

# Determinants of natural HIV-1 control

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## Abstract

**HIV-1 infection usually progresses to AIDS within 10 years in antiretroviral therapy untreated individuals, but there is a group of infected individuals, known as controllers, who maintain low plasma HIV-1 RNA levels and normal CD4+ T-cell counts for many years. Evidence suggests that the mechanisms of viral control in these individuals are heterogeneous. In this review, we highlight the viral and host factors, particularly host immunological and immunogenetic factors that are associated with controller status. Despite the broad heterogeneity within controllers, there is compelling evidence that cytotoxic CD8+ T lymphocyte responses act as the main driver of control in the majority of these individuals, especially in those with protective HLA-I alleles. Further investigation of controllers without protective HLA-I alleles is required as it seems that this subset exhibits more durable control of HIV-1 disease progression. Understanding the immune defense mechanisms in controllers provides hope for harnessing these responses in the general population, either for protective or therapeutic vaccines or to achieve a functional cure in infected individuals.**

## Keywords

**HIV-1. Disease progression. Controllers. Non-progressors.**

## Introduction

HIV infection remains a global epidemic with approximately 39.6 million people living with the virus worldwide. The course of infection varies greatly between individuals, where a combination of host genetic, host immunological and viral factors contribute to differences in HIV-1 disease progression patterns<sup>1-3</sup>. Multiple studies have sought to determine these factors and understand their impact on disease progression, with the hope of harnessing these factors to control progression even in the absence of ARVs<sup>2,4-7</sup>. Various types of disease classifications have been used based on clinical and/or diagnostic criteria, years of follow-up, and viral load quantification<sup>1</sup>. The classifications in-

clude long-term non-progressors (LTNPs), long-term survivors, HIV-1 controllers (HICs), elite controllers (ECs), viremic controllers (VCs), viremic non-controllers, chronic progressors (CPs), and rapid progressors (RPs). Table 1 describes the criteria used to define these different terms and simplifies the classification of disease progression phenotypes (controllers, CP, and RP), with the goal of clarifying the terminology used to describe disease progression.

The mechanisms underlying natural HIV-1 control are not fully understood. Multiple factors are at play in different individuals; the achievement of control cannot be explained by one single factor<sup>2,5</sup> (Fig. 1). The purpose of this review is to give a concise overview of the different viral and host factors associated with differences in HIV-1 disease progression rate to date. While

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Table 1. HIV-1 disease progression classifications and criteria

Name	CD4+ counts (cells/mm <sup>3</sup> )	Years of follow-up	Viral load (plasma HIV RNA) (copies/ml)	ART	Symptomatic infection
Controllers <sup>a</sup>					
Elite controller (EC)	> 350 <sup>54</sup> /> 400-500 <sup>5,13</sup>	1 <sup>2</sup> /> 10 <sup>1,3,5</sup> /From months to years <sup>13,55</sup>	< 50 <sup>1,2,5,13,54,55</sup>	No <sup>1,3,5,13,54,55</sup>	No <sup>1,5</sup>
Viremic controller (VC)	> 350 <sup>13,54</sup>	*/> 10 <sup>1</sup>	50-2000 <sup>1,13,54,55</sup>	No <sup>1,54,55</sup>	No <sup>1</sup>
Long-term non-progressor (LTNP)	> 350 <sup>54</sup> /> 500 <sup>13,55</sup>	> 7 <sup>54</sup> /> 10 <sup>13,55</sup>	> 2000 <sup>54</sup> /≤ 10 000 <sup>13</sup>	No <sup>13,54</sup>	No <sup>55</sup>
Long-term survivor (LTS)	500 <sup>2,13,55</sup>	10 <sup>55</sup>	*	No	No symptoms/ AIDS-free <sup>55</sup>
HIV-1 controller (HIC)	*	1 <sup>55</sup> /≥ 5 <sup>2</sup> /10 <sup>55</sup> /	< 400 <sup>2</sup> /2000 <sup>55</sup>	No <sup>55</sup>	*
Viremic non- controller (VNC)	*	> 10 <sup>1</sup>	> 2000 <sup>1</sup>	No <sup>1</sup>	No
Chronic progressor (CP) <sup>1</sup>	*	*	> 2000	No	Yes
Rapid progressor (RP) <sup>1,55</sup>	- ≥2 CD4 T-cell measurements < 350 within 3 years after seroconversion, with no value > 350 afterward in the absence of antiretroviral therapy (ART). - And/or, ART initiated within 3 years after seroconversion, and at least one preceding CD4 < 350. - And/or, AIDS or AIDS-related death within 3 years after seroconversion and at least one preceding CD4 < 350.	3 (time to end point)	*	No	Death, AIDS, or ART initiation used as endpoints.

