Opinion

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Elite control of HIV: is this the right model for a functional cure?

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A cure for HIV is still greatly needed and has become a global research priority. A unique subset of HIV-infected individuals who spontaneously control HIV exists, and these are known as 'elite controllers'. They may represent a natural model for a 'functional cure' in which there is long term control of viral replication and remission from symptoms of HIV infection in the absence of antiretroviral therapy. However, controllers have evidence of ongoing inflammation, CD4$^+$ T cell depletion, and perhaps even inflammation-associated cardiovascular disease, suggesting that this natural long term virologic control may be coming at an immunologic and clinical cost. These individuals may continue to provide continued insights into mechanisms of host control; however, they may not represent the best model of a functional cure, if we believe that a cure should require a disease-free (and not just a treatment-free) state.

HIV cure is a research priority

The use of antiretroviral therapy (ART) has resulted in the marked decline in the morbidity and mortality associated with HIV infection for individuals with access to therapy [1,2]. Many antiretroviral-treated individuals achieve substantial reconstitution of CD4$^+$ T cell counts and near-complete suppression of viral replication. However, despite this achievement, ART is not curative. Interruption of therapy results in the rapid rebound of viral replication in most HIV-infected individuals due to the presence of a long-lived infected cell population that harbors replication-competent virus known as the latent viral reservoir (see Glossary) [3]. Furthermore, even in those individuals who are successfully treated, ART does not fully restore health or normal immune function as HIV-infected individuals still experience increased non-AIDS-related morbidity and mortality compared to HIV-uninfected individuals [4–7]. Lastly, there are still a large number of individuals who do not have access to ART, which contributes to morbidity and subsequent transmission events [8,9]. Therefore, there is a great need for a cure for HIV infection and this has become a global research priority [10].

A cure may be feasible and elite controllers may be a potential model for functional cure

The case of the 'Berlin patient' has provided evidence to suggest that a cure for HIV infection may be possible in some individuals [11]. The Berlin patient is thought to have achieved a 'sterilizing cure' given that no replication-competent virus has been found, despite vigorous study several years after the discontinuation of ART [12,13]. The circumstances which led to this apparent cure were incredibly unique, however, because this patient: (i) was heterozygous for the CCR5 delta-32 (Δ32) deletion at baseline (a genetic factor known to confer a favorable HIV disease course); (ii) received an extensive conditioning regimen that included whole body irradiation to deplete the hematopoietic system; (iii) received two allogeneic bone marrow transplants from a donor who was homozygous for the CCR5 Δ32 deletion; (iv) exhibited graft-versus-host disease (and perhaps as a consequence 'graft-versus-HIV-reservoir responses'); and (v) received immune-modulating therapies after transplant. It is unclear whether one, or all, of these factors was necessary to achieve a sterilizing cure. Furthermore, many of the interventions in this unique case have substantial risks associated with them, making this scenario difficult to replicate in a wider population. A sterilizing cure, therefore, is likely to be more difficult to achieve and may not be possible for most HIV-infected individuals.

There exists a population of HIV-infected individuals who spontaneously control their virus, termed 'HIV controllers'. This group may represent a natural model for a 'functional cure' in which there is long term control of viral replication and remission from symptoms of HIV infection in the absence of ART. It is likely that a functional cure will be more feasible than a sterilizing cure. Understanding the

Glossary

Elite controller: a subset of HIV-infected individuals who maintain plasma viral loads to levels below the limits of clinical detection (<50–75 copies/ml) in the absence of anti-retroviral therapy.
Functional cure: long term host control of viral replication and remission from symptoms of HIV-infection in the absence of ART, but replication-competent HIV remains detectable.
Latent viral reservoir: an HIV-infected cell population that harbors integrated, replication-competent HIV virus.
Long term nonprogressors (LTNPs): individuals with long term clinical and immunologic stability, usually over a period of several years, in the absence of ART. These individuals may or may not have a low HIV plasma viral load as there is usually no viral load requirement in this definition.
Sterilizing cure: complete eradication of replication-competent HIV from the body.

biologic mechanisms of HIV control is an area of intense research focus as it may inform future therapeutic strategies.

