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Progress in achieving long-term HIV remission

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Abstract

Purpose of review—The purpose of the present review is to describe the major barriers to HIV eradication and assess the most promising cure strategies under investigation.

Recent findings—There are significant challenges to achieve HIV eradication. These include the establishment of persistent latently infected cells, systemic chronic immune activation, and immune dysfunction. Since the announcement of the first HIV cure involving the Berlin patient, several attempts to reproduce these results have failed. Thus, it is widely accepted that long-term HIV remission would be a more feasible approach. Optimization of ART, immune-based therapies, therapeutic vaccinations, and gene editing, amongst others, are strategies aimed at controlling HIV in the absence of ART. These new strategies alone or in combination are being developed in preclinical studies and clinical trials and will provide further insight into whether long-term HIV remission is possible.

Summary—The present review discusses several mechanisms that mediate the persistence of the HIV reservoir, clinical cases that provide hope in finding a functional cure of HIV, and promising interventional strategies being tested in preclinical studies and clinical trials that attempt to reduce the HIV reservoirs and/or boost the immune responses to control HIV in the absence of ART.

Keywords

gene therapy; HIV remission; immune-based therapies; therapeutic vaccination; viral reservoirs

INTRODUCTION

When optimally administered, antiretroviral therapy (ART) can successfully control viral replication, reduce the risk of viral transmission, and improve morbidity and mortality for individuals living with HIV infection [1,2]. However, ART interruption leads almost

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Conflicts of interest

There are no conflicts of interest.

invariably to viral rebound, thus, life-long adherence to ART is necessary. Long-term ART in HIV-positive individuals is an enormous challenge to optimal adherence and can result in cumulative drug toxicities and the emergence of HIV drug resistance. Although one person has experienced viral eradication, this remains an elusive target because the therapeutic strategy employed is not feasible on a large scale. For these reasons, achieving sustained viral remission upon ART discontinuation has been the primary focus of the HIV scientific community.

In this review, we will address the major obstacles to achieving long-term HIV remission, clinical cases that provide insight towards this goal, and which strategies appear most promising.

THE OBSTACLES

There are several substantial barriers to achieve HIV remission. The key challenges are described in this review: [1] the establishment of a reservoir of latently infected cells, [2] persistent immune activation and chronic systemic inflammation, and [3] functional exhaustion of HIV-specific CD4 and CD8 T cells.

Reservoir

Soon after it was demonstrated that effective ART could result in the suppression of viral replication for HIV-positive individuals, it was recognized that interruption of therapy resulted in rebound of viremia. This viral rebound confirmed the existence of a reservoir of long-lived, quiescent cells that harbour-integrated, latent HIV proviruses [3,4]. Although the precise source of this reservoir is not clear, it is widely believed that latently infected, resting $CD4^+$ T cells are the major cellular reservoirs for HIV [5]. However, other cell types can also constitute part of the HIV reservoir [6,7]. Several mechanisms contribute to the maintenance of the viral reservoir such as intrinsic stability of resting $CD4^+$ T cells [8]; antigenic and homeostatic proliferation of infected cells [9]; localization of the pool of infected cells in anatomic sanctuary sites, where drug concentrations could be suboptimal [10,11]; and cell-to-cell viral transmission [12]. Furthermore, HIV can integrate into specific genomic sites that extend survival or enhance cell proliferation, thereby inducing a clonal expansion of memory $CD4^+$ T cells [13]. The concept of low-level viral replication that could replenish viral reservoirs during suppressive ART remains controversial. Several studies quantifying two long terminal repeat (2-LTR) circles and measuring HIV evolution for patients virologically suppressed on ART as a surrogate marker of ongoing viral replication produced conflicting results [14■■, 15–18].

Immune activation

HIV infection causes a progressive impairment of the immune system characterized by massive $CD4^+$ T-cell depletion, sustained immune activation, and systemic inflammation. ART suppresses viral replication, reduces immune activation, and permits the recovery of $CD4^+$ T-cell counts in HIV-positive individuals but does not normalize these processes for all patients. In fact, this immunocompromised state may contribute to the persistence of the viral reservoir [19].