<sup>a</sup>Includes all patients with lack of disease progression.

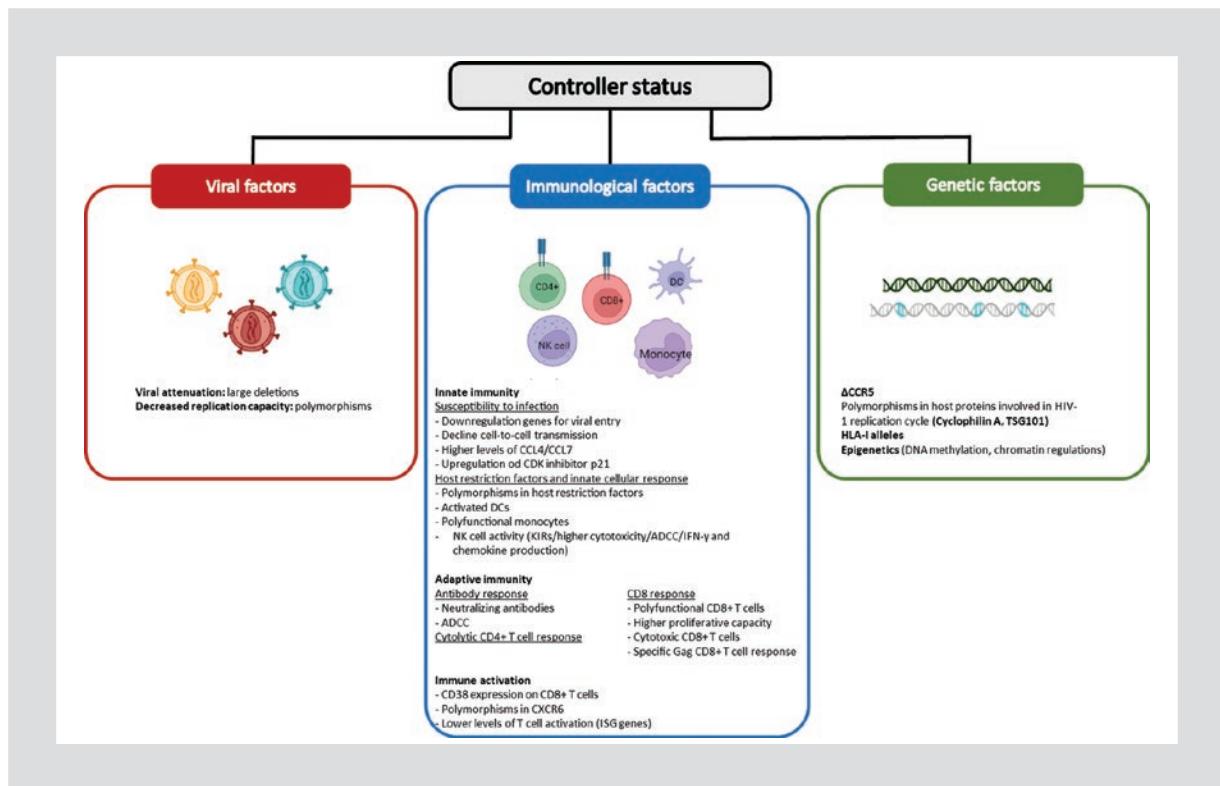
\*Parameter not used in this definition.

these factors are discussed separately, it is important to note that they are closely interlinked: the majority of host genetic factors linked to altered disease progression mediate their effect through influencing host immune responses to HIV-1; similarly, most viral genetic factors associated with slower or faster rates of disease progression are themselves consequences of host im-

mune responses and/or affect pathogenesis through altering the effectiveness of host immune responses.