Defining elite control

HIV controllers are HIV-infected individuals who, in the absence of therapy, are able to maintain low levels of plasma HIV RNA. They are often distinct from 'long term nonprogressors' (LTNPs) who are generally defined as untreated individuals who have long term clinical and immunologic stability over a period of several years, without a viral load requirement. The term 'elite controllers' usually refers to the subset of controllers who maintain plasma viremia to levels below the limits of clinical detection (<50–75 copies/ml). This a rare group, comprising <1% of the HIV-infected population [14]. There is an over-representation of certain MHC class 1 alleles in elite controllers, including class I HLA-B*57 and HLA-B*27 alleles [15–17]. Enrichment of specific natural killer (NK) cell immunoglobulin-like receptors (KIR) has also been seen in one study of LTNPs [18], although this finding was not seen in a small cohort of elite controllers [19]. These data argue that sustained host immune responses are a mechanism by which virus is controlled in these individuals. However, not all HIV controllers possess these protective alleles, and some individuals with favorable genetics have normal progression of disease, suggesting that these genetic factors are neither necessary nor sufficient for immune control [20]. Thus, elite controllers are likely a heterogeneous group with multiple potential mechanisms of control and this group of individuals provides a unique opportunity to better understand viral persistence and host control.

Potential mechanisms of viral control

The precise mechanism of viral control in elite controllers is unknown and may be multifactorial with different factors playing a role in different individuals [21]. Host genetics and how they shape the response of the different arms of the immune system: adaptive, innate, and intrinsic, are all possible areas in which elite controllers may have unique ways to maintain control of viral replication (Figure 1).

One potential mechanism of control is the $CD8^+$ T cell response. The presence of specific MHC class 1 alleles has been one of the most consistent factors associated with host control. It may be that $CD8^+$ cytotoxic T lymphocytes (CTLs) restricted by the class I molecules such as HLA-B*57 and HLA-B*27 are more potent and polyfunctional [22–24]. Previous studies have found that although the frequency of HIV specific $CD8^+$ CTLs is not elevated in elite controllers [25], their CTLs seem to produce more cytolytic proteins, such as perforin and granzyme B, [23,26] and more pro-inflammatory cytokines, including interleukin (IL-2) and interferon-gamma (IFN-γ) [24]. However, a strong CTL response is unlikely to be the only factor leading to viral control, as elite controllers have been shown to maintain viral suppression even in the setting of viral escape mutations [27].

The role of antibodies in achieving viral suppression in elite controllers is unclear. Several studies have shown that the levels of neutralizing antibodies (antibodies that bind to the HIV envelope and block viral entry into target cells) are either similar or lower in elite controllers compared to viremic individuals [28,29]. However, antibodies could also contribute to viral control via antibody-dependent cell-mediated cytotoxicity (ADCC). In ADCC, cells coated with antibodies are destroyed by NK cells. It is unclear, however, whether elite controllers have increased ADCC activity, as studies have had conflicting results [28,30].

Another mechanism by which elite controllers may achieve viral suppression is via the innate immune system. HLA class 1 molecules can also bind to KIRs that are expressed by NK cells. HLA-B*57 is a Bw4 allele, which is a natural ligand for several KIRs including KIR3DS1 and KIR3DL1, and this combination has been associated with delayed progression to AIDS in noncontrollers [31,32]. It is possible that this relationship is explained by linkage disequilibrium with HLA-B alleles, but a previous study found that these KIRs were enriched in a population of LTNPs who did not possess the HLA-B*57 allele [18]. NK cells expressing the KIR3DS1 allele strongly inhibit HIV replication in target cells *in vitro* and may be a mechanism of elite control apart from its association with HLA-B alleles [33]. Further studies are needed to better understand the contribution of KIRs to viral control in elite controllers.

