Role of therapeutic vaccines in the control of HIV-1

S. Kinloch-de Loes*

Department of HIV/Thoracic Medicine, Department of Medicine and Department of Immunology and Molecular Pathology, The Royal Free Centre for HIV Medicine, Royal Free Campus, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK

The recent success of highly active antiretroviral therapy (HAART) has altered the prognosis of patients living with HIV-1 infection. However, there are still many challenges to be addressed if we want to develop long-term therapeutic strategies for patients, in both the Western world and resource-poor countries. In this review, the potential role for HIV-1 therapeutic vaccines in the era of HAART will be discussed in the light of the present efforts at developing immune-based therapies to complement antiviral treatment and minimize the duration of exposure to antiviral drugs.

Keywords: immune control, immune-based therapies, HIV, highly active antiretroviral therapy

Introduction

HIV-1 is a major pandemic which is presently out of control worldwide. Highly active antiretroviral therapy (HAART) has revolutionized the care of the patients to whom it has been accessible. The potency and short-term clinical benefit of these new regimens have now become a daily reality in the clinic. However, their benefits are limited both by problems over long-term use of these regimens as well as the lack of access for the majority of infected patients. These realities have prompted a renewed interest for testing alternative forms of treatment such as active specific immunotherapy.

In this review, I shall describe the attempts at translating the present understanding of the immune processes at play during the course of HIV-1 infection into new treatment strategies. HAART has provided an opportunity to attempt to recover or boost immune responses, which are instrumental in the control of viral replication, when the bulk of HIV replication is suppressed by antivirals and immune reconstitution is taking place.

Natural history of HIV-1 and the HAART revolution

HIV-1 infection can schematically be divided into four phases: primary or acute infection (PHI), the first 6 months of the infection, the chronic stage and finally the acquired immune deficiency syndrome (AIDS) phase when the majority of opportunistic infections and cancers occur. Viral replication is an on-going process throughout these stages with the highest levels of viraemia found during PHI and AIDS.

Since the early years of the pandemic, considerable efforts have been made to try to control the progressive, virally-induced decline in immune defences which characterizes HIV-1 infection. HIV replication is understood to drive the immunological abnormalities associated with the infection, in particular the profound depletion in CD4 cells.

If left untreated, HIV-1 infection leads to AIDS and death in the majority of patients over a period of several years. A very small proportion of infected patients the so-called 'long-term non-progressors' (LTNPs) remain free of disease, with a stable high CD4 count. They are able to control viral replication to low levels in the absence of treatment and represent one of the paradigms of immune control of HIV.

The initial efficacy of HAART was dramatic on both laboratory markers, such as viral replication and CD4 depletion, and opportunistic infections. Mortality and morbidity were decreased by about 70% when two nucleoside analogues and a protease inhibitor were used simultaneously. Immune responses against common pathogens were also restored, resulting in the possibility of discontinuing primary and secondary prophylaxes against some AIDS-defining infections. However, HIV-1-specific T cell immune responses were initially not recovered in late infection.

Absence of eradication and HAART toxicity

Evidence showing the persistence of integrated, replication-competent virus in long-lived resting CD4+ memory T cells and other reservoirs has highlighted that eradication will not be feasible in the majority of patients with antiretroviral therapy alone. Mathematical modelling to assess the duration of treatment for the eradication of the virus predicted a minimum of 6–10 years if HAART was started in the early stages of infection and of several decades if initiated during the chronic phase of the infection, as it is presently recommended.

The long-term use of the present components of HAART regimens is raising grounds for concern. Although the efficacy of initial HAART can last for at least 4 years and clinical experience shows that highly compliant patients can remain aviraemic for longer periods...
of time, there are serious doubts about the feasibility of managing HIV infection with the very prolonged and continuous use of antiretroviral agents. Short-term lack of compliance jeopardizes antiviral efficacy. Resistance to antivirals, mitochondrial toxicity and lipoatrophy will all require the continuous development of new antiviral agents with different resistance and toxicity profiles with an emphasis on limiting the duration of drug exposure. Finally, costs and the absence of access to antiviral therapy for the majority of patients affected by HIV-1 make new and simplified treatment strategies a particular priority.

Immune responses and HIV

The initial encounter of the virus with the immune system during PHI is temporally associated with the development of a CD8+ T lymphocyte and an HIV-specific cytotoxic T cell (CTL) response while viraemia levels decrease sharply in the following weeks. CTLs are understood to be a major player in the acute decline of viraemia. The role of neutralizing antibodies in viraemia control at this stage had long been thought negligible as titres rise slowly and remain low. However, recent evidence indicates that they play a part in applying selective pressure on viral evolution.