## Viral factors

The impact of the virus strain on HIV-1 disease progression is clearly demonstrated by non-progression to dis-



**Figure 1.** Factors involved on the control of HIV-1 disease progression. Certain factors have been associated with the presence of controller status to date, including viral (red), immunological (blue) or genetic (green) factors. It should be noted that factors have been distributed into the different categories for easy visualization, and there may be some overlap between genetic and immunological factors (genetic traits may have a direct impact on immune responses, e.g., single nucleotide polymorphisms may impact on expression levels of immunological mediators).

ease in individuals infected with strains containing large deletions in the *nef* gene. Control in these cases may be explained by significant attenuation of the virus replication due to the deletions, as well as the absence of the many antagonistic effects of Nef, such as CD8+ cytotoxic T lymphocyte (CTL) evasion through Nef-mediated downregulation of HLA Class I (HLA-I) in infected cells. However, large viral deletions or gross sequence defects of the transmitted virus account for the minority of control cases<sup>3</sup>. Nevertheless, transmission of viruses with decreased replication capacity due to single-nucleotide polymorphisms rather than gross defects has also been shown to result in benefit to the host. For example, transmission of strains with attenuating CTL escape mutations in *gag* to HLA-mismatched hosts has been shown to result in lowered viral load set point or slower CD4+ T-cell decline in the host, and this may even facilitate development of controller status in some cases<sup>8,9</sup>. However, an attenuated virus alone is not sufficient for control, as is evidenced by loss of viral control when effective CTL responses are lacking despite virus attenuation<sup>10</sup>. While

numerous studies have shown an overall tendency for attenuated function of various proteins isolated from the plasma of EC during chronic infection<sup>7</sup>, it is likely that this is due to the immune responses of the EC attenuating the plasma virus, while replication competent virus is archived in the proviral DNA, rather than the attenuated virus being the cause of the control<sup>3</sup>. Furthermore, the isolation from some EC of replication competent viruses with replication/pathogenic potential equivalent to that of laboratory strains or viruses isolated from CP<sup>11</sup>, as well as transmission of replication competent viruses from EC to others who become progressors, illustrates that the development of controller status is likely to depend more on host factors than virus factors.

## Host factors

### Host genetics

Polymorphisms in host proteins that are involved in the replication cycle of HIV-1, such as CCR5 (a core-

ceptor for virus entry), cyclophilin A (promotes HIV-1 infectivity by facilitating viral uncoating), and Tsg101 (participates in HIV-1 budding by interacting with viral proteins), have been associated with differences in susceptibility to HIV-1 infection or in the rate of progression to AIDS<sup>12</sup>. CCR5 is the most well-known example here, where individuals who are homozygous for a 32-base pair deletion in the CCR5 gene show almost complete protection against CCR5-tropic HIV-1 acquisition<sup>5,13</sup> and bone marrow transplantation from donors homozygous for the CCR5 deletion mutation has led to the only 2 known cases of complete cure of HIV-1 – the “Berlin patient” and the “London patient”<sup>14</sup>. In addition, those who are heterozygous for the CCR5 deletion mutation show delayed progression to AIDS<sup>13</sup>. Interestingly, lower levels of CCR5 gene DNA methylation have also been associated with viral control<sup>15</sup>, indicating that epigenetics (modifications, determined by DNA methylation or chromatin regulations, that regulate gene transcription and expression without changing the DNA sequence) could also play a role in clinical course of HIV-1 infection<sup>4,16</sup>.

