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## Emerging Therapies in HIV Infection: Is the Immune Response the Answer?

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### Abstract

After 35 years of research in HIV infection, resulting in the development of almost 30 disease-specific drugs, the infection has evolved, from a lethal disease, to a chronic state that in many cases does not compromise life expectancy of infected individuals. Despite this immense progress, a widespread mechanism of virus eradication has not yet been recorded, rendering individuals committed to combined drug regimens for life. As a result, these patients often face several difficulties that are associated with side effects, adherence to therapy and/or emerging resistance of the virus to the applied regimen.

On this regard, scientists have recently focused on manipulating responses of the hosts' immune system, in order to control viral replication and eventually succeed in eliminating the virus in infected individuals. Research will verify the rationale of this syllogism, which according to the authors of this article, is the only approach that can permanently heal infected patients from HIV.

either NNRTI or PI) reduced mortality and induced viral load suppression [3]. However, the initial enthusiasm would soon be moderated, as ART administration was often accompanied by severe side effects and the austere regimens with the multiple pill doses per day were a hindrance to the effective adherence to the therapy. These difficulties made clear the need for simplification of ART [4]. For this purpose, fixed drug combinations (FDCs) were produced, with Atripla<sup>®</sup> being the first to gain approval from the FDA in 2006. Despite the side effects, ART has been successful towards controlling HIV, rendering this infection from a fatal disease to a chronic, manageable condition. On this regard, development of new agents intervening in totally different stages of HIV replication than NRTIs or NNRTIs, have enriched the armament of anti-HIV drugs. Among these agents are the approved chemokine receptor antagonists and treatments that are still in different stages of development that target both the viral cycle and the immune system.

### History of Chemokine Therapies

The relation between chemokines and HIV infection became known in 1996, two years after scientists managed to isolate a surface receptor that would be later called CXCR4 [5]. Furthermore, it was found that several chemokines (RANTES, MIP- $\alpha$  and MIP- $\beta$ ) could inhibit the entry of M-tropic HIV [6]. The last led to the recognition of CC chemokine receptor R5 (CCR5) as the main co-receptor for HIV, followed by the discovery that individuals homozygous for the 32bp deletion in the *CCR5* gene (*CCR5 $\Delta$ 32*) showed resistance to HIV infection [7]. CCR5 is expressed in various cell types and plays a wider role in inflammatory conditions. Potential therapeutic use of most of these chemokines had to do with being used as adjuvant for vaccines, though this concept was soon abandoned, since on one hand they did not achieve viral load suppression, on the other hand, their application deregulated physiological responses of the immune system. Research on a CCR5 antagonist led to the approval of Maraviroc in 2007, a small compound that can inhibit HIV fusion with the host cell [8].

### Introduction

The discovery, in 1983, that HIV was the cause of the acquired immunodeficiency syndrome (AIDS) [1] was followed by immense research and progress towards finding an effective therapy for a new lethal disease. The first compound that clinically achieved partial viral suppression was zidovudine (AZT), an old anticancer agent, though it was soon abandoned due to insufficient effectiveness and induction of viral resistance [2]. Despite the widespread use of AZT, which is a nucleoside reverse transcriptase inhibitor (NRTI), it was soon obvious that monotherapy would not be enough for retaining low viremia, as resistance to drugs and viral mutation emerged.

The breakthrough in AIDS therapy in 1995-1996, with the approval of more antiretroviral classes (non-nucleoside reverse transcriptase inhibitors-NNRTIs and protease inhibitor- PIs) led to combination therapy, which would be later called HAART (highly active antiretroviral therapy) and eventually ART (Anti-Retroviral therapy). The combination of three different antiretroviral agents (two of which are NRTIs and the other one

## Current Trends and Challenges

To date, more than 30 drugs have been approved and are distributed [9]. Also, commercially available are multi-class combination therapies, as Atripla<sup>®</sup> described above and Striblid<sup>®</sup>, the Quad pill [10]. The use of FDCs also provides the ability to incorporate new classes of antiretroviral agents, thus enhancing therapeutic results.

