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A Shot at Dendritic Cell-Based Vaccine Strategy against HIV-1

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ABSTRACT

Introduction: Despite considerable efforts to control AIDS pandemic, it is still one of the significant infectious concerns worldwide. The advance in medical research has led to the development of highly active antiretroviral therapy with a considerable effect to suppress the disease. However, an effective vaccine capable of eradication the HIV pandemic is not available yet. Failure to develop a prophylactic vaccine diverted the efforts to clinical trials of therapeutic vaccines. **Methods**: Here, we review different approaches to dendritic cell-based HIV therapeutic vaccines. We have summarized the dendritic cell-based trials as HIV therapeutic vaccination, registered in the United States clinical trial database. **Results and Conclusion**: The strategies applied in the clinical trials were mostly of low success rates; however, by using dendritic cell therapy, they could trigger the host immune response against HIV-1 infections.

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1), the causative agent of AIDS, has infected about 50 million individuals over nearly 40 years. Despite the massive effort to overcome the virus, about 38 million people were living with HIV infection by 2019 [1, 2]. The infection is manageable by antiretroviral therapy (ART) [3], but this approach is not able to eliminate the virus and cure infected individuals. Though the virus is undetectable in blood, several host organs serve as HIV reservoirs [4]. HIV vaccines were initially designed based on different preventive strategies. However, failure to achieve a successful formulation draw attention to therapeutic strategies with the hope of a cure. HIVcomplicated features and its ability to escape host immunity pose several challenges [5, 6]. The lack of available funding and the ideal animal models are the other obstacles [7, 8]. Besides, clinical trials of these kinds of vaccines are very costly and time-consuming [9, 10].

When the virus infects the cells, HIV specific CD8+ and CD4+ T cells are generated following the viremia. The viral load decreases by the T-cell mediated responses, and antibodies can be detected six weeks to three months post-infection [11, 12]. However, HIV is capable of evading both immune arms due to its envelope diversity and several protein products that change the cell cycle. Consequently, the burst of viremia happens, and the immune system fails to make any progress [13-15]. An efficient therapeutic vaccine is supposed to induce host immune responses by broadly neutralizing antibodies expression. In the case of HIV, due to the virus complicated capabilities to evade the immune system, the humoral immunity activation is not sufficient alone. Therefore, cell-mediated immune induction is essential, along with the humoral responses [16-19]. Several approaches were investigated to come up with a way to cure HIV infected population; among them, one of the most successful is dendritic cell (DCs) therapy, which is used to trigger the immune response against antigens in many studies. Initially, DC therapy was used for cancer treatment [20]. Dendritic cells, as the most professional antigen-presenting cells (APCs), can induce T cells, which are crucial in pathogen-specific immune responses in both innate and adaptive pathways [21, 22]. HIV evades innate immune sensing by the DCs, which leads to inefficient maturation and results in a weak adaptive immune response [23]. Therefore, the sensitized DC administration might drive the immune response to the desired specific target and improve anti-HIV-specific response [24]. Various strategies, mostly with autologous DCs obtained from patients were conducted, in which the DCs were loaded with plasma-derived target antigens followed by giving back to the sample donor [25]. There are some variations among DC-based clinical trials, e.g., the type of antigen, the DC maturation method, and *in-*

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vivo or *ex-vivo* targeting [26, 27].

DCs are required to induce T-cell responses against intracellular pathogens. Moreover, *in vitro* studies have demonstrated that loaded DCs with HIV-1 virions is needed to activate naïve HIV-1-specific CD8 and CD4 T cells. Therefore, DCs play a crucial role in HIV infection since they are essential for strong HIV-specific CD4 T-cell responses and also specific $CD8^+$ cytotoxic T-lymphocyte (CTL) induction to control HIV replication. Clinical trials that have applied DC therapy mostly used autologous MD-DCs, which were pulsed *ex-vivo* with a variety of inactivated virus products [28].

Here, we review the clinical trials that applied dendritic cells with results reflected in the US National Library of Medicine (clinicaltrials.gov) [29]. Table 1 shows a summary of these trials.

DCV-2. Dendritic cell vaccine (DCV-2) was the study conducted to evaluate the efficacy of a therapeutic HIV vaccine composing of MD-DCs (autologous myeloid dendritic cells). DCs were pulsed with a high dosage of heat-inactivated autologous HIV-1 *ex-vivo*, at very early stages of the disease (CD4>450 x 10^6 /L) in HIV-1 infected patients. A significant reduction of plasma viral load occurred among the recipients, which were related to persistent enhancement in HIV-1 specific T cell responses. These results suggest that HIV-1 proper immune responses were induced by therapeutic DC vaccines, which is capable of changing plasma viral load set point post cART interruption in treated patients at early stages [30, 31].

AGS-004. The therapeutic vaccine AGS-004 studied in the phase IIb clinical trials, was based on applying autologous DCs. The DCs were initially loaded with the patient's derived HIV-1 RNA encoding some HIV-1 antigens and also CD40L using co-electroporation. The study evaluated the safety and activity of AGS-004 among successfully ART-treated patients followed by ART interruption. The vaccine-induced HIV-specific effector and memory CD8 T-cell responses efficiently, but there was no significant antiviral effect post-administration compared to the placebo recipients [32].