The intrinsic immune system may also play a role in the control of HIV in elite controllers. Cell-intrinsic mechanisms, such as restriction factors, can limit HIV's ability to replicate in target cells and could theoretically lead to control of plasma viremia. However, one study which looked at one of the most well-characterized restriction factors, APOBEC3G, did not find a higher frequency of hypermutated proviral genomes in elite controllers compared to ART-treated individuals, suggesting that enhanced APOBEC activity alone could not account for the control of viral replication in elite controllers [34]. Another recent study examined 34 anti-HIV host restriction factors and did not find an increase in the overall expression of restriction factors in elite controllers [35]. However, a single factor, schlafen 11, was expressed at a significantly higher level in $CD4^+$ T cells from elite controllers compared to both untreated and ART suppressed subjects. It may be that the expression of specific host restriction factors, rather than the overall frequency of expression, is important for viral control. Additional examination of restriction factors could lead to the development of curative strategies.

Translating mechanisms of viral control to cure research

There are potentially several factors that allow elite controllers to maintain undetectable viral loads and that may be relevant for cure research. These factors include $CD8^+$ CTL responses, KIRs, and intrinsic restriction factors. Eliciting strong CTL responses will likely be a part of future cure strategies. Recent cure efforts have focused on reactivation strategies; however, a recent study found that reactivation alone in the presence of autologous $CD8^+$ T cells did not result in effective killing [36]. Prestimulation of $CD8^+$ T cells or using CTLs from elite controllers
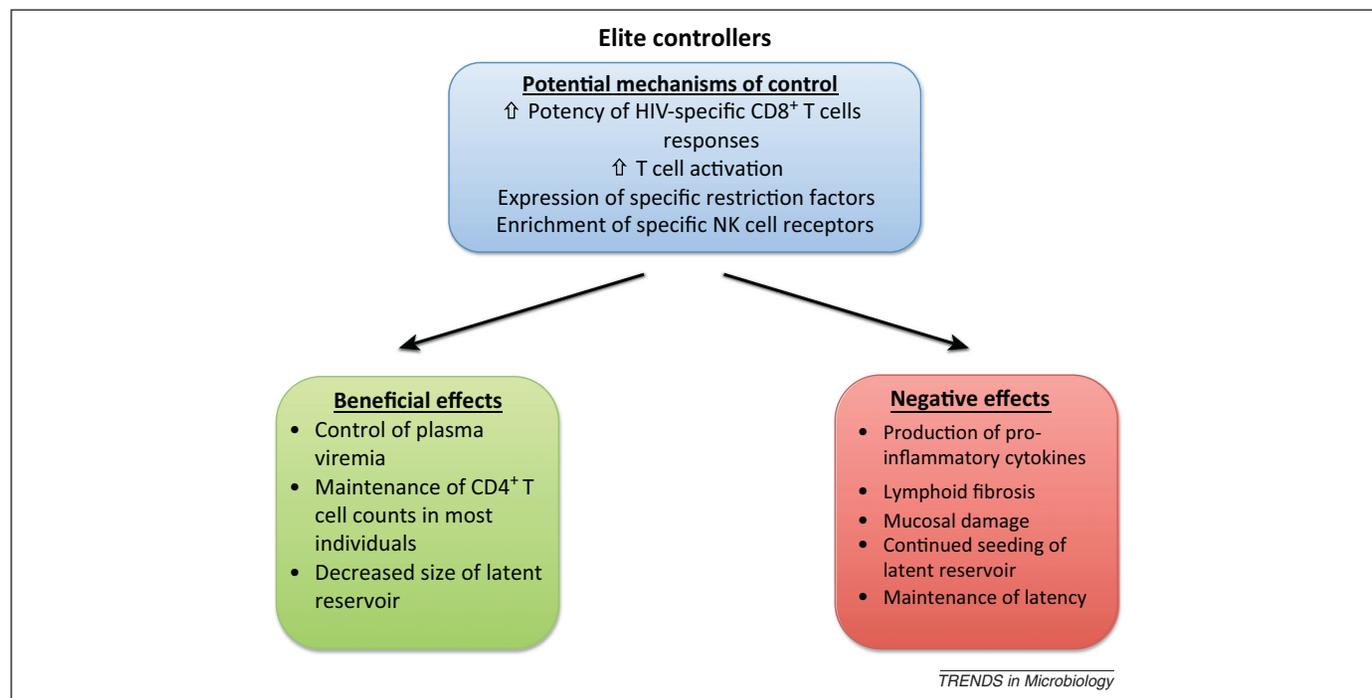
Figure 1. Mechanisms of host viral control may have both beneficial and negative effects for elite controllers. Potential mechanisms of host control of plasma viremia are noted in the blue box. These factors may have beneficial effects for these individuals (green box). However, there may also be immunologic consequences of the immune response that lead to inflammation and viral persistence (red box).

