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# Cellular and Immune Therapy for Treating HIV-1 Infection

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## Abstract

***At present, HIV-1 infection is treated with combined antiretroviral therapy (cART). cART greatly improves the life quality and outcome of infected individuals but cannot eradicate the virus from the hosts. Therefore, new treatment methods that can clear the virus are needed. In this review, we summarized four novel approaches that have the potentials to cure HIV infection, which are dendritic cell targeting, CCR5 editing, LASER ART and CRISPR-Cas9 dual therapy and broad neutralization antibodies.*** ***(AIDS Rev. 2021;23:59-64)***

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## Key words

***HIV-1. Dendritic cell. CCR5 editing. CRISPR-cas9. LASER ART. bNAbs.***

## Introduction

HIV-1 infection has caused a number of deaths worldwide and remains a global health concern. Combined antiretroviral therapy (cART) inhibits viral replication, prevents $CD4^+$ T cell loss, and thus slows HIV disease progression. However, cART does not eradicate HIV-1. Infected individuals must remain on treatment for their entire lives and treatment interruption will result in viral rebound.

In 2009, the first patient cured of AIDS caught the world's attention. This patient had acute myeloid leukemia and HIV-1 infection. He received allogeneic hematopoietic stem cell (HSCs) transplantation from a donor carrying a homozygous CCR5Δ32 mutation making him resistant to HIV infection. This patient stopped cART after the transplantation, and no viral rebound was detected throughout his body till his death. This patient makes people believe that cure of HIV-1 infection is possible. Over the past decade, our understanding of where and how HIV-1 persists in the hosts has dramatically improved, and many scientific breakthroughs have been developed into potential treatment methods for the cure of HIV-1 infection. Here we briefly reviewed four of these new methods that may end the HIV pandemic in the future, and they are dendritic cell targeting, CCR5 editing, LASER ART and CRISPR-cas9 dual therapy, and broad neutralization antibodies (bNAbs).

## Dendritic cell targeting therapy

Autologous dendritic cells expressing HIV-antigens can activate latent HIV reservoir making cytotoxic T lymphocytes (CTLs) much easier to clear the viruses. However, the effect was short-lived as the virus rebounded a few weeks after discontinuation of cART. In consideration of the good tolerance and safety of dendritic cell-based HIV therapy and to improve its efficacy,

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Guardo et al. proposed a new strategy of directly targeting dendritic cells[1] and the idea was combining TRIMIX with HIV-1 T cell immunogen (HTI). TRIMIX is the mixture of mRNA encoding CD40L, CD70, and TLR-4. Induction of CD40L by IL-12 allows dendritic cells to activate T helper cells. By activating HIV-1 specific $CD8^+$ T cells, CD40L-stimulated DCs induce antiviral cytotoxic T cell response, which kills HIV-infected $CD4^+$ T cells more effectively than previously existing virus-specific memory T cells. CD40L stimulation also results in the formation of a large number of nanotubular network structures between dendritic cells[2]. These structures facilitate signal communication between dendritic cells and potentially T lymphocytes during immunotherapy. TLR-4 can activate and cause dendritic cells to mature. CD70 binds to CD27, a co-stimulatory molecule on primary T lymphocytes. However, CD70 sometimes plays a negative role in chronic viral infection by activating programmed cell death protein 1 (PD-1) and other immune checkpoint molecule[3]. Therefore, it is necessary to assess whether these mRNAs activate PD-1 and other immune checkpoint molecules such as CTLs-associated antigen 4[4]. If so, this method could be combined with one or more checkpoint inhibitors to maximally activate immune responses, which shows a new hope for clearing the HIV reservoir.

