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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/mm^3 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

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

Author Year [ref]	Study design	Location	Study population	*n**	Criteria for elite control	ART prescribed	Study endpoint(s)	Key findings
Hsue 2009 [59]	Cross-sectional	San Francisco, USA	UCSF-affiliated clinics in the SCOPE cohort	33/494	HIV RNA <75 copies/mm^3 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. Findings were similar for elite controllers, viraemic PLWH, and PLWH who were well controlled on ART
Pereyra 2012 60]	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/mm^3 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

Table 2. Summary of studies reporting clinical outcomes among elite controllers

Author Year [ref]	Study design	Location, years of conduct	Study population	*n**	Criteria for elite control	ART prescribed	Study endpoint(s)	Key findings
Okulicz 2009 [1]	Cohort	USA 1986–2006	PLWH in the US military healthcare system	25/4,586	≥3 undetectable HIV RNA measurements over ≥12 months in absence of ART	No, elite control data censored at time of ART initiation	Death, AIDS, hospitalisation	Elite controllers had fewer deaths, fewer AIDS-defining events, and a longer time to death and AIDS diagnosis as compared to non-controllers. No difference was seen in proportion of subjects hospitalised in the elite control group as compared to other cohort participants
Lucero 2013 [61]	Cohort	Barcelona, Spain 1996–2011	PLWH with CD4 >500 cells/mm^3 at a university hospital	64/574	Undetectable HIV RNA throughout first year of study in absence of ART	Yes, during usual care	Death, hospitalisation	Risk of non-AIDS-related hospitalisation similar between controllers and non-controllers. ART did not alter risk of non-AIDS hospitalisation for those with nadir CD4 <350 cell/mm^3, but reduced risk for those with higher CD4 nadir. No deaths or hospitalisations were seen among 25 elite controllers who maintained virological suppression for the entire study period
Crowell 2014 [4]	Cohort	USA 2005–2011	PLWH with CD4 >350 cells/mm^3 at 11 HIV care sites in the HIV Research Network	149/23,461	≥3 consecutive undetectable HIV RNA measurements over ≥12 months in absence of ART	No, elite control data censored at time of ART initiation	Hospitalisation	Higher risk of all-cause, cardiovascular, and psychiatric hospitalisations among elite controllers as compared to persons medically controlled with ART

* number of elite controllers/total number of participants.

resulted in 64 participants being categorised as elite controllers. The second definition required undetectable HIV RNA measurements throughout the study period and only 25 participants met this stricter criterion. No deaths or hospitalisations were seen among the 25 elite controllers meeting the stricter criteria. Using the less strict definition of elite control, investigators observed a similar risk of non-AIDS-related hospitalisations between elite controllers and non-controllers. Of note, in this study, elite controllers could be prescribed ART during usual care. ART did not alter the risk of non-AIDS hospitalizsations for those with a nadir CD4+ T cell count <350 cell/mm^3, but ART reduced the risk for those with a higher CD4+ T cell nadir, underscoring the importance of early ART even among elite controllers.

Crowell *et al*. reported rates and reasons for hospitalisation for PLWH at 11 US clinical care sites in the HIV Research Network (HIVRN), including 149 elite controllers [4]. Elite controllers had an increased rate of all-cause hospitalisations as compared to PLWH who were well-controlled with ART, even after adjusting for other factors such as age, race, gender, injection drug use, CD4+ T cell count, hepatitis status and insurance. The adjusted rate of cardiovascular hospitalisations was over three times higher for elite controllers compared to other PLWH treated with ART. Elevated rates of psychiatric hospitalisations were also observed among untreated elite controllers as compared to treated PLWH. Interestingly, non-AIDS-defining infections were the most common reason for hospitalisation overall, but were responsible for only 2.7% of hospitalisations among elite controllers.

The excess risk of non-AIDS events (as compared to HIV-uninfected persons) and all-cause and cardiovascular hospitalisations (as compared to other treated PLWH) are consistent with prior studies showing increased subclinical cardiovascular disease and inflammatory markers among elite controllers. Although clinical data are limited, they suggest that elite controllers may be at heightened risk of illnesses that are not traditionally considered to be HIV-related, including cardiovascular disease. Moreover, because immune activation is likely to be a systemic process, it is possible that the consequences of elevated immune activation in elite controllers could extend beyond the cardiovascular system. This then raises the question of whether 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

Table 3. Summary of studies of ART in elite controllers

Author Year [ref]	Study design	Location	Study population	*n**	Criteria for elite control	ART prescribed	Study endpoint(s)	Key findings
Greenough 1999 [64]	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 [25]	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, CD3, 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 [63]	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 [65]	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, quantitiative 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 [66]	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, CD8, 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 [62]	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.