resulted in improved killing. Less is understood about antibodies, KIRs, and restriction factors and further studies will be needed to better understand their role in viral control and potentially apply this to the cure effort.

Elite control but not cure

Although elite controllers have undetectable viremia by standard clinical assays, when using more sensitive assays for RNA detection in the plasma, almost all elite controllers have detectable levels of plasma viremia [37,38] and viral 'blips' of >50 copies/ml occur in controllers [37,39]. Previous studies have detected HIV RNA and DNA in peripheral blood mononuclear cells (PBMCs) [40] and shown that virus from controllers is replication-competent [41,42] and has no substantial genetic defects [43]. Furthermore, there is evidence of ongoing viral replication in HIV controllers based on the presence of genetic viral divergence over time [44,45]. Elite controllers also have detectable levels of HIV RNA and DNA in rectal cells [46], although levels are lower than HIV-infected individuals on ART. Therefore, it seems clear that even though elite controllers maintain low levels of plasma RNA, HIV virus is easily detectable in most controllers and is likely to be replication-competent.

Ongoing viral replication and immune control may have consequences

There is growing evidence to suggest that ongoing viral replication, even at low levels, may have detrimental immunologic consequences. Markers of T cell activation (CD4$^+$ and CD8$^+$ T cells co-expressing HLA-DR and CD38), inflammation and coagulation (e.g., interleukin-6 and D-dimer) and microbial translocation (e.g., soluble CD-14) have all been associated with increased morbidity and mortality in HIV infection [47–50]. Although elite controllers maintain

viral loads under the limit of detection, they too have elevated levels of CD4$^+$ T cell activation compared to HIV-uninfected individuals and higher CD8$^+$ T cell activation compared to both HIV-uninfected as well as HIV-infected persons with viral suppression on ART [51,52]. One study also found that elite controllers had significantly higher levels of D-dimer and soluble tissue factor, compared to both HIV-negative controls and ART-suppressed HIV-infected individuals [53]. Elevated levels of soluble CD163 have also been observed in elite controllers [54]. They also have increased levels of lymphoid tissue fibrosis compared to people uninfected with HIV [55]. It is possible that continued exposure to virus, albeit at low levels, results in the production of inflammatory cytokines, elevated levels of T cell activation and coagulation factors, and ongoing damage to areas such as the mucosal surfaces of the gastrointestinal (GI) tract, vascular endothelium and lymphoid tissue.

This increased immune activation and inflammation may affect clinical outcomes as well. Despite the lack of detectable viremia by clinical assays and the lack of exposure to ART which, theoretically, could have cardiovascular side effects, elite controllers have higher levels of coronary atherosclerosis, as measured by carotid artery intima media thickness (IMT) and coronary computed tomography angiography (CTA), compared to HIV-uninfected individuals [54,56]. Although further studies are needed, these data suggest that the increased inflammation in controllers may have clinically relevant consequences and contribute to nonAIDS morbidity and mortality. Lastly, a small proportion of HIV controllers progress immunologically despite maintaining low plasma RNA levels, and this decline in CD4$^+$ T cell count is associated with T cell activation [51]. This observation raises the possibility that, even in the absence of measurable plasma viremia, a mechanistic link

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may exist between chronic inflammation and progressive immunodeficiency.

