

# Elite Controllers and Long-term Nonprogressors: Models for HIV Vaccine Development?

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## Abstract

Elite controllers and Long-term nonprogressors (LTNP) are uncommon subgroups of HIV-infected individuals that are typically associated with improved clinical outcomes compared to other members of the HIV-infected population. These groups have particularly desirable characteristics for developing a therapeutic vaccine for HIV infection, namely spontaneous virologic suppression in elite controllers and prolonged elevation in CD4 cell counts in LTNP. Despite these favorable characteristics, some individuals in these groups experience HIV disease progression including virologic escape, CD4 decline, and the development of AIDS and serious non-AIDS events. Due to the heterogeneity observed in these populations, it is essential to select individuals with durable virologic control and/or CD4 cell count trajectories when considering elite controllers and LTNP as models for development of therapeutic vaccines.

## Introduction

The pathogenesis of HIV infection involves the depletion of CD4+ T-cells resulting in immunodeficiency. For the vast majority of patients infected with HIV, ongoing viral replication and CD4 cell count declines eventually lead to the development of acquired immune deficiency syndrome (AIDS) and ultimately death in the absence of antiretroviral therapy (ART). Elite controllers are a subset of HIV-infected persons who have the ability to spontaneously control plasma viral load without ART. Although defined by virologic criteria, typically the presence of serial viral load measurements below the limit of detection for prolonged periods, elite controllers are also associated with elevated CD4 cell counts and reduced risk of AIDS and death [1]. Elite controllers comprise a very small subgroup with most HIV cohorts reporting a prevalence of <1% [1,2]. Despite the rarity of this phenotype, elite controllers are being aggressively studied to determine the mechanisms responsible for spontaneous virologic control with the hope of developing novel treatment strategies and perhaps even a therapeutic vaccine to treat patients infected with HIV.

In contrast to the virologic criteria used to define elite controllers, long-term nonprogressors (LTNP) are classically defined as having prolonged elevation in CD4 cell counts for many years in the absence of ART. This immunologic-based phenotype, first recognized in the pre-ART era, consists of an uncommon subset of HIV-infected individuals with most studies reporting a prevalence of 2-15% [1,3-5]. With widespread availability of viral load testing after the mid 1990s, most LTNP were found to have low to moderate levels of viremia [3,6-8]. Despite differing definitions, an exceedingly rare group of individuals can be characterized by both elite controller and LTNP definitions. For example, the U.S. Military HIV Natural History Study and SEROCO/HEMOCO cohorts demonstrated that the percentage of LTNP also meeting elite controller criteria was 4% and 12%, respectively [1,3]. This review highlights the utility of studying these uncommon HIV phenotypes as potential models for vaccine development, with a particular emphasis on the study of elite controllers due to the expanding knowledge and interest in this phenotype.

## Elite Controllers and LTNP: Variability of Definitions

The identification of well-characterized phenotypes is essential when considering elite controllers and LTNP as models for vaccine development. The lack of uniformity in the literature for defining both

elite controllers and LTNP represents a potential pitfall for studying these groups. For example, elite controllers typically have undetectable viral loads, but there have been differences in the limit of detection for viral load assays over the past decade. Thus, an elite controller defined by viral load <400 copies/mL may not be similar to another defined by viral load <20 copies/mL. The duration of virologic control may also differ [1,9-12]. Similarly for LTNP, there are differences in the magnitude and possibly the slope of CD4 counts over time [1,3,13-15]. These differences in elite controller and LTNP definitions used in the literature are summarized in Table 1. Due to the variability of definitions and follow-up time in elite controller and LTNP cohorts, it is paramount to select patients with durability of these phenotypes, particularly the duration of spontaneous virologic control in elite controllers.