Besides polymorphisms in host proteins involved in virus replication, polymorphisms in host proteins key in the immune response against HIV-1 are associated with differences in disease progression rate. Indeed, the most significant genetic determinant of clinical outcome in HIV-1 infection is the HLA-I profile of the host<sup>3</sup>. HLA-I molecules present viral peptides to HIV-specific CTLs, allowing for recognition and elimination of infected cells. “Protective” HLA-I alleles, such as HLA-B\*27, HLA-B\*57, HLA-B\*58:01, HLA-B\*81:01, and HLA-A\*74, have been associated with low viral loads and slower progression to AIDS, while “risk” HLA-I alleles, such as HLA-B\*35, HLA-B\*08, HLA-B\*58:02, and HLA-B\*18, have been associated with a susceptibility to rapid disease progression<sup>17</sup>. The amino acid variants at positions in the peptide binding groove appear to distinguish these “protective” and “risk” HLA-I alleles<sup>3</sup>. Protective HLA-I alleles in conjunction with specific natural killer (NK) receptors, known as killer inhibitory receptors (KIRs), have also been shown to increase the likelihood of achieving controller status<sup>3</sup>. For example, KIR3DS1 and KIR3DL1, when interacting with HLA-B alleles, are associated with delayed disease progression in cohorts of HIV-1-positive individuals with spontaneous control of viral load<sup>18</sup>. In addition, HLA-B\*57 expressed in combination with KIR3DL1\**h/y*, as well as a higher KIR3DS1/L1 ratio (corresponding to a lower threshold for NK activation)<sup>19</sup>, is more prevalent in exposed seronegative individuals, suggesting

that these characteristics may contribute to HIV-1 resistance. The underlying basis for the particularly strong association between HLA-I alleles and HIV-1 disease progression (and/or resistance to HIV-1 infection) is not fully understood but appears to involve the specificity and quality of the CTL response, the interaction between HLA-I alleles and NK cells, as well as the relationship between HLA-I alleles and immune activation status as further discussed below.

## **Host immune response**

Consistent with the strong association between different HLA-I alleles and differences in clinical course, the CTL response, which is determined in part by HLA-I alleles, is the dominant feature of immune defense in EC<sup>20</sup>. However, there is considerable heterogeneity between controllers, and additional factors may act together with or independently of CTLs to achieve virus control<sup>21</sup>. In addition, a subset of EC may eventually lose control while others maintain durable control<sup>6,22</sup>. More recently, transcriptome studies have identified genes that are differentially expressed in CP and controllers, thereby contributing to the understanding of pathogenesis as well as potential mechanisms involved in control of disease progression and these studies are highlighted below. A discussion on various immune responses and their role in determining rate of disease progression, as well as durability of virus control, follows.

## **Innate immunity**

### **Susceptibility to infection**

Data suggest that ECs have a reduced susceptibility of target cells to support HIV-1 infection. Zhang et al. (2018)<sup>16</sup> performed transcriptome analysis and observed that CXCR6 and SIGLEC1 genes were down-regulated in EC, suggesting that a mechanism for increased control in EC is decreased susceptibility of T lymphocytes to HIV-1 entry and declined cell-to-cell transmission mediated by myeloid cells<sup>23</sup>. They also describe higher levels of CCL4 and CCL7 in EC than CP; CCL4 and CCL7 are chemokines that bind to CCR5, one of the coreceptors used by HIV-1 to enter the cell<sup>16</sup>. Multiple studies show that CD4+ T cells from EC are resistant to HIV-1 infection in culture, and some have associated this phenotype with increased levels of cyclin-dependent kinase (CDK) inhibitor p21. It has been suggested that p21 may indirectly block HIV-1

reverse transcription by inhibiting CDK2-dependant phosphorylation<sup>24</sup>.

### **Host restriction factors and innate cellular response**

Host restriction factors constitute a first line of defense; they block steps in the viral replication cycle, and some can also act as sensors that trigger innate responses against infections. Polymorphisms in the interferon (IFN- $\alpha$ ) receptor as well as restriction genes upregulated by IFN- $\alpha$ , namely, APOBEC3G, SAMHD1, tetherin, and TRIM5a, have been linked to differences in disease progression<sup>25</sup>. However, it appears that polymorphisms in identified restriction factors are not the cause of viral control in the majority of EC<sup>26</sup>.