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 and magnetic resonance imaging for carotid artery disease. The results of this study could inform the use of aspirin and/or atorvastatin as adjunctive therapies in the management of elite controllers to mitigate the risk of cardiovascular disease in this population.

Conclusions

The relative rarity of elite control among PLWH makes the execution of a large, randomised trial of ART with clinical endpoints virtually impossible. Clinicians caring for elite

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 control. 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.

References

1. Okulicz JF, Marconi VC, Landrum ML *et al*. Clinical outcomes of elite controllers, viremic controllers, and long-term nonprogressors in the US Department of Defense HIV natural history study. *J Infect Dis* 2009; **200**: 1714–1723.
2. Grabar S, Selinger-Leneman H, Abgrall S *et al*. Prevalence and comparative characteristics of long-term nonprogressors and HIV controller patients in the French Hospital Database on HIV. *AIDS* 2009; **23**: 1163–1169.
3. Sajadi MM, Constantine NT, Mann DL *et al*. Epidemiologic characteristics and natural history of HIV-1 natural viral suppressors. *J Acquir Immune Defic Syndr* 2009; **50**: 403–408.
4. Crowell TA, Gebo KA, Blankson JN *et al*. Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection. *J Infect Dis* 2014.
5. Okulicz JF, Lambotte O. Epidemiology and clinical characteristics of elite controllers. *Curr Opin HIV AIDS* 2011; **6**: 163–168.
6. Torres RA, Barr M. Impact of combination therapy for HIV infection on inpatient census. *N Engl J Med* 1997; **336**: 1531–1532.
7. Lewden C, May T, Rosenthal E *et al*. Changes in causes of death among adults infected by HIV between 2000 and 2005: The 'Mortalite 2000 and 2005' surveys (ANRS EN19 and Mortavic). *J Acquir Immune Defic Syndr* 2008; **48**: 590–598.
8. Palella FJ, Jr., Baker RK, Moorman AC *et al*. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006; **43**: 27–34.
9. Smit C, Geskus R, Walker S *et al*. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. *AIDS* 2006; **20**: 741–749.
10. Crum NF, Riffenburgh RH, Wegner S *et al*. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006; **41**: 194–200.
11. Smith CJ, Ryom L, Weber R *et al*. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet* 2014; **384**: 241–248.
12. Weber R, Ruppik M, Rickenbach M *et al*. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Med* 2013; **14**: 195–207.
13. Palella FJ, Jr., Delaney KM, Moorman AC *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338**: 853–860.
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services.
15. Williams I, Churchill D, Anderson J *et al*. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). *HIV Med* 2014; **15 Suppl 1**: 1–85.
16. Aberg JA, Gallant JE, Ghanem KG *et al*. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis* 2014; **58**: e1–34.
17. World Health Organization. WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Geneva: World Health Organization; 2013. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/en/ (accessed March 2015).
18. Walker BD. Elite control of HIV infection: implications for vaccines and treatment. *Top HIV Med* 2007; **15**: 134–136.
19. Pereyra F, Jia X, McLaren PJ *et al*. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science* 2010; **330**: 1551–1557.
20. Lambotte O, Boufassa F, Madec Y *et al*. HIV controllers: a homogeneous group of HIV-1-infected patients with spontaneous control of viral replication. *Clin Infect Dis* **2005**; 41: 1053–1056.
21. Hatano H, Delwart EL, Norris PJ *et al*. Evidence for persistent low-level viremia in individuals who control human immunodeficiency virus in the absence of antiretroviral therapy. *J Virol* 2009; **83**: 329–335.
22. Pereyra F, Palmer S, Miura T *et al*. Persistent low-level viremia in HIV-1 elite controllers and relationship to immunologic parameters. *J Infect Dis* 2009; **200**: 984–990.