## Elite Controllers and LTNP as Models for Functional Cure of HIV Infection

The term "functional cure" is typically defined as the ability to achieve persistent control of HIV infection without the need for treatment such as ART. Elite controllers and LTNP often have desirable characteristics that warrant consideration as potential models for functional cure. Elite controllers typically have undetectable viral loads which is a current treatment goal for patients on ART [16]. The goal of achieving undetectable viral load by means other than ART is an important goal for vaccine development. The mechanisms leading to spontaneous virologic control have not been fully described; however recent data suggests low T cell regulatory responses may be involved

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Characteristic	Elite Controllers	Long-term Nonprogressors	Comments
Magnitude of viral load	Typically below the limit of detection of the clinical assay (i.e. <50 copies/mL)	N/A	Low to moderate viremia is common in LTNP
Longitudinal characteristics of viral load suppression	Varying definitions: a) ≥3 undetectable VLs over ≥12 months <sup>1,9</sup> b) Undetectable VLs for ≥2 years <sup>11</sup> c) >90% with undetectable VLs for ≥10 years <sup>12</sup>	N/A	
Magnitude of CD4 cell count	N/A	≥500 cells/uL most common	CD4 cell counts typically elevated in elite controllers
Longitudinal characteristics of CD4 cell count	N/A	Varying definitions: a) All CD4 counts ≥600 cells/uL for ≥7 years <sup>13</sup> a) All CD4 values ≥500 cells/uL for ≥8 years <sup>3</sup> b) All CD4 values ≥500 cells/uL for ≥10 years <sup>1</sup> c) Definitions including both magnitude and slope of CD4 over time <sup>14,15</sup>	
Antiretroviral therapy	No therapy	No therapy	
AIDS-defining illness	Absent	Absent	

**Table 1:** Variability of Definitions in the Literature for Elite Controllers and Long-term Nonprogressors.

[17]. Although the presence of defective HIV virus was considered a possible contributor to elite controller status, several studies have shown recovery of replication-competent virus [18,19].

Although formerly termed “aviremic controllers”, many elite controllers have detectable virus with one longitudinal study showing that only 6 of 11 elite controllers had a viral load <1 copy/mL with serial measurements during follow-up [20]. It is unclear whether a proportion of elite controllers are persistently <1 copy/mL or if all elite controllers have detectable virus by single-copy assay at some point during the course of untreated HIV infection. Interestingly, a French study showed that elite controllers with transient low-level viremia, termed “blips”, do not experience CD4 declines compared to those who do not have detectable viremia [21]. In contrast to elite controllers, LTNP are typically viremic by standard clinical viral load assays. Since viremic individuals are more likely to transmit HIV to seronegative sexual contacts [22], this distinction has important public health implications.

Elite controllers are not defined by CD4 criteria and may experience CD4 declines over time and eventually require ART [23]. AIDS events have also been described in elite controllers, either by CD4 criteria or development of AIDS-defining events such as Kaposi sarcoma and pulmonary tuberculosis [1,24]. The determinants of CD4 decline in elite controllers have not been fully characterized. Although HIV

infection typically causes immunodeficiency, there is also persistent inflammation and activation of the immune system which may have many detrimental effects including cardiovascular disease, renal dysfunction, neurocognitive decline, liver failure, and osteoporosis [25]. Elite controllers have been shown to have a greater magnitude of immune activation compared to those with suppressed viral load on ART [24]. Despite this finding, however, one study showed that T cell activation was not a driver of CD4 decline in elite controllers [26]. Since HIV is a chronic inflammatory disease, the development of a therapeutic vaccine that can reduce immune activation as well as reduce plasma viremia would be highly advantageous.

LTNP have prolonged, stable elevation in CD4 cell counts which is also characteristic of patients on ART. Although some LTNP may have a potential disadvantage of low to moderate level viremia, CD4 stability is an important outcome for vaccine research. Viral load-independent mechanisms are likely involved in determining CD4 slope, with one study demonstrating that steady state viral load contributes only 4% towards CD4 decline [27]. Conversely, it also appears that the magnitude of CD4 cell count does not determine virologic control. A recent study in macaque elite controllers showed that reduction of CD4 cells *in vivo* did not affect viral load [28]. Thus, it is attractive to pursue vaccine strategies aimed at attaining durable CD4 cell counts and stable trajectories but such an approach may not impact plasma viral load.