HTI is the mixture of 16 mRNAs encoding antigen fragments of Gag, Pol, Vif, and Nef. These HIV antigens are relatively conserved[5]. Guardo et al. showed that monocyte-derived dendritic cells expressed activation markers *in vitro* after electroporation of TRIMIX/HTI mRNA into these cells and induced a relatively weak antigen-specific, proliferative response of $CD4^+$ T cells, which may be due to a relatively insufficient number of $CD4^+$ T cells that were targeting epitopes in HTI mixture. However, the number of such epitopes has not yet been revealed, and the low response may also be due to its weak expression of the major histocompatibility complex (MHC) class II molecules. Since mRNA is translated in the cytoplasm, this antigen expression pattern facilitates its presentation through MHC class I molecules. On the other hand, exogenous antigens are mainly presented through MHC class II on dendritic cells although MHC class I molecules are sometimes used through cross-presentation. In general, it is difficult for dendritic cells to present endogenous antigens through MHC class II molecules. Therefore, to increase the frequency of antigen presentation through MHC class II, $CD4^+$ T cell targeting epitopes can be modified to facilitate its entry into the lysosome and MHC class II loading regions. Finally, therapeutic mRNA should be of high purity and not contain any double-stranded RNA because double-stranded RNA can induce type I interferon response by activating TLR-3 and interferon will inhibit mRNA translation and reduce its therapeutic effect.

## CCR5 editing

CCR5 and CXCR4 are the co-receptors required for HIV-1 to infect target cells. Attempts to make CCR5-deficient HSCs and $CD4^+$ T cells have been achieved with different gene-editing methods, which makes functional cure of HIV-1 infection on the horizon.

CCR5, a type of integrin on cell surface, acts as the initial docking site of HIVgp120/gp41 and CD4. Interaction between gp120/gp41 of HIV-1 and CD4/ CCR5 on cell surface allows for viral invasion and subsequent infection. The important site on CCR5 for binding to HIV is called 2D7. It is located on the third extracellular element (second loop) of CCR5 and works with the PA12 binding site and the G protein linkage domain on the first extracellular element of CCR5. The CCR5-Δ32 mutation refers to the missing 32 bases just before the 2D7 ring structure, which leads to stop codon and subsequent loss of the 2D7 loop that renders CCR5 cytosolic and cannot be bound by HIV anymore[6].

CRISPR/Cas, zinc-finger nucleases and transcription activator-like effector nuclease are the gene-editing systems that can edit the genome at a fixed location and achieve gene specific knockout, knock-in, or repair. CRISPR-based gene editing technology recently draws a lot of attention and will be the focus of this manuscript. The CRISPR system consists of single guided RNA (sgRNA) that mediates targeting and recognition and Cas9 protein for editing. Therefore, only designing sgRNA is needed and Cas9 protein is universal. With CRISPR/Cas9 gene-editing technology Deng's team knocked out CCR5 gene in human HSCs and then transplanted these cells into immune deficient mice. These CCR5-deficient HSCs persisted for a long time in the humanized mice making these mice resistant to HIV-1 infection. This study provides support for translating CCR5-edited HSC transplantation into clinic for HIV cure[7]. A human trial was conducted in a patient with HIV-1 infection and acute lymphoblastic leukemia. This patient was transplanted with CCR5-edited, MHC matched HSCs, and leukemia was then in complete remission. Full donor chimerism with donor cells carrying ablated CCR5 gene lasted for more than 19 months, and no adverse events related to gene editing were observed in this patient during this period[8].

Meanwhile, Hou et al. efficiently disrupted CXCR4 expression on $CD4^+$T cells from both human and rhe-

