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REVIEW

The latest evidence for possible HIV-1 curative strategies

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Abstract

Human immunodeficiency virus type 1 (HIV-1) infection remains a major health issue worldwide. In developed countries, antiretroviral therapy has extended its reach from treatment of people living with HIV-1 to post-exposure prophylaxis, treatment as prevention, and, more recently, pre-exposure prophylaxis. These healthcare strategies offer the epidemiological tools to curve the epidemic in rich settings and will be concomitantly implemented in developing countries. One of the remaining challenges is to identify an efficacious curative strategy. This review manuscript will focus on some of the current curative strategies aiming at providing a sterilizing or functional cure to HIV-1-positive individuals. These include the following: early treatment initiation in post-treatment controllers as a long-term HIV-1 remission strategy, latency reversal, gene editing with or without stem cell transplantation, and antibodies against either the viral envelope protein or the host integrin α4β7.

Keywords: antiretroviral, antiretroviral treatment intensification, broadly neutralizing antibodies, CRISPR/Cas9, dolutegravir, HIV-1 infection, HIV-1 latency, HIV-1 persistence, shock and kill.

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Introduction

Human immunodeficiency virus (HIV) infects approximately 37 million individuals worldwide. HIV is highly genetically diverse and can be found in the form of two types HIV-1 and -2, and numerous subtypes. HIV-1 is the most common HIV type and is also the most studied; it is the focus of the current review. In the absence of treatment, HIV infection is typically fatal because of progressive decline in CD4-positive T cells and acquisition of opportunistic infections. In most cases, daily use of combinations of antiretroviral drugs subdues viral replication and prevents mortality. However, this treatment is not curative; following treatment interruption or treatment failure, viral replication resumes to levels comparable to those that existed before treatment, typically within a few weeks. This is attributed to the existence of HIV proviral DNA, which is produced by integration within the host's genome of the reverse transcribed viral genome. Proviral DNA can be actively transcribed or not, the latter situation giving rise to latently infected cells that are insensitive to antiretroviral treatment and virtually invisible to the host's immune system. In addition to the fact that some latently infected cells can live for decades, latency is a reversible state. The molecular mechanisms behind latency and persistence are extensively studied. Various curative strategies have been designed against these two issues.

Sterilizing cure: the battle against HIV-1 persistence

Antiretroviral therapy (ART) effectively controls HIV-1 replication and provides durable suppression of plasma viremia in HIV-1-infected individuals. However, ART cannot cure HIV-1 infection. The majority of individuals on ART frequently experience viral rebound within a few weeks after treatment interruption. This is evidently due to the replication competence of integrated HIV-1 genomes in small subsets of latently infected memory CD4+ T-cell populations [1,2]. It is still controversial whether latency occurs in cells of myeloid lineage including monocytes, macrophages and dendritic-infected cells. The complicated mechanisms involved in the establishment and stabilization of latency are major hurdles for scientists to find ways to eliminate these cells from latent

Table 1. Summary of possible HIV-1 curative strategies.