Several issues have lately emerged regarding HIV therapy. Primarily, selection of first line regimen in the treatment of ART-naïve patients. Current guidelines suggest administration of two NRTIs, while the third agent could be a NNRTI or a ritonavir-boosted PI, or even the lately approved integrase inhibitor raltegravir. Another very important issue in the era of ND-ART patients is the therapy-related side effects. Optimizing dosage and drug combinations that will both be effective in controlling viral replication and will limit side effects incidence is an open challenge. Moreover, the use of boosted protease inhibitors monotherapy as maintenance therapy after the initial suppression of viral load with ART has been achieved, is under research, though PIs' ability to sustain HIV load suppression for a long time is limited [11]. Another major issue, especially for the developing countries is the lowering of ART costs, suggesting the use of generic drugs. In this review we focus on the emerging immunological therapies of HIV infection. This issue is a key factor in achieving not only suppression of viral replication, but actually eradication of HIV. Only an HIV-targeted immune response can lead to therapy from the virus. This is the issue of the development of "clever" therapies that will involve mobilization of effector responses of the immune system. Nevertheless, few reports have been published discussing the immunomodulating aspect of new potential anti-HIV agents [12].

## HIV Treatment and Innate Immunity

On discussing HIV infection and innate immunity, the main feature of 'reservoirs' comes at the front line. Reservoirs can be cells like macrophages and dendritic cells infected by HIV, in which the virus remains in latency. They create a major problem for HIV eradication because ART does not affect latent form of the virus. On the contrary, the more ART extinguishes viral replication, the more HIV reservoirs give a feedback of new viruses. Thus, the idea of HIV eradication can be achieved by only one strategy: targeting the reservoirs [13].

On this regard, a first approach could be that of preventing reservoir creation. This can be achieved by blocking the integration of virus' RNA to the DNA of the cell, which is catalyzed by an enzyme called integrase. Inhibitors of integrase (INSTIs) have been used successfully for this purpose [14]. It has been reported that the primary human macrophages obtain resistance to INSTIs by a single-point mutation of the virus [15]. Another technique which prevents the integration allosterically has also been suggested. LEDGINS molecules have been used to intervene to the attachment of the LEDGF (lens epithelium-derived growth factor), a co-transactivator of the integrase, with the integrase and as a result to prevent the integration [16,17].

Nevertheless, reservoir creation is an early phenomenon on HIV infection, thus this strategy cannot be effective in the majority of newly diagnosed cases, where infection has already evolved beyond the first stage. On these cases the only effective approach for reservoir depletion is to activate the latent virus and then eliminate it with ART. Inhibitors of histone deacetylase (HDACi), an enzyme which blocks the expression of the HIV proviral DNA, promote reactivation of HIV from latency. HDACi have been tested successfully in monocytes and macrophages *in vitro* [18,19]

Activation of latent HIV can be induced by cytokine stimulation. Research data have shown that CXCL8 chemokine raises the levels of HIV p24 antigen in peripheral blood and enhances the cellular expression in infected monocytes and macrophages. Additionally, CXCL8 enhances the formation of 2-LTR circle, which is created by cDNA that has not integrated to the DNA of the cell. Thus, 2-LTR circles can be used as a marker for the nuclear import of viral DNA. CXCL8 has the same results either it is has endogenous or exogenous origin. Moreover, a raise in the production of CXCL8 can be caused by the activation of the NF- $\kappa$ B transcriptional factor [20]. Taking all these into consideration, researchers conclude that another therapeutic strategy that could lead to HIV activation of latent reservoirs, should be based on blocking the production or the effects of CXCL8. Limitations on this approach include the complex signaling pathways in the production of CXCL8, thus complete blocking of the CXCL8 production *in vivo* is not feasible. As a result indirect approaches need to be employed, such as targeting the CXCR1 and CXCR2 receptors.