Although the CD4 cell count rebounds to lower levels than those measured pre-infection, during the phase of resolution of the acute phase, natural history shows a subsequent chronic CD4 cell decline in the absence of therapy. The erosion of immune function occurs in the presence of a detectable CTL response against the virus until the very late stage of the infection. This paradox has led to several hypotheses for the various mechanisms leading to the CTL dysfunction which allows the virus to escape immune responses. HIV-1 mutational escape from host cytolytic specificities in peripheral blood and impaired cytotoxicity in lymphoid tissue occur rapidly after acute infection. Defects in antigen presenting cells may also hinder CTL function through a lack of appropriate co-stimulation.

The present consensus is that CD4 help is crucial for CTL’s functional activity for viraemia control in HIV-1 infection as in other viral infections. Activated HIV-specific CD4 cells are understood to be the main target of the virus, starting at the earliest stages of infection, and to be progressively deleted in the absence of antiviral intervention. These responses have been reported at high frequencies in PHI and human studies in PHI and LTNPs, using CD8 cell depletion and antigenic stimulation. Therefore, the re-exposure of the immune system to viral antigens as a therapeutic intervention represents an attempt at the boosting of the CD4 and CD8 HIV-specific responses in HAART-treated patients in order to strengthen the immune control against the virus.

Modalities and aims of therapeutic vaccination

The aim of therapeutic vaccination is to induce or augment immune responses involved in the control of HIV-1 replication with a planned exposure to viral antigens. Two modalities have been considered recently. The first one is feasible with HAART interruption and viral rebound and involves autologous virus. The second is the exposure of the immune system to heterologous virus using vaccines.

The main aim of such an intervention in the HAART era is to attempt the partial, temporary or total control of viral replication after the discontinuation of antiviral therapy. If successful, this strategy should in turn decrease or stop the CD4 loss and potentially delay or stop clinical progression. In clinical terms, it might allow patients to discontinue their antiviral therapy for a given period of time with the added benefit of a ‘drug-holiday’, and cause a decrease in HAART-induced toxicity and costs. An optimistic aim for this type of strategy would be to transform patients into LTNPs, besides viral eradication which would be the most successful outcome. This paradigm may be more realistically entertained in the very early stages of infection, in particular in PHI.

The strengthening of immune responses through re-exposure to heterologous antigens could also be envisaged to enhance viral control in patients on HAART in order to decrease treatment failure. Lastly, for the patients who remain untreated, particularly when antiviral drugs are unavailable, a potential role for therapeutic vaccines would be to allow for the delay of HAART initiation.

Autoologous vaccines or ‘auto-vaccination’

Some case reports and small studies of patients at the chronic stage of the infection have led to several studies of structured treatment interruption in order to evaluate the possibility of viral control and type of immune responses generated by this strategy during both chronic and acute infection.

In chronic infection, a Swiss-Spanish, prospective study (SSTI) enrolled a cohort of 133 patients on long-term HAART who underwent several treatment interruptions followed by treatment re-initiation and subsequent discontinuation of antiviral therapy. Ninety patients
completed the four cycles and stopped HAART at week 40.43 Twenty-three of the 79 patients who could be evaluated 12 weeks after stopping treatment had a viraemia level below 5000 copies/mL and were considered as responders. Although there were increases in HIV-specific CD8 cells during treatment interruptions, these did not prevent viraemia rebound.44 These results and others, which have shown the possibility of emergence of viral resistance, clinical progression and new infections in partners of previously aviraemic patients, have generated a cautious approach towards this form of intervention outside clinical trials.

When testing this strategy in very early infection, the most quoted cohort includes 14 patients treated with HAART during PHI.42 A substantial proportion of these patients continued to maintain viral loads below 5000 HIV copies/mL up to 3 years after one to four treatment interruptions.45 However, there is presently no controlled trial which allows firm conclusions to be drawn on the effect of such a strategy in very early infection. It is not known whether prolonged antiviral therapy without treatment interruptions might be able to achieve similar results through CD4 help rescue and the decrease in viral differentiation.36

In conclusion, this form of approach has been conducted with mixed success although there are some encouraging results in acute infection. Further evaluation is needed to better define the role of planned therapeutic interruption in the treatment of HIV infection and the potential for combining it with immunomodulatory strategies.43

**Heterologous vaccines**

**Numerous new vaccine candidates.** There are presently no licensed prophylactic or therapeutic vaccines against HIV. None of the therapeutic vaccine candidates has shown long-term efficacy on the viral set-point, CD4 count or disease progression in a randomized trial. However, in the past few years, there has been an explosion in the number of new vaccine candidates [recombinant proteins, synthetic peptides, HIV peptides or lipopeptides, viral or bacterial vectors expressing HIV antigen(s), DNA vaccines and virus-like particles]. They are about to be or have been piloted in more than 60 Phase I trials since the beginning of the epidemic. Several Phase II trials are ongoing, and one Phase III trial has been completed while another is ongoing.46-48 Efforts have concentrated on devising vaccines which can produce neutralizing antibodies and stimulate cell-mediated immunity. However, because of the difficulty in generating antibodies capable of neutralizing primary HIV-1 isolates, there has been a recent emphasis on T cell responses.