Type of cure	Mechanisms		Advantages/Disadvantages	References
Sterilizing cures	Latency activating agents	– HDAC inhibitors (valproic acid, vorinostat, panobinostat, romidepsin)	Weak, nonspecific (valproic acid) Upregulate HIV transcription May or may not reduce the size of the latent reservoir May need boosting or combination for effective HIV-1 transcription activation	[9–14]
		– NF-kB inducing agents (prostatin, bryostatin)	Upregulate HIV-1 expression May downregulate expression of CD4, CXCR4 and CCR5 receptors (prostratin) Synergistic activation with some HDAC inhibitors	[11,12,14,112]
		– Immune modulators (anti-CTLA-4 mAb, anti-PD-1 mAb)	Upregulate HIV-1 expression Enhance immune-mediated clearance of infected cells. May have severe adverse effect	[28,30,33,34,113]
		– Other molecules		
		• BET bromodomain inhibitor – JQ1	Upregulate HIV-1 expression specifically by suppression of Tat transactivation	[17]
		• TLR agonists	Upregulate HIV-1 expression Induce antiviral innate immune responses	[13,22,114]
		• Histone methyltransferase inhibitors	Upregulate HIV-1 expression Synergistic effect in combination with some HDAC inhibitors	[18,115]
		• Cytokines and chemokines (IL-2, IL-6, IL-7)	Upregulate HIV-1 expression May or may not reduce the size of latently infected cells	[19,116,117]
	Gene therapy/ stem cell transplantation	– Targeting HIV-1 receptors/ co-receptors		
		• CCR5Δ32-homozygous transplantation	Long-term viral remission achieved in the unique 'Berlin case' but viral rebound following ART interruption in most other cases Low prevalence of resistant phenotype Severe or fatal potential side effects and expensive Concern about safety and efficacy *in vivo*	[35,37,38]
		• Endonuclease to knock-out CCR5 /CXCR4 expression (ZFNs, TALENS, CRISPR/Cas9	Efficient *in vitro* but need a safe and effective delivery system *in vivo* or side effects and expensive cost due to transplantation Tropism switch from CCR5 to CXCR4 viruses is a possible viral escape route Undemonstrated safety and efficacy *in vivo*	[41–43,45,47,48]
		– Targeting HIV-1 genome (PBS sequence, HIV-1 protein coding sequences by ZFNs, TALENS or CRISPR/ Cas9)	Rapid development of HIV-1 resistant strains (e.g. against CRISPR/Cas9) Need a safe and effective delivery system Unproven safety and efficacy *in vivo*	[58–61,65]

Table 1. (*Continued*)

Functional cures	Early treatment: after birth or at primary HIV-1 infection period	Long-term viral remission can be achieved but viral rebound can also occur HIV-1 reservoirs cannot be eliminated Problem in persistent immune activation in patients with undetectable plasma viremia Safety concerned following treatment interruption	[67,70,71]
	Intensification of ART or treatment with multiple drug classes	May or may not reduce HIV-1 latent reservoirs Possitive effects should be validated Possible side effects of added drugs Increasing the number of drugs can be problematic in older patients with polypharmacy	[73,74,76,78]
	Broadly neutralizing antibodies	Potential for rapid development of HIV-1 resistant strains Better neutralizing activity when combination of multiple bNAbs or engineered 'bi- or tri-specific bNAbs' Well tolerated, can be combined with other strategies (ART intensification) High manufacturing costs Optimal bNAb half-life and better delivery method should be identified	[86,95,97,98,103]
	Anti-α4β7 antibody therapy	Does not target a viral protein; consequently, immune to escape viral mutations No data from patients to date	[109–111]

reservoirs. Significant advances in our knowledge about HIV-1 latency and immune system from the last decades have provided a scientific basis on the road to finding a cure for HIV-1. In this review, we focused on what we believe are the most interesting and relevant strategies for an HIV cure as summarized in Table 1.