Innate cells, including dendritic cells (DC), monocytes, and NK cells, may play a role in determining the rapidity of disease progression. HIV-1 activates DCs through toll-like receptors (TLRs) and induces the secretion of cytokines, such as type 1 IFN. Studies show an increase in the antigen-presenting properties of myeloid DCs of EC, while their TLR-dependent secretion of pro-inflammatory cytokines is reduced<sup>27</sup>. Multiple studies have shown that ECs have higher levels of plasmacytoid DCs than CP, and similar levels to uninfected individuals, with preserved functionality that translates into sustained secretion of type 1 IFN and induction of T-cell apoptosis, thereby reducing viral production<sup>28,29</sup>. Superior monocyte function is also indicated in controllers; specifically, transcriptomic studies suggest that monocytes may contribute to the phenotype of viral control. In monocytes from LTNP, compared with CP, there is an upregulation of inter-related pathways of TLR signaling (with downstream expression of antiviral cytokines), cytokine-cytokine receptor interactions, the cell cycle pathway, apoptosis, and transendothelial migration, which indicate superiority in the innate immune response in monocytes from LTNP compared to CP<sup>30</sup>. Furthermore, a longitudinal single-cell transcriptomic analysis suggests that monocytes, as well as NK cells, acting alongside T cells could play a role in the development of the controller phenotype<sup>31</sup>. In that study, the hyperacute phase was characterized by pro-inflammatory T-cell differentiation, prolonged monocyte MHC II upregulation, and persistent NK cell cytolytic killing. During the early weeks of infection in two individuals who became VC, the authors identified polyfunctional monocytes, as well as a subset of cytotoxic, proliferating NK cells, and suggest that the proliferating NK cells may function

alongside CTLs early in infection, thereby mitigating CTL antigenic load and subsequent exhaustion.

Various other studies have also linked better NK functionality with VC<sup>18,19,32</sup>. As described in the host genetics section of this review, specific NK receptors in conjunction with protective HLA-I alleles have been shown to increase the likelihood of achieving controller status<sup>18</sup>. These receptor-HLA combinations may associate with better NK functionality. For example, controllers expressing HLA-Bw4\*801 on target cells and KIR3DL1 on NK cells displayed a stronger target cell-induced NK cytotoxicity compared with CD8+ T cells of the same individuals<sup>33</sup>. A study evaluating the phenotypic and functional properties of CD56/CD16 NK cells, found higher IFN- $\gamma$  expression and cytolytic activity in the CD3-CD56+ NK subset in LTNP and controllers than in CP<sup>34</sup>. This subset of NK cells usually diminishes with HIV-1 infection<sup>34</sup>. Further, increased IFN- $\gamma$  and chemokine production (CCL3, CCL4, and CCL5; natural ligands of CCR5) of NK cells have been associated with resistance to HIV-1 infection and delayed disease progression<sup>18</sup>.

### **Adaptive immunity**

#### **Antibody response**

Several studies have shown that ECs have lower titers of broadly neutralizing antibodies and similar levels of autologous neutralizing antibodies when compared with CP<sup>35</sup>, suggesting that neutralizing antibody responses are not a main determinant of EC of HIV-1 replication. Data suggest that sufficient antigenic stimulation is generally required to develop broadly neutralizing antibody activity<sup>36</sup>, however, there is considerable heterogeneity in controllers, and although less common, broadly neutralizing antibodies have been detected in EC<sup>36</sup>. Interestingly, neutralizing antibodies to a conserved gp41 epitope were reported to be more common in LTNP (24%) than CP (<5%) and hypothesized to contribute to long-term control in these individuals<sup>37</sup>.