### Host and Immunologic Factors Associated With Elite Controllers and LTNP

Specific demographic characteristics, such as age, race, gender, and mode of HIV transmission, have not been observed in elite controllers and LTNP [1,3,20]. There have been a number of host genetic and immunologic characteristics reported, particularly in the more extensively studied elite controller population. Protective MHC class I alleles, including HLA B57 and B27 containing the Bw4 motif, are overrepresented in elite controllers [10,12,29]. In European and North American cohorts, HLA B5701 is enriched while HLA B5703 is observed with greater frequency in those of African descent [19,30,31]. Although studies have shown enrichment for these protective alleles, some elite controllers lack these alleles suggesting they are not necessarily required for host virologic control. Similarly, CCR5 Delta 32 gene deletion has been reported in only a small proportion of LTNP and elite controllers [30,32-34].

There is evidence suggesting that an adaptive MHC class I-restricted CD8-mediated control is operating, given the linkage between the MHC class I locus and elite controllers [9,35-37]. Strong CD8 responses to HIV-gag are often reported in elite controllers with subsequent production of cytotoxic granules, IL-2 and IFN-g, and cell surface expression of CD27 leading to high functional avidity [35,37-39]. CD8 cells also demonstrate antiviral effects by inhibiting virus production from super-infected CD4 cells in elite controllers [36,38]. The intense cell-mediated response to HIV infection has not been demonstrated in all elite controllers suggesting that other viral control mechanisms are in effect [9,40]. Other possible mechanisms may include innate immunity mediated by natural killer cells, as evidenced by the strong association of KIR3DL1 allele in HLA B57 positive individuals [41-43]. Neutralizing antibodies have not been shown to have a major role, as these antibodies may be nearly absent in some elite controllers [10,44,45] and perhaps have a positive correlation with viral load as reported in studies involving LTNP [46,47]. Also, some studies of broadly neutralizing antibodies in elite controllers have shown these antibodies to contain a narrow spectrum of activity [48,49].

## Elite Controllers and LTNP as Models of Vaccine Design

Both elite controllers and LTNP exhibit a high degree of heterogeneity in many different areas, including demographic characteristics, host genetics, immunologic characteristics, rates of HIV disease progression and clinical outcomes, and even by criteria used in the literature to define these groups. Each phenotype possesses a desirable target for vaccine development: virologic suppression in elite controllers and stable, elevated CD4 cell counts for prolonged periods in LTNP. As previously discussed, the overlapping population meeting criteria for both elite controllers and LTNP is exceedingly rare. However, this combined phenotype likely represents the most advantageous approach for vaccine development research in these groups since this combined phenotype has a greater number of desirable characteristics than the singular elite controller and LTNP phenotypes. Due to the stability and durability inherent in a combined definition, this combination elite controller/LTNP phenotype has also been proposed in the literature [50]. In particular, the trait of spontaneous virologic control demonstrated in elite controllers is of lesser value if HIV disease progression occurs despite a suppressed viral load. It is also likely that viral load-independent mechanisms are involved in the magnitude and maintenance of CD4 cell counts. Thus, a vaccine aimed to accomplish both virologic suppression and CD4 stability may not be feasible and single approaches targeting either viral load suppression or CD4 maintenance may be preferred.

In summary, elite controllers and LTNP represent uncommon subgroups of the HIV-infected population that are typically associated with improved clinical outcomes. However, lack of HIV disease progression and both AIDS and serious non-AIDS outcomes can also occur in these populations. The heterogeneous nature of these groups poses significant challenges for vaccine development. Well-defined and characterized phenotypes are necessary if elite controllers and/or LTNP are to be considered as a potential model for vaccine development.

### Conflict of Interest

The content of this publication is the sole responsibility of the author and does not necessarily reflect the views or policies of the Department of Defense or the Departments of the Army, Navy or Air Force.

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