Shock and kill

The idea of the 'shock and kill' strategy is to purge the integrated proviruses in long-lived cells constituting the HIV-1 reservoirs to become transcriptionally active and then eliminate them through the combined effects of current therapy and HIV1-specific cytotoxic CD8+ T cells of the immune system. Numerous attempts to employ this technique for the clearance of viral reservoir have been made (Table 1). The common approach is to upregulate transcription by modifying the host chromatin. Histone deacetylases (HDAC) are one of the key enzymes that increase chromatin condensation and inhibit cellular transcription. Thus, the ability of latency reactivating agents (LRAs) with HDAC inhibitory activity such as valproic acid (VPA), bultyric acid, trichostatin, panobinostat (PNB) and romidepsin (RMD) to reverse latency and to trigger HIV-1 transcription has been investigated [3–7]. Most of these compounds have been approved for cancer treatment and differ in their toxicological profile. VPA had been first used for the treatment of epilepsy and psychiatric disorders. To date, the anticancer effect of VPA has been studied in several cancer models. Moreover, it has been introduced in the clinical treatment of different types of solid tumor and leukemia [8]. VPA was the first HDAC inhibitor tested to activate HIV-1 transcription in latently infected cells; conflicting results have been reported regarding its ability to reduce HIV-1 reservoirs in patients receiving ART. In fact, in recent studies, VPA displayed no ability to reduce the size of the HIV-1 reservoir [9,10]. It is possible that VPA has a weak and/or nonspecific HDAC inhibitory activity *in vivo*. It now appears that HDAC inhibitors can be combined either with boosting compounds with different activities such as bryostatin-1 or prostratin (NF-κB inducers) or with another HDAC inhibitor (e.g. romidepsin with panobinostat) in order to induce efficient HIV-1 transcription [11–14]. These strategies have the potential to improve the activity and specificity of LRAs. For

example, the combination of VPA or vorinostat with prostratin, a nontumor-promoting nuclear factor NF-κB inducer, was shown to reactivate provirus transcription more efficiently than single compound in latently infected U1 and J-Lat cell lines and in CD8-depleted peripheral blood mononuclear cells (PBMCs) isolated from ART-treated patients with undetectable viremia [11]. The glutathione synthesis inhibitor buthionine sulfoximine (BSO) favored the HIV-1 activating effects of MS-275 (Class I-selective HDAC inhibitors) in a Jurkat cell clone by depleting the intracellular levels of glutathione that are further consumed by activated viruses [15]. BSO was also found to induce the recruitment of HDAC inhibitor-insensitive cells into the responding cell population in Jurkat cell models of HIV-1 quiescence.

Apart from well-known HDAC inhibitors, other categories of potent LRAs have been characterized such as bromodomain and extraterminal (BET) inhibitors [16] – JQ1, DNA methytransferases (DNMT) inhibitors, protein kinase C (PKC) agonist, toll-like receptor (TLR) agonists, cytokines and chemokines as well as unclassified reagents [17–22] (Table 1). Similar to HDAC inhibitors, the use of single LRAs typically showed limited clinical efficacy, though combining them can result in an enhanced activation of viral transcription [14]. Most recently, PEP005, a compound that was previously approved by Food and Drug Administration (FDA) for the treatment of precancerous actinic keratosis (PICATO), was shown to effectively reactivate HIV-1 reservoirs [23]. In the same study, the combination of JQ1 and PEP005 was showed to exhibit synergism in reactivating latent HIV-1.

Despite these progresses, the 'shock and kill' strategy using HDAC inhibitors experiences several challenges. Studies have shown that as HDAC inhibitors are nonspecific, they may cause active transcription of cellular genes [24,25]. In addition, findings indicated that HDAC inhibitors romidepsin can 'kick' the latent HIV-1 from infected resting T cells without reducing the size of the viral reservoir [26,27]. This suggests that the host immune response may not always be sufficiently potent to destroy the artificially activated cells. Accordingly, more potent activators may increase the viral reservoir instead of decreasing it, on account of the inability of the immune system to fully control activated cells.

Another approach to deal with the viral reservoir is the use of antibodies against immune checkpoint (IC) blockage (ICB) proteins in order to inhibit the IC-mediated negative regulation of TCR-induced NF-κB dependent signaling in CD4+ T cells and thus to potentially enhance viral transcription [28]. During HIV-1 infection, particularly during the acute phase, the expression of immune checkpoint proteins including programmed death (PD1), CD160, 2B4, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation protein (LAG-3), T-cell immune receptor with Ig and ITIM domains (TIGIT), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) is upregulated in both $CD4^+$ and $CD8^+$ T cells and varies in levels within different T-cell subsets [28–31]. Following ART treatment, the upregulation of IC molecules in HIV-1-infected individuals declines, however, persistent elevated levels can be observed whether patients started ART early or not [32].

