Clinical outcomes and antiretroviral therapy in ‘elite’ controllers: a review of the literature

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Abstract

Elite controllers naturally suppress HIV viraemia below the level of detection using standard methods, but demonstrate persistent inflammation and low-level viraemia that is detectable via ultrasensitive assays. These factors may contribute to an increased risk of non-AIDS-related morbidity and mortality among elite controllers. Data suggest that cardiovascular disease may be of particular concern in elite controllers, as evidenced by an increased burden of subclinical cardiovascular disease upon radiographic screening and an elevated rate of hospitalisations for cardiovascular disease as compared to non-controllers who are treated with antiretroviral therapy (ART). Widespread use of ART among non-controllers has led to significant declines in morbidity and mortality, but guidelines are generally silent on the role of ART in the care of elite controllers. Multiple small studies have demonstrated that laboratory markers of inflammation, immune activation and HIV burden improve after initiation of ART in elite controllers. Clinicians must consider these potential benefits of ART when deciding whether to initiate treatment in asymptomatic elite controllers.

Introduction

Elite controllers are a unique subgroup of persons living with HIV (PLWH). For most PLWH, untreated HIV infection is characterised by the detection of HIV across multiple compartments, gradual CD4+ T cell count decline, and progression to clinical AIDS. In contrast, ‘elite’ controllers, who comprise less than 1% of PLWH, are able to suppress HIV in the plasma to levels below the limit of detection via conventional assays [1–5]. Even in the absence of antiretroviral therapy (ART), elite controllers experience relative CD4+ T cell preservation and delayed disease progression [5]. For individuals with access to ART, there have been significant reductions in AIDS-related morbidity and mortality [6–13]. For elite controllers, however, the best practices for care remain unknown.

National and international guidelines are generally silent about the role of ART in the management of elite controllers [14–17]. Guidelines from the US Department of Health and Human Services, for example, note only that ART should be initiated in elite controllers who demonstrate other criteria for ART initiation, such as CD4+ T cell depletion or HIV-related complications, and otherwise state that ‘the Panel has no recommendations on managing controllers with high CD4 counts’ [14]. The paucity of data on clinical outcomes among elite controllers and the effects of ART in this population create a challenge for patients and healthcare providers who must make decisions with few guidelines to support them. The purpose of this review is to summarise the existing data on clinical outcomes and the impact of ART among elite controllers.

Definition of elite control

Elite controllers have undetectable plasma HIV RNA by conventional assays for prolonged periods in the absence of ART. Different research groups have employed different definitions of ‘elite’ control, with subtle variations in the plasma HIV RNA threshold used to classify an ‘undetectable’ viral load (generally <50 copies/mL with modern laboratory methods) and in the duration of spontaneous virological suppression required (anywhere from 1 to 10 years) [1–4,18–20]. Elite controllers may experience occasional viral load ‘blips’ above the level of detectability by conventional assays and most have low-level viraemia detectable by ultrasensitive assays [20–22]. In fact, the low-level viraemia observed among elite controllers often exceeds that seen in persons who are well controlled on ART [21]. Virological control also does not necessarily persist indefinitely and eventual loss of control has been documented in several controller cohorts [1,23,24].

In contrast to long-term non-progressors (another unique subgroup of PLWH, characterised by delayed disease progression and a preserved CD4+ T cell count), elite controllers are not defined by CD4+ T cell count criteria. While many elite controllers maintain a normal or near-normal CD4+ T cell count, slowly progressive CD4+ T cell decline may also be observed [3,19,22,25]. Progression to clinical AIDS has even been described in elite controllers, with complications such as pulmonary tuberculosis, Kaposi sarcoma and Candida oesophagitis [1,4,26,27].

Immunological and inflammatory consequences of elite control

The mechanisms underlying spontaneous virological control are poorly understood and are likely to be multifactorial. Certain HLA alleles, such as HLA-B57 and HLA-B27, are overrepresented among elite controllers [19,20,28–30]. This may result in populations of CD8+ T cells that are more potent and polyfunctional [31–33]. Elite controllers are also more likely to have specific natural killer cell genotypes that are associated with strong HIV-specific immune responses [34–37]. High levels of HIV-specific T cells have also been observed among elite controllers [28,31,32,38–42]. There is no doubt that the immune response to HIV infection exhibited by elite controllers is unique, but the effects of this response may not all be beneficial.