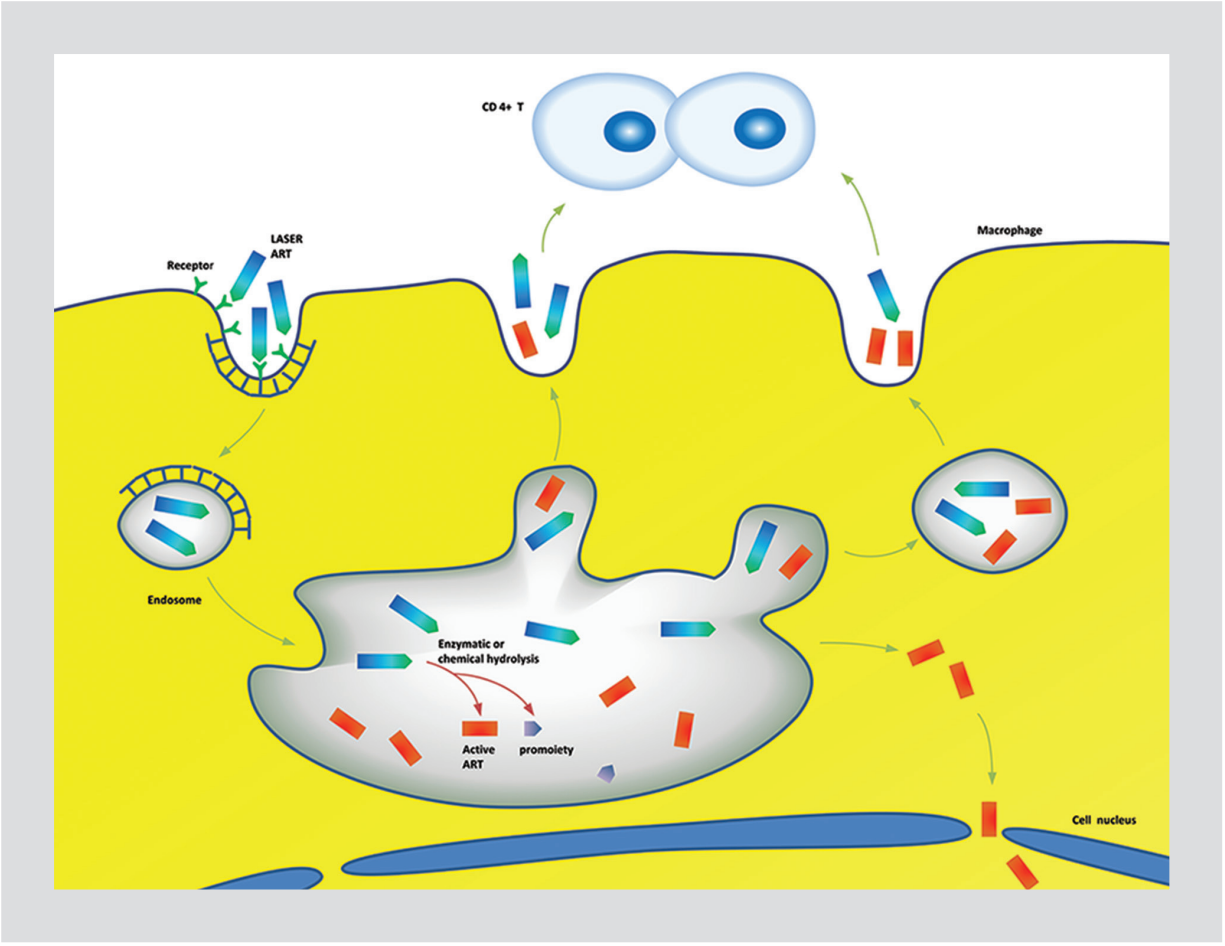


**Figure 1.** *Delivery of LASER ART. The LASER ART transport system is specifically modified to target macrophages. LASER ART recognizes specific receptors on macrophages and then is endocytosed into macrophages and stored in endosomes. After LASER ART is hydrolyzed by enzymes or chemicals in the macrophages, antivirals containing in LASER ART become active and then are slowly released to adjacent CD4+ T cells.*

sus macaques using the CRISPR/Cas9 system delivered by lentiviruses. Human CD4+T cells with CXCR4 knockout showed reduced p24 production after infection by X4-tropic HIV-1, suggesting that CXCR4-modified cells resisted X4-tropic HIV-1 infection[9]. In addition, CD4+T cells that had CXCR4 edited by CRISPR/Cas9 showed normal proliferation without obvious toxicity and off-target effect on CD4+ T cells being observed[9].