There is evidence to support the use of antibodies against ICB proteins to reverse latency and potentially target the viral reservoir, including a recent case study that showed an increase in cell-associated unspliced HIV-1 RNA in sorted $CD4^+$ T cells in an HIV-1-infected patient on ART who received ipilimumab (an anti-CTLA-4 mAb) for the treatment of metastatic melanoma [33]. Similarly, anti-PD-1 antibodies (nivolumab) can also reverse latency *in vivo* and *in vitro*. However, latency reversal was only observed in nonproliferating and not in proliferating latently infected cells [28,34]. Concurrent results were obtained with ipilimumab. Further studies are essential to determine whether this antibody could have an activity in the elimination of HIV-1 latent reservoir. Notably, IC antibodies have been successfully used in cancer treatment and are generally considered safe although immune reactions have been reported. When used for the treatment of infectious diseases, several studies have suggested that the use of antibodies against IC proteins provides clinical benefits beyond latency reversal because they can also enhance immune-mediated clearance of infected cells via the recovery of HIV-1 specific CD8+ T-cell function from exhaustion. Thus, these antibodies may be used as part of a possible strategy for HIV-1 elimination. A potential drawback of this approach though is that, as latently infected T cells also express IC proteins, the administration of these antibodies may lead to the expansion of the pool of latently HIV-1-infected cells.

To date, ART has been commonly used as the 'kill' agent; however, this treatment has demonstrated that it cannot clear either the latent virus or the infected cells. Therefore, one challenge that remains is to find a more effective 'kill' agent to eradicate the reactivated latent reservoir. Some of the proposed strategies include broadly neutralizing antibodies (bNAbs), non-neutralizing antibodies, generating specific HIV-1 CTLs using modified peripheral CD8 lymphocytes or the creation of a therapeutic vaccine. Recent studies in this field have shown promising results. However, despite extensive *in vitro* and *ex vivo* investigation of combinations of 'shock' and 'kill' agents, the safety and efficacy of this approach are far from being validated.

Gene editing and stem cell transplantation

The inspiring case of the 'Berlin patient', Timothy Ray Brown, who was diagnosed with acute myeloid leukemia and became HIV-1-negative after receiving hematopoietic stem cell transplantation (HSCT) from a CCR5Δ32 homozygous donor, has raised hope for the possibility of developing an HIV-1 cure [35,36]. Similar attempts to use autologous or allogeneic HIS transplantation to eradicate HIV-1 from infected patients with lymphoma and/or leukemia diseases have been made.

Unfortunately, these attempts have been unsuccessful given the common detection of HIV-1 replication whether ART was continued or discontinued, as exemplified by the 'Boston patients' [37]. It is noted that the two Boston patients had remained on ART throughout the transplant process. Moreover, ART interruption was applied only 2–4 years after transplantation. Both patients experienced viral rebound, and they also developed symptoms of acute retroviral syndrome after week 12 or 32 so they had to reinitiate ART. Another case was reported by the Mayo Clinic in Minnesota of a HIV-1-positive bone marrow transplant recipient who experienced viral remission for 10 months before loss of viral control [38]. This was despite the fact that researchers found a progressive decline in the frequency of CD4 T cells with replication competent virus as measured through a quantitative outgrowth assay, as well as reduced plasma HIV-1 DNA and RNA levels during the post-transplant period. The research team also assumed that suppressed viral replication in allogeneic peripheral blood stem cells transplantation may be associated with loss of HIV-1-specific immunity which may subsequently favor homeostatic proliferation of latently infected cells, altogether decreasing the chances of HIV-1 eradication. Further studies are underway to explain the delay in viral rebound observed in this patient. Although unsuccessful, these attempts at eliminating HIV-1 can be informative through the extensive characterization of the viral reservoirs, as well as CD8+ T-lymphocyte reactivity and other immunological parameters of various patients.