Elite controllers have elevated markers of microbial translocation, T cell activation, activation of the coagulation cascade and systemic inflammation as compared to those observed among HIV-uninfected persons and PLWH who are well-controlled on ART [26,43,44]. Separately, these markers have each been associated with increased morbidity and mortality among PLWH [45–48]. These observations raise concern that elite

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controllers may be at increased risk of morbidity and mortality not due to progression of HIV disease but rather due to increased immune activation and inflammation.

**Markers of cardiovascular disease**

Several studies have demonstrated that PLWH have a higher risk of both clinical and subclinical cardiovascular disease than do HIV-uninfected individuals [49–53]. These findings have been attributed to direct effects of HIV [54,55], side effects of ART [56,57], and a high prevalence of traditional cardiovascular risk factors among PLWH [58]. Two studies have specifically investigated subclinical cardiovascular disease among elite controllers (Table 1).

Hsue et al. measured carotid intima-media thickness (IMT) in 33 elite controllers, 96 untreated non-controllers, 180 treated non-controllers who were virologically suppressed on ART, 92 non-controllers who were viraemic despite ART, and 93 HIV-negative controls [59]. They observed significantly higher median IMT values among PLWH as compared to HIV-negative controls and this relationship persisted after adjusting for traditional cardiovascular risk factors such as age, gender, family history, smoking, hypertension and dyslipidaemia. Elite controllers appeared much like the overall HIV-infected population, demonstrating significantly increased IMT compared to HIV-negative controls even after controlling for traditional risk factors. Interestingly, elite controllers also demonstrated a trend toward higher median IMT than untreated non-controllers. Among elite controllers, C-reactive protein (CRP) levels were elevated as compared to HIV-uninfected controls and essentially indistinguishable from those observed in the other HIV-seropositive groups, regardless of viraemia or ART use.

Pereyra et al. used coronary computed tomography angiography (CTA) to assess subclinical atherosclerosis in 10 elite controllers and compared their findings to historical controls from other studies of 103 non-controllers who were virologically suppressed on ART and 49 HIV-negative controls [60]. The prevalence of atherosclerotic plaques was significantly increased in elite controllers compared with HIV-negative controls and was also increased compared to treated non-controllers, although the latter association did not meet the threshold for statistical significance. There were also non-significant trends towards higher calcium scores and more stenosis among elite controllers as compared to either HIV-negative controls or treated non-controllers. Inflammatory markers such as sCD163, sCD14, hsIL6, and CXCL10 were all higher among elite controllers as compared to HIV-negative controls. Elite controllers also had significantly higher sCD163 levels compared to treated non-controllers and trends towards higher levels of other inflammatory markers.

These two relatively small studies suggest that elite controllers have a significant burden of cardiovascular disease, despite demonstrating good virological control, relatively preserved CD4+ T cell counts, and no confounding ART exposure. The immune response that enables spontaneous virological control among elite controllers may create an environment of immune activation and inflammation that predisposes them to accelerated cardiovascular disease.

**Clinical outcomes**

Few studies have assessed clinical outcomes among elite controllers as compared to non-controllers, due to the relative rarity of elite control. No study, for example, has evaluated rates of myocardial infarction among elite controllers despite concerning evidence that suggests accelerated coronary atherosclerosis. Only three studies have provided some information about clinical outcomes among elite controllers within larger cohorts of PLWH (Table 2).

Okulicz et al. reported clinical outcomes among 25 elite controllers in the US Department of Defense HIV Natural History Study (NHS) [1]. They observed fewer deaths and fewer AIDS-defining events among elite controllers as compared to other PLWH in usual care. Similarly, in survival analyses, the time to death and time to AIDS-defining events were longer for elite controllers than for other PLWH. The percentage of elite controllers hospitalised during the study period was similar to other PLWH. No specific assessment of cardiovascular outcomes or reasons for hospitalisation was reported.

Lucero et al. reported clinical outcomes among elite controllers at a single university hospital in Barcelona, Spain [61]. The study population included both elite controllers and non-controllers, but all participants in this study were required to have a CD4+ T cell count >500 cells/mm³ during the study period. Two different definitions of elite control were employed. The first definition required undetectable HIV RNA measurements in the absence of ART during only the first year of the study and those with undetectable HIV RNA measurements in the first year of the study.