High levels of $CD4^+$ T-cell activation enhances the transcription of integrated virus, and therefore the production of new virions that can infect additional target cells. Furthermore, activation of T cells makes them more susceptible to infection via increased expression of CCR5 and homing of T cells to anatomic locations where replication is ongoing, establishing a vicious cycle during whereby HIV replication promotes immune activation and immune activation promotes HIV replication [20]. Residual immune activation during ART can promote viral persistence through several mechanisms. Pro-inflammatory cytokines can sustain the reservoir through homeostatic proliferation, and cycling of $CD4^+$ T cells can result in clonal expansion of the latent reservoir. Immune activation also leads to a functional exhaustion of T cells, which in turn reduces HIV-specific T-cell responses, and can promote $CD4^+$ T-cell latency by increasing the fraction of these cells expressing co-inhibitory receptors that have been associated with viral persistence, such as PD-1, CTLA-4, LAG-3, TIM-3 and TIGIT [21■■,22■■,23■,24–28]. Furthermore, HIV-associated immune activation stimulates collagen deposition in secondary lymphoid organs, which causes tissue fibrosis. Tissue fibrosis can result in significant architectural damage of lymphatic tissues that impairs $CD4^+$ T-cell reconstitution, antigen-lymphocyte interaction, and access of cytotoxic $CD8^+$ T cells into areas where HIV reservoirs are localized [29–31]. It is conceivable that tissue fibrosis may also contribute to a sub-optimal concentration of antiretroviral drugs in these tissues.

Functional exhaustion of T cells

Persistent immune activation in HIV-positive individuals results in a reduction of T-cell renewal and a progressive enrichment of terminally differentiated T cells with reduced antiviral function, a process known as immunosenescence. HIV-associated immunosenescence contributes to persistent immunodeficiency, early onset of age-associated diseases, and diminished HIV-specific T-cell responses [32].

Chronic exposure to antigens leads to T-cell exhaustion, described as a dysfunction of antigen-specific T cells. Loss of $CD8^+$ T-cell function can promote the persistence of viral reservoirs by the inability to kill both productively infected cells and reactivated latently infected cells during ART.

T-cell exhaustion is also associated with the upregulation of negative costimulatory molecules of T-cell activation (PD-1, CTLA-4, LAG-3, TIM-3, and TIGIT), which in turn, is correlated with the persistence of latently infected T cells in HIV-positive individuals. Otherwise, upregulation of CTLA-4 and PD-1 expression in $CD4^+$ T cells correlates directly with parameters of disease progression, viral loads, and inversely with T-cell counts. An increase of these molecules may inhibit HIV replication and promote latency [21■■,22■■,23■,24–28].

Therefore, finding novel therapeutic strategies aimed at reducing the survival of infected cells, limiting residual inflammation, and improving antiviral responses should bring us closer to a ‘functional cure’ for HIV. Clinical trials and preclinical studies testing distinct therapeutic strategies discussed in this review are summarized in Table 1.

ENCOURAGING CASES OF VIROLOGIC REMISSION

The first case that invigorated the scientific community to believe that a cure was possible was the ‘Berlin patient.’ An adult with chronic HIV infection developed acute myeloid leukemia and underwent myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT). The donor was screened for homozygosity of the CCR5Δ32 allele, which renders cells resistant to HIV infection [61]. A decade after this procedure, the ‘Berlin patient’ is still in remission from both cancer and HIV in the absence of ART. The ‘Berlin patient’ was considered as the first patient cured of HIV infection [62]. Since then, several efforts have been attempted to reproduce the same results with little success [63].

The ‘Boston patients,’ two individuals with chronic HIV infection underwent allogeneic HSCT for treatment of refractory lymphoma. Contrary to the Berlin patient, these two patients received a reduced-intensity conditioning allogeneic HSCT from donors with wild-type CCR5+ cells and received ART until full chimerism from the transplanted donor cells was achieved. During this period, HIV could not be detected from plasma or rectal mucosa samples. However, both patients experienced viral rebound 12 and 32 weeks after ART cessation [64,65]. These results demonstrated that allogeneic HSCT reduced considerably the HIV reservoir, but not completely. The reason why the Berlin patient may be the only example of HIV eradication is not clearly understood. Factors such as cell type donors (heterozygous/homozygous for CCR5Δ32), graft-versus-host disease reaction, pretreatment conditioning, emergence of hematologic CXCR4-tropic minority variants, and regimen during transplantation and engraftment, could have influenced the outcome of the combined procedures [66].