Most transmitted types of HIV-1 are R5 tropic viruses, a dominant viral population during early phases of clinical HIV-1 infection and individuals who are homozygous for the CCR5Δ32 allele are naturally resistant to HIV-1 infection [39,40]. Many efforts aim to generate this resistant phenotype by disruption or suppression of CCR5 receptor in CD4+ T cells by Zinc finger nuclease (ZFN), a class of engineered DNA-binding proteins that facilitate gene editing in a highly efficient manner [41,42]. Similar strategies aiming at disrupting the CCR5 genes include shRNA, transcription activator-like effector nucleases (TALENS) and more recently, Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein nuclease-9 (CRISPR/Cas9) [43–45] (Table 1). The engineered CD4+ T cells are always of autologous origin and are typically infused into HIV-1 patients by a delivery system. Studies in the last few years have shown encouraging results, including a 50% knockout efficacy in primary T cells with a CCR5-targeting TALEN, using electroporation for mRNA delivery [43]. Both lentiviral and chimeric adenoviral vector systems have also been found to successfully deliver agents to CD4+ T cells [42,46,47]. The latter strategy has been tested in patients in the context of a Phase 1 clinical trial (NCT00842634) that looked at the efficacy of the infusion of autologous CD4+ T cells in which CCR5 gene was suppressed by ZFN [48]. However, only 4/6 immune responders (defined as having CD4 counts greater than 450 cells/mm^3 and documented CD4 nadir of not lower than 300 cells/mm^3) who were eligible to undergo the 12-week analytical treatment interruption could complete the study that was designed to assess the safety and antiviral effects of autologous CD4-enriched T cells modified at the CCR5 gene by ZFN. The other two patients had to reinitiate ART following rapid increase of HIV-1 RNA viral loads greater than 100,000 copies/mL. A serious adverse event was reported in another patient after transplantation, altogether raising concerns in regard to the safety of the overall process as a treatment for HIV-1 infection. Regardless, CCR5-modified CD4+ T cells were found to be persistent and present in higher numbers than unmodified cells. HIV-1 rebounded in all patients who had been infused with modified CD4+ T cells after ART withdrawal. In later time points, viremia in those patients decreased continuously and even reached undetectable level in one participant at the endpoint of the trial, suggesting that this intervention could potentially be used to functionally cure HIV-1, granted that these results could be extended beyond one single case.

Similar strategies include studies on modified hematopoietic stem cells (HSC) derived from bone marrow or peripheral blood. In a 2014 study, researchers used the CRISPR/Cas9 and guide RNA to efficiently disrupt CCR5 in hematopoietic stem and progenitor cells [49]. It was showed that this system could also generate transplanted mice that are functionally resistant to infection by a CCR5-tropic HIV-1 [50]. So far, this approach has been used in the laboratory with cells and animal models, although its applicability remains doubtful, in particular to a large population of HIV-1-positive individuals. Aside from the side effects, complex procedure and expensive costs of autologous transplantation, another major limitation is potential viral escape from the CCR5-based entry restriction. This has been reported in one patient who received a transplantation of homozygous CCR5Δ32 cells only to see the virus shift to an X4-tropic HIV-1 [51,52]. It is evident that HIV-1 can change tropism during infection (as well as *in vitro*), although this was not observed in the 'Berlin patient' even after ART discontinuation [35]. In addition, it is important to note that patients undergoing transplantation should be on ART until the successful engraftment.

Targeting both CCR5 and CXCR4 is a strategy to avoid the issue of tropism switch [53]. Alternative strategies that also make use of engineering target cells include the expression of chimeric antigen receptor (CAR) in T cells [54]. Rather than a tumor-specific antigen, the CAR, composed of CD4 linked to the CD3ζ signaling chain (CD4ζ), targets the HIV-1 gp120 envelop glycoprotein on the surface of infected cells. CAR-T cells may act as specific cytotoxic killer cells and persist at detectable levels in peripheral blood mononuclear cells from patients for at least 11 years after the infusion [55]. Furthermore, the combination of CAR expression and CCR5 suppression successfully abolished HIV-1 replication in transplanted mice [56].