**Table 1. Summary of studies reporting surrogate endpoints for cardiovascular disease among elite controllers**

| Author   | Year | Study design | Location | Study population | n*   | Criteria for elite control | ART prescribed | Study endpoint(s) | Key findings                                      |
|----------|------|--------------|----------|------------------|------|-----------------------------|----------------|-------------------|---------------------------------------------------|
| Hsue     | 2009 | Cross-sectional | San Francisco, USA | UCSF-affiliated clinics in the SCOPE cohort | 33/494 | HIV RNA <75 copies/mm³ and never prescribed ART | No | Carotid IMT, CRP | Elite controllers had higher IMT and CRP than did HIV-negative controls after adjustment for traditional risk factors. |
| Pereyra  | 2012 | Cross-sectional | Boston, USA | Elite controllers selected from the International HIV Controllers Study, historic comparisons to PLWH on ART and HIV-uninfected controls from other studies | 10/162 | HIV RNA consistently <48 copies/mm³ in absence of ART | No | Coronary CTA, CAC, inflammatory markers | Elite controllers had more atherosclerosis on CTA than did HIV-negative controls and a trend towards more atherosclerosis than in non-controllers on ART. Elite controllers had higher inflammatory markers than did HIV-negative controls and sCD163 was also higher than in non-controllers on ART. |

* number of elite controllers/total number of participants. IMT: intima-media thickness, CRP: C-reactive protein, CTA: computed tomography angiography, CAC: coronary artery calcium
including 149 elite controllers [4]. Elite controllers had PLWH at 11 US clinical care sites in the HIV Research Network. Cardiac hospitalisations (as compared to other treated PLWH) are elevated rates of psychiatric hospitalisations were also observed for elite controllers compared to other PLWH. Although clinical data are limited, they suggest that elite controllers may benefit from ART or other therapies to reduce this risk and improve clinical outcomes.

**Antiretroviral therapy**

Several small studies have evaluated the effects of ART in elite controllers (Table 3). The largest of these was an observational study conducted by Boufassa et al. that included 34 elite controllers pooled from a variety of cohorts around the world [62]. CD4+ T cell counts before and after initiation of ART during usual care were compared to values obtained from 478 non-controllers in the French ANRS COPANA cohort. Investigators found that the magnitude of CD4+ T cell reconstitution after ART initiation was reduced among elite controllers as compared to non-controllers. This finding was consistent with observations of blunted CD4+ T cell response to ART among elite controllers in several smaller reports [25,63,64]. ART has been prospectively administered to elite and viraemic controllers in two single-arm clinical trials. Chun et al. administered a 9-month course of raltegravir and tenofovir/emtricitabine to three elite controllers and one viraemic controller [65]. They observed a significant decline in immune activation and level of replication competent virus after ART initiation. By 3 months after cessation of ART, however, the viral burden returned to baseline in all participants and immune activation rebounded in three of the four participants. Hatano et al. gave the same ART regimen to four elite controllers.
and 12 viraemic controllers for 24 weeks [66]. A similar decrease in viral burden and markers of immune activation was seen after ART initiation. Moreover, these effects in the peripheral blood were mirrored by similar trends in the gut-associated lymphoid tissue, which is one of the first sites infiltrated by HIV during acute infection and serves as an important reservoir for HIV persistence [67–71].

These data indicate that although elite controllers spontaneously control HIV viraemia to levels below the limit of detection by standard assays, ART is effective at further reducing viraemia to even lower levels in these patients. Furthermore, ART reduced markers of inflammation and immune activation that have previously been associated with increased risks of morbidity and mortality among PLWH [45–48]. A larger, ongoing study (NCT01777997) is prospectively treating elite controllers with ART and monitoring for changes in inflammatory markers, CD4+ T cell count, and HIV viral load. If the findings of this study are consistent with prior investigations, this could bolster the argument for initiating ART in asymptomatic elite controllers.

It is possible that therapies other than ART may also have a role in the care of elite controllers. Since much of the concern about these patients is focused on chronic inflammation and immune activation with associated risk of cardiovascular disease, agents with anti-inflammatory effects and promoters of cardiovascular health could provide a theoretical benefit to elite controllers. One ongoing study (NCT02081638) is randomising both elite controllers and treated non-controllers to receive either aspirin or atorvastatin. The study will measure changes in inflammatory markers in blood and colon and the burden of replication competent virus in all participants. Markers of immune activation and HIV burden rebounded to pre-therapy level after discontinuation of ART.