Another clinical case that increased expectations of the scientific community was the Mississippi baby. The Mississippi baby was a perinatally infected child that initiated ART at 30h of life until 18 months of age. The child had undetectable viral loads in plasma for 27 months without ART [67]. However, when the child was nearly 4 years of age, HIV RNA became detectable in plasma, and HIV-specific antibodies were detected [68]. This case provided evidence that very early ART could result in transient HIV remission.

Not only has the efficacy of very early ART to achieve HIV remission been investigated in newborns, but also in adults. The French VISCONTI group reported a subset of 20 ‘Posttreatment controllers’ (PTC). PTC are individuals that received ART at the time of primary HIV-infection, whom after treatment discontinuation presented an unusual and sustained virologic control. Only 5–15% of people who start early treatment are able to control viremia without ART. As opposed to ‘HIV controllers,’ these individuals lacked the protective HLA class I alleles, but rather risk-associated HLA alleles, and had weak $CD8^+$ T-cell responses. To date, median time of remission is 9.3 years, with the longest period of control greater than 12 years [69,70■■].

CURRENT DIRECTIONS OF THE CURE AGENDA

Early therapeutic antiretroviral therapy

Since the Mississippi baby and the VISCONTI cohort, several studies have been conducted with the hypothesis that early intensive ART can result in broad and strong HIV-specific immune responses, reduced immune activation, and limited establishment of viral reservoirs. However, it is unclear how much viral exposure is necessary to 'prime' the HIV-specific response while simultaneously minimizing reservoir expansion.

Additional cases focused on initiating ART in newborns have been reported. A HIV-positive baby in Milan initiated ART within 12h of life. At 3 years of age, the baby was undetectable on several HIV assays. However, two weeks after ART cessation, viremia rebound occurred [71]. Several studies are currently investigating whether early intensive ART among newborn infants infected perinatally can achieve long-term viral remission (IMPAACT TRIAL NCT02140255) [72,73].

A recent study described two HIV-positive adults that initiated ART 10 and 12 days after HIV infection. Although for one of the patients, HIV was not detectable in plasma or tissues, HIV rebounded 225 days following cessation of ART [74■■]. This delayed rebound in viremia was similar to that observed in one of the Boston patients. In another report, eight Thai patients started ART during Fiebig stage-I infection and the median time to viral rebound upon ART interruption was only 26 days [75■].

The effect of very early ART within hours of infection in adults has been well established in the setting of postexposure prophylaxis (PEP). PEP strategies have successfully demonstrated that ART can preventviral replication within the first infected cells following viral exposure in adults. If PEP strategies are able to prevent the establishment of a latent reservoir, it is not clear why cases such as the Mississippi baby did not succeed. This could suggest that immune responses in newborns are not mature enough to control viremia compared with the PTC in the Visconti Cohort.

Over the past several years, it is clear that reaching a functional cure could be facilitated by the rapid initiation of ART, which could reduce the size of the viral reservoir, limit damage to the immune system, and prevent onward viral propagation. Thus, it is critical that clinicians continue to screen for HIV among high-risk populations in order to facilitate early diagnosis and immediate ART initiation in order to achieve viral remission.

Immune-based therapies

Immune-based therapies aim to diminish HIV-associated immune activation and boost immune responses in order to achieve control over HIV infection, and/or target the HIV reservoir.

Cytokine therapies

Recombinant cytokines have been used for the expressed purpose to improve immunologic outcomes by increasing CD4 and CD8 T-cell expansion and function. In several phase III studies, the use of interleukin-2 (IL-2) in ART-suppressed, HIV-positive patients

increased peripheral CD4 T-cell counts, but failed to reduce the risk of HIV-associated opportunistic diseases or death (ESPRIT/SIL-CAAT NCT00004978 and NCT00013611; ANRS119 NCT00120185; ANRS118- ILIADE NCT00071890) [33,34,76]. Similarly, increased reconstitution of $CD4^+$ T cells was observed when administering IL-7 in HIV-positive individuals (INSPIRE NCT00099671) [35–37].

