Title

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Journal

Current Treatment Options in Infectious Diseases, 10(2)

ISSN

1523-3820

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Publication Date

2018-06-01

DOI

10.1007/s40506-018-0158-8

Peer reviewed

HHS Public Access

Author manuscript

Curr Treat Options Infect Dis. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Curr Treat Options Infect Dis. 2018 June ; 10(2): 302–309. doi:10.1007/s40506-018-0158-8.

Current Treatment Options for HIV Elite Controllers: a Review

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Abstract

Opinion statement—Initiating antiretroviral therapy (ART) in human immunodeficiency virus (HIV) elite controllers remains controversial, because current evidence does not definitively demonstrate that the benefits of ART outweigh risk in this patient population. However, it is the opinion of the authors that in developed countries, where first-line ART regimens have minimal toxicities, treatment of elite controllers should be strongly considered. Treatment of elite controllers has the potential to minimize the size of the HIV reservoir, which benefits elite controllers who choose to pursue future cure, dampen immune activation, diminish risk of transmission, and encourage linkage and engagement in care allowing HIV providers the opportunity to address HIV-associated non-AIDS conditions and other co-morbidities.

Purpose of review—This review aims to summarize literature relevant to the management of elite controllers for clinicians caring for patients living with HIV. Key topics include timing of antiretroviral therapy (ART) and ART in the unique populations of elite controllers with concomitant cardiovascular disease and hepatitis C co-infection, and undergoing immunosuppressive therapy for other co-morbidities.

Recent findings—The persistent HIV reservoir in elite controllers has two main implications. First, increased immune activation appears to adversely impact clinical outcomes in elite controllers, but the role of ART in addressing this effect remains unclear. Second, elite control duration can be limited, but certain factors may help to predict disease progression with implications on timing of ART.

Summary—Initiation of ART during elite control remains controversial, although there are multiple theoretical benefits. Elite controllers comprise a heterogeneous population of patients living with HIV, and optimal management involves weighing the risk and benefit of ART as well as monitoring of clinical consequences of increased immune activation.

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Conflict of Interest

Dr. Katherine Promer declares that she has no conflicts of interest.

Dr. Maile Y Karris has served as an advisory board memory for Gilead Sciences and receives research funding to the institution from Gilead Sciences.

This article is part of the Topical Collection on *HIV Medicine*

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Elite controllers; HIV; Antiretroviral therapy; Treatment options; Cardiovascular disease; Hepatitis C; Immunosuppression

Introduction

In the last decade, the strategy for timing of initiation of ART for the treatment of HIV has shifted from a cutoff $CD4^+$ T cell count to immediate initiation. This shift occurred as a result of better-tolerated ART options and from findings in multiple randomized clinical trials. The Strategic Timing of Antiretroviral Treatment (START) trial demonstrated that patients who start ART with $CD4^+$ T cell counts above 500 cells/μL experience lower rates of serious AIDS-related and non-AIDS-related events than patients who wait for a $CD4^+$ count decline to 350 [1•]. In the Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO) trial, patients who received immediate initiation of ART suffered lower rates of severe illness in comparison to those who waited for a decline in $CD4^+$ count to less than 500 cells/μL [2•]. From a public health perspective, early initiation of ART also diminishes HIV transmission in sero-discordant couples by 96% in the HIV Prevention Trials Network (HPTN) 052 Trial [3].

The most beneficial course of action becomes less clear for those who spontaneously control HIV viral load below the limit of detection for long periods of time in the absence of ART, a group known as “elite controllers.” Generally regarded as rare, estimated prevalence ranges from 0.15 to 1.5% of all patients living with HIV (PLWH) [4, 5, 6••, 7••]. Cutoffs for viral load and time period of follow-up differ between various definitions of elite control, which contributes to the range of prevalence among these studies. However, most experts agree that the definition for elite control is demonstration of multiple consecutive undetectable viral loads for at least 6 months or undetectable viral loads on at least 90% of measurements over 10 years [8]. The classification “viremic controller” is similar but allows a higher RNA cutoff of 2000 copies/mL [9, 10, 11••]. The term “long-term non-progressor” refers to immunologic control with a nadir $CD4^+$ T cell count of at least 500 cells/μL over more than 8 years [4]. “Chronic progressors,” also referred to as “non-controllers,” do not fulfill any of the above definitions of spontaneous control.