There is some evidence that non-neutralizing antibody activity may play a role in viral control. NK cells can mediate antibody-dependent cellular cytotoxicity (ADCC), linking innate and adaptive immunity, and these responses were reported to be stronger in HIC<sup>35</sup>. ADCC against Env and Vpu proteins, which is mediated largely by NK cells, is also associated with EC<sup>5</sup>. However, the causal link between ADCC and EC is not determined, particular since, compared with EC,

equally potent ADCC activity was shown in some acutely infected individuals and individuals on ART, which may suggest that persistent viremia is responsible for a loss in ADCC activity<sup>38</sup>.

### **CD4+ T-cell responses**

HIV-specific CD4+ T-cell responses of EC and LTNPs have a higher cytolytic response and proliferative potential than those of CP, and also result in the secretion of multiple cytokines, including IL-2, on stimulation, while CD4+ T cells from CP mostly secrete IFN- $\gamma$ <sup>26,39</sup>. Further, there are preserved central memory and activated effector memory CD4+ T-cell subsets in HICs<sup>40,41</sup>. The preservation of a strong CD4+ T-cell response in controllers may be important for CD8+ T-cell-mediated control of virus replication, but whether or not it is crucial is unknown<sup>6,42</sup>. However, a study has shown that IL-21-secreting CD4+ T cells (preserved in EC) may contribute to viral control through enhancing CD8+ T-cell function<sup>43</sup>. It is also unclear whether preserved CD4+ T-cell responses in controllers are a cause or consequence of low viremia and there are conflicting data in this regard<sup>26,44</sup>. It is clear at least that the proliferative capacity of HIV-specific CD4+ T cells can be restored by ART to levels observed in LTNPs, suggesting that this characteristic is influenced by the level of viremia<sup>3</sup>.

### **CD8+ T-cell responses**

Most of the immunological studies focus on CD8+ T cells as there is a consensus that they are the main immunological driver of control. As with HIV-specific CD4+ T-cell responses, there are qualitative differences in HIV-specific CD8+ T-cell responses between EC or VC and CP. HIV-specific CD8+ T cells from EC and/or LTNPs are more polyfunctional (can secrete multiple cytokines)<sup>20</sup>, have a higher proliferative capacity when stimulated, are more efficient at lytic granule loading, and have a higher per cell killing capacity<sup>20</sup>. Interestingly, some studies have found restoration of CD8+ T-cell polyfunctionality by ART, suggesting that polyfunctionality might be a consequence rather than cause of low viremia<sup>45</sup>. It is argued that polyfunctionality is not likely to be an important determinant of immune control as polyfunctional cells form a small subset of the total HIV-specific CD8+ T-cell response<sup>46</sup>. However, proliferative and cytotoxic capacities of CD8+ T cells were superior in LTNPs when compared with patients on ART and

these characteristics may contribute to immune control of HIV-1<sup>2,26</sup>.

Several studies show that Gag-specific CD8+ T-cell responses are associated with better suppression of viral replication<sup>2,3</sup>. In particular, ECs with protective HLA-I alleles have CD8+ T-cell responses focused on key Gag epitopes which have limited toleration to sequence variation due to structural and functional constraints, thereby allowing them to maintain immune pressure on the virus<sup>20</sup>. Furthermore, CD8+ T cells from controllers present a higher capacity to suppress viral infection *ex vivo*<sup>6,21</sup>, which is suggested to be the primary mechanism of control in VC with protective HLA-I alleles, but not in those without protective alleles<sup>21</sup>. Furthermore, CD8+ T cells restricted by the protective HLA-I alleles are not suppressed by T regulatory cells, in contrast with those restricted by non-protective alleles<sup>47</sup>. Specific TCR clonotypes that interact with the peptide-HLA-I allele complex, together with protective HLA-I alleles, may also determine the antiviral efficacy<sup>48</sup>.