In addition to targeting cell surface receptors, direct targeting of the provirus from latently infected cells is also a feasible

approach. Theoretically, targeting the proviral DNA within latently infected cells will prevent it from acting as a source for viral rebound after treatment cessation. Several technologies have been employed to eradicate proviral HIV-1 DNA from the reservoirs, such as Tre-recombinase (HIV-1 long terminal repeat site-specific recombinase), ZFN, TALENs and CRISPR/Cas9 using specific HIV-1 target sequences [57–62]. Most recent works have been focused on some regions of the HIV-1 LTR that are highly conserved across HIV-1 clades [60,61,63,64]. These studies revealed that, in general, gene-editing techniques can prevent HIV-1 replication in T-cell lines and primary CD4+ T cells. However, complete silence of HIV-1 production was not attained, as HIV-1 quickly escaped from the programmed CRISPR/Cas9 system [65,66]. Scientists are now combining the latter approach with other gene-editing therapies that target different steps of the viral replication cycle or host genes such as CCR5. The rationale behind combining several such approaches is that it would decrease the chances of viral rebound through resistance.

As discussed earlier, there are many obstacles in addition to the complicated transplantation procedure. One last point is that the health risks for patients who undergo ART interruption in the context of the above-mentioned procedures could make this type of clinical trials unethical.

Functional cures: to achieve a durable remission of HIV-1 infection

Early treatment and intensification of ART as a cure

The purpose of a functional cure is to allow HIV-1-positive patients to attain viral remission without taking ART, which is similar to those observed in 'HIV controllers' or 'elite controllers'. This can be obtained in a small patient population who initiate ART very early during primary infection, while their CD4 cell counts are still high. These 'post-treatment HIV-1 controllers' can be virologically suppressed for long periods of time after ART withdrawal. In a study called 'VISCONTI', 14 patients with different genetic backgrounds were enrolled. Most of them lacked the protective HLA B alleles that are overrepresented in HIV-1 controllers [67]. The VISCONTI cohorts started ART within 10 weeks of primary infection and discontinued ART 3 years after. For a median of 7 years, they maintained undetectable HIV-1 viral loads. Thus, early and prolonged ART may allow some individuals to achieve long-term HIV-1 remission. In the START study that enrolled 4685 HIV-1-positive participants across 35 countries, early ART initiation was found to lower the risk of serious AIDS-related events and death by 72 and 57%, respectively, regardless of age, gender and baseline characteristics, as well as geography and country income level [68].

Benefits of early treatment have also been observed in pediatric HIV-1 cases, including in the case of the 'Mississippi child' who initiated ART 30 h after birth and continued treatment until 18 months of age when she was lost to follow up. The child subsequently remained free of ART for more than 2 years without detectable HIV-1 [69]. Unfortunately, the virus eventually rebounded, and treatment was reinitiated [70]. Recently, a unique pediatric HIV-1 patient who was infected with HIV-1 at birth and received early treatment was reported to have been living with undetectable viral loads in the absence of ART for 12 years [71].

These cases provided proof of concept that viral remission is possible following very early treatment. However, as exemplified by the case of the 'Mississippi child', permanent remission does not always occur in patients who started very early treatment. Moreover, early ART treatment is not always sufficient to eliminate the viral reservoir. Accordingly, several questions remain in regard to post-treatment controllers, including are there host-specific mechanisms that defined post-treatment control or is it only a consequence of early treatment effects on the establishment of viral reservoirs? Importantly, most of these post-treatment controllers have, in effect, not experienced acute infection. This might be beneficial for the immune system to maintain higher competency to fight HIV-1 infection. It was also hypothesized that the latent reservoir might not be the exclusive source of viral rebound in these cases [72].

