role in identifying determinants of the infection and its control. Similarly, much of the molecular and cellular knowledge of HIV has been instrumental in achieving practical clinical outcomes, and it is crucial that the translational science involving multidisciplinary collaborations between basic scientists, epidemiologists, and clinical, social and public health researchers is maintained, and even reinforced. This translational and multidisciplinary aspect should go beyond this particular field, as research on HIV could benefit other biomedical areas (as has been the case for viral hepatitis, for example) and could itself benefit from interaction with and insight from other research fields, including those of chronic infections and inflammatory diseases.

The shift from a lethal infection to a manageable chronic disease should be a reminder of the effect that biomedical research has had on the lives of those who are infected with HIV. HIV clinical and operational research in low-income countries has been integral to saving the lives of millions of people and has helped to reinforce the general healthcare system in several countries. Despite the undeniable progress that has been made, we cannot forget that 34 million people are still living with HIV, and although incidence rates have decreased in many countries, transmission remains high in specific populations. Alongside a strong political agenda and continued commitment from civil society (BOX 3), science must continue to deliver new and simpler treatments as well as novel preventive options, identify new biomarkers to predict and monitor the host response to current and future interventions, and investigate the implementation of combination approaches, pushing towards a potential cure for HIV.

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Competing interests statement
The authors declare no competing interests.