In preclinical studies of simian-immunodeficiency virus (SIV)-infected rhesus macaques who had been virologically suppressed on ART for an extended period of time, IL-15 treatment-enhanced activation, function, and proliferation of natural killer, and $CD8^+$ T cells [38], but failed to reconstitute SIV-specific or total $CD4^+$ T cells. Consequently, IL-15 treatment delayed viral suppression and accelerated the loss of T cells upon ART interruption. Other preclinical studies in chronic simian–HIV (SHIV)-infected rhesus macaques have demonstrated the effect of a human hetIL-15 superagonist ALT-803, which directs antiviral $CD8^+$ T cells into B-cell follicles, in reducing SHIV RNA in plasma and LN [39■■]. ALT-803 is being tested in ART-suppressed, HIV-positive individuals (NCT02191098).

IL-21 administration in early chronically SIV-infected rhesus macaques resulted in a significant reduction of T-cell immune activation (as measured by HLA-DR and CD38 expression) and cycling (as measured by Ki-67 expression) in blood and intestinal mucosa, SIV RNA in plasma, and SIV DNA content in gut, as well as reduced levels of $CD4^+$ T cells harboring replication-competent virus during ART [40,77]. Furthermore, a combined IL-21 and probiotic therapy limited microbial translocation in ART-treated, SIV-infected macaques [78■].

Janus kinase (Jak) 1/2 inhibitors are capable of decreasing circulating levels of several cytokines (e.g. IL-6, IL-7, and IL-15), which could impact both systemic inflammation and maintenance of the HIV reservoir. Preclinical studies have shown the ability of Jak inhibitors to block reservoir establishment, maintenance, and expansion [79■], and are currently being explored for HIV-positive patients (ACTG 5336 NCT02475655).

Development of cytokine-based therapies requires a more nuanced understanding of the role of cytokines in the setting of HIV/SIV infection either with or without ART. Furthermore, use of cytokines should not only restore the quantity but also improve the quality of T cells, and their ability to migrate to tissues where HIV reservoirs persist. Thus, the efficacy of cytokine therapies alone or in conjunction with other immune-based strategies should be further tested in preclinical and clinical studies as a potentially effective approach to reduce long-term viral reservoirs in HIV-positive individuals.

Anti-immune checkpoint molecules (anti-CTLA-4, PD-1, LAG-3, TIM-3)

Immune checkpoint molecules, such as CTLA-4 and PD-1, are co-inhibitory receptors, which down-modulate immune responses to prevent hyperimmune activation. Overexpression of these molecules is associated with T-cell exhaustion and dysfunction in cancer and chronic viral infections, including HIV [80]. Furthermore, $CD4^+$T cells that express PD-1, CTLA-4, LAG-3, and TIM-3 alone or in combination are major contributors of the viral reservoirs in ART-suppressed, HIV-positive patients and rhesus macaques

[21■■,22■■,23■]. Several immune checkpoint blockers have been successfully used for cancer therapy, encouraging their use in HIV/SIV infection to restore the loss of $CD4^+$ T-cell functions, and therefore to perturb viral reservoirs.

Blockade of CTLA-4 with ipilimumab in a HIV-positive individual on ART had increased effects on $CD4^+$ T-cell activation levels and induced an increase in cell-associated unspliced HIV RNA that was associated with a subsequent decline in plasma HIV RNA [81]. This was the first evidence that immune checkpoint blockers could be used to activate latently infected cells. Similar results were reported after blocking PD-1 with nivolumab [82■]. Ongoing clinical studies are being conducted to determine the efficacy of two immune checkpoint blockers, alone or in combination, for the ability to activate latently infected cells and reduce the latent HIV reservoir (NCT02408861, NCT03354936).