## LASER ART and CRISPR-Cas9 dual therapy

cART cannot eradicate HIV from the host. Thus, it is difficult or even impossible to achieve virological cure by cART in a patient's lifetime[10-12]. Long-acting Slow Effective Release Anti-retroviral Therapy (LASER ART) delivery platform is expected to provide new options for the treatment and prevention of HIV-1 infection, and new strategies to address poor compliance. LASER ART is characterized for slow drug dissolution, enhanced lipophilicity, increased bioavailability, and limited off-target toxicity. With this delivery platform active ingredients of antiretroviral drugs can be slowly released, the half-lives of the drugs will be increased and thus the frequency of cART use will be reduced. The drug carrier technology of LASER ART is characterized by a high load of antiretroviral drugs in a single carrier. Ideally, hydrophobic antiretroviral pro-drugs are packaged into particles and transported through the carrier[11]. By this way, the accuracy of targeting different stages of viral replication cycle can be optimized, emergence of viral resistance can be minimized, and patient compliance can be improved[13]. LASER ART uses drug carrier technology and carrier surface modification to target macrophages so that macrophages can absorb a number of antiretroviral drug crystals and then slowly release and transfer these drug crystals to adjacent CD4+ T cells through cell-cell

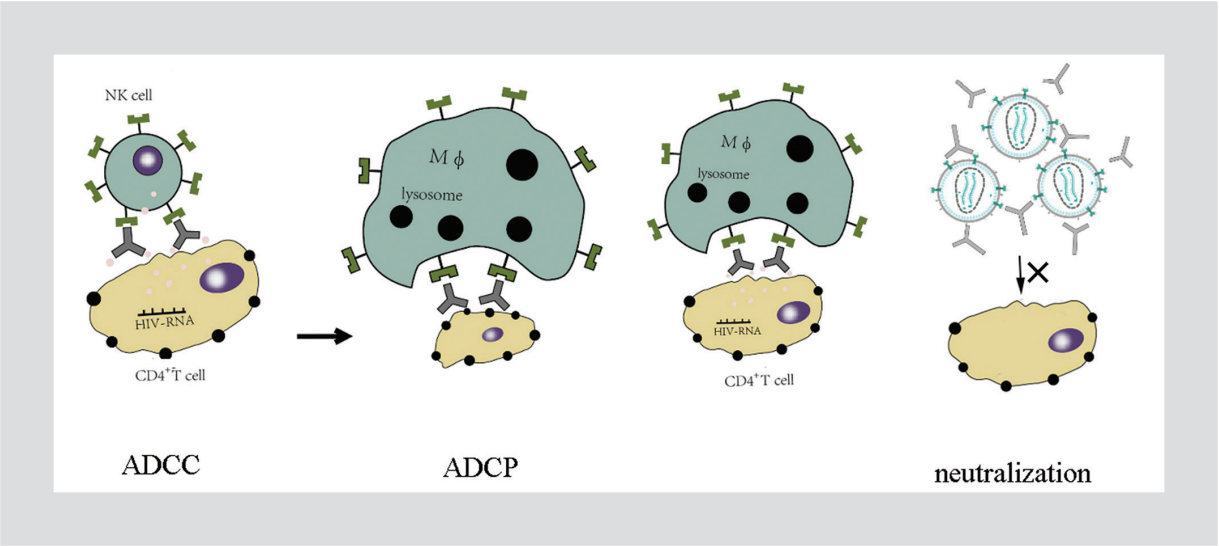


**Figure 2**. *Functions of bNAbs. The Fc fragment of bNAbs binds to the FcR on NK cells enabling NK cells to release cytotoxins. (ADCC) Cytotoxins kill infected CD4+ T cells and these dead CD4+ T cells are then phagocytosed by macrophages. (ADCP) Macrophages can also directly engulf infected CD4+ T cells with the help of bNAbs. bNAbs can also directly bind to and neutralize viruses making viruses lose the ability to invade CD4+ T cells. (neutralization).*