Elite controllers may benefit from ART

Given the concern that even very low levels of viral replication may lead to disproportionately high levels of immune activation and inflammation (which, in turn, may lead to an increased risk of AIDS and nonAIDS defining events), a prospective study of ART initiation was recently conducted in a cohort of asymptomatic HIV-infected controllers, including four elite controllers [57]. Participants were treated with an antiretroviral regimen of raltegravir and tenofovir/emtricitabine for 24 weeks and underwent blood collection and, in some instances, colorectal biopsies. Despite having low plasma HIV RNA levels at baseline before starting ART, controllers had an early and persistent decrease in ultrasensitive plasma HIV RNA levels and HIV antibodies levels. Controllers also had a significant decrease in the percentage of CD4+ and CD8+ T cells co-expressing HLA-DR and CD38 as well as programmed death-1 (PD-1) in PBMCs. In the rectum, controllers had a decrease in CD8+ T cell activation. This study showed that antiretroviral therapy in controllers leads to significant decreases in ultrasensitive plasma and rectal HIV RNA, as well as markers of immune activation/dysfunction in blood and gut.

Even in the subset of the four elite controllers, a significant decrease in ultrasensitive plasma HIV RNA levels was seen after the initiation of ART [57]. Similarly, this subset of controllers had a decrease in HIV antibody levels. There was also a trend toward decreased levels of immune activation in CD8+ T cells in these four elite controllers. These data suggest that, even in the subset of elite controllers who maintain undetectable HIV viral loads, HIV replication persists and contributes to a chronic inflammatory state.

Another recent study treating three elite controllers and one viremic controller with the same antiretroviral regimen for 9 months found >1 log decrease in the frequency of CD4+ T cells carrying replication-competent HIV in three out of four subjects after the initiation of ART [58]. Interestingly, after the discontinuation of therapy, levels rebounded back to their pre-ART baseline.

Collectively, these studies provide further support that elite controllers harbor replication-competent virus and that residual viral replication is occurring in the absence of ART, despite undetectable plasma RNA levels. The data also suggest host rather than virologic factors account for the remarkable degree of viral control in these unique individuals. Furthermore, the decrease in markers of immune activation with the addition of ART suggests that there may be immunologic consequences to even very low levels of viral replication (Figure 1). It is still unclear, however, whether the initiation of ART in elite controllers would provide clinical benefits that outweigh any adverse effects associated with antiretroviral drugs. A larger study examining the effect of ART on immunologic and virologic parameters in controllers is currently underway.

Concluding remarks

Elite controllers are a rare group of individuals who control viral replication in the absence of ART and are thought to

Box 1. Outstanding questions
- What mechanism(s) allow elite controllers to maintain undetectable HIV viral loads?
- Can these mechanisms of virologic control be induced in noncontrollers and result in a functional cure?
- What are the immunologic consequences of host viral control?
- Would elite controllers benefit from antiretroviral therapy?

potentially represent a model for a functional cure. Recent studies of these individuals have shown that a complete block of viral replication is not necessary to achieve long term virologic control. However, the evidence also suggests that the immune responses that allow elite controllers to limit viral replication may also result in increased inflammation and immune activation, leading potentially to negative clinical consequences (Figure 1). In other words, this natural long term virologic control appears to be coming at an immunologic and/or clinical cost. This is not to say that further study of controllers is unwarranted. Additional study of these individuals may provide continued insights into mechanisms of host control that could inform future therapeutics (Box 1). Understanding why some mechanisms of viral control are associated with negative inflammatory consequences is also an important issue. It may be, however, that untreated HIV-infected controllers may not represent the best model of a functional cure, if we believe that a cure should require a disease-free (and not just a treatment-free) state.