In patients on ART with undetectable plasma viremia, persistent immune activation can be observed. This could be due in part because of potential low levels of ongoing *de novo* viral replication or residual plasma viremia that is lower than the limit detection of available clinical tests (less than 20 copies/mL). This residual viremia may be due to partial suppression and/or suboptimal drug concentrations in some deep tissues such as gut-associated lymphoid tissues, deep tissue lymph nodes, bone marrow or the central nervous system. In this regard, therapy intensification has aimed at targeting the source of residual replication to possibly decrease the latent reservoir following long-term treatment. Therapy intensification has been studied with raltegravir, abacavir, maraviroc or darunavir/ritonavir [73–78]. Although evidence showed that therapy intensification might benefit HIV-1-infected individuals, it is unlikely to reduce the residual viral load, immune activation or the size of the latent reservoir. Thus, it is important to further study the positive effects of treatment intensification with multiple drug classes or with more potent drugs especially during early primary HIV-1 infection. Currently, the NCT00908544 and NCT02500446 clinical trials are ongoing to explore these questions. The NCT00908544 is a multicenter, open-label, nonrandomized proof-of-concept trial to evaluate treatment with multiple drug class therapies that include two nucleoside-reverse-transcriptase inhibitors (NRTIs), one protease inhibitor (PI), a CCR5-inhibitor and integrase inhibitor in HIV-1-infected patients with either arms, primary infection and chronic infection or suppressed plasma viral load under continuous ART. The NCT02500446 trial is a randomized

controlled study that assesses the impact of dolutegravir (DTG) intensification on residual replication of HIV-1 in patients with suppressive ART. Because of its efficacy and high genetic barrier to the development of resistance, DTG is one of the preferred options for HIV-1 treatment in both naïve and experienced individuals [79,80]. As we have discussed in our previous reviews, it will also be important to study the effects of DTG in combination with other novel approaches toward HIV-1 eradication [79,81–84].

Broadly neutralizing antibodies (bNAbs)

HIV-1 employs multiple strategies to evade the humoral and adaptive immune systems, including evolutionary escape through rapid replication and the accumulation of mutations. The discovery of broadly neutralizing, specific monoclonal antibodies against HIV-1 envelope proteins has opened an alternative and innovative approach to promising therapeutic reagents. During natural infection, only 10–30% of HIV-1-infected individuals can produce bNAbs, mostly directed against the Env protein [85]. Most antibodies have been found not to provide protection for patients who developed them. Early studies using first generation neutralizing antibodies, including b12, 2G12, 2F5, Z13 and 4E10, to target Env showed that they only moderately inhibit HIV-1 replication *in vitro* [86,87]. Combination of b12, 2F5, 2G12 and 4E10 provided complete protection against SIH89.6P in macaques [88–91]. In clinical trials, treatments using a combination of these bNAbs were safe and well tolerated and could reduce HIV-1 RNA in plasma of HIV-1-infected patients [92–95]. However, viral escape with resistance mutation against bNAbs caused viral rebound in some of the patients who stopped ART after infusions of the bNAb cocktail [96,97]. In response to this, several approaches to identify and produce bNAbs with enhanced potency or/and to combine bNAbs with different approaches to achieve long-term viral suppression have been investigated.

Advances in B-cell cloning method to identify genes encoding immunoglobulin heavy and light chains have led to the discovery and generation of numerous highly potent bNAbs. VRC01 (targeting CD4 binding site) and PG9/PG16 (binding monomeric $gp120_{JR\text{-}CSF}$ or $gp41_{HxB2}$) bNAbs are among the second generation bNAbs that have strong neutralization profiles against different HIV-1 isolates [98,99]. The combination of b12, PGT121 and 3BC117 was found to suppress viral rebound in SHIV-infected rhesus macaques [100]. In humans, bNAb monotherapy was not sufficient to prolong viral suppression without ART owing to the rapid emergence of bNAb-resistant HIV-1 [101]. Current research is also focusing on the development of bNAbs that target more than one specific regions of HIV-1 Env for greater neutralizing ability. The combination of antigen-binding fragments from VRC07 and PG9-16 in a single immunoglobulin recombinant protein is an example of bispecific bNAb that showed better neutralization profile in the TZM-bl system [102]. More recently, researchers have engineered a single molecule of 'trispecific bNAb' that target three independent HIV-1 Env regions: the CD4 binding site, the membrane-proximal external region (MPER) and the V1V2 glycan site. This trispecific bNAb exhibited potent SHIV protection in macaques up to 99% neutralizing activity against over 200 HIV strains [103].