contact or direct absorption to strictly control ongoing viral replication[14-16] (Fig. 1). Academic laboratories and pharmaceutical industry are working to develop personalized drug delivery systems that can target specific parts of the body where the virus hides in a latent, restricted, or non-productive state. The main purpose is to improve cART compliance, optimize therapeutic index, and maximize virus control[17-19]. Studies have shown that LASER ART can reduce the incidence of HIV-associated co-morbidities in small animals and effective antiretroviral drug concentrations can be maintained in blood and tissues for days to weeks[14,16,20]. The chemical and biological properties of LASER ART make its antiretroviral activity increased by 30 folds. Compared with conventional ART, the pharmacokinetics (PK) and pharmacodynamics (PD) curves of LASER ART in mice were significantly improved: the half-life of the drugs was extended by 5.3 times and the drugs were widely distributed throughout the tissues. These results indicated that the efficacy of the antiretrovirals was improved in LASER ART. Therefore, LASER ART has the potential to further reduce the incidence and mortality of HIV infection. However, it is noted that no matter how successfully it can inhibit viral replication, LASER ART alone cannot clear latent HIV-1[21]. Therefore, CRISPR-Cas9-based gene-editing technology which was delivered by AAV9 was employed and specifically and efficiently excised integrated HIV-1DNA from the host genome[22,23]. It was confirmed that the combination of LASER ART and CRISPR-Cas9 cleared the virus with replication capability in experimental models of HIV-1 infection. With an ultrasensitive HIV-1 nucleic acid detection method elimination of HIV-1 was confirmed in various organs of HIV-1 infected humanized mice treated with LASER ART and AAV9-CRISPR-Cas9. Adoptive transfer of human immune cells from HIV-1 infected humanized mice undergoing double treatments to uninfected animals did not result in productive infection in the recipient animals. Prasanta used a variety of highly sensitive methods to evaluate the effect of combinational LASER ART and AAV9-CRISPR-Cas9 on HIV-1 elimination. Two out of seven double-treated, HIV-infected mice showed no rebound of HIV-1 replication in the plasma, bone marrow, spleen, brain, intestine, liver, kidney, and lung. To further confirm these observations, they tested the ability of LASER ART and CRISPR-Cas9 to eliminate HIV-1 in ten humanized mice infected with HIV-1. Virological tests showed that after withdrawal of the dual treatments four animals still showed no sign of replication-competent viruses. In contrast, other HIV-1 infected animals that either did not receive the dual treatments or received only a single treatment all showed viral rebound after treatment withdrawal[21]. Taken together, these data indicate that the dual therapy is capable of effectively eradicating HIV-1. However, although this treatment strategy is effective in small animals, safety and efficacy data in humans are still needed.

In addition, studies showed that under suboptimal conditions ART treatment of cells improved editing

efficiency[24,25]. Compared with conventional ART, LASER ART has a stronger inhibitory effect on HIV-1 replication suggesting that LASER ART increase the ability of CRISPR-Cas9 to edit pre-integrated viral DNA and thereby keep the number of integrated HIV to minimum. Therefore, LASER ART and CRISPR-Cas9 dual therapy increases the chance of eradicating HIV.

## Broadly neutralizing antibodies (bNAbs)

Studies have shown that bNAbs enhanced antibody responses and reduced viral load in the plasma. Activation of the host immune system is likely due to the immune complexes formed by antibodies and viruses.