Another approach that could lead to elimination of HIV reservoirs consists in activating these cells so that they express the virus' antigens on their surface, rendering them targets for cytotoxic T lymphocytes. Unfortunately, such scenario is not confirmed *in vivo*. A more effective strategy seems to be that of combining on the same cells activation of the virus with means of boosting the apoptosis with "apoptosis inducing agents". This procedure seems to render reservoir cells more recognizable from cytotoxic T lymphocytes, with the latest providing an effective form of reservoir depletion. This strategy is called "Prime, Shock and Kill Strategy" [21]. In other words, reactivation the virus is followed by a procedure that makes the reservoirs prone to apoptosis. Some examples of apoptosis inducing agents are Bcl2 inhibitors, surviving inhibitors, PI3K/ATP inhibitors. These agents have been used to promote apoptosis in cancer cells and they are proposed for use on this regard. Nevertheless, monocytes and macrophages, especially when HIV infects them, have been proved to be more resistant to apoptosis caused by DNA damaging agents [22]. A thorough experimentation on this field could reveal a new approach on targeting HIV reservoirs [23].

When applying this strategy *in vivo*, one has to consider that the core of this procedure involves boosting the homeostatic proliferation of reservoirs, a mechanism that can lead to cancer development, especially in HIV patients who are already susceptible to cancer due to immunosuppression [24]. Targeting directly only the infected cells could spare *in vivo* cancer development. This is a realistic option, since monocytes and

macrophages have different program cell death signature depending on their infection by HIV [25].

## Adaptive Immunity

Adaptive immunity is a potential field for developing effective therapies for HIV infection. Medical research has already been conducted with controversial findings, leaving space for more specific research in the future. Both compartments of adaptive immunity, cell mediated and humoral mediated responses, could be used as therapeutical approaches of HIV infection, with the so far conducted research presenting controversial results when referring to different cell types that compose the compartment of the adaptive immunity [26,27].

## Cell Mediated Immunity (T-lymphocytes)

Potential immunotherapeutic goals of the adaptive immunity include CD8<sup>+</sup> T-cells, T regulatory cells, and the Treg/Th17 axis, which has been shown to play a crucial role in the early events of systemic intracellular infections.

CD8<sup>+</sup> cytotoxic T lymphocyte (CTL) activity is essential in controlling HIV replication. Clinical data has shown that individuals that naturally control HIV infection, the so-called "HIV elite-controllers", have robust CTL activity [28]. CD8<sup>+</sup> cytotoxic effect is closely related to the expression of CD56 cell surface glycoprotein. According to Poonia and colleagues, CD8 T cells from ART treated patients show sharply reduced expression of CD56 whereas elite patients who control HIV, in the absence of ART, retain CD56<sup>+</sup>CD8 T cell levels similar to uninfected controls [29]. Experimental data show that factors that boost CD56 expression, such as IL-15, might be used for augmenting CD8<sup>+</sup> cytotoxicity. On a clinical regard, these data suggest that reconstitution of the cytotoxic effector ability of CD8 T cells may increase the elite-controller status amongst HIV patients.

Other findings are more contradictory. Some studies indicate that trials to restore T cell function by use of negative signalling from ligands such as PD-1 can lead to better function and longer survival of CD8 T cells, whereas others note that this approach seems to be insufficient in inhibiting HIV viremia [30,31].

T regulatory cells (Tregs), seem to play a controversial role in both pathophysiology, and treatment of HIV infection. This controversial action is attributed to the different effects that Treg induced immunosuppression has according to different phases of the infection. During the short phase of primary infection, Treg action can be of benefit, by suppressing HIV-1-associated immune activation thus suppressing disease progression. On the other hand, in the chronic phase, Treg induced immunosuppression can minimize responses to HIV, promoting viral persistence [32]. Their controversial role is further supported by the fact that in some studies a decline in Tregs number is observed during progressive HIV-1 infection whereas in others, increased numbers are reported [33].

Therapeutic application of Treg function is further compromised by the fact that local tissue microenvironment is what promotes Tregs to acquire immunosuppressive or not activity.

According to some reports, Tregs/Th17 balance is of great importance concerning progression of HIV infection, as the ratio between uninfected and HIV elite controller individuals was similar [34]. More specifically,IDO enzyme and by-products of its activity, such as tryptophan catabolite kynurenine, appear to be a potential goal on influencing Tregs/Th17 balance that may be of therapeutic interest in the future [35].