23. Goujard C, Chaix ML, Lambotte O *et al*. Spontaneous control of viral replication during primary HIV infection: when is 'HIV controller' status established? *Clin Infect Dis* 2009; **49**: 982–986.
24. Bailey JR, Zhang H, Wegweiser BW *et al*. Evolution of HIV-1 in an HLA-B*57-positive patient during virologic escape. *J Infect Dis* 2007; **196**: 50–55.
25. Sedaghat AR, Rastegar DA, O'Connell KA *et al*. T cell dynamics and the response to HAART in a cohort of HIV-1-infected elite suppressors. *Clin Infect Dis* 2009; **49**: 1763–1766.
26. Hunt PW, Brenchley J, Sinclair E *et al*. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis* 2008; **197**: 126–133.
27. Chen A, Shieh E, Brinkley S, Blankson JN. Candida esophagitis in a human immunodeficiency virus-1-positive elite controller with hepatitis C virus cirrhosis. *Open Forum Infectious Diseases* 2014; **1**: ofu111.
28. Pereyra F, Addo MM, Kaufmann DE *et al*. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. *J Infect Dis* 2008; **197**: 563–571.
29. Migueles SA, Sabbaghian MS, Shupert WL *et al*. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. *Proc Natl Acad Sci U S A* 2000; **97**: 2709–2714.
30. Han Y, Lai J, Barditch-Crovo P *et al*. The role of protective HCP5 and HLA-C associated polymorphisms in the control of HIV-1 replication in a subset of elite suppressors. *AIDS* 2008; **22**: 541–544.
31. Saez-Cirion A, Lacabaratz C, Lambotte O *et al*. HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. *Proc Natl Acad Sci U S A* 2007; **104**: 6776–6781.
32. Betts MR, Nason MC, West SM *et al*. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. *Blood* 2006; **107**: 4781–4789.
33. Migueles SA, Osborne CM, Royce C *et al*. Lytic granule loading of CD8+ T cells is required for HIV-infected cell elimination associated with immune control. *Immunity* 2008; **29**: 1009–1021.
34. Martin MP, Qi Y, Gao X *et al*. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. *Nat Genet* 2007; **39**: 733–740.
35. Qi Y, Martin MP, Gao X *et al*. KIR/HLA pleiotropism: protection against both HIV and opportunistic infections. *PLoS Pathog* 2006; **2**: e79.
36. Alter G, Martin MP, Teigen N *et al*. Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes. *J Exp Med* 2007; **204**: 3027–3036.
37. Jiang Y, Chen O, Cui C *et al*. KIR3DS1/L1 and HLA-Bw4-80I are associated with HIV disease progression among HIV typical progressors and long-term nonprogressors. *BMC Infect Dis* 2013; **13**: 405.
38. Boaz MJ, Waters A, Murad S *et al*. Presence of HIV-1 Gag-specific IFN-gamma+IL-2+ and CD28+IL-2+ CD4 T cell responses is associated with nonprogression in HIV-1 infection. *J Immunol* 2002; **169**: 6376–6385.
39. Emu B, Sinclair E, Favre D *et al*. Phenotypic, functional, and kinetic parameters associated with apparent T-cell control of human immunodeficiency virus replication in individuals with and without antiretroviral treatment. *J Virol* 2005; **79**: 14169–14178.
40. Harari A, Petitpierre S, Vallelian F, Pantaleo G. Skewed representation of functionally distinct populations of virus-specific CD4 T cells in HIV-1-infected subjects with progressive disease: changes after antiretroviral therapy. *Blood* 2004; **103**: 966–972.
41. Migueles SA, Laborico AC, Shupert WL *et al*. HIV-specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors. *Nat Immunol* 2002; **3**: 1061–1068.
42. Carriere M, Lacabaratz C, Kok A *et al*. HIV 'elite controllers' are characterized by a high frequency of memory CD8+CD73+ T cells involved in the antigen-specific CD8+ T-cell response. *J Infect Dis* 2013; **209**: 1321–1330.
43. Hunt PW, Landay AL, Sinclair E *et al*. A low T regulatory cell response may contribute to both viral control and generalized immune activation in HIV controllers. *PLoS One* 2011; **6**: e15924.
44. Krishnan S, Wilson EM, Sheikh V *et al*. Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J Infect Dis* 2014; **209**: 931–939.
45. Kelesidis T, Kendall MA, Yang OO *et al*. Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. *J Infect Dis* 2012; **206**: 1558–1567.
46. Sandler NG, Wand H, Roque A *et al*. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* 2011; **203**: 780–790.