The major challenges facing this field include extension of the bNAb half-life, the mode of bNAb delivery to patients instead of multiple intravenous injections and reduction of manufacturing costs for these bNAbs [104].

Anti-α4β7 antibody therapy

As mentioned earlier, one of the risks associated with the use of antibodies directed against viral proteins is the possibility for the virus to evolve to become resistant against neutralization through a process that is identical to the development of drug resistance. Accordingly, resistance against antibody neutralization has been found to result in transmission of resistant strains in the context of preventative vaccine. However, it also can cause viral escape when neutralizing antibodies are used in an attempt to cure HIV-1 infection. Another avenue is to target human proteins that can be incorporated and expressed at the surface of viral particles. Such avenue is explored with the testing of anti-α4β7 integrin antibodies against SIV and HIV-1 infections. Integrin α4β7 is a heterodimer of α4 (CD49d) and β7 that are both present at the surface of lymphocytes. The idea of using such antibodies to fight HIV-1 infections originated from the facts that α4β7 is a lymphocytic gut homing integrin while HIV-1 pathogenesis is essentially lymphocytic and gut-centric. Accordingly, preventing CD4+ cells from accessing the gut-associated lymphoid tissue as a major site of active replication could have a protective or restorative effect on CD4+ cell numbers. Surprisingly, initial exploration of this hypothesis led to the identification of a specific interaction between the viral gp120 envelope protein and α4β7 integrin at the cell surface of CD4+ lymphocytes that contributed to HIV-1 infection [105,106]. Concomitantly, the development of a humanized monoclonal antibody that targets α4β7 was reported [107]. The development of a similar rhesus macaque antibody led to findings that administration of such antibody intravenously to macaques had a protective effect against SIV transmission and could reduce SIV pathogenesis, by preserving CD4+ T cells in the blood and gut-associated tissues and impeding viral loads and DNA levels [108–110]. Remarkably, transient administration of the anti-α4β7 antibody was sufficient to establish long-term virological control even when the antibody itself had waned [108,110]. The contribution of NK cells and plasmacytoid DC to this protective and/or curative approach has been discussed [110,111]. Notably, although this hypothesis has not been proven, the extraordinary results obtained with anti-α4β7 antibodies support the possibility of persistence of CD4+ lymphocyte infection through the percolation of these cells through the gut-associated lymphoid tissues as part of their normal trafficking, despite ART. Human trials are now

underway to examine how anti-α4β7 might lead to prolonged virological control in a classical clinical setting (NCT02788175, clinicaltrial.gov).

Conclusions

In this review, we have examined several curative strategies, which are summarized in Table 1. From 'shock and kill', a compound-based approach aiming at reversing HIV latency, to gene therapy and cell transplants, the field of HIV cure encompasses a variety of evidence-based strategies. The development of such strategies is complex and difficult, as illustrated by the fact that 'Shock and kill' is now confronted with serious concerns about the safety of some latency reversing agents. Among various antibody-based strategies, the use of anti-α4β7 antibodies has the advantage of not targeting a viral protein and thus to be immune to the development of escape resistance mutations. Early treatment would require healthcare payers to invest in prevention. In addition, there are additional approaches that we did not discuss here, including inhibiting HIV-1 reactivation by using Tat inhibitors that is still in early development.

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