While some individuals are able to maintain control for long periods of time, a proportion of controllers eventually lose control<sup>6</sup>. Loss of control in controllers has been associated with CD8+ T-cell activity. In controllers, before loss of control, a decrease in antiviral *in vitro* capacity of CD8+ T cells, together with an increase in expression of T-cell activation and exhaustion markers (high levels of PD-1 expressing CD8+ T cells), is a predictor of failing immune control<sup>22</sup>. CTL escape mutations were not, however, significantly correlated with loss of control in that study<sup>22</sup>. A longitudinal study of EC identified the characteristics of those individuals that eventually lose control, termed as “transient EC,” showing that these individuals present lower Gag-specific T-cell polyfunctionality, a higher viral diversity, and a profile of higher pro-inflammatory cytokine levels before loss of control, when compared to persistent EC<sup>6</sup>. Interestingly, a decrease on CD8+ T-cell breadth has been associated with a loss of control in VC with protective HLA-I alleles, while individuals without HLA-I protective alleles exhibit durable control which appears to be independent of CD8+ T-cell responses<sup>21</sup>.

It is worth noting that most studies have focused on studying CD8+ T cells responses in blood, however, a recent study has associated EC with distinct functional and transcriptional signatures of CD8+ T cells in lymphoid tissue<sup>49</sup>. That study showed higher levels of memory and follicle homing HIV-specific CD8+ T cells in lymph nodes of EC when compared to CP. These cells suppressed viral replication without demonstrable

cytolytic activity and presented a downregulation of inhibitory receptors and cytolytic molecules as well as an upregulation of multiple cytokines. This suggests that the CTL-mediated mechanisms of action may differ somewhat between blood and tissues, and more studies of cells in tissues are warranted.

## Immune activation

There is much evidence supporting that immune activation plays a role in HIV-1 disease progression. The expression of CD38 (a marker of activation) on CD8+ T cells can predict progression to AIDS to a similar degree as HIV-1 viral load in early infection and is the strongest predictor in later infection<sup>50</sup>. In addition, polymorphisms in the CXCR6 receptor (a mediator of inflammation) are strongly associated with LTNP<sup>13</sup>, and polymorphisms in genes encoding pro-inflammatory (e.g., tumor necrosis factor- $\alpha$ ) and anti-inflammatory cytokines (e.g., IL-10) have been associated with altered rates of disease progression<sup>51</sup>. ECs have lower levels of HIV-specific CD8+ and CD4+ T-cell activation<sup>2</sup>, and have immune activation restricted to the T-cell effector compartment and not a generalized pattern of immune activation<sup>40</sup>. T-cell transcriptome analysis shows a role of reduced IFN-stimulated genes (ISGs) associated with non-progressor status in LTNP and EC, and the reduction of ISG genes expression translates in a reduction of the immune system activation<sup>4</sup>. Whole-blood transcriptome studies describe a novel ISG gene (LY6E), which restrains the hyperactivation of monocytes during HIV-1 infection, which was upregulated in CP<sup>52</sup>. Activation markers, such as the above-mentioned CD38, as well as LAG-3 (coinhibitory molecule) were also downregulated in controllers<sup>4</sup>. Recently, a novel mechanism of HLA-I-mediated protection was described for certain HLA alleles; namely, the reduction of microbial translocation and consequently reduction in immune activation during acute HIV-1 infection<sup>53</sup>. Collectively, these studies highlight that restriction of immune activation is a key feature in controllers.

## Conclusions

The existence of individuals able to control HIV-1 infection in the absence of ARVs provides evidence that natural control of disease progression is possible. Despite the broad heterogeneity within controllers, there is compelling evidence that CTL responses act as the main driver of control in the majority of these

individuals, especially in those with protective HLA-I alleles. However, not all controllers rely on protective HLA-I alleles and CD8+T cells as mechanisms of control. Further investigation of controllers without protective HLA-I alleles is required as it seems that this subset of controllers exhibits more durable control of HIV-1 disease progression. Understanding the immune defense mechanisms in these individuals perhaps also provides more hope for harnessing a response in the general population, either for protective or therapeutic vaccines or to achieve a functional cure in infected individuals, that does not rely on the expression of protective HLA-I alleles.

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