47. Hunt PW, Cao HL, Muzoora C *et al*. Impact of CD8+ T-cell activation on CD4+ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy. *AIDS* 2011; **25**: 2123–2131.
48. Kuller LH, Tracy R, Belloso W *et al*. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008; **5**: e203.
49. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007; **92**: 2506–2512.
50. Currier JS, Taylor A, Boyd F *et al*. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003; **33**: 506–512.
51. Bonnet D, Aggoun Y, Szezepanski I *et al*. Arterial stiffness and endothelial dysfunction in HIV-infected children. *AIDS* 2004; **18**: 1037–1041.
52. Kaplan RC, Sinclair E, Landay AL *et al*. T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. *J Infect Dis* 2011; **203**: 452–463.
53. Karim R, Mack WJ, Kono N *et al*. T-cell activation, both pre- and post-HAART levels, correlates with carotid artery stiffness over 6.5 years among HIV-infected women in the WIHS. *J Acquir Immune Defic Syndr* 2014; **67**: 349–356.
54. Oliviero U, Bonadies G, Apuzzi V *et al*. Human immunodeficiency virus per se exerts atherogenic effects. *Atherosclerosis* 2009; **204**: 586–589.
55. Triant VA, Regan S, Lee H *et al*. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. *J Acquir Immune Defic Syndr* 2010; **55**: 615–619.
56. Sabin CA, Worm SW, Weber R *et al*. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; **371**: 1417–1426.
57. Friis-Moller N, Sabin CA, Weber R *et al*. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349**: 1993–2003.
58. Currier JS, Kendall MA, Zackin R *et al*. Carotid artery intima-media thickness and HIV infection: traditional risk factors overshadow impact of protease inhibitor exposure. *AIDS* 2005; **19**: 927–933.
59. Hsue PY, Hunt PW, Schnell A *et al*. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS* 2009; **23**: 1059–1067.
60. Pereyra F, Lo J, Triant VA *et al*. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS* 2012; **26**: 2409–2412.
61. Lucero C, Torres B, Leon A *et al*. Rate and predictors of non-AIDS events in a cohort of HIV-infected patients with a CD4 T cell count above 500 cells/mm$^{(3)}$. *AIDS Res Hum Retroviruses* 2013; **29**: 1161–1167.
62. Boufassa F, Lechenadec J, Meyer L *et al*. Blunted response to combination antiretroviral therapy in HIV elite controllers: an international HIV controller collaboration. *PLoS One* 2014; **9**: e85516.
63. Okulicz JF, Grandits GA, Weintrob AC *et al*. CD4 T cell count reconstitution in HIV controllers after highly active antiretroviral therapy. *Clin Infect Dis* 2010; **50**: 1187–1191.
64. Greenough TC, Sullivan JL, Desrosiers RC. Declining CD4 T-cell counts in a person infected with nef-deleted HIV-1. *N Engl J Med* 1999; **340**: 236–237.
65. Chun TW, Shawn Justement J, Murray D *et al*. Effect of antiretroviral therapy on HIV reservoirs in elite controllers. *J Infect Dis* 2013; **208**: 1443–1447.
66. Hatano H, Yukl SA, Ferre AL *et al*. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. *PLoS Pathog* 2013; **9**: e1003691.
67. Nilsson J, Kinloch-de-Loes S, Granath A *et al*. Early immune activation in gut-associated and peripheral lymphoid tissue during acute HIV infection. *AIDS* 2007; **21**: 565–s574.
68. Anton PA, Elliott J, Poles MA *et al*. Enhanced levels of functional HIV-1 co-receptors on human mucosal T cells demonstrated using intestinal biopsy tissue. *AIDS* 2000; **14**: 1761–1765.
69. Guadalupe M, Reay E, Sankaran S *et al*. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol* 2003; **77**: 11708–11717.
70. Mehandru S, Poles MA, Tenner-Racz K *et al*. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* 2004; **200**: 761–770.
71. Poles MA, Elliott J, Taing P *et al*. A preponderance of CCR5(+) CXCR4(+) mononuclear cells enhances gastrointestinal mucosal susceptibility to human immunodeficiency virus type 1 infection. *J Virol* 2001; **75:** 8390–8399.