As immune checkpoint blockers have not received Food and Drug Administration (FDA) approval for the indication to treat HIV infection, all ongoing clinical trials are occurring in HIV-positive patients who are receiving immune checkpoint blockers for advanced cancers. The benefits of immune checkpoint blockers compared with conventional chemotherapy in advanced tumors eclipse the risks. As immune checkpoint molecules are involved in antigen self-tolerance, disruption of these molecules can lead to autoimmune or inflammatory side-effects, reactivation of underlying autoimmune conditions, or the precipitation of new autoimmune conditions such as type 1 diabetes mellitus. As immune checkpoint blockers have not been tested in the context of HIV-infection alone, additional preclinical studies should be performed to monitor these side effects in an already activated immune system.

Other antibodies (anti-α4β7)

Recently, immunotherapy has provided a new direction in HIV cure research for the scientific community. Blocking of α4β7, a gut-homing integrin, together with ART in SIV-infected rhesus macaques lead to undetectable viral loads and normal $CD4^+$ T-cell counts in plasma and gut for more than 9 months after withdraw of both ART and monoclonal antibody (mAb) antiα4β7 [83■■]. The precise mechanisms by which ART plus α4β7 mAb therapy promoted virologic control remains to be defined. Currently, a clinical trial is testing whether a short-term treatment with the humanized analog of α4β7 mAb, vedolizumab, in combination with ART can generate sustained HIV remission in HIV-positive individuals (the HAVARTI TRIAL NCT03147859; NCT02788175).

Therapeutic vaccines

Therapeutic HIV vaccination is designed to improve HIV-specific immune responses (both humoral and cellular immune responses) and/or direct reactivation of HIV-specific $CD4^+$ T cells that harbor latent HIV. Although around 200 HIV vaccine candidates have been clinically tested since 1986, there are no therapeutic HIV vaccines approved by the FDA. Only one HIV vaccine demonstrated modest efficacy in preventing HIV acquisition [41–43,84–87].

Eliciting nonneutralizing antibodies

The RV144 study in Thailand consisted of a prime-boost regimen of a canarypox viral vector (ALVAC vCP1521canarypox Env/Gag/Pro) with the HIV Envelope (Env) subunit protein gp120 clade B/E (AIDSVAX). This study demonstrated a 31% reduction in new infections compared with the placebo group (NCT00223080) [41]. Subsequent analysis showed that nonneutralizing IgG antibodies capable of mediating polyfunctional responses or antibody-dependent cellular cytotoxicity (ADCC) responses correlated with a lower risk of HIV acquisition [85,86]. Subsequent vaccine trials have improved the ALVAC/AIDSVAX B/E vaccine by adapting the RV144 regimen to different geographic regions by changing the HIV clade used, using different adjuvants, prolonging the boost durability, and so forth.

Therapeutic vaccines also aimed at eliciting polyfunctional antibody responses, including adenovirus serotype 26 (Ad26)/modified vaccinia Ankara (MVA) prime/boost regimens, mosaic immunogens, and Env gp140 protein subunit immunogens, were associated with increased protection from intra-rectal SIV challenge and improved virologic control in NHP studies [42,43]. These novel vaccine strategies are currently being evaluated in clinical studies (reviewed in [87]).

Eliciting or delivery of broadly neutralizing antibodies

Another approach in HIV therapeutic vaccination is to elicit or deliver broadly neutralizing antibodies (bNAbs) by immunization, gene delivery, or passive administration. These bNAbs provide highly potent cross-reactivity that targets Env epitopes shared amongst different HIV clades.

In one study, bNAbs elicited protection against SHIV challenge in NHPs (reviewed in [88]). Passive administration of bNAb PGT121, which targets a V3-glycan site of Env, together with a TLR7 agonist (GS-9620) resulted in a decline in plasma viremia to undetectable levels and a decrease in proviral DNA in blood and tissues of SHIV-infected rhesus macaques. This team found that 55% of PGT121+GS-9620 treated animals rebounded by day 140 following ART discontinuation [44■■,89]. VRC01 and 3BNC117, bNAbs targeting the CD4-binding site, have been shown to slightly delay plasma viral rebound upon ART interruption in HIV-positive individuals with suppressed viremia [45,46■].