LIPO-5. In the LIPO-5 clinical trial, which developed to phase II, HIV-1 lipopeptides were applied to load dendritic cells. This trial assessed the safety and efficiency of dendritic cell administration as a therapeutic vaccine in infected individuals. For doing this, *ex-vivo* generated DCs were loaded with HIV-1 lipopeptides comprising five HIV-1-antigen peptides [Gag (17-35), Gag (253-284), Nef (66-97), Nef (116-145), Pol (325-355)] and an Analytical Treatment Interruption (ATI) was conducted on the vaccine recipients at the week 24. The regimen was well-tolerated and elicited polyfunctional HIV-specific responses, but the virus rebound was observed after 14 days [33].

ApB DC. Another DCs based trial that developed to phase I and II was the autologous HIV-1 ApB DC vaccine. In this trial, the safety and antiviral activity of this therapeutic vaccine were assessed. The autologous dendritic cells were loaded with patients' derived HIV-1 infected apoptotic cells. The vaccine was safe, well-tolerated and led to induce T-cell activation; however, it was not able to prevent viral rebound after treatment interruption [34, 35].

PARC002. This clinical trial evaluated the safety of the experimental autologous dendritic cell vaccine and its ability to enhance the immune system response against HIV. The autologous DCs loaded with mRNA encoding HIV-1 Gag and Nef were applied along with the placebo in two groups randomly. The mRNA for loading the DCs was selected based on several criteria; first of all, lysosomal targeting sequences in the transfected mRNA can be induced so that antigen can be directed to lysosomal degradation and therefore stimulate antigen-specific CD4 cell responses. Moreover, the transfected mRNA is directly delivered into the cytoplasm to be translated with no need for codon optimization. Finally, immunization with mRNA-loaded DCs facilitates the delivery of whole viral gene products. The result of the study showed that the CD4 and CD8 proliferative responses enhanced 2.4 and 2.5 folds, respectively, though not long-lasting. There were increases in proliferative responses against HIV-1 antigens but were transient [36].

Other studies on DC therapy against HIV infection are in progress (Table 2). The DC-HIV04 in HIV-infected patients evaluates safety and tolerance. This study assesses the vaccine among six groups [group 1: receive enhanced DC-HIV vaccine with inactive HIV, group 2: receive enhanced DC-HIV vaccine with HIV peptide, group 3: receive enhanced DCs only (control), Group 4: receive classic DC-HIV vaccine with inactive HIV, group 5: receive classic DC-HIV vaccine with HIV peptides, and group 6: receive only classic DCs (control)]. Autologous DCs will be loaded with whole inactivated autologous HIV or only the conserved HIV peptides. The control group will receive DCs with no antigen, according to different time tables in ART-treated HIV-infected Adults [29].

Table 1. Completed clinical trials based on DCs vaccination

Registry Identifier	Trial	Phase	Status	Last Update	References
NCT00402142	DCV-2	II	completed	2014	[30,31]
NCT00672191	AGS-004	IIb	completed	2013	[32]
NCT00796770	LIPO5	I	completed	2017	[32]
NCT00510497	ApB DC	II	completed	2016	[34,35]
NCT00833781	PARC002	II	completed	2016	[36]

Table 2. Active DC-based clinical trials

Registry Identifier	Trial	Phase	Status	Last Update
NCT03758625	DC-HIV04	I	Recruiting	2019
NCT02961829	SPARC-7	-	Active, not recruiting	2018

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In Brazil, another ongoing trial on chronically infected individuals (an interventional study) use HIV-RNA loaded DCs in order to provide a synergistic effect leading to the eradication of HIV infection [29]

CONCLISION

Due to failures in developing a preventive or therapeutic vaccine and lack of access to medical care, particularly in developing countries, HIV has remained one of the most challenging deadly infections for four decades. Dendritic cells (DCs) as the most important mediators of humoral and cellular immune responses offer a promising strategy toward a therapeutic approach. The current information about the function of dendritic cells and their subsets are crucial to apply the full potency of these cells for immune-stimulatory. There are some considerable elements to develop efficient immunotherapy, including antigen selection and its delivery method, optimization of T cells and antigenic peptide interaction, and avoidance of tolerogenic responses [37-39].

By looking at different strategies in completed clinical trials that investigated DC therapy, we realize that the vaccines did not work as expected. Generally, the safety profiles of these trials were acceptable with minor local side effects in some clinical trials. Although they showed limited success rates, there proved that host immune response could be recovered against HIV-1. Some modifications in the main steps of protocols and standardization of trial design can improve the efficacy of these vaccines. First of all, the criteria for patient selection should be reconsidered by the investigation of the patients' genome and also HLA-typing due to their roles in vaccine response. Secondly, antigen selection is crucial in the case of HIV-1. Due to antigens variations among the isolates, the most conserved regions must be chosen. The procedures of dendritic cell culture and the determination of the dosage might also affect the immune response [27, 39]. *Ex-vivo* manipulation of autologous DCs individually may be prohibitive since specific facilities are required, and this limits its application to only facilitated centers. Therefore, *in-vivo* targeting by direct administration of immunogens to DCs has been developed in some studies which seem to be more efficient than the conventional strategy and will improve the DCs antigen presentation and capture by avoiding the inconvenient manipulation of them [28, 40]. Novel strategies considering all these criteria that modulate DC functions will be eventually able to induce a robust, broadly cellular response against T cell in the near future.

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CONFLICT OF INTEREST

The authors declare that there is no issue related to this article to be conceived as a conflict of interest.

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