## Humoral Immunity (B-cells & antibodies)

B-cells constitute a fundamental population in HIV infection pathophysiology, with functions that could be exploited for developing therapeutic strategies. Studies on B cell related cytokines, such as IL-21, have raised interest upon their effect on both B-cells (proliferating effect) and on T-cells, mainly Treg cells (inhibitory effect). A special B cell subpopulation, B regulatory cells (Bregs), according to Siewe and colleagues, hinder function of APC cells and CD4<sup>+</sup> T cells proliferation, promoting viral persistence and progress of HIV infection [36]. In contrast to Tregs, Bregs, according to the above findings, may be a more efficient therapeutic target in limiting HIV infection.

Another B cell dependent function, the antibody dependent cellular cytotoxicity (ADCC) can be of therapeutic interest by HIV infections. Nevertheless, recent data suggests that HIV infected cells may escape ADCC [37].

## Stem Cells

In 2009 an HIV patient who underwent bone marrow transplantation due to acute leukaemia, the so-called "Berlin patient" was the first patient to be reported as cured from HIV infection. The patient received bone marrow transplant from an unrelated donor, who was homozygous for the CCR5Δ32/Δ32 gene. This therapeutic intervention resulted in the elimination of the HIV-1, and the patient remained undetectable for over 4 years, without receiving ART. A year later, two HIV-1 infected patients in Boston received wild type Hematopoietic Stem Cells (HSCs), but in this case they were kept on ART throughout the procedure. After a considerable period of follow up, the patients remained non-detectable and discontinued ART therapy, showing that in the allogeneic HSCs transplantation genetic modification may be avoided. In both interventions full donor chimerism and GVHD were noticed. Despite the ambitious efforts, two more patients treated as the Boston patients showed relapse, setting the approach into doubt.

Alongside with these efforts, studies focus on autologous stem cell transplantation. For this therapeutic method to succeed, genetic modification of the HSCs is necessary, and is accomplished by transporting genes that prevent the early stages of the HIV-1 infection. On this regard, CCR5Δ32/Δ32 and *TRIM5* gene, seem to be more effective. Unfortunately, the presence of the provirus in the reservoirs impedes this approach. Hence, it is incumbent on myeloblastic chemotherapy alone or combined with other type of depletion therapies to eliminate all the harboring provirus cells. Some researches question even the safety of the modified HSCs mentioning that these cells can also be infected by HIV-1, while other studies suggest that a number of macrophages originate not only from

HSCs, but also from other sources during embryogenesis, a fact that triggers the efforts of destroying all of the virus reservoirs [38]. Taking into consideration the failure of this method to result in undetectable levels of virus in the patients blood, more studies should be conducted and non-human primate (NHP) models could be a helpful tool in achieving undetectable levels of viral load.

## Chemokine Receptors CCR5

As stated above, FDA has approved only the small molecule in 2007 for use in HIV infected people [8]. The discovery of the CCR5 $\Delta$ 32 mutation in people that provides them with more resistance to HIV infection led scientists to focus on the receptor, by targeting the receptors' intracellular biosynthetic pathway. The first study took place in 2003 [39] with the use of truncated CCR5 molecules, followed by other studies in 2009 [40] and 2010 [41], applying this time RNA interference, a mechanism used to target the transcripts of HIV proteins or host cellular components causing their subsequent degradation and reduction of the respective protein expression. All studies resulted in reduction of CCR5 expression, leading to the acquirement of resistance to HIV infection.

A more sophisticated approach is the use of modified CD4+ T cells. This method includes extracting large amounts of CD4+ cells and cultivating them with zinc finger nucleases (ZFNs) that target and disrupt CCR5. Then, the genetically modified cells are injected back to the patient. The infusions became well tolerated except from a severe side effect, a transfusion reaction of arthritis. This study showed in general good results in keeping low viremia and so it raises hopes for future use [42].