By using adenoassociated virus (AAV) vectors carrying transgenes that encode for bNAbs, these antibodies can be produced directly from the muscle tissue where the AAV were delivered. This novel strategy, also called vectored immunoprophylaxis (VIP), has been demonstrated to produce and maintain titers of bNAbs that confer protection from HIV/SHIV challenges in preclinical studies [90–92].

Shock and kill strategies

The ‘shock and kill’ strategy consists of [1] reversing the latent HIV proviral DNA-containing $CD4^+$ T cells and [2] killing the reactivated virus by cytopathic effect or by HIV-specific cytotoxic T-cell response. Latency reversing agents (LRAs) are compounds identified to potentially reactivate latently infected cells and are involved in gene transcription regulation.

In-vivo studies testing valproic acid, vorinostat, disulfiram, panabinostat, and romidepsin have demonstrated the ability of LRAs to reverse latency by initiating HIV transcription and thus increasing cell-associated HIV RNA in total and resting $CD4^+$ T cells. However, none of these have shown a decrease in the size of the latent reservoir [47–51,93]. Thus, further LRA studies are needed to fully understand the mechanism of action for LRA targeting the latent HIV reservoir.

Recently, it is being recognized that latency disruption ('the shock') should be combined with immune therapies that could boost the clearance of reactivated virus ('the kill').

Few 'shock and kill' clinical trials are ongoing (reviewed in [94]). In the REDUC Phase IB/IIA clinical trial, HIV-positive patients virologically suppressed on ART were vaccinated with Vacc-4x (a synthetic gag peptide) and recombinant human granulocyte macrophage colony-stimulating factor (rhuGM-CSF) as adjuvant followed by infusions of the HDAC inhibitor romidepsin. The results showed a 40% reduction of total HIV DNA after romidepsin, but it did not have any effect in time to rebound after ATI compared with patients from previous trials who received no intervention (NCT02092116) [52■].

In the BCN02-Romi study, 15 patients virologically suppressed from BCN01 trial, were immunized with ChAd.HIVconsv/MVA.HIVconsv prime/boost followed by 3 weekly doses of romidepsin and by a second MVA.HIVconsv vaccination. Follow-up results will explore the efficacy of this therapeutic combination (NCT02616874) [53■].

Administration of LRAs by themselves has proved to reactivate HIV reservoirs, but once the virus is reactivated, viral cytopathic effect and/or HIV-specific cytolytic T cells are not sufficient to kill the infected cells. Thus, a strategy combining LRAs and other immune-based strategies that could boost cytolytic T-cell responses should be further studied.

Cellular or gene therapy

Gene editing (zinc finger nucleases and CRISPR)—Curing HIV via allogeneic HSCT from a CCR5Δ32 donor pushed the development of genome-editing techniques to create permanent CCR5-negative autologous T cells that could be transferred to HIV-positive patients avoiding allogeneic transplantations.

The first genome-editing technique evaluated was zinc finger nucleases (ZFNs). ZFNs are engineered restriction enzymes that include a DNA-binding domain together with a DNA-nuclease domain that cleaves DNA at specific locations. Infusion of CCR5-disrupted ZFN-modified cells on HIV-positive patients on ART proved to be safe and well tolerated, engrafted in all patients, and persisted for more than 42 months (NCT00842634) [54]. Further clinical trials are improving this approach with different preconditioning prior to the infusion of ZFN-modified cells and with increasing number of CCR5 ZFN-modified cells infusions (reviewed in [95]).

One important state-of-the-art genome-editing technology involves the CRISPR/Cas9 system, which consists of a Cas endonuclease that is directed to cleave a target sequence by a guide RNA (gRNA). Most of the clinical trials employing CRISPR/Cas9 are directed

at deleting PD-1 in T cells or generating CAR-T cells to treat cancer. One study in China has been evaluating the safety and feasibility of CRISPR/Cas9 *CCR5* gene modified CD34+ HSPCs transplantation in ART suppressed HIV-positive patients that developed AIDS and hematological malignances (NCT03164135). Clinical implementation of gene-editing techniques requires further optimization of delivery of nucleases to target cells by maximizing biallelic disruption, while limiting off-target genome modifications that could result in viral resistance or/and side effects of the treatment. We should also take into consideration the scalability and cost of gene therapy in order to make these promising treatments deliverable to HIV-positive individuals worldwide.

