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# Optimizing the efficiency of therapeutic HIV vaccine trials: A case for CTN 173

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ABSTRACT

*Background:* The introduction of highly active antiretroviral therapy (HAART) has enabled the dramatic reduction in viral replication and the partial restoration of host immune function, albeit at the expense of drug toxicity. Strategies to enhance HIV-specific immunity are required in order to limit ART exposure. Therapeutic vaccination is a promising new approach to enhance immunogenicity and anti-viral activity in people infected with HIV.
*Purpose:* Efficient clinical trial designs are required to optimize therapeutic HIV vaccination strategies. Herein, we describe unique design features and investigational procedures that were applied to a prime-boost therapeutic vaccine trial (CTN 173) to enhance HIV immunity.
*Methods:* CTN 173 was a multicentre, randomized, 3-arm, double-blind placebo controlled trial to evaluate anti-viral activity of therapeutic vaccination with ALVAC ± Remune in chronically infected individuals on HAART. CTN 173 was developed with the specific aim to better characterize patient factors and immunologic parameters associated with vaccine response. This paper discusses the relevance of choice of primary endpoint and statistical approach used in this trial, in relation to vaccine response, patient safety and the identification of optimal target populations for future vaccine trials.
*Results:* Time to event surrogate endpoints of viral response and frequent immunologic monitoring allow for a better characterization of immunologic correlates of vaccine response.
*Limitations:* The clinical implications of delayed viral rebound associated with therapeutic vaccination with ALVAC + Remune are not yet known and will need to be evaluated on long-term follow-up.
*Conclusions:* Randomized controlled trials such as CTN 173, with well-defined surrogate endpoints and frequent immunologic and virologic monitoring, are necessary to streamline the approach to effective vaccine discovery and to ensure patient safety.



## 1. Background

On-going HIV replication following initial infection leads to progressive immune deficiency. Highly active antiretroviral therapy (HAART) can effectively maintain HIV RNA at undetectable levels (<50 copies/ml) and allows for the preservation of general and HIV-specific immunity. HIV-infected individuals on HAART may therefore be amenable to strategies capable of further enhancing immune function. Novel approaches to strengthen immune responses to HIV may allow for limited ART exposure.

Re-exposure to the HIV antigen using structured treatment interruptions (STI), often referred to as autoimmunization, is a strategy that has been to tested to boost anti-HIV immunity [1,2]. Despite the potential benefits of this approach in limiting the time on therapy and the associated cost and toxicity of treatment, the evidence to support the immunologic benefit of STI remains equivocal [3,4]. Further, the absence of durable virologic control of HIV after ART discontinuation combined with the associated declines in CD4 count and worse clinical outcomes, has prevented this strategy from being recommended in the routine management of patients with HIV infection [5,6]. Nonetheless, in the context of the controlled clinical setting, analytic treatment interruption (ATI) continues to be acceptable in the testing of therapeutic HIV vaccines [5].

Therapeutic immunization strategies designed to stimulate anti-viral activity by enhancing HIV-specific immune response

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have also been proposed [7–11]. Guided by the immune modulating characteristics of successful preventative vaccines, putative therapeutic HIV vaccines have been chosen based on their ability to enhance cytotoxic T lymphocyte (CTL) responses and CD4 T cell help. Most recently, vaccination strategies of multiple vaccines and/or immune modulating agents have been undertaken in order to enhance and expand the breadth of the HIV-specific immune response [9–12] and because of the limited clinical efficacy of single agent trials.

Efficient clinical trial designs are required to optimize therapeutic HIV vaccine strategies, as optimal target populations and immunologic correlates of vaccine response remain poorly defined. CTN 173 was a randomized double-blinded placebo controlled trial of ALVAC (a modified recombinant canarypox virus) and Remune (whole killed HIV) in chronically HIV-infected individuals on ART. This study was undertaken to better characterize clinical features of the host and immunologic responses associated with control of HIV following ATI of HAART, using well defined endpoints, frequent immunologic monitoring and stringent eligibility criteria. Herein, following a brief study overview, we explore the unique design features of CTN 173 that enhanced the design efficiency of this therapeutic HIV vaccine trial.