References
1 Palella, F.J., Jr *et al.* (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N. Engl. J. Med.* 338, 853–860
2 Lohse, N. *et al.* (2007) Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann. Intern. Med.* 146, 87–95
3 Chun, T.W. *et al.* (1997) Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature* 387, 183–188
4 Phillips, A.N. *et al.* (2008) The role of HIV in serious diseases other than AIDS. *AIDS* 22, 2409–2418
5 Currier, J.S. *et al.* (2008) Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation* 118, e29–e35
6 Choi, A.I. *et al.* (2009) HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy. *AIDS* 23, 2143–2149
7 Triant, V.A. *et al.* (2008) Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J. Clin. Endocrinol. Metab.* 93, 3499–3504
8 Gardner, E.M. *et al.* (2011) The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin. Infect. Dis.* 52, 793–800
9 Piot, P. and Quinn, T.C. (2013) Response to the AIDS pandemic – a global health model. *N. Engl. J. Med.* 368, 2210–2218
10 Deeks, S.G. *et al.* (2012) Towards an HIV cure: a global scientific strategy. *Nat. Rev. Immunol.* 12, 607–614
11 Hutter, G. *et al.* (2009) Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.* 360, 692–698
12 Allers, K. *et al.* (2011) Evidence for the cure of HIV infection by CCR5Delta32/Delta32 stem cell transplantation. *Blood* 117, 2791–2799
13 Yukl, S.A. *et al.* (2013) Challenges in detecting HIV persistence during potentially curative interventions: a study of the Berlin Patient. *PLoS Pathog.* 9, e1003347
14 Okulicz, J.F. and Lambotte, O. (2011) Epidemiology and clinical characteristics of elite controllers. *Curr. Opin. HIV AIDS* 6, 163–168
15 Pereyra, F. *et al.* (2010) The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science* 330, 1551–1557

16 Migueles, S.A. *et al.* (2000) 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.* 97, 2709–2714

17 Dean, M. *et al.* (1996) Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the *CKR5* structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* 273, 1856–1862

18 Jiang, Y. *et al.* (2013) KIR3DS1/L1 and HLA-Bw4-80I are associated with HIV disease progression among HIV typical progressors and long-term nonprogressors. *BMC Infect. Dis.* 13, 405

19 O'Connell, K.A. *et al.* (2009) Role of natural killer cells in a cohort of elite suppressors: low frequency of the protective KIR3DS1 allele and limited inhibition of human immunodeficiency virus type 1 replication *in vitro*. *J. Virol.* 83, 5028–5034

20 Emu, B. *et al.* (2008) HLA class I-restricted T-cell responses may contribute to the control of human immunodeficiency virus infection, but such responses are not always necessary for long-term virus control. *J. Virol.* 82, 5398–5407

21 Walker, B.D. and Yu, X.G. (2013) Unravelling the mechanisms of durable control of HIV-1. *Nat. Rev. Immunol.* 13, 487–498

22 Saez-Cirion, A. *et al.* (2007) 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.* 104, 6776–6781

23 Migueles, S.A. *et al.* (2008) Lytic granule loading of CD8+ T cells is required for HIV-infected cell elimination associated with immune control. *Immunity* 29, 1009–1021

24 Betts, M.R. *et al.* (2006) HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. *Blood* 107, 4781–4789

25 Hersperger, A.R. *et al.* (2011) Qualitative features of the HIV-specific CD8+ T-cell response associated with immunologic control. *Curr. Opin. HIV AIDS* 6, 169–173

26 Hersperger, A.R. *et al.* (2010) Perforin expression directly *ex vivo* by HIV-specific CD8 T-cells is a correlate of HIV elite control. *PLoS Pathog.* 6, e1000917

27 Bailey, J.R. *et al.* (2006) Maintenance of viral suppression in HIV-1-infected HLA-B*57+ elite suppressors despite CTL escape mutations. *J. Exp. Med.* 203, 1357–1369

28 Lambotte, O. *et al.* (2009) Heterogeneous neutralizing antibody and antibody-dependent cell cytotoxicity responses in HIV-1 elite controllers. *AIDS* 23, 897–906

29 Doria-Rose, N.A. *et al.* (2010) Breadth of human immunodeficiency virus-specific neutralizing activity in sera: clustering analysis and association with clinical variables. *J. Virol.* 84, 1631–1636

30 Smalls-Mantey, A. *et al.* (2012) Antibody-dependent cellular cytotoxicity against primary HIV-infected CD4+ T cells is directly associated with the magnitude of surface IgG binding. *J. Virol.* 86, 8672–8680