CONCLUSION

Achieving complete elimination of HIV reservoirs from the body appears remote. Alternatively, eliciting long-term control of infection in the absence of ART appears more feasible. Early ART initiation has demonstrated a reduction in the establishment of viral reservoir and preservation of immune responses in HIV-positive individuals. Thus, prevention, early diagnosis, and early treatment should be a priority for HIV medical care. However, most HIV-positive individuals are diagnosed at chronic stages of HIV infection. Various HIV therapeutic approaches have been able to elicit immunological responses, but only a few of them have succeeded in reducing viral reservoirs and achieving viral remission. Combined strategies, such as therapeutic vaccines with cytokine therapies/LRAs, could be an effective approach. Follow-up studies will demonstrate whether cell and gene therapies are well tolerated, effective, scalable, and affordable cure strategies. Incredible achievements have been accomplished during the last 30 years in the HIV field; however, many aspects of the interaction between HIV and the host are not completely understood and pose a challenge to eradicate or control HIV.

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KEY POINTS

- The main obstacle to HIV cure is the establishment of HIV reservoirs that persist in HIV-positive individuals despite virologic suppression on ART.
- The most feasible therapeutic approach in HIV care is the achievement of long-term drug-free remission for HIV-positive individuals.
- Several cases have proven that HIV can be eradicated or controlled in the absence of ART. To date, several therapeutic strategies have demonstrated improved immunological responses, but few of them have proved to reduce viral reservoirs and/or transiently control viremia.
- Preclinical studies are of key importance in testing the safety and efficacy of new therapies in development.
- Ongoing clinical trials based on optimization of ART, immune-based therapies, therapeutic vaccinations, and gene editing will further provide insight into whether long-term HIV remission is possible.

Table 1.

Preclinical and clinical studies of different therapeutic strategies to achieve long-term HIV remission

Trial	Product	Number trial	Phase	Results	References
Early ART					
IMPAACT PI 115	Early ART in newborn infants	NCT02140255	I/ll	Currently recruiting participants	-
Immune-based therapies					
ESPRIT/SILCAAT	IL-2	NCT00004978/ NCT00013611	III	Increase in the CD4+ cell count, no clinical benefit	The INSIGHT—ESPRIT Study Group and SILCAAT Scientific Committee. 2009
ANRS 119	IL-2	NCT00120185	I	Increase in the CD4+ cell count, no clinical benefit	Molina *et al.* [33]
ANRS 118-NIH ILIADE	IL-2	NCT00071890	ll/lll	Delay HAART resumption following ATI. No effect on viral load.	Levy *et al.* [34]
INSPIRE	IL-7	NCT00099671	I	Increased number of CD4 and CD8 T cells	Sereti 1, *et al.* [35]
EudraCT	IL-7	NCT00099671	I/I la	Expansion of naive CD4 and CD8 T cells	Imamichi *et al.* [36]
	IL-7	-	Preclinical study in rhesus macaques	Increasing circulating CD4 T cells	Parker *et al.* [37]
	IL-15	-	Preclinical study in rhesus macaques	Proliferation of HIV-specific CD8+ T cells but not CD4+ T cells. Upon ART interruption, faster drop in CD4+ T cells No effect on viral load	Lugli E *et al.* [38]
	hetIL-15 ALT-803	-	Preclinical study in rhesus macaques	Increased Gran B+ CD8 T cells within B-cell follicle, decreased viral RNA in LN	Watson *et al.* [39■■]
ACTG 5336	Jak 1/2 inhibitors (Ruxolitinib)	NCT02475655	Pilot study	-	
	IL-21	-	Preclinical study in rhesus macaques	Reduction of immune activation. Reduced plasma viremia, and cell- associated SIV DNA	Micci *et al.* [40]
	Ipilimumab (anti-CTLA-4) + Nivolumab (anti-PD-1)	NCT02408861	I	Currently recruiting participants	-
ANRS C024 OncoVIHAC (Onco VIH Anti Checkpoint)	Ipilimumab (anti-CTLA-4) or Nivolumab (anti-PD-1) or pembrolizumab (anti-PDL-1)	NCT03354936	Observational	Currently recruiting participants	-
	Vedolizumab (antia4b7)	NCT03147859	I	Currently recruiting participants	-
Therapeutic vaccine					
VAX 003	Recombinant gpl 20 (B/E) (AIDSVAX B/E)	NCT00006327	III	Antibody responses (binding and neutralizing antibodies to gpl 20)	Pitisuttithum et al, [55]
VAX 004	Recombinant gpl 20 (B/B) (AIDSVAX B/B)	NCT00002441	III	Antibody responses (binding and neutralizing antibodies to gpl 20)	Flynn *et al.*, [56] Gilbert *et al.* [57]
STEP study	rAd5 (Gag/Pol/Nef) (B)	NCT00095576	lib	T-cell response	Buchbinder *et al.* [58]