One of the approaches shown to increase T cell responsiveness is a prime-boost strategy using a DNA prime followed by boosting with a viral vector.49 Among the numerous new vaccine candidates for use with this type of approach are several avipox-based vector vaccines with inserted HIV genes such as modified virus Ankara (MVA), NYVAC and fowlpox and a new replication-defective adenovirus 5-based vaccine.46

Although the vaccine effort has mostly been geared towards the creation of one or several prophylactic vaccines, some of the new compounds are also in the process of being tested in the therapeutic arena. These complement others which have been more extensively piloted in the pre-HAART period such as Remune (a gp120 depleted whole inactivated virus), envelope-based recombinant gp120 and gp160 compounds, a core-based p24 virus-like particle vaccine (p24-VLP vaccine), and DNA plasmid compounds.50-54

**Therapeutic vaccines in the pre-HAART era.** Initial vaccine candidates have demonstrated their safety and immunogenicity in HIV-positive individuals. However, when used on their own, some have shown a limited ability to generate HIV-specific immunity or neutralizing antibodies and led to rather disappointing therapeutic benefits in terms of CD4 increase, viral load decrease or delay in disease progression.55-57

However, the general antigenic overload in the absence of control of HIV replication by powerful antiviral treatment, the various CD4 counts and viraemia levels of vaccinees and biases introduced by the introduction of HAART in some of these studies have precluded firm conclusions from being drawn about their efficacy and best clinical and immunological settings for their use in the HAART era.58-60 A review suggested that the best immunogenicity for gp120 (envelope)-based vaccines might be achieved in patients with a baseline CD4 count of more than 350 cells/mm³ and a low level of viraemia.61 In a recent study, the best predictor of efficacy for Remune was the baseline CD4 count.61

**The HAART era.** Studies in animal models have recently supported the rationale for testing the association of antiretroviral therapy and therapeutic immunization in both early and chronic infection.62,63

The availability of HAART and the present focus on the importance of HIV-specific T cell immunity in the immune control of HIV viraemia have targeted new vaccine compounds for their potential to elicit strong and broad cellular immune responses for therapeutic use.46,47

Several generations of the recombinant canarypox-based vector (ALVAC-HIV) with various inserted HIV genes have shown their safety and immunogenicity in humans and HIV-1-infected individuals.64 The ALVAC-HIV vCP 1452 was recently piloted in early HIV infection in association with rgp160 or Remune.65,66 ALVAC vCP 1433 has also been used in two French studies in association with HAART or HAART, lipopeptides and cycles of interleukin-2 (IL-2).67,68

Other vaccine candidates which are in the pipeline for therapeutic use include the protein-based env-tat-net compound developed by GlaxoSmithKline and a DNA-based vaccine administered intradermally.59,60 The latter encompasses the entire sequence of the HIV genome with deletion in the integrase gene. It has shown extremely encouraging results in terms of viraemia control at the late stage of infection in the monkey model in association with structured treatment interruptions.60

It remains to be shown whether the addition of immunostimulatory strategies to vaccines such as cytokines in association with DNA alone or in prime-boost strategies with viral vectors will lead to an increased efficacy as suggested by some animal models.65,60,71 IL-2 was administered after immunization with a canarypox vaccine (ALVAC-HIV vCP 1433) and lipopeptides in a recent trial with encouraging results in terms of the possibility of treatment interruption.68 The description of the effect of cell-based vaccines using autologous dendritic cells pulsed with a chemically inactivated HIV in early SIV infection also deserves further studies.72

**Conclusions**

We are still at the initial steps of the testing of immune strategies such as the planned re-exposure to autologous or heterologous virus in the HAART era. Many issues remain open when using vaccine compounds in humans, such as the best clinical setting, the optimal mode, dose and timing of administration and potential for cross-clade
efficacy. Their efficacy and role in therapy for HIV-1-infected individuals remain to be defined through clinical trials. One can hope that these issues will be addressed with the urgency demanded by the epidemic and that the interplay between clinical testing and further elucidation of immunological parameters will allow for the improved long-term care of patients.

References