In 1996, phase I clinical trial of F105 was completed. This is the bNAb capable of binding to the CD4 binding site of gp120, neutralizing HIV-1 and thus protecting $CD4^+$ T cells[26,27]. More and more bNAbs have since then been found including KD-247, 3BNC117, and VRC01. KD-247 can efficiently neutralize CXCR4- and CCR5-tropic primary HIV-1 clade B isolates[28]. In the clinical trial, subjects were randomly assigned into the groups of injecting 4, 8, or 16 mg/kg of KD-247 or placebo, and received three injections within 2 weeks. The results showed that HIV RNA was significantly reduced in the groups of injecting 8 mg/kg and 16 mg/kg of KD-247[28]. 3BNC117 is another neutralizing antibody against the CD4 binding site of Env. Twelve healthy controls and seventeen HIV-1-infected patients were intravenously injected with 1, 3, 10, or 30 mg/kg of 3BNC117, respectively[29,30]. The results showed that the antibody not only was safe for use and had a strong inhibitory effect on viral replication but also could enhance host immune responses to the virus. VRC01 is similar to 3BNC117 in effect and viral load was decreased immediately after injection. VRC01 allows HIV remission by stopping viral replication and clearing infected cells. It can prevent vertical transmission of HIV-1[31]. Besides binding to the outer V2/V3 ring of gp120 and the gp120/gp41 interface, bNAbs can also bind to the fusion peptide or outer proximal membrane region of gp41[32]. Neutralization is not the only working mechanism of bNAbs against viruses and they can act as a bridge linking immune cells and viruses together. The Fc domain of IgG binds to the specific domain of FcR causing the aggregation of macrophages and NK cells nearby and then inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cytophagocytosis (ADCP) against infected $CD4^+$ T cells (Fig. 2).

## Conclusions

The novel strategy taking advantage of mRNA and dendritic cells developed by Guardo and his colleagues represents a major advance in the development of effective and expanded immunotherapy approaches for HIV-1 infected individuals. However, it is unknown whether this strategy is effective against viral relapse after cART interruption. If so, how long can the inhibitory effect last? If not, this strategy will not be of much significance.

With the rapid development of gene-editing technology and HSCs transplantation in recent years, HSCs-based gene therapy has the potential to be developed for the treatment of a variety of diseases. CCR5 gene deletion confers susceptible cells resistant to not only HIV but also other viruses such as Zika, dengue, West Nile, and smallpox viruses[33]. However, CCR5-Δ32 deletion also is a risk factor for certain biological processes such as an early onset of clinical manifestations in West Nile viral infection[34], 4 times increased mortality rate in influenza infection[35], and osteoclast dysfunction[36]. In 2018, the birth of a baby whose CCR5 gene was edited by CRISPR-Cas9 technology during the embryonic stage sparked widespread criticism in the scientific community. This baby is the first artificially modified, “anti-HIV” baby. Hence, the area of CCR5 editing for the treatment of HIV-1 infection faces upfront both enormous challenges and prospects.

LASER ART and CRISPR-Cas9 dual therapy may provide an effective way to eliminate HIV-1. Such a strategy will help improve patient adherence to the treatment and bio-distribution of the drugs inside the body, maintain a higher drug concentration for a longer period of time, reduce viral resistant mutations, and finally improve the efficacy of antiretroviral therapy and patient outcomes[20]. In the future, more studies are needed to optimize drug formulation and delivery methods. Therefore, successful clearance of HIV-1 from the host results from the interactions of multiple factors including the set-points of viral replication, size of latent viral reservoirs, the efficacy of delivery of LASER ART to tissues and cells and strong inhibition of viral growth[21]. However, it is important to understand that this joint method still has many potential risks: LASER ART may have an immunosuppressive effect on NK cells and other effector cells; CRISPR-Cas9 technology may cause harmful mutations in HIV that can trigger enhanced viral pathogenicity and a wider viral escaping mechanism; gene-editing technology may also lead to oncogene activation and destruction of tumor suppressor genes facilitating tumor development[37,38]; and finally gene editing has the risk of off-target effects with

unpredictable consequences. These risks all need to be studied further to avoid.

In many clinical trials, bNAbs have been shown to be very effective in reducing peripheral viral load and the size of viral reservoirs and enhancing host immunity. However, a series of modifications are still needed to improve their antiviral potency and avoid the emergence of viral resistance. We also need to explore the issue of secondary antibodies that are produced against bNAbs and will undoubtedly reduce the efficacy of the bNAbs. To increase the efficacy of bNAb treatment, one strategy is to use several antibodies in combination but the best formulation still needs to be explored[39].

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