## 2. Methods

### 2.1. Design overview

CTN 173 was designed as a multicentre, randomized, double-blind placebo controlled trial to evaluate anti-viral activity of therapeutic vaccination with ALVAC ± Remune in chronically infected individuals on HAART. This 3-arm study (1:1:1) was designed to evaluate the individual and additive effect of complementary vaccines on HIV-specific immunity, with the expectation that combined vaccination (ALVAC + Remune) would induce the greatest treatment effect. Briefly, Remune™ is a chemically and physically inactivated gp120-depleted HIV-1 adjuvanted with Incomplete Freund's Adjuvant (IFA) that has been shown to enhance cellular immune responses [13,14] and has a good safety profile [15–17]. In CTN 173, Remune™ or its placebo, IFA, were administered (1 ml i.m.) at weeks 0, 12 and 20. ALVAC (vCP1452) is a preparation of a modified recombinant canarypox virus, expressing the gene products of the HIV-1 *env* and *gag* genes and a synthetic polypeptide encompassing the known human CTL epitopes from the *nef* and *pol* gene products, which can be safely be administered to HIV-infected adults to target CTL responses [11,18,19]. In CTN 173, ALVAC or its placebo (saline) was administered (1 ml i.m.) at weeks 8, 12, 16 and 20.

HIV-infected individuals (aged >18 years) were able to participate in CTN 173 if they were receiving at least three antiretrovirals and had a plasma HIV RNA level <50 copies/ml for a minimum of 2 years. CD4 eligibility criteria at baseline consisted of absolute CD4 count >500 cells/μl, CD4 to CD8 ratio >0.5 and CD4+ T cell nadir (lowest CD4 count ever) >250 cells/μl. Study participants received vaccination or placebo for 20 weeks, while continuing on ART. At week 24, ART was discontinued and study participants were monitored for viral rebound and CD4 decline, which precipitated ART re-initiation. Protocol defined criteria for re-initiating ART are presented in Fig. 1. The primary endpoint was time to detectable levels of HIV RNA (>50 copies/ml).

To characterize immunologic responses associated with control of HIV study participants underwent frequent virologic monitoring and immunologic investigations during vaccination and following ART withdrawal. Specifically, CD4 counts and viral load testing began 4 weeks before the first vaccination and continued every 4 weeks until week 24 in all subjects. At the time of ATI, viral load measurements were scheduled twice a week for 4 weeks (weeks 25–28 inclusive) and then weekly during weeks 29–36, or until the patient reached one of the conditions to restart ART. Viral loads were then evaluated monthly after week 36 for study participants who continued off ART. CD4 counts in all patients were carried out every 4 weeks from week 24 to 48. Finally, immunologic investigations were performed in all patients at screening and 4 weeks before vaccination as well as at weeks 0, 12 and 20 (during vaccination) and weeks 24, 28, 32, 36 and 48, after ART was discontinued, and included evaluations of HIV-specific CTL and T helper cell responses. All study participants were monitored during ATI until week 48, at which point study participants with detectable HIV RNA were to re-initiated ART (Fig. 1). The primary analysis of virologic, clinical and immunological endpoints was conducted upon the completion of 48 weeks of follow-up in all study participants. Additional analyses were also proposed after 3 years of follow up, to evaluate the potential lasting clinical impact of early vaccine response. This study was conducted in accordance with the ethical standards on human experimentation of the Declaration of Helsinki and was approved by the local research ethics board at each participating centre.

## 3. Design efficiency in therapeutic HIV vaccine trials

To streamline the approach to vaccine discovery, trials of putative HIV therapeutic vaccines must be designed to not only accurately quantify vaccine immunogenicity and anti-viral activity but must also help define optimal target populations and identify immunologic correlates of vaccine responsiveness, all the while preserving patient safety. CTN 173 was novel in its application of design features to specifically address these issues. A review of design features that will optimize and advance therapeutic HIV vaccine discovery is presented below, using CTN 173 as a case in point.

### 3.1. Randomized clinical trial

Therapeutic vaccine trials have been plagued with many of the well-known biases inherent in single arm observational studies. To date, only a limited number of randomized therapeutic HIV vaccine trials have been carried out [20–26]. Despite the added complexity of randomized controlled trials, their use in the study of vaccine response provides a unique opportunity to accurately quantify treatment effect (without the confounding effects introduced by the use of historical controls) and to identify host immunologic responses associated with the control of viral replication – both critical to effective vaccine development. Using a placebo-controlled randomized study design, CTN 173 was able to accurately quantify the delay of viral rebound associated with vaccination and identify vaccine-induced immunologic responses associated with improved control of HIV replication on ART withdrawal [26]. Through standard blinding procedures, CTN 173 also minimized the ascertainment and selection biases of previous open-label trials.

### 3.2. Choice of primary endpoint

The choice of primary endpoint is critical to the testing of new vaccines. Although a demonstration of clinical benefit is the ultimate goal of therapeutic vaccination, predictive markers of HIV disease progression are required as surrogate endpoints in vaccine trials to streamline the approach to effective vaccine discovery. Plasma viral load has been proposed as a viable primary endpoint in therapeutic vaccine trials [27] based on its strong association with disease progression [28]. Steady state viral load