| Author   | Year | Study design | Location   | Study population | n* | Criteria for elite control | ART prescribed | Study endpoint(s) | Key findings                                                                 |
|----------|------|--------------|------------|------------------|----|---------------------------|----------------|------------------|-----------------------------------------------------------------------------|
| Greenough | 1999 | Case report  | Worcester, USA | One elite controller followed at the Medical Center of Central Massachusetts in Worcester | 1/1 | Undetectable HIV RNA over 15 years in absence of ART | Yes, zidovudine, lamivudine, nevirapine during usual care | CD4, CD8, HIV RNA, immune activation markers | No change in CD4, CD8, or immune activation in one patient started on ART due to declining CD4 count. HIV RNA remained undetectable before and after ART initiation. |
| Sedaghat  | 2009 | Cohort       | Baltimore, USA | Nine elite controllers followed at Johns Hopkins Medical Clinics | 9/9 | HIV RNA <50 copies/mL in absence of ART during ≥10 years of follow-up | Yes, one patient prescribed efavirenz, tenofovir, emtricitabine during usual care | CD4, CD8, HIV RNA, immune activation markers | HIV RNA and markers of immune activation decreased after ART initiation in one patient started on ART due to declining CD4 count. CD4 did not significantly increase after 1 year of ART |
| Okulicz   | 2010 | Cohort       | USA         | PLWH in the US military healthcare system | 6/1127 | ≥3 undetectable HIV RNA measurements over ≥12 months in absence of ART | Yes, during usual care | CD4 | 62 HIV controllers (including six elite controllers) demonstrated CD4 increase after ART initiation, but not as large an increase as was seen in non-controllers |
| Chun      | 2013 | Single-arm clinical trial | Canada | PLWH in the US military healthcare system | 6/1127 | Sustained HIV RNA <50 copies/mL with ≤1 blip above this level in absence of ART | Yes, prospectively given tenofovir, emtricitabine and raltegravir for 9 months | CD4, HIV RNA, quantitative co-culture assay, HIV DNA, immune activation markers in blood and colon | ART reduced immune activation and the burden of replication competent virus in all participants. Markers of immune activation and HIV burden rebounded to pre-therapy level after discontinuation of ART |
| Hatano    | 2013 | Single-arm clinical trial | Canada | 16 asymptomatic HIV controllers | 4/16 | HIV RNA <1000 copies/mL for ≥12 months, HIV RNA <40 copies/mL at study start, and never prescribed ART | Yes, prospectively given tenofovir, emtricitabine and raltegravir for 24 weeks | CD4, HIV RNA, HIV DNA, immune activation markers in blood and colon | HIV RNA and markers of immune activation decreased in the blood and colonic mucosa of HIV controllers after ART initiation |
| Boufassa  | 2014 | Cohort       | Worldwide   | Elite controllers pooled from several studies and non-controllers who were prescribed ART in the ANRS COPANA cohort | 34/512 | ≥5 HIV RNA measurements <400 copies/mL during at least a 5-year period and never prescribed ART | Yes, during usual care | CD4 trajectory | Non-controllers experienced a rapid rise in CD4 after ART initiation followed by a more gradual phase of progressive CD4 reconstitution. Elite controllers had a blunted response to ART without an initial phase of rapid CD4 reconstitution |

* number of elite controllers/total number of participants.
controllers must work with limited data regarding clinical outcomes among elite controllers and the potential impact of ART initiation in this population. The available data suggest that elite controllers experience a uniquely activated immune system that may predispose to long-term complications such as cardiovascular disease. Observational data on clinical outcomes are mixed, but the largest study to date also suggests a heightened risk of clinically relevant cardiovascular disease among elite controllers as compared to other PLWH who are well controlled on ART. Clinical data on the impact of ART among elite controllers do not exist, but laboratory markers of inflammation, immune activation and HIV burden improved after initiation of ART in elite controllers across multiple studies. Furthermore, the blunted CD4+ T cell reconstitution that has been described after ART initiation among elite controllers suggests that delaying initiation of therapy until CD4+ T cell decline has occurred may be detrimental. In order to provide the best possible care to elite controllers, we must learn how to mitigate the adverse effects associated with chronic inflammation and immune activation while preserving the otherwise beneficial effects of elite controllers. Clinicians must consider the potential benefits of ART when deciding whether to initiate treatment in asymptomatic elite controllers.

Disclaimer
The views expressed are those of the authors and should not be construed to represent the positions of the US Army or the Department of Defense.

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