## HIV-1 Vaccine

The epidemic character of the HIV infection directed early the research towards the development of a vaccine that would protect the population from the virus. Protective vaccines aim to halt HIV-1 infection and provide sterilizing immunity, while therapeutic vaccines motivate immune responses against virus' proteins in order to control viral replication.

To date, three concepts have been supported with six efficacy clinical trials for models of protective vaccines. Vax003/Vax004 were based on the idea of a gp120 Env protein inducing antibody production [43]. The Step and Phambili trials proposed the use of an adenovirus type 5 (Ad5) vaccine that showed induction of cell mediated immune response by CTLs [44], while the HVTN505 combined those two concepts in a DNA prime/rAd5 boost vaccine regimen [45]. Each of the above trials either failed to show satisfactory results or was stopped due to increased risk of vaccine induced HIV-1 infection [46]. Last but not least, in 2009 the RV144 trial in Thailand tested a recombinant canarypox vector vaccine prime regimen and showed 31,2% efficacy [47]. These were the first promising results for a safe and effective protective vaccine and were followed by significant correlates of risk: plasma IgG antibodies against Env variable region 1 and 2 correlated with lower risk of HIV-1 infection, while vaccine efficacy was reduced by high levels of plasma IgA Env-specific antibodies, that did not result though

in higher infection rates [48]. Despite the encouraging but statistically not significant results of the RV144 trial, the obstacles in the vaccine construction are yet many, including the unnoticed induction of neutralizing antibodies, the virus' complicated morphology (many subtypes, sequence diversity, the immune dominant and cryptic epitopes on the envelope, the virus' ability to create quickly viral reservoirs, the incompletely studied immune responses triggered by the infection, the lack of a suitable animal model) and other, non-scientific issues [49]. However, it has become clear that broader, more powerful and more prolonged humoral as well as cellular responses should be induced by an effective HIV-1 vaccine, especially at the mucosal level. Hence, efforts lean mainly towards three directions: Heterologous vectors and inserts, replicating vectors and broadly neutralizing antibodies elicited by immunogens, as noticed in mice [50].

Little progress has been made in testing HIV-1 therapeutic vaccines. Such vaccines aim in re-inducing the immune response against the HIV-1 virus offering prolonged periods of non-detectable viral load to infected patients, without ART therapy. The most ambitious strategies involve synthetic peptide vaccines that direct the immune response against virus' proteins or peptides. P17, a matrix protein originating from Gag gene, that plays a great role in both virus' life circle and immune response during HIV-1 infection, is the main target of the studies [51]. This protein is considered to induce the migration of monocytes and dendritic cells and the proliferation of NK and T-cells by increasing the expression of IL-2, IL-12, IL-15, MCP1 and CCR7, and by decreasing IL-4 levels, an anti-inflammatory cytokine [52]. Studies show that p17 may be chronically found in the microenvironment of infected patients, regardless of ART treatment and that Abs against p17 may halt the progression to AIDS, findings that imply that a P17 related intervention could have a therapeutic effect [53]. Other clinical trials test the effectiveness of immunotherapies against viruses' reservoirs using dendritic cell-based vaccines [54]. These vaccines provide autologous dendritic cells that have been pulsed *in vitro* either with autologous inactivated whole HIV, which may lead to a decrease of viremia, or with autologous HIV sequences for Gag, Nef, Rev and Vpr [55]. This last method, combined with the use of a vector that induces the expression of CD40 ligand on the dendritic cell-surface, initiated the presentation of the viral peptides and enhanced the immune response [56]. It is encouraging enough that most novel interventions are immune-based and that the construction of multi-epitope-based vaccines is a very promising concept.

## Conclusion

In Internal Medicine, the concept of treating a specific condition not only by targeting the etiological factor, but trying to induce homeostasis by manipulating aspects of the immune system, is a modern approach that has given very promising therapeutic results in autoimmunity and cancer. After 35 years of research on HIV therapy, it is evident that although the development of many regimens targeting viral replication has led the HIV infection to be considered a chronic disease, a

definitive eradication of HIV can be achieved only by manipulating the hosts' immune response.

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