Mechanism of elite control

Efforts to discover additional options for the treatment and cure of HIV have revealed some of the complex facets of the mechanism of elite control. One hypothesis has been that viral strains infecting elite controllers are defective and incapable of replication. Host factors also play a role in elite control and are likely more important than virologic fitness [12]. For example, elite controllers exhibit epigenetic modifications with a higher degree of 5′ long terminal repeat methylation than medical controllers, leading to silencing of HIV promoters and limitation of active replication [13]. Several genetic alleles also occur in greater frequency in elite controllers, including HLA-B57*01, HLA-B27-*05, and HLA-C2 [14, 15]. These rare HLA types drive additional HIV evolution and help to overcome the HIV escape variant defense mechanism by leading to selection of variants with diminished

replication capacity [16]. In ex vivo studies, $CD8^+$ T cells from elite controllers showed more sustained polyfunctionality, as measured by CD107a, IFN-γ, and MIP-1β, than $CD8^+$ T cells from chronic progressors which had a higher tendency to undergo apoptosis [17]. This implies that elite controllers have a more robust and sustained cytotoxic T cell response to HIV infection. A stronger rectal mucosal gag-specific $CD8^+$ T cell response for IFN-γ, MIP-1β, CD107a, and TNF-α compared to medical controllers on ART appears to play a role in elite control as well [18]. A study on gut microbiota diversity found elite controllers more resembled the healthy HIV-negative control group than viremic patients on short-term ART, further suggesting a distinction in mucosal immunity compared to non-controllers [19]. The unique cytotoxic T cell responses (both peripheral and mucosal) often described in this population may in part be due to other unique aspects of the adaptive immune system. A study on dendritic cells of elite controllers demonstrated enhanced type 1 interferon secretion response to HIV-1 leading to enhanced induction of HIV-1 specific $CD8^+$ T cells [20]. Lastly, the innate immune system of elite controllers may also contribute to their unique phenotype. A study on expression of NK cell receptors found that elite controllers demonstrate impaired NKp44 inducibility in the elimination of infected and uninfected $CD4^+$ T cells, which could result in dampening of $CD4^+$ T cell depletion [21]. Together, these studies reflect the complexity behind the underlying mechanism for elite control and highlight the heterogeneity of this population.

Characteristics of elite controllers

By definition, elite controllers maintain undetectable HIV viral load in routine assays, but persistent HIV reservoirs provide potential for disease progression and role of ART. Sequencing of *gag* clones in elite controllers has revealed significant evolution in plasma virus but not in proviral clones, suggesting ongoing replication without reseeding of the latent reservoir [22]. Levels of several inflammatory markers including soluble CD14, IFN-γ, IFN-γ-inducible protein-10, IL-4, IL-10, soluble CD40L, and granulocyte-macrophage colony-stimulating factor are twice as high in elite controllers compared with those of medical controllers and HIV-negative persons [23]. Elite controllers exhibit abnormally high T cell activation levels, which may contribute to progressive $CD4^+$ T cell loss even in the absence of measurable viremia [24]. ART in elite controllers decreases the number of $CD4^+$ T cells carrying replication-competent HIV (i.e., the HIV reservoir), which rebounds following ART cessation [25]. This is important because potential for HIV cure will likely depend on the size of the HIV reservoir [26]. Moreover, abnormally high $CD8^+$ T cell activation in elite controllers may contribute to ongoing $CD4^+$ T cell depletion [24]. ART initiation in elite controllers decreases $CD8^+$ T cell activation [27] and increases $CD4^+$ T cell count, albeit to a lesser degree compared to chronic progressors [28, 29]. Elite controllers do represent a diverse group of individuals with varying rates of $CD4^+$ T cell decline, so identifying factors associated with more rapid HIV progression helps to determine prognosis. Based on longitudinal observational data from a cohort of elite and viremic controllers, variables associated with higher risk of disease progression include shorter length of follow-up, sexual mode of transmission (both homosexual and heterosexual), and hepatitis C co-infection [7••]. Moreover, HLA*B57 and IFNL-4 related genotypes correlate with a lower risk of $CD4^+$ T cell decline [30•]. Thus, multiple variables contribute to

determining prognosis and ideal timing of ART initiation in the management of elite controllers.

Clinical outcomes

The clinical consequences of increased immune activation of elite controllers remain unclear, but multiple studies have evaluated major end points such as mortality, hospital admissions, and AIDS-defining events in this population. A retrospective cohort study by the HIV Research Network demonstrated higher all-cause, cardiovascular, and psychiatric admissions in elite controllers compared to medical controllers. Study design, however, is important to consider in the interpretation of these results as only patients actively engaged in care enrolled in the study, suggesting a possible bias in choosing elite controllers with medical co-morbidities that have more incentive to engage in care [6••]. Of note, the elite controller group did have a higher proportion of cigarette use and there was a lack of information on additional confounders of cardiovascular disease (CVD) [31]. Several factors contribute to the development of CVD in PLWH. Rates of myocardial infarction as well as traditional CVD risk factors such as hypertension, hyperlipidemia, and diabetes are often higher in PLWH patients than those in HIV-negative patients [32]. Furthermore, cross-sectional surveys demonstrate that HIV-infected adults are more likely to smoke cigarettes and less likely to quit than the general population [33]. HIV itself is thought of as an independent risk factor for the development of atherosclerosis [34] with participants in the Observation Study of the Consequences of Protease Inhibitor Era (SCOPE) cohort demonstrating a strong association between HIV sero-status and carotid intima-media thickness irrespective of viral load, $CD4^+$ T cell count, ART, and other confounders of arterial inflammation [35]. Despite viral suppression, elite controllers appear to have similar levels of coronary atherosclerosis to medical controllers, but statistically higher levels than sero-negative individuals [36]. Thus, elite controllers may indeed be at higher risk for CVD; however, it is unknown if ART in elite controllers impacts CVD risk. Of note, an additional study that evaluated low-level viremic HIV controllers found no difference in all-cause and cardiovascular hospitalization rates compared to medical controllers. However, power was insufficient and data on additional cardiovascular confounders, such as tobacco use, was incomplete [11••].