Trial	Product	Number trial	Phase	Results	References
Phambili study HVTN 503	rAd5 (Gag/Pol/Nef) (B)	NCT00413725	lib	T-cell response	Gray *et al.* [59]
HVTN 505	DNA (Gag/Pol/Nef) (B) + DNA (Env) (A/B/C) + Ad5 (Gag/Pol) (B) + Ad5 (Env) (A/B/C)	NCT00865566	lib	T cell and antibody responses (gp 140 binding IgG)	Hammer *et al.* [60]
RV144 (Phase Ill/ prophylactic)	ALVAC-HIV vCPl 521 / AIDSVAX-gpl 20 B/E	NCT00223080	III	T cell and antibody responses (nonneutralizing antibodies to the V1V2 loop)	Rerks-Ngarm *et al.* [41], 31,2% efficacy
	Ad26 (Mosaic Env/Gag/Pol) + MVA/Ad35 (Mosaic Env/Gag/Pol)	-	Preclinical study in rhesus macaques	Protection of intrarectal SHIV challenges	Barouch *et al.* [42]
	Ad26 (Env/Gag/Pol) + Env gpl40	-	Preclinical study in rhesus macaques	Protection of intrarectal SHIV challenges	Barouch *et al.* [43]
	PGT121 bNAbs+TLR-7 agonist (GS-9620)	-	Preclinical trial in rhesus macaques	Delay in cell-associated DNA in plasma and tissues. Delay in viral rebound	Borducchi *et al.* [44■■]
	3BNC117 bNAb		lia	Delay in viral rebound during ATI	Scheid *et al.* [45]
ACTG A5340	VRC01 bNAbs	NCT02463227/ NCT2471326	lib	Delay of viral rebound during ATI	Bar *et al.*, [46■]
Shock and kill strategies					
	Valproic acid	NCT00289952	I/ll	No changes in cell-associated DNA	Routy *et al.* [51]
	Vorinostat	NCT01319383	I/ll	Increased HIV RNA in plasma	Archin *et al.* [47]
	Disulfiram	NCTO1944371	II	Increased cell-associated HIV RNA	Elliott *et al.* [49]
	Panabinostat	NCTO1680094	I/ll	Increased HIV RNA in plasma, but no changes in total HIV DNA.	Rasmussen *et al.* [48]
REDUC	Romidepsin	NCT02092116	lb/lla	Increase HIV RNA in plasma, but no changes in cell-associated HIV DNA.	Sogaard *et al.* [50]
REDUC	Vacc-4x/rhuGM-CSF+ Romidepsin	NCT02092116	lb/lla	Moderate reduction of total HIV- DNA, but no effects in ATI	Leth *et al.* [52■]
BCN02-Romi	ChAd.HIVconsv/MVA.HIVconsv + Romidepsin	NCT02616874	I	Four patients remain in ATI	Mothe *et al.* [53■]
Gene editing					
	CCR5 ZFN-modified cells	NCT00842634	I	Therapy proved to be well tolerated	Tebas *et al.* [54]
	CCR5 CrispR/Cas9	NCT03164135	I	-	-