31 Martin, M.P. *et al.* (2007) Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. *Nat. Genet.* 39, 733–740

32 Qi, Y. *et al.* (2006) KIR/HLA pleiotropism: protection against both HIV and opportunistic infections. *PLoS Pathog.* 2, e79

33 Alter, G. *et al.* (2007) Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes. *J. Exp. Med.* 204, 3027–3036

34 Gandhi, S.K. *et al.* (2008) Role of APOBEC3G/F-mediated hypermutation in the control of human immunodeficiency virus type 1 in elite suppressors. *J. Virol.* 82, 3125–3130

35 Abdel-Mohsen, M. *et al.* (2013) Expression profile of host restriction factors in HIV-1 elite controllers. *Retrovirology* 10, 106

36 Shan, L. *et al.* (2012) Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. *Immunity* 36, 491–501

37 Pereyra, F. *et al.* (2009) Persistent low-level viremia in HIV-1 elite controllers and relationship to immunologic parameters. *J. Infect. Dis.* 200, 984–990

38 Hatano, H. *et al.* (2010) Evidence of persistent low-level viremia in long-term HAART-suppressed, HIV-infected individuals. *AIDS* 24, 2535–2539

39 Pereyra, F. *et al.* (2008) Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. *J. Infect. Dis.* 197, 563–571

40 Hatano, H. *et al.* (2009) Evidence for persistent low-level viremia in individuals who control human immunodeficiency virus in the absence of antiretroviral therapy. *J. Virol.* 83, 329–335

41 Blankson, J.N. *et al.* (2007) Isolation and characterization of replication-competent human immunodeficiency virus type 1 from a subset of elite suppressors. *J. Virol.* 81, 2508–2518

42 Lamine, A. *et al.* (2007) Replication-competent HIV strains infect HIV controllers despite undetectable viremia (ANRS EP36 study). *AIDS* 21, 1043–1045

43 Miura, T. *et al.* (2008) Genetic characterization of human immunodeficiency virus type 1 in elite controllers: lack of gross genetic defects or common amino acid changes. *J. Virol.* 82, 8422–8430

44 Mens, H. *et al.* (2010) HIV-1 continues to replicate and evolve in patients with natural control of HIV infection. *J. Virol.* 84, 12971–12981

45 O'Connell, K.A. *et al.* (2010) Control of HIV-1 in elite suppressors despite ongoing replication and evolution in plasma virus. *J. Virol.* 84, 7018–7028

46 Hatano, H. *et al.* (2013) Comparison of HIV DNA and RNA in gut-associated lymphoid tissue of HIV-infected controllers and noncontrollers. *AIDS* 27, 2255–2260

47 Kelesidis, T. *et al.* (2012) Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. *J. Infect. Dis.* 206, 1558–1567

48 Sandler, N.G. *et al.* (2011) Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J. Infect. Dis.* 203, 780–790

49 Hunt, P.W. *et al.* (2011) Impact of CD8+ T-cell activation on CD4+ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy. *AIDS* 25, 2123–2131

50 Kuller, L.H. *et al.* (2008) Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med.* 5, e203

51 Hunt, P.W. *et al.* (2008) 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.* 197, 126–133

52 Hunt, P.W. *et al.* (2011) A low T regulatory cell response may contribute to both viral control and generalized immune activation in HIV controllers. *PLoS ONE* 6, e15924

53 Krishnan, S. *et al.* (2014) Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J. Infect. Dis.* 209, 931–939

54 Pereyra, F. *et al.* (2012) Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS* 26, 2409–2412

55 Sanchez, J.L. *et al.* (2014) Lymphoid fibrosis occurs in long-term nonprogressors and persists with antiretroviral therapy, but may be reversible with curative interventions. *J. Infect. Dis.* Published online October 24, 2014. (http://dx.doi.org/10.1093/infdis/jiu586)

56 Hsue, P.Y. *et al.* (2009) Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS* 23, 1059–1067

57 Hatano, H. *et al.* (2013) Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. *PLoS Pathog.* 9, e1003691

58 Chun, T.W. *et al.* (2013) Effect of antiretroviral therapy on HIV reservoirs in elite controllers. *J. Infect. Dis.* 208, 1443–1447