Co-infection with hepatitis C

Hepatitis C is one clinical condition that impacts elite controllers more significantly than medical controllers and may influence decisions about ART. Worldwide, PLWH have an estimated 2.4% prevalence of co-infection with hepatitis C, and this rate increases to 82.4% with associated injection drug use [37]. Given this high overall prevalence, hepatitis C co-infection poses a clinical challenge in the management of HIV elite controllers. Compared to co-infected patients with uncontrolled HIV viremia, elite controllers and medically controlled patients with co-infection have less associated liver fibrosis [38]. However, co-infected elite controllers and medical controllers do demonstrate differences in immune activation. For example, HIV/HCV co-infection is associated with lower $CD4^+$ and $CD8^+$ T cells [39] and increased $CD8^+$ T cell apoptosis [38] in elite controllers compared to medical controllers. These differences do not translate to a loss in elite controller status, but co-

infected patients were 4.78 times as likely to develop complications such as cancer, cardiovascular disease, organ failure, and cirrhosis than elite controllers without hepatitis C [40]. An additional cohort study demonstrated co-infection to be the main factor associated with both hepatic and extra-hepatic non-AIDS-defining events in elite controllers [41••]. These studies suggest a complex response to HIV and hepatitis C co-infection and highlight the importance in curative treatment of hepatitis C to minimize complications in this patient population but do not provide definitive evidence that ART would benefit elite controllers with hepatitis C.

Immunosuppression

The need for immunosuppressive therapy is another situation that influences decisions around ART in elite controllers. The prevalence of elite controllers who undergo immunosuppressive therapy for cancer, autoimmune conditions, or transplantation is very low; research is limited to case reports. In one report, an elite controller who previously had a short trial of ART underwent chemotherapy with cyclophosphamide, vincristine, prednisone, rituximab, and plasmapharesis for treatment of Waldenstrom's macroglobulinemia. At follow-up 1 year later, viral load remained undetectable and $CD4^+$ T cell count stable [42]. In a second case report, an elite controller refused ART both before and after kidney transplant. On follow-up, the HIV viral load became detectable but then rapidly declined; simultaneously, his $CD4^+$ T cell count transiently fell in the immediate post-transplant period but subsequently recovered [43]. In a third case report, an ART-naive elite controller underwent autologous stem cell transplant with melphalan. By post-transplant day 13, HIV viral load had reached 28,000 copies but subsequently became undetectable by day 37 without use of ART. Given the timing of onset and resolution of viremia, the cytotoxic effect of $CD8^+$ T cells on productively infected $CD4^+$ T cells likely played a major role [44]. These case reports illustrate examples of recovery of elite control after an intense period of immunosuppression without the use of ART, but further research will be needed to determine if there is a role for ART in elite controllers undergoing immunosuppression.

Future directions

In elite controller patients, the long-term clinical consequences of increased immune activation remain unclear at this time. Additional clinical trials comparing immediate initiation of ART to watchful waiting would potentially help determine optimal timing of therapy. Special attention to confounding factors for CVD would additionally determine the significance of prior study findings attributing increased risk in elite controllers. However, obtaining a sufficient number of study participants would be a potential barrier to completion of these studies. Although there are no current clinical trials assessing ideal timing of ART, one ongoing trial is focusing on the effect of aspirin and statins on immune and clotting systems in elite and medical controllers, with enrollment expected to end in 2019 [45••]. Such investigations will help to determine the role of pharmacologic therapy beyond ART in management of elite controllers.

Conclusions

Improved clinical outcomes with initiation of ART at higher $CD4^+$ T cell counts and the impact of ART on HIV transmission have resulted in current guidelines recommending immediate ART initiation [46•, 47•]. The Department of Health and Human Services (DHHS) guidelines note the insufficient number of elite controllers in clinical trials prevents an adequate comparison of the risks and benefits of ART in this population, but note that ART should not be delayed in an effort to see if a patient is an elite controller [46•]. For those who were identified before the change in guidelines or those who qualify as elite controllers after delay in treatment for another reason, one option is to monitor $CD4^+$ T cell count and viral load off ART. The International Antiviral Society USA Panel suggests ART initiation may address increased immune activation but also summarizes ART in this population is controversial [47•]. Given potential for loss of elite control, patients should be regularly monitored for signs of loss of control, which would definitively justify initiation of ART.

Acknowledgments

Funding information

Dr. Katherine Promer is supported by a grant from the National Institutes of Health: T32 AI 007036.

Dr. Maile Y Karris is supported by grants from the National Institutes of Health: R01 AI28803, R21 AI134295, R01 MH110057